

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-024/S008

Trade Name: PRIFTIN®

Generic Name: rifapentine

Sponsor: Sanofi Aventis US

Approval Date: 6/1/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:
21-024/S008**

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-024/S008

APPROVAL LETTER



NDA 21-024/S-008

Sanofi-Aventis U.S. LLC
Attention: Mr. John Cook
Senior Manager, US Regulatory Affairs Marketed Products
55 Corporate Drive
Bridgewater, NJ 08807

Dear Mr. Cook,

Please refer to your supplemental new drug application dated July 12, 2007, received July 13, 2007, and 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 March 11, 2008, May 9, 2008, May 22, 2008, April 23, 2009 and May 29, 2009.

Your application dated July 12, 2007, contained the results of US Public Health Service (USPHS) Study 22 which addressed the efficacy and relapse rates in subjects in whom rifapentine once-weekly dosing was used for 4 months as a component of the continuation phase of anti-tuberculosis treatment with isoniazid (INH) and compared to the standard continuation regimen of rifampin and INH twice a week for 4 months.

We reviewed this information and on May 13, 2008, issued an approvable letter stating that before the application may be approved, you must submit draft labeling as revised in the package insert enclosed with the approvable letter.

Your submission dated April 23, 2009 constituted a complete response to our May 13, 2008 action letter.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions as agreed in the communication dated June 1, 2009. The revisions are listed below (~~strikethrough~~ = deleted text):

1. The 6th paragraph of section **6.2 Clinical Trials Experience** has been revised as follows:

Seven patients had adverse reactions: (b) (4) associated with an overdose. In the rifampin combination group these reactions included hematuria, anorexia, back pain, arthralgia, and myalgia. In the rifapentine combination

group these reactions included hematuria, neutropenia, hyperglycemia, ALT increased, hyperuricemia, pruritus, and arthritis.

2. The labeling should not have the lines in the left margin which denote that new information has been added to the labeling. These lines were deleted from the labeling.

We approved this NDA on June 22, 1998 under 21 CFR 314.510 of Subpart H-Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses. Approval of this supplemental application fulfills your commitments made under 21 CFR 314.510.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. This application was granted Orphan Designation on June 1995 and therefore is exempt from this requirement.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>, that is identical in content to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate these submissions “**SPL for approved supplements NDA 21-024/S-008.**”

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Hyun Son, Pharm.D., Senior Regulatory Management Officer, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Package Insert

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this page is the manifestation of the electronic signature.**

/s/

Renata Albrecht
6/1/2009 05:08:59 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-024/S008

OTHER ACTION LETTER(s)



NDA 21-024/S-008

Sanofi-Aventis U.S. LLC
Attention: Mr. John Cook
Senior Manager
US Regulatory Affairs Marketed Products
55 Corporate Drive
Bridgewater, NJ 08807

Dear Mr. Cook

Please refer to your supplemental new drug application dated July 12, 2007, received July 13, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Priftin[®] (rifapentine) 150 mg Tablets.

This application is subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

We acknowledge receipt of your submissions dated March 11, 2008 and May 9, 2008.

This supplemental new drug application contains results of US Public Health Service (USPHS) Study 22 which addresses the issue of efficacy and relapse in subjects in whom rifapentine once a week dose was utilized as a component of the Continuation phase (last 4 months) of anti-tuberculosis treatment with INH as compared to the standard Continuation regimen of rifampin and INH twice a week for 4 months.

We completed our review of this application, as amended, and it is approvable. Before this application may be approved, however, you must submit draft labeling as revised in the enclosed package insert.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
 4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
 5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
 6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
 7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

If you have any questions, call Hyun Son, Pharm.D., Senior Regulatory Management Officer, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Proposed Package Insert

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this page is the manifestation of the electronic signature.**

/s/

Renata Albrecht
5/13/2008 07:25:52 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-024/S008

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PRIFTIN® safely and effectively. See full prescribing information for PRIFTIN.

Priftin (rifapentine) Tablets

Initial U.S. Approval: 1998

INDICATIONS AND USAGE

- Rifapentine is a rifamycin antimycobacterial indicated for the treatment of pulmonary tuberculosis caused by *Mycobacterium tuberculosis* in combination with one or more antituberculosis drugs. (1)

DOSAGE AND ADMINISTRATION

- PRIFTIN has been studied for the treatment of tuberculosis caused by drug-susceptible organisms as part of regimens consisting of an initial 2 month phase followed by a 4 month continuation phase. (2.1)
- PRIFTIN should not be used alone in either the initial or the continuation phases of antituberculous treatment. (2.1)
- Initial Phase (2 Months):** 600 mg twice weekly for two months by direct observation of therapy, with an interval of no less than 3 consecutive days (72 hours) between doses, in combination with other antituberculosis drugs. (2.1)
- Continuation Phase (4 Months):** 600 mg once weekly for 4 months by direct observation therapy with isoniazid or another appropriate antituberculous agent. (2.1)
- Concomitant administration of pyridoxine (Vitamin B6) is recommended in order to avoid INH-associated peripheral neuropathy. (2.2)
- Take with food. (2.2)

DOSAGE FORMS AND STRENGTHS

- 150 mg tablets. (3)

CONTRAINDICATIONS

Known hypersensitivity to any rifamycin. (4.1)

WARNINGS AND PRECAUTIONS

- Do not use as a once weekly Continuation Phase regimen with isoniazid in HIV seropositive patients due to the risk of failure and/or relapse with rifampin-resistant organisms. (5.1, 14)

- Co-administration with Protease Inhibitors and Reverse Transcriptase Inhibitors. (5.2, 7.1)
- Higher relapse rates occur in patients with cavitary pulmonary lesions and/or positive sputum cultures after the initial phase of treatment or those with evidence of bilateral pulmonary disease: Use cautiously. (5.3)
- Hepatotoxicity: In patients with abnormal liver tests/disease monitor liver tests prior to therapy and every 2-4 weeks during therapy. If signs of disease occur or worsen, discontinue therapy. (5.4)
- Hyperbilirubinemia: Repeat testing and reassess patient. (5.5)
- Discoloration of body fluids: May permanently stain contact lenses or dentures red-orange. (5.6)
- Porphyria: Avoid use in these patients. (5.7)
- Clostridium difficile*-associated colitis: Evaluate if diarrhea occurs. (5.8)

ADVERSE REACTIONS

The most common adverse reactions ($\geq 10\%$) are hyperuricemia, pyuria, hematuria, urinary tract infection, proteinuria, lymphopenia, neutropenia, anemia, and hypoglycemia. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis U.S. LLC at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Protease Inhibitors and Reverse Transcriptase Inhibitors. (5.2, 7.1)
- Hormonal Contraceptives: Use another means of birth control. (7.2)
- May increase metabolism and decrease the activity of drugs metabolized by cytochrome P450 3A4 and 2C8/9. Dosage adjustments may be necessary if given concomitantly. (7.3)

USE IN SPECIFIC POPULATIONS

- Pediatrics: The safety and effectiveness under the age of 12 has not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: June 2009

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

PRIFTIN[®] is indicated for the treatment of pulmonary tuberculosis caused by *Mycobacterium tuberculosis*. PRIFTIN must always be used in combination with one or more antituberculosis drugs to which the isolate is susceptible depending on the phase of treatment [*see Dosage and Administration (2) and Clinical Studies (14)*].

Limitations of Use

PRIFTIN should not be used as a once weekly Continuation Phase regimen in combination with isoniazid in HIV seropositive patients with pulmonary tuberculosis because of a higher rate of failure and/or relapse documented with the presence of rifampin-resistant organisms [*see Warnings and Precautions (5.1) and Clinical Studies (14)*].

PRIFTIN has not been studied as part of the Initial Phase treatment regimen in HIV seropositive patients with pulmonary tuberculosis.

PRIFTIN should not be used as monotherapy in either the initial or the continuation phases of antituberculous treatment.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

PRIFTIN has been studied for the treatment of tuberculosis caused by drug-susceptible organisms as part of regimens consisting of an initial 2 month phase followed by a 4 month continuation phase.

These recommendations apply only to the treatment of patients with drug-susceptible organisms.

Initial Phase (2 Months) of short course treatment for pulmonary tuberculosis:

PRIFTIN should be administered at a dose of 600 mg (4 x 150 mg tablets) twice weekly for two months by direct observation of therapy, with an interval of no less than 3 consecutive days (72 hours) between doses, in combination with other antituberculosis drugs as part of an appropriate regimen which includes daily companion drugs such as ethambutol, pyrazinamide, and streptomycin.

The determination of the companion drugs to be used should be made by the treating physician and depends on the results of susceptibility testing as well as the phase of treatment. PRIFTIN has been studied as part of the initial regimen with isoniazid, pyrazinamide and ethambutol [*see Clinical Studies (14)*].

Continuation Phase (4 Months) of short course treatment for pulmonary tuberculosis:

Following the Initial Phase (2 months), Continuation Phase (4 months) treatment may consist of PRIFTIN 600 mg once weekly for 4 months in combination with isoniazid or an appropriate antituberculosis agent for susceptible organisms by direct observation therapy.

PRIFTIN was studied as a component of a 4 month continuation phase in conjunction with INH 900 mg once a week in two clinical studies [see *Clinical Studies (14)*].

The prescribing physician is directed to current guidelines for further direction on other possible components of the Continuation Phase regimen as well as for directions on extending this phase.

2.2 Administration

Take PRIFTIN with meals. Administration of rifapentine with a meal increases oral bioavailability and may reduce the incidence of gastrointestinal upset, nausea, and/or vomiting. [see *Clinical Pharmacology (12.3)*].

In patients with conditions which predispose them to neuropathy (e.g., nutritional deficiency, HIV infection, renal failure, alcoholism, as well as pregnant and breastfeeding women), concomitant administration of pyridoxine (Vitamin B6) is recommended in order to avoid INH-associated peripheral neuropathy (see American Thoracic Society/Centers for Disease Control/Infectious Disease Society of America Guideline for the Treatment of Tuberculosis and Tuberculosis Infection in Adults and Children).

3 DOSAGE FORMS AND STRENGTHS

PRIFTIN is supplied as 150 mg round normal convex dark-pink film-coated tablets debossed “Priftin” on top and “150” on the bottom.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

PRIFTIN is contraindicated in patients with a history of hypersensitivity to rifamycins.

5 WARNINGS AND PRECAUTIONS

5.1 HIV Seropositive Patients

PRIFTIN should not be used as a once weekly Continuation Phase regimen in combination with isoniazid in HIV seropositive patients with pulmonary tuberculosis because of a higher rate of failure and/or relapse documented with the presence of rifampin-resistant organisms [see *Clinical Studies (14)*].

PRIFTIN has not been studied as part of the Initial Phase treatment regimen in HIV seropositive patients with pulmonary tuberculosis.

5.2 Protease Inhibitors and Reverse Transcriptase Inhibitors

Rifapentine is an inducer of CYP450 enzymes. Concomitant use of PRIFTIN with other drugs metabolized by these enzymes, such as protease inhibitors and reverse transcriptase inhibitors, may cause a significant decrease in plasma concentrations and loss of therapeutic effect of the

protease inhibitor or reverse transcriptase inhibitor. [see *Drug Interactions (7.1 and 7.2)* and *Clinical Pharmacology (12.3)*]

5.3 Relapse of Tuberculosis

PRIFTIN should be used cautiously in subjects with cavitory pulmonary lesions and/or positive sputum cultures after the initial phase of treatment or in those with evidence of bilateral pulmonary disease due to higher rates of relapse. [see *Clinical Studies (14)*].

Poor compliance with the dosage regimen, particularly during the initial phase in the companion antituberculosis drugs administered with rifapentine, is associated with late sputum conversion and a high relapse rate. Therefore, compliance with the full course of therapy must be emphasized, and the importance of not missing any doses must be stressed [see *Patient Counseling Information (17)*].

Higher relapse rates have also been seen in HIV positive patients receiving PRIFTIN during the continuation phase. Risk factors for relapse included the presence of both pulmonary and extrapulmonary disease at baseline, low CD4 counts, use of azole antifungals and age (younger) [see *Clinical Studies (14)*].

5.4 Hepatotoxicity

Since antituberculous multidrug treatments, including the rifamycin class, are associated with serious hepatic events, patients with abnormal liver tests and/or liver disease should only be given rifapentine in cases of necessity and then with caution and under strict medical supervision. In these patients, careful monitoring of liver tests (especially serum transaminases) should be carried out prior to therapy and then every 2 to 4 weeks during therapy. If signs of liver disease occur or worsen, rifapentine should be discontinued. Hepatotoxicity of other antituberculosis drugs (eg, isoniazid, pyrazinamide) used in combination with rifapentine should also be taken into account.

5.5 Hyperbilirubinemia

Hyperbilirubinemia resulting from competition for excretory pathways between rifapentine and bilirubin cannot be excluded since competition between the related drug rifampin and bilirubin can occur. An isolated report showing a moderate rise in bilirubin and/or transaminase level is not in itself an indication for interrupting treatment; rather, the decision should be made after repeating the tests, noting trends in the levels and considering them in conjunction with the patient's clinical condition.

5.6 Discoloration of Body Fluids

PRIFTIN may produce a predominately red-orange discoloration of body tissues and/or fluids (eg, skin, teeth, tongue, urine, feces, saliva, sputum, tears, sweat, and cerebrospinal fluid). Contact lenses or dentures may become permanently stained.

5.7 Porphyria

PRIFTIN should not be used in patients with porphyria. Rifampin has enzyme-inducing properties, including induction of delta amino levulinic acid synthetase. Isolated reports have

associated porphyria exacerbation with rifampin administration. Based on these isolated reports with rifampin, it may be assumed that rifapentine has a similar effect.

5.8 *Clostridium difficile*-Associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including the rifamycins, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

6 ADVERSE REACTIONS

6.1 Serious and Otherwise Important Adverse Reactions

The following serious and otherwise important adverse drug reactions are discussed in greater detail in other sections of labeling:

- Hypersensitivity [see *Contraindications (4.1)*]
- Hepatotoxicity [see *Warnings and Precautions (5.4)*]
- Hyperbilirubinemia [see *Warnings and Precautions (5.5)*]
- Discoloration of Body Fluids [see *Warnings and Precautions (5.6)*]
- Porphyria [see *Warnings and Precautions (5.7)*]
- *Clostridium difficile*-Associated Diarrhea [see *Warnings and Precautions (5.8)*]

6.2 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to PRIFTIN in a randomized, open label, active-controlled trial of patients with pulmonary tuberculosis, excluding those with HIV-infection. The population consisted of primarily of male subjects with a mean age of 37 ± 11 years. In the initial 2 month phase of treatment (60 days), 361 patients received rifapentine 600 mg twice a week in combination with daily isoniazid, pyrazinamide, and ethambutol and 361 subjects received rifampin in combination with isoniazid, pyrazinamide and ethambutol all administered daily. Ethambutol was discontinued when drug susceptibility testing was completed. During the 4

month continuation phase, 321 patients in the rifapentine group continued to receive rifapentine 600 mg dosed once weekly with isoniazid and 307 patients in the rifampin arm received twice weekly rifampin and isoniazid. Both treatment groups received pyridoxine (Vitamin B6) over the 6 month treatment period.

Twenty-two deaths occurred in the study (eleven in the rifampin combination therapy group and eleven in the rifapentine combination therapy group).

In the study, 18/361 (5.0%) rifampin combination therapy patients discontinued the study due to an adverse reaction compared to 11/361 (3.0%) rifapentine combination therapy patients. Three patients (two rifampin combination therapy patients and one rifapentine combination therapy patient) were discontinued in the Initial Phase as a result of hepatitis with increased liver function tests (ALT, AST, LDH, and bilirubin). Concomitant medications for all three patients included isoniazid, pyrazinamide, ethambutol, and pyridoxine. The two rifampin patients and one rifapentine patient recovered without sequelae.

As shown in Table 1, hyperuricemia was the most frequently reported reaction and was most likely related to the pyrazinamide since only two cases were reported in the Continuation Phase when this drug was no longer included in the treatment regimen.

Seven patients had adverse reactions associated with an overdose. In the rifampin combination group these reactions included hematuria, anorexia, back pain, arthralgia, and myalgia. In the rifapentine combination group these reactions included hematuria, neutropenia, hyperglycemia, ALT increased, hyperuricemia, pruritus, and arthritis.

The following table (Table 1) presents treatment-emergent adverse reactions associated with the use of any of the four drugs in the regimens (rifapentine/rifampin, isoniazid, pyrazinamide, or ethambutol) which occurred in $\geq 1\%$ of patients during treatment and post-treatment through the first three months of follow-up.

System Organ Class Preferred Term	<i>Initial Phase¹</i>		<i>Continuation Phase²</i>		<i>Total³</i>	
	<i>Rifapentine Combination (N=361) N(%)</i>	<i>Rifampin Combination (N=361) N(%)</i>	<i>Rifapentine Combination (N=304) N(%)</i>	<i>Rifampin Combination (N=317) N(%)</i>	<i>Rifapentine Combination (N=361) N(%)</i>	<i>Rifampin Combination (N=361) N(%)</i>
RENAL & URINARY						
Pyuria	39 (10.8)	56 (15.5)	47 (14.8)	36 (11.8)	78 (21.6)	83 (23.0)
Proteinuria	36 (10.0)	53 (14.7)	14 (4.4)	27 (8.9)	47 (13.0)	71 (19.7)
Hematuria	39 (10.8)	38 (10.5)	32 (10.1)	27 (8.9)	64 (17.7)	61 (16.9)
Urinary Tract Infection	32 (8.9)	24 (6.6)	23 (7.3)	10 (3.3)	48 (13.3)	32 (8.9)
Urinary Casts	20 (5.5)	22 (6.1)	11 (3.5)	7 (2.3)	29 (8.0)	28 (7.8)
Cystitis	5 (1.4)	6 (1.7)	1 (0.3)	1 (0.3)	6 (1.7)	7 (1.9)
METABOLIC & NUTRITIONAL						
Hyperuricemia	115 (31.9)	83 (23.0)	0 (0.0)	2 (0.7)	115 (31.9)	83 (23.0)
Hyperkalemia	14 (3.9)	22 (6.1)	20 (6.3)	21 (6.9)	33 (9.1)	41 (11.4)
Hypoglycemia	22 (6.1)	27 (7.5)	15 (4.7)	11 (3.6)	36 (10.0)	35 (9.7)
Nonprotein Nitrogen Increased	4 (1.1)	3 (0.8)	10 (3.2)	15 (4.9)	14 (3.9)	17 (4.7)
Hyperglycemia	10 (2.8)	8 (2.2)	4 (1.3)	2 (0.7)	13 (3.6)	9 (2.5)
LDH Increased	5 (1.4)	7 (1.9)	0 (0.0)	2 (0.7)	5 (1.4)	9 (2.5)
Hyperphosphatemia	2 (0.6)	1 (0.3)	3 (0.9)	5 (1.6)	5 (1.4)	6 (1.7)

HEMATOLOGIC						
Anemia	41 (11.4)	41 (11.4)	5 (1.6)	10 (3.3)	44 (12.2)	51 (14.1)
Lymphopenia	38 (10.5)	37 (10.2)	10 (3.2)	9 (3.0)	46 (12.7)	45 (12.5)
Neutropenia	22 (6.1)	21 (5.8)	27 (8.5)	24 (7.9)	45 (12.5)	41 (11.4)
Leukopenia	16 (4.4)	11 (3.0)	11 (3.5)	9 (3.0)	24 (6.6)	17 (4.7)
Leukocytosis	6 (1.7)	13 (3.6)	5 (1.6)	2 (0.7)	11 (3.0)	15 (4.2)
Neutrophilia	5 (1.4)	11 (3.0)	4 (1.3)	2 (0.7)	9 (2.5)	13 (3.6)
Thrombocytosis	20 (5.5)	13 (3.6)	1 (0.3)	0 (0.0)	20 (5.5)	13 (3.6)
Thrombocytopenia	6 (1.7)	6 (1.7)	4 (1.3)	6 (2.0)	9 (2.5)	11 (3.0)
Polycythemia	3 (0.8)	2 (0.6)	5 (1.6)	3 (1.0)	8 (2.2)	5 (1.4)
Lymphadenopathy	4 (1.1)	2 (0.6)	0 (0.0)	2 (0.7)	4 (1.1)	4 (1.1)
BODY AS A WHOLE - GENERAL						
Back Pain	15 (4.2)	11 (3.0)	11 (3.5)	4 (1.3)	25 (6.9)	15 (4.2)
Pain	14 (3.9)	17 (4.7)	8 (2.5)	5 (1.6)	22 (6.1)	22 (6.1)
Chest Pain	10 (2.8)	11 (3.0)	10 (3.2)	5 (1.6)	20 (5.5)	16 (4.4)
Injury Accident	5 (1.4)	5 (1.4)	12 (3.8)	14 (4.6)	17 (4.7)	17 (4.7)
Abdominal Pain	3 (0.8)	3 (0.8)	4 (1.3)	4 (1.3)	7 (1.9)	7 (1.9)
Fever	5 (1.4)	7 (1.9)	1 (0.3)	1 (0.3)	5 (1.4)	7 (1.9)
Fatigue	3 (0.8)	1 (0.3)	1 (0.3)	3 (1.0)	4 (1.1)	4 (1.1)
Edema Dependent	4 (1.1)	1 (0.3)	0 (0.0)	1 (0.3)	4 (1.1)	2 (0.6)
DERMATOLOGIC						
Rash	15 (4.2)	26 (7.2)	8 (2.5)	8 (2.6)	22 (6.1)	33 (9.1)
Sweating Increased	19 (5.3)	18 (5.0)	5 (1.6)	4 (1.3)	23 (6.4)	22 (6.1)
Pruritus	10 (2.8)	16 (4.4)	3 (0.9)	0 (0.0)	13 (3.6)	16 (4.4)
Acne	9 (2.5)	5 (1.4)	0 (0.0)	3 (1.0)	9 (2.5)	8 (2.2)
Skin Disorder	2 (0.6)	3 (0.8)	3 (0.9)	5 (1.6)	5 (1.4)	8 (2.2)
Rash Maculopapular	6 (1.7)	3 (0.8)	0 (0.0)	1 (0.3)	6 (1.7)	4 (1.1)
Eczema	2 (0.6)	2 (0.6)	3 (0.9)	2 (0.7)	4 (1.1)	3 (0.8)
RESPIRATORY						
Hemoptysis	27 (7.5)	20 (5.5)	6 (1.9)	6 (2.0)	30 (8.3)	25 (6.9)
Coughing	21 (5.8)	8 (2.2)	9 (2.8)	11 (3.6)	29 (8.0)	17 (4.7)
Upper Respiratory Tract Infection	5 (1.4)	9 (2.5)	12 (3.8)	15 (4.9)	17 (4.7)	22 (6.1)
Bronchitis	1 (0.3)	1 (0.3)	8 (2.5)	1 (0.3)	9 (2.5)	2 (0.6)
Pharyngitis	5 (1.4)	0 (0.0)	2 (0.6)	5 (1.6)	7 (1.9)	5 (1.4)
Epistaxis	2 (0.6)	2 (0.6)	3 (0.9)	1 (0.3)	5 (1.4)	3 (0.8)
Pleuritis	4 (1.1)	1 (0.3)	0 (0.0)	1 (0.3)	4 (1.1)	2 (0.6)
GASTROINTESTINAL						
Dyspepsia	6 (1.7)	11 (3.0)	4 (1.3)	6 (2.0)	10 (2.8)	17 (4.7)
Vomiting	6 (1.7)	14 (3.9)	3 (0.9)	3 (1.0)	9 (2.5)	17 (4.7)
Nausea	7 (1.9)	3 (0.8)	2 (0.6)	1 (0.3)	9 (2.5)	4 (1.1)
Constipation	6 (1.7)	1 (0.3)	2 (0.6)	1 (0.3)	7 (1.9)	2 (0.6)
Diarrhea	5 (1.4)	2 (0.6)	2 (0.6)	0 (0.0)	7 (1.9)	2 (0.6)
Hemorrhoids	4 (1.1)	0 (0.0)	1 (0.3)	0 (0.0)	5 (1.4)	0 (0.0)
INFECTIOUS DISEASE						
Influenza	9 (2.5)	8 (2.2)	22 (6.9)	12 (3.9)	28 (7.8)	20 (5.5)
Infection Tuberculosis	0 (0.0)	5 (1.4)	9 (2.8)	4 (1.3)	9 (2.5)	9 (2.5)
Infection	1 (0.3)	2 (0.6)	4 (1.3)	4 (1.3)	5 (1.4)	6 (1.7)
Herpes Zoster	2 (0.6)	0 (0.0)	2 (0.6)	3 (1.0)	4 (1.1)	3 (0.8)
HEPATIC & BILIARY						
ALT Increased	18 (5.0)	23 (6.4)	7 (2.2)	10 (3.3)	25 (6.9)	32 (8.9)
AST Increased	15 (4.2)	18 (5.0)	7 (2.2)	8 (2.6)	21 (5.8)	26 (7.2)
NEUROLOGIC						
Headache	11 (3.0)	13 (3.6)	3 (0.9)	7 (2.3)	14 (3.9)	20 (5.5)
Dizziness	5 (1.4)	5 (1.4)	1 (0.3)	1 (0.3)	6 (1.7)	6 (1.7)
Tremor	3 (0.8)	1 (0.3)	2 (0.6)	0 (0.0)	5 (1.4)	1 (0.3)
PSYCHIATRIC						
Anorexia	14 (3.9)	18 (5.0)	8 (2.5)	6 (2.0)	21 (5.8)	22 (6.1)
Insomnia	2 (0.6)	2 (0.6)	2 (0.6)	2 (0.7)	4 (1.1)	4 (1.1)
MUSCULOSKELETAL						
Arthralgia	13 (3.6)	13 (3.6)	3 (0.9)	5 (1.6)	16 (4.4)	18 (5.0)
Arthritis	4 (1.1)	5 (1.4)	1 (0.3)	0 (0.0)	4 (1.1)	5 (1.4)
Arthrosis	4 (1.1)	1 (0.3)	0 (0.0)	1 (0.3)	4 (1.1)	2 (0.6)
Gout	3 (0.8)	1 (0.3)	1 (0.3)	0 (0.0)	4 (1.1)	1 (0.3)
CARDIOVASCULAR						

Hypertension	3 (0.8)	5 (1.4)	3 (0.9)	2 (0.7)	6 (1.7)	7 (1.9)
OPHTHALMOLOGIC						
Conjunctivitis	8 (2.2)	2 (0.6)	1 (0.3)	1 (0.3)	9 (2.5)	3 (0.8)
Note: $\geq 1\%$ refers to rifapentine in the TOTAL column.						
1 Initial Phase consisted of therapy with either rifapentine or rifampin combined with isoniazid, pyrazinamide, and ethambutol administered daily (rifapentine twice weekly) for 60 days.						
2 Continuation Phase consisted of therapy with either rifapentine or rifampin combined with isoniazid for 120 days. Rifapentine patients were dosed once weekly; rifampin patients were dosed twice weekly.						
3 A patient may have experienced the same adverse reaction more than once during the course of the study, therefore, patient counts across the columns may not equal the patient counts in the TOTAL column.						

In addition to the adverse reactions reported in Table 1, adverse reactions were reported post-treatment during the 3 month through 24 month follow-up period. Although the protocol for this study specified collection of serious adverse reactions during this period, some non-serious adverse reactions were reported as well. For the rifapentine combination group these included the following: hematuria, infection tuberculosis, proteinuria, urinary casts, hyperkalemia, hypoglycemia, injury accident, skin disorder, respiratory disorder, stupor, prostatic disorder.

Treatment-emergent adverse reactions reported during treatment and post-treatment through the first three months of follow-up in $<1\%$ of the rifapentine combination therapy patients are presented below by body system in order of frequency.

Renal & Urinary: urethral disorder, dysuria, pyelonephritis, urinary incontinence, urination disorder.

Metabolic & Nutritional: weight decrease, BUN increased, diabetes mellitus, alkaline phosphatase increased, hypophosphatemia, hypercalcemia, hypovolemia, weight increase.

Hematologic: lymphocytosis, hematoma, purpura, anemia hypochromic, anemia normocytic, thrombosis.

Body as a Whole - General: laboratory test abnormal, edema legs, asthenia, edema face, abscess, edema peripheral, malaise.

Dermatologic: skin ulceration, urticaria, dry skin, furunculosis, skin discoloration, dermatitis fungal, nail disorder, alopecia, rash erythematous.

Respiratory: abnormal breath sounds, pneumothorax, pneumonia, pleural effusion, rhinitis, dyspnea, pneumonitis, sinusitis, sputum increased, pulmonary fibrosis, upper respiratory congestion, asthma, chest x-ray abnormal, bronchospasm, laryngeal edema, laryngitis, respiratory disorder,

Gastrointestinal: tooth disorder, gastroenteritis, gastritis, esophagitis, cheilitis, dry mouth, pancreatitis, proctitis, salivary gland enlargement, tenesmus, gastrointestinal disorder not specified.

Infectious Disease: infection fungal, infection parasitic, infection protozoan.

Hepatic & Biliary: bilirubinemia, hepatomegaly, jaundice.

Neurologic: somnolence, seizure not specified, dysphonia, hypoesthesia, torticollis, hypertonia, hyporeflexia, meningitis, migraine headache, stupor.

Psychiatric: anxiety, confusion, drug abuse, aggressive reaction, agitation.

Musculoskeletal: myalgia, myositis, bone fracture, muscle weakness, muscle spasm.

Cardiovascular: syncope, tachycardia, palpitation, hypotension orthostatic, pericarditis.

Reproductive Disorders: penis disorder, vaginitis, vaginal hemorrhage, cervical smear test positive, leukorrhea, mastitis male, prostatic disorder.

Hearing & Vestibular: ear disorder not specified, otitis media, earache, otitis externa, tympanic membrane perforation.

Ophthalmologic: eye pain, eye abnormality.

Neoplasms: pulmonary carcinoma, neoplasm not specified, carcinoma, lipoma.

Vascular (Extracardiac): thrombophlebitis deep, vascular disorder, vasodilation.

Special Senses Other: taste loss.

Pregnancy, puerperium and perinatal conditions: abortion

In another randomized, open-label trial in 1075 HIV seronegative and seropositive patients with pulmonary tuberculosis the overall adverse event rate did not differ substantially from the previous trial. Patients who had completed an initial 2 month phase of treatment with 4 drugs were randomly assigned to receive either rifapentine 600 mg and isoniazid once weekly or rifampin and isoniazid twice weekly for the 4 month continuation phase.

In the rifapentine arm, 502 HIV seronegative and 36 HIV seropositive patients were randomized and in the rifampin arm 502 HIV seronegative and 35 HIV seropositive patients were randomized to treatment.

The death rate among all study participants was 71/1075 (6.6%) and did not differ between the two treatment groups (6.5% for the rifapentine combination regimen compared to 6.7% for the rifampin combination regimen; $P = 0.87$).

There were 526 treatment-emergent adverse events regardless of causality reported from 251 patients treated with the rifapentine combination regimen and 513 adverse events reported from 248 patients treated with the rifampin combination regimen. On both study arms the most frequently reported adverse events were hyperglycemia, pneumonia, liver toxicity, and death and

were consistent with concurrent underlying conditions that included alcohol abuse, pancreatitis and HIV.

There was a greater percentage of patients in the rifampin combination arm who developed hepatic adverse events (35/513; 6.8 %) compared to 20/526 (3.8%) in the rifapentine combination arm. The types of other adverse events were similar between the treatment arms.

Hyperuricemia was not reported as an adverse reaction in this study of continuation phase therapy. In the previous study which evaluated initial therapy containing pyrazinamide, hyperuricemia was reported in 32% of rifapentine and 23% of rifampin combination treated patients (see Table 1).

7 DRUG INTERACTIONS

7.1 Protease Inhibitors and Reverse Transcriptase Inhibitors

Rifapentine is an inducer of CYP450 enzymes. Concomitant use of PRIFTIN with other drugs metabolized by these enzymes, such as protease inhibitors and reverse transcriptase inhibitors, may cause a significant decrease in plasma concentrations and loss of therapeutic effect of the protease inhibitor or reverse transcriptase inhibitor. [see *Warnings and Precautions (5.2)* and *Clinical Pharmacology (12.3)*]

7.2 Hormonal Contraceptives

PRIFTIN may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to change to non-hormonal methods of birth control.

7.3 Cytochrome P450 3A4 and 2C8/9

Rifapentine is an inducer of cytochromes P4503A4 and P4502C8/9. Therefore, rifapentine may increase the metabolism of other coadministered drugs that are metabolized by these enzymes. Induction of enzyme activities by rifapentine occurred within 4 days after the first dose. Enzyme activities returned to baseline levels 14 days after discontinuing rifapentine. In addition, the magnitude of enzyme induction by rifapentine was dose and dosing frequency dependent; less enzyme induction occurred when 600 mg oral doses of rifapentine were given once every 72 hours versus daily.

In vitro and in vivo enzyme induction studies have suggested rifapentine induction potential may be less than rifampin but more potent than rifabutin.

Rifampin has been reported to accelerate the metabolism and may reduce the activity of the following drugs; hence, rifapentine may also increase the metabolism and decrease the activity of these drugs. Dosage adjustments of the drugs in Table 2 or of other drugs metabolized by cytochrome P4503A4 or P4502C8/9 may be necessary if they are given concurrently with rifapentine.

Table 2. Drug Interactions with PRIFTIN: Dosage Adjustment may be Necessary

Drug Class	Examples of Drugs Within Class
-------------------	---------------------------------------

Antiarrhythmics	Disopyramide, mexiletine, quinidine, tocainide
Antibiotics	Chloramphenicol, clarithromycin, dapsone, doxycycline; Fluoroquinolones (such as ciprofloxacin)
Oral Anticoagulants	Warfarin
Anticonvulsants	Phenytoin
Antimalarials	Quinine
Azole Antifungals	Fluconazole, itraconazole, ketoconazole
Antipsychotics	Haloperidol
Barbiturates	Phenobarbital
Benzodiazepines	Diazepam
Beta-Blockers	Propranolol
Calcium Channel Blockers	Diltiazem, nifedipine, verapamil
Cardiac Glycoside Preparations	Digoxin
Corticosteroids	Prednisone
Fibrates	Clofibrate
Oral Hypoglycemics	Sulfonylureas (e.g., glyburide, glipizide)
Hormonal Contraceptives/ Progestins	Ethinyl estradiol, levonorgestrel
Immunosuppressants	Cyclosporine, tacrolimus
Methylxanthines	Theophylline
Narcotic analgesics	Methadone
Phosphodiesterase-5 (PDE-5) Inhibitors	Sildenafil
Thyroid preparations	Levothyroxine
Tricyclic antidepressants	Amitriptyline, nortriptyline

7.4 Other Interactions

The conversion of rifapentine to 25-desacetyl rifapentine is mediated by an esterase enzyme. There is minimal potential for rifapentine metabolism to be inhibited or induced by another drug, or for rifapentine to inhibit the metabolism of another drug based upon the characteristics of the esterase enzymes.

Rifapentine does not induce its own metabolism [*see Clinical Pharmacology (12.3)*].

Since rifapentine is highly bound to albumin, drug displacement interactions may also occur [*see Clinical Pharmacology (12.3)*].

7.5 Interactions with Laboratory Tests

Therapeutic concentrations of rifampin have been shown to inhibit standard microbiological assays for serum folate and Vitamin B₁₂. Similar drug-laboratory interactions should be considered for rifapentine; thus, alternative assay methods should be considered.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well controlled studies of rifapentine use during pregnancy. In animal reproduction and developmental toxicity studies, rifapentine

produced fetal harm and was teratogenic. However, because animal studies are not always predictive of human response, rifapentine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When administered during the last few weeks of pregnancy, rifampin, another rifamycin, may increase the risk for maternal postpartum hemorrhage and bleeding in the exposed infant. Therefore, pregnant women and their infants, who are exposed to rifapentine during the last few weeks of pregnancy, should have appropriate monitoring of clotting parameters. Treatment with Vitamin K may be indicated.

Six patients randomized to rifapentine became pregnant during a study of initial treatment of tuberculosis. Two delivered normal infants; two had first trimester spontaneous abortions; one had an elective abortion; and one patient was lost to follow-up. The two patients who spontaneously aborted had co-morbid conditions: One patient abused ethanol and the other patient was HIV positive.

Animal studies in rats and rabbits revealed embryofetal toxicity in both species. Pregnant rats given rifapentine during organogenesis at doses 0.6 times the human dose (based on body surface area), produced pups with cleft palates, right aortic arch, increased incidence of delayed ossification, and increased numbers of ribs. When rifapentine was administered to mated female rats late in gestation, at 0.3 times the human dose (based on body surface area), pup weights and gestational survival (live pups born/pups born) were reduced compared to controls. Increased resorptions and post implantation loss, decreased mean fetal weights, increased numbers of stillborn pups, and slightly increased pup mortality during lactation were also noted. When pregnant rabbits received rifapentine at doses 0.3 to 1.3 times the human dose (based on body surface area), major fetal malformations occurred including: ovarian agenesis, pes varus, arhinia, microphthalmia and irregularities of the ossified facial tissues. At the higher dose, there were increases in post-implantation loss and the incidence of stillborn pups.

8.3 Nursing Mothers

It is not known whether rifapentine is excreted into human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother and the benefits of breastfeeding. Since rifapentine may produce a red-orange discoloration of body fluids, there is a potential for discoloration of breast milk.

A slight increase in rat pup mortality was observed during lactation when dams were dosed late in gestation through lactation.

8.4 Pediatric Use

The safety and effectiveness of rifapentine in pediatric patients under the age of 12 have not been established. A pharmacokinetic study was conducted in 12- to 15-year-old healthy volunteers and the pharmacokinetics of rifapentine were similar to those observed in healthy adults [*see Clinical Pharmacology (12.3)*].

8.5 Geriatric Use

The Clinical studies of PRIFTIN did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy [*see Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

There is no experience with the treatment of acute overdose with rifapentine at doses exceeding 1200 mg per dose.

In a pharmacokinetic study involving healthy volunteers (n=9), single oral doses up to 1200 mg have been administered without serious adverse events. The only adverse events reported with the 1200 mg dose were heartburn (3/8), headache (2/8) and increased urinary frequency (1/8). In clinical trials, tuberculosis patients ranging in age from 20 to 74 years accidentally received continuous daily doses of rifapentine 600 mg. Some patients received continuous daily dosing for up to 20 days without evidence of serious adverse effects. One patient experienced a transient elevation in SGPT and glucose (the latter attributed to pre-existing diabetes); a second patient experienced slight pruritus. While there is no experience with the treatment of acute overdose with rifapentine, clinical experience with rifamycins suggests that gastric lavage to evacuate gastric contents (within a few hours of overdose), followed by instillation of an activated charcoal slurry into the stomach, may help adsorb any remaining drug from the gastrointestinal tract.

Rifapentine and 25-desacetyl rifapentine are 97.7% and 93.2% plasma protein bound, respectively. Rifapentine and related compounds excreted in urine account for only 17% of the administered dose, therefore, neither hemodialysis nor forced diuresis is expected to enhance the systemic elimination of unchanged rifapentine from the body of a patient with PRIFTIN overdose.

11 DESCRIPTION

PRIFTIN (rifapentine) for oral administration contains 150 mg of the active ingredient rifapentine per tablet.

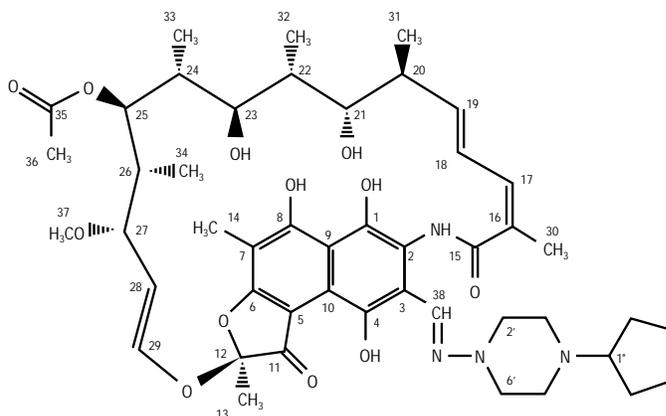
The 150 mg tablets also contain, as inactive ingredients: calcium stearate, disodium EDTA, FD&C Blue No. 2 aluminum lake, hydroxypropyl cellulose, hypromellose USP, microcrystalline cellulose, polyethylene glycol, pregelatinized starch, propylene glycol, sodium ascorbate, sodium lauryl sulfate, sodium starch glycolate, synthetic red iron oxide, and titanium dioxide.

Rifapentine is a rifamycin derivative antibiotic and has a similar profile of microbiological activity to rifampin (rifampicin). The molecular weight is 877.04.

The molecular formula is $C_{47}H_{64}N_4O_{12}$.

The chemical name for rifapentine is rifamycin, 3-[[[(4-cyclopentyl-1-piperazinyl)imino]methyl]-

or 3-[N-(4-Cyclopentyl - 1-piperazinyl)formimidoyl] rifamycin or 5,6,9,17,19,21-hexahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-8-[N-(4-cyclopentyl-1-piperazinyl)-formimidoyl]-2,7-(epoxypentadeca[1,11,13]trienimino)naphtho[2,1-b]furan-1,11(2H)-dione 21-acetate. It has the following structure:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rifapentine, a cyclopentyl rifamycin, is an antimycobacterial agent [see *Clinical Pharmacology, Microbiology* (12.4)].

12.3 Pharmacokinetics

Absorption

The absolute bioavailability of rifapentine has not been determined. The relative bioavailability (with an oral solution as a reference) of rifapentine after a single 600 mg dose to healthy adult volunteers was 70%. The maximum concentrations were achieved from 5 to 6 hours after administration of the 600 mg rifapentine dose.

The administration of rifapentine with a high fat meal (850 total calories: 33 g protein, 55 g fat and 58 g carbohydrate) increased AUC(0-∞) and C_{max} by 43% and 44%, respectively over that observed when administered under fasting conditions.

When oral doses of rifapentine were administered once daily or once every 72 hours to healthy volunteers for 10 days, single dose AUC(0-∞) value of rifapentine was similar to its steady-state AUC_{ss} (0-24h) or AUC_{ss} (0-72h) values, suggesting no significant auto-induction effect on steady-state pharmacokinetics of rifapentine. Steady-state conditions were achieved by day 10 following daily administration of rifapentine 600 mg.

The pharmacokinetic parameters of rifapentine and 25-desacetyl rifapentine (active metabolite) on day 10 following oral administration of 600 mg rifapentine every 72 hours to healthy volunteers are contained in Table 3.

Table 3. Pharmacokinetics and rifapentine and 25-desacetyl rifapentine in healthy volunteers.		
Parameter	Rifapentine	25-desacetyl Rifapentine

	Mean ± SD (n=12)	
C _{max} (µg/mL)	15.05 ± 4.62	6.26 ± 2.06
AUC (0-72h)(µg*h/mL)	319.54 ± 91.52	215.88 ± 85.96
T _{1/2} (h)	13.19 ± 1.38	13.35 ± 2.67
T _{max} (h)	4.83 ± 1.80	11.25 ± 2.73
Cl _{po} (L/h)	2.03 ± 0.60	--

Distribution

In a population pharmacokinetic analysis in 351 tuberculosis patients who received 600 mg rifapentine in combination with isoniazid, pyrazinamide and ethambutol, the estimated apparent volume of distribution was 70.2 ± 9.1 L. In healthy volunteers, rifapentine and 25-desacetyl rifapentine were 97.7% and 93.2% bound to plasma proteins, respectively. Rifapentine was mainly bound to albumin. Similar extent of protein binding was observed in healthy volunteers, asymptomatic HIV-infected subjects and hepatically impaired subjects.

Metabolism/Excretion

Following a single 600 mg oral dose of radiolabeled rifapentine to healthy volunteers (n=4), 87% of the total ¹⁴C rifapentine was recovered in the urine (17%) and feces (70%). Greater than 80% of the total ¹⁴C rifapentine dose was excreted from the body within 7 days. Rifapentine was hydrolyzed by an esterase enzyme to form a microbiologically active 25-desacetyl rifapentine. Rifapentine and 25-desacetyl rifapentine accounted for 99% of the total radioactivity in plasma. Plasma AUC(0-∞) and C_{max} values of the 25-desacetyl rifapentine metabolite were one-half and one-third those of the rifapentine, respectively. Based upon relative in vitro activities and AUC(0-∞) values, rifapentine and 25-desacetyl rifapentine potentially contributes 62% and 38% to the clinical activities against *M. tuberculosis*, respectively.

Special Populations

Gender: In a population pharmacokinetics analysis of sparse blood samples obtained from 351 tuberculosis patients who received 600 mg rifapentine in combination with isoniazid, pyrazinamide and ethambutol, the estimated apparent oral clearance of rifapentine for males and females was 2.51 ± 0.14 L/h and 1.69 ± 0.41 L/h, respectively. The clinical significance of the difference in the estimated apparent oral clearance is not known.

Elderly: Following oral administration of a single 600 mg dose of rifapentine to elderly (≥65 years) male healthy volunteers (n=14), the pharmacokinetics of rifapentine and 25-desacetyl metabolite were similar to that observed for young (18 to 45 years) healthy male volunteers (n=20).

Pediatric (Adolescents): In a pharmacokinetics study of rifapentine in healthy adolescents (age 12 to 15), 600 mg rifapentine was administered to those weighing ≥45 kg (n=10) and 450 mg was administered to those weighing <45 kg (n=2). The pharmacokinetics of rifapentine were similar to those observed in healthy adults.

Renal Impaired Patients: The pharmacokinetics of rifapentine have not been evaluated in renal impaired patients. Although only about 17% of an administered dose is excreted via the kidneys, the clinical significance of impaired renal function on the disposition of rifapentine and its 25-desacetyl metabolite is not known.

Hepatic Impaired Patients: Following oral administration of a single 600 mg dose of rifapentine to mild to severe hepatic impaired patients (n=15), the pharmacokinetics of rifapentine and 25-desacetyl metabolite were similar in patients with various degrees of hepatic impairment and to that observed in another study for healthy volunteers (n=12). Since the elimination of these agents are primarily via the liver, the clinical significance of impaired hepatic function on the disposition of rifapentine and its 25-desacetyl metabolite is not known.

Asymptomatic HIV-Infected Volunteers: Following oral administration of a single 600 mg dose of rifapentine to asymptomatic HIV-infected volunteers (n=15) under fasting conditions, mean C_{max} and AUC(0-∞) of rifapentine were lower (20-32%) than that observed in other studies in healthy volunteers (n=55). In a cross-study comparison, mean C_{max} and AUC values of the 25-desacetyl metabolite of rifapentine, when compared to healthy volunteers were higher (6-21%) in one study (n=20), but lower (15-16%) in a different study (n=40). The clinical significance of this observation is not known. Food (850 total calories: 33 g protein, 55 g fat, and 58 g carbohydrate) increases the mean AUC and C_{max} of rifapentine observed under fasting conditions in asymptomatic HIV-infected volunteers by about 51% and 53%, respectively.

Drug-Drug Interactions: Rifapentine is an inducer of cytochrome P4503A4 and 2C8/9. Therefore, it may increase the metabolism and decrease the activity of other co-administered drugs that are metabolized by these enzymes. Dosage adjustments of the co-administered drugs may be necessary if they are given concurrently with rifapentine [see *Drug Interactions (7.3)*].

Indinavir: In a study in which 600 mg rifapentine was administered twice weekly for 14 days followed by rifapentine twice weekly plus 800 mg indinavir 3 times a day for an additional 14 days, indinavir C_{max} decreased by 55% while AUC reduced by 70%. Clearance of indinavir increased by 3-fold in the presence of rifapentine while half-life did not change. But when indinavir was administered for 14 days followed by coadministration with rifapentine for an additional 14 days, indinavir did not affect the pharmacokinetics of rifapentine [see *Warnings and Precautions (5.2)* and *Drug Interactions (7.1)*].

12.4 Microbiology

Mechanism of Action

Rifapentine, a cyclopentyl rifamycin, inhibits DNA-dependent RNA polymerase in susceptible strains of *Mycobacterium tuberculosis* but not in mammalian cells. At therapeutic levels, rifapentine exhibits bactericidal activity against both intracellular and extracellular *M. tuberculosis* organisms. Both rifapentine and the 25-desacetyl metabolite accumulate in human monocyte-derived macrophages with intracellular/extracellular ratios of approximately 24:1 and 7:1, respectively.

In Vitro Activity

Rifapentine and its 25-desacetyl metabolite have demonstrated *in vitro* activity against rifamycin-susceptible strains of *Mycobacterium tuberculosis* including cidal activity against phagocytized *M. tuberculosis* organisms grown in activated human macrophages.

The correlation between rifapentine MICs and clinical cure has not been established. Interpretive criteria/breakpoints to determine whether clinical isolates of *M. tuberculosis* are susceptible or resistant to rifapentine have not been established.

***In Vivo* Activity**

In mouse infection studies a therapeutic effect, in terms of enhanced survival time or reduction of organ bioburden, has been observed in *M. tuberculosis*-infected animals treated with various intermittent rifapentine containing regimens. Animal studies have shown that the activity of rifapentine is influenced by dose and frequency of administration.

Drug Resistance

In the treatment of tuberculosis, a small number of resistant cells present within large populations of susceptible cells can rapidly become predominant. Rifapentine resistance development in *M. tuberculosis* strains is principally due to one of several single point mutations that occur in the *rpoB* portion of the gene coding for the beta subunit of the DNA-dependent RNA polymerase. The incidence of rifapentine resistant mutants in an otherwise susceptible population of *M. tuberculosis* strains is approximately one in 10^7 to 10^8 bacilli.

Cross Resistance

M. tuberculosis organisms resistant to other rifamycins are likely to be resistant to rifapentine. A high level of cross-resistance between rifampin and rifapentine has been demonstrated with *M. tuberculosis* strains. Cross-resistance does not appear between rifapentine and non-rifamycin antimycobacterial agents.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility Fertility, Carcinogenesis, Mutagenesis

Hepatocellular carcinomas were increased in male NMRI mice (Harlan Winkleman) which were treated orally with rifapentine for two years at or above doses of 5 mg/kg/day (equivalent to a human dose of 0.4 mg/kg/day or 1/5 th of the recommended human dose, in the intensive phase, based on body surface area conversions). In a two year rat study, there was an increase in nasal cavity adenomas in Wistar rats treated orally with rifapentine at 40 mg/kg/day (equivalent to a human dose of 6.5 mg/kg/day or 3 times the recommended human dose in the intensive phase, based on body surface area conversions).

Rifapentine was negative in the following genotoxicity tests: in vitro gene mutation assay in bacteria (Ames test); in vitro point mutation test in *Aspergillus nidulans*; in vitro gene conversion assay in *Saccharomyces cerevisiae*; host-mediated (mouse) gene conversion assay with *Saccharomyces cerevisiae*; in vitro Chinese hamster ovary cell/hypoxanthine-guanine-phosphoribosyl transferase (CHO/HGPRT) forward mutation assay; in vitro chromosomal aberration assay utilizing rat lymphocytes; and in vivo mouse bone marrow micronucleus assay.

The 25-desacetyl metabolite of rifapentine was positive in the *in vitro* mammalian chromosome aberration test in V79 Chinese Hamster cells, but was negative in the in vitro gene mutation assay in bacteria (Ames test), the in vitro Chinese hamster ovary cell/hypoxanthine-guanine-

phosphoribosyl transferase (CHO/HGPRT) forward mutation assay, and the in vivo mouse bone marrow micronucleus assay. Fertility and reproductive performance were not affected by oral administration of rifapentine to male and female rats at doses of up to one-third of the human dose (based on body surface area conversions).

14 CLINICAL STUDIES

Rifapentine was studied in two randomized, open-label controlled clinical trials.

The first trial was an open-label, prospective, parallel group, active controlled trial in patients with pulmonary tuberculosis, excluding those with HIV-infection. The population was mostly comprised of Black (> 60%) or Multiracial (>31%) patients. Treatment groups were comparable for age and sex and consisted primarily of male subjects with a mean age of 37 ± 11 years. In the initial 2 month phase of treatment (60 days), 361 patients received rifapentine 600 mg twice a week in combination with daily isoniazid, pyrazinamide, and ethambutol and 361 subjects received rifampin 600 mg in combination with isoniazid, pyrazinamide and ethambutol all administered daily. The doses of the companion drugs were the same in both treatment arms during the initial phase: isoniazid 300 mg, pyrazinamide 2000 mg, and ethambutol 1200 mg. For patients weighing less than 50 kg, the doses of rifampin (450 mg), pyrazinamide (1500 mg) and ethambutol (800 mg) were reduced. Ethambutol was discontinued when isoniazid and rifampin susceptibility testing results were confirmed. During the 4 month continuation phase, 321 patients in the rifapentine group continued to receive rifapentine 600 mg dosed once weekly with isoniazid 300 mg and 307 patients in the rifampin arm received twice weekly rifampin and isoniazid 900 mg. For patients weighing less than 50 kg, the doses of rifampin (450 mg) and isoniazid (600 mg) were reduced. Both treatment groups received pyridoxine (Vitamin B6) over the 6 month treatment period. Treatment was directly observed. Despite observed therapy, 65/361 (18%) of patients in the rifapentine arm and 34/361 (9%) in the rifampin arm received overdoses of one or more of the administered study medications during the initial or continuation phase of treatment. Only seven of these patients had adverse reactions reported with the overdose (5 in the rifapentine group and 2 in the rifampin group).

Table 4 below contains assessments of sputum conversion at end of treatment (6 months) and relapse rates at the end of follow-up (24 months).

Table 4. Clinical Outcome in HIV Negative Patients with Pulmonary Tuberculosis

	Rifapentine Combination Treatment % and (n/N*)	Rifampin Combination Treatment % and (n/N*)
Status at End of 6 months of Treatment		
Converted	87% (248/286)	80% (226/283)
Not Converted	1% (4/286)	3% (8/283)
Lost to Follow-up	12% (34/286)	17% (49/283)
Status Through 24 Month Follow-up**:		

Relapsed	12% (29/248)	7% (15/226)
Sputum Negative	57% (142/248)	64% (145/226)
Lost to Follow-up	31% (77/248)	29% (66/226)

* All data for patients with confirmed susceptible *M. tuberculosis* (rifapentine combination treatment, N=286; rifampin combination treatment, N=283).

** Twenty-two (22) deaths occurred during the study; 11 in each treatment arm

Risk of relapse was greater in the group treated with the rifapentine combination. Higher relapse rates were associated with a lower rate of compliance with the companion antituberculosis drugs as well as a failure to convert sputum cultures at the end of the initial 2 month treatment phase. Relapse rates were also higher for males in both regimens. Relapse in the rifapentine group was not associated with development of mono-resistance to rifampin.

In vitro susceptibility testing was conducted against *M. tuberculosis* isolates recovered from 620 patients enrolled in the study. Rifapentine and rifampin MIC values were determined employing the radiometric susceptibility testing method utilizing 7H12 broth at pH 6.8 (CLSI procedure M24-A; (1)). Six hundred and twelve patients had *M. tuberculosis* isolates that were susceptible to rifampin (MIC < 0.5 µg/ml). Of these patients, six hundred and ten had *M. tuberculosis* isolates (99.7%) with rifapentine MICs of < 0.125 µg/ml. The other two patients that had rifampin susceptible *M. tuberculosis* isolates had rifapentine MICs of 0.25 µg/ml. The remaining eight patients had *M. tuberculosis* isolates that were resistant to rifampin (MIC > 8.0 µg/ml). These *M. tuberculosis* isolates had rifapentine MICs of > 8.0 µg/ml. In this study high rifampin and rifapentine MICs were associated with multi-drug resistant *M. tuberculosis* (MDR-TB) isolates. Rifampin monoresistance was not observed in either treatment arm. This information is provided for comparative purposes only as rifapentine breakpoints have not been established.

The second trial was a randomized, open-label trial in 1075 HIV seronegative and seropositive patients with pulmonary tuberculosis. Patients with culture-positive, drug-susceptible pulmonary tuberculosis who had completed the initial 2 month phase of treatment with 4 drugs (rifampin, isoniazid, pyrazinamide, and either ethambutol or streptomycin) under direct observation were randomly assigned to receive either rifapentine 600 mg and isoniazid 15 mg/kg (max 900 mg) once weekly or rifampin 10 mg/kg (max 600 mg) and isoniazid 15 mg/kg (max 900 mg) twice weekly for the 4 month continuation phase. Study drugs were given under direct observation therapy in both arms.

In the rifapentine arm, 502 HIV seronegative and 36 HIV seropositive patients were randomized and in the rifampin arm 502 HIV seronegative and 35 HIV seropositive patients were randomized to treatment. Enrollment of HIV seropositive patients was stopped when 4 of 36 patients in the rifapentine combination group developed rifampin monoresistance.

Table 5 below contains assessments of sputum conversion at the end of treatment (6 months total: 2 months of initial and 4 months of randomized continuation treatment) and relapse rates at the end of follow-up (24 months) in all HIV seronegative patients randomized to treatment. The failure and relapse rates reported in this study could be underestimated due to the limitation of the microbiologic methods used in the study. Positive culture was based on either one

sputum sample with >10 colonies on solid media OR at least 2 positive sputum samples on liquid or solid media. However, only one sputum sample was collected at each visit in a majority of patients.

Table 5: Clinical Outcome in HIV Negative Patients with Pulmonary Tuberculosis

	Rifapentine Combination Treatment % (n/N)	Rifampin Combination Treatment % (n/N)
Status at End of 4 Months Continuation Phase		
Treatment Response *	93.8% (471/502)	91.0% (457/502)
Not Converted	1.0% (5/502)	1.2% (6/502)
Did Not Complete Treatment**	4.2% (21/502)	7.0% (35/502)
Deaths	1.0 % (5/502)	0.8% (4/502)
Status Through 24 Month Follow-up:		
Relapsed	8.7% (41/471)	4.8% (22/457)
Sputum Negative	79.4% (374/471)	80.1% (366/457)
Lost to Follow-up	7.9% (37/471)	9.8% (45/457)
Deaths	4.0% (19/471)	5.3% (24/457)

* Treatment response was defined as subjects who responded successfully after 16 doses of rifampin and isoniazid or after 8 doses of rifapentine and isoniazid, and remained sputum negative through the end of continuation phase therapy.

** Due to drug toxic effects, non-adherence, withdrawal of consent, receipt of nonstudy regimen, other.

Higher relapse rates in HIV seronegative patients were seen in patients with a positive sputum culture at 2 months (i.e., at the time of study randomization), cavitation on chest x-ray, and bilateral pulmonary involvement.

Seventy-one HIV seropositive patients were enrolled into the study. There were no treatment failures during the study phase therapy. Sixty-one patients completed therapy and were assessed for relapse. The rates of relapse were 16.7% (5/30) in the rifapentine group and 9.7% (3/31) in the rifampin group.

Risk factors that predisposed to relapse in the HIV seropositive patients included the presence of both pulmonary and extrapulmonary disease at baseline, low CD4 counts, use of azole antifungals and younger age.

In HIV seropositive patients, 4 of the 5 relapses from the rifapentine combination group involved *M. tuberculosis* strains with rifampin monoresistance (RMR). No relapse strain in the twice weekly rifampin/isoniazid group had acquired drug resistance. These data are consistent with other documented acquired rifampin monoresistance in HIV seropositive adults who fail or relapse after treatment with intermittent regimens with isoniazid and other rifamycins (rifampin and rifabutin).

The death rate among all study participants did not differ between the two treatment groups.

15 References

1. Clinical and Laboratory Standards Institute. M24-A Susceptibility Testing of Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes; Approved Standard. 23 ed. 2003. Clinical Laboratory Standards Institute, Wayne, PA

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

PRIFTIN is supplied as 150 mg round normal convex dark-pink film-coated tablets debossed “Priftin” on top and “150” on the bottom, packaged in aluminum formable foil blister strips placed in cartons of 32 tablets (4 strips of 8). Each strip of 8 tablets is inserted into an aluminum foil laminated pouch. (NDC 0088-2100-03).

Storage

Store at 25°C (77°F); excursions permitted 15-30°C (59-86°F) (see USP Controlled Room Temperature). Protect from excessive heat and humidity.

17 PATIENT COUNSELING INFORMATION

17.1 Compliance

Compliance with the full course of therapy must be emphasized to the patient, and the importance of not missing any doses of the daily administered companion medications in the Initial Phase must be stressed.

17.2 Drug Interactions

Rifapentine may increase the metabolism and decrease the activity of other drugs that are metabolized by the P4503A4 and 2C8/9 pathways. Dosage adjustments of the co-administered drugs may be necessary. Patients should be advised to discuss with their physician the other medications they are taking before starting treatment with rifapentine.

Concomitant use of rifapentine with protease inhibitors or reverse transcriptase inhibitors may cause a significant decrease in plasma concentrations and loss of therapeutic effect of the protease inhibitor or reverse transcriptase inhibitor.

Rifapentine may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to change to non-hormonal methods of birth control.

17.3 Discoloration of Body Fluids

The patient should be informed that PRIFTIN may produce a reddish coloration of the urine, sweat, sputum, tears, and breast milk and the patient should be forewarned that contact lenses or dentures may be permanently stained.

17.4 Adverse Reactions

Patients should be instructed to notify their physician promptly if they experience any of the following: fever, loss of appetite, malaise, nausea and vomiting, darkened urine, yellowish discoloration of the skin and eyes, and pain or swelling of the joints.

17.5 Administration with Food

For those patients with a propensity to experience nausea, vomiting, or gastrointestinal upset, inform those patients that administration of PRIFTIN with food may be useful.

Revised June 2009

Sanofi-Aventis U.S. LLC
Bridgewater, NJ 08807
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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-024/S008

OFFICER/EMPLOYEE LIST

OFFICER/EMPLOYEE LIST
APPLICATION: NDA 21-024/S-008

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified:

- 1. Alivisatos, Regina**
- 2. Jang, Seong**
- 3. Myer, Joette**
- 4. Higgins, Karen**
- 5. Li, Xianbin**
- 6. Davidson, Maureen**
- 7. Delasko, Jeanne**
- 8. Bala, Shukal**

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-024/S008

OFFICE DIRECTOR MEMO

Division Director Review

APPLICANT: Sanofi-Aventis Pharmaceuticals
NDA: NDA 21-024/S-008
DRUG: Rifapentine
TRADE NAME: Priftin®
Date of Submission: July 12, 2007
PDUFA Goal Date: May 13, 2008
Indication: Treatment of pulmonary tuberculosis caused by *Mycobacterium tuberculosis*,
Dosage form: Tablets, 150 mg
Regimen: 600 mg twice a week (first 2 months), 600 mg once a week (subsequent 4 months),
in combination with other anti-tuberculous drugs
Designation: Standard review
Related Material: **Material Reviewed:**
Clinical: Regina Alivisatos, TL: Joette Meyer
Clinical Pharmacology: Seong Jang, TL: Phil Colangelo
Statistics: Xianban Li, TL: Karen Higgins
Microbiology: Maureen Davidson, TL: Shukal Bala
Pharmacology/Toxicology: Owen McMaster, TL: Bill Taylor
Administrative Action Package, including reviews and records from
Original approval of NDA 21-024

RECOMMENDATIONS:

The applicant should be issued an approvable letter for this efficacy supplement, requesting that the 6.2 Adverse Reactions section and Table 1 for Study 8 be updated with “treatment-emergent” adverse reactions, as outlined in the Guidance to Industry document on *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*, dated January 2006.

The draft labeling has already been updated to reflect the findings of the submitted information and complete report of Study 22. Information from the previously submitted carcinogenicity study in rats is also included.

Postmarketing commitments – fulfilled:

Priftin was approved under Subpart H on June 22, 1998. The surrogate endpoint used for approval was the relapse rate at 6 months after completion of treatment, in lieu of the 2 year relapse rate. The current submission of the report for Study 22 completes the post-marketing commitments (PMC) required from Sanofi-Aventis as condition of “full approval” of this application, once labeling is finalized. The other commitment, to provide 2 year follow up data for Study 8 submitted in the original NDA was fulfilled with the submission dated December 17, 1999, NDA 21-024/S-005. Therefore, the studies required of Sanofi-Aventis under 21 CFR 314.510 have been submitted.

Postmarketing commitments – outstanding issues:

The other remaining postmarketing commitments listed in the June 22, 1998 letter will be addressed separately.

BACKGROUND:

Prifin (rifapentine) is a rifamycin antibiotic developed by Hoechst-Marion Roussel and CDC for the treatment of pulmonary tuberculosis. Tuberculosis is caused by *Mycobacterium tuberculosis*, and while uncommon in the US, is one of the most common infectious diseases worldwide causing millions of infections and deaths. In contrast, a total of 13,767 tuberculosis cases were reported in 2006 in the United States, a decline since the 1990’s. Rifapentine has a longer half-life than rifampin, and was developed with the goal of better compliance in mind. The original NDA was submitted December 22, 1997. With the repeal of Section 507 of the Act, the application was given NDA 21-024 (to replace 50-752). The application was presented to the Anti-Viral Advisory Committee on May 5, 1998. The committee members recommended approval, but cautioned that rifapentine use in HIV positive patients because rifapentine reduced the AUCs of Indinavir, a protease inhibitor in the treatment of HIV, and because 4 HIV-positive patients developed rifamycin mono-resistance in the rifapentine arm.

The recommendation for treatment of tuberculosis are provided by the CDC, American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) at <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm#tab1> (accessed May 8, 2008), underscoring the importance of treating this contagious disease. Based on these recommendations, rifampin is a cornerstone of tuberculosis treatment, Rifapentine is an acceptable alternative product for HIV negative patients but should not be given to HIV positive patients.

Efficacy and Safety Information from Study 008 (from labeling and previous reviews):

Study 008 involved 722 patients, it was open label, prospective, and randomized. Most of the patients were Black (>60%) or Multiracial (>31%), the mean age was 37, 73-80% were male. patients and the mean ± standard deviation age was 37 ± 11 years. Treatment groups were comparable with respect to age and race. For the first two months, patients received a four drug regimen of rifapentine (twice weekly), isoniazid, pyrazinamide, and ethambutol for 60 days (361 patients) or rifampin (daily), isoniazid, pyrazinamide, and ethambutol for 60 days. (361 patients). Ethambutol was to be discontinued once baseline susceptibility test results were available. During the next 4 months, the Continuation Phase, patients continued on rifapentine and isoniazid once weekly for up to 120 days or rifampin and isoniazid twice weekly for up to 120 days. Additionally, both treatment groups received pyridoxine (Vitamin B6) over the 180-day treatment period.

Clinical outcome in Study 008*

	Rifapentine Combination	Rifampin Combination
Status of End of Treatment		
Converted	87% (248/286)	80% (226/283)
Not Converted	1% (4/286)	3% (8/283)
Lost to Follow-up	12% (34/286)	17% (49/283)
Status Through 24 Month Follow-up		
Relapsed	12% (29/248)	7% (15/226)
Sputum Negative	57% (142/248)	64% (145/226)
Lost to Follow-up	31% (77/248)	29% (66/226)

*Data from patients with confirmed TB

Although conversion at end of treatment was higher in the rifapentine arm, the relaps rate was higher in the rifapentine arm. This application was presented before the May 5, 1998 Antiviral Advisory Committee for discussion, and the members recommended approval. The members also expressed concerned about use of rifapentine in HIV positive patients because of drug interactions, rifapentine decreased the AUC of protease inhibitors, and information from CDC that 4 HIV positive patients developed rifamycin-mono-resistance during therapy with rifapentine in a CDC study (Study 22). The committee discussed whether alternative regimens of rifapentine (one, two or three times weekly) may have less relapse or resistance, although an optimal regimen was not determined. Labeling therefore reflected the findings available and stressed the importance of compliance.

Microbiology information was summarized in labeling as follows: “In vitro susceptibility testing was conducted against *M. tuberculosis* isolates recovered from 620 patients enrolled in the study. Rifapentine and rifampin MIC values were determined employing the radiometric susceptibility testing method utilizing 7H12 broth at pH 6.8 (NCCLS procedure M24-T). Six hundred and twelve patients had *M. tuberculosis* isolates that were susceptible to rifampin (MIC < 0.5 µg/ml). Of these patients, six hundred and ten had *M. tuberculosis* isolates (99.7%) with rifapentine MICs of < 0.125 µg/ml. The other two patients that had rifampin susceptible *M. tuberculosis* isolates had rifapentine MICs of 0.25 µg/ml. The remaining eight patients had *M. tuberculosis* isolates that were resistant to rifampin (MIC > 8.0 µg/ml). These *M. tuberculosis* isolates had rifapentine MICs of > 8.0 µg/ml. In this study high rifampin and rifapentine MICs were associated with multi-drug resistant *M. tuberculosis* (MDRTB) isolates. Rifamycin mono-resistance was not observed in either treatment arm. This information is provided for comparative purposes only as rifapentine breakpoints have not been established.”

The safety information from the study reported on treatment-related adverse reactions and showed a comparable safety profile between the two arms, with the exception of hyperuricemia in the rifapentine arm (21% vs 15%) during the first 2

months of treatment, and therefore thought to be due to pyrazinimide use. Although not significantly different, there was a slight increase in hepatic events and allergic reactions in the rifampin arm of the study. At the end of the 24 month follow up, reported mortality was 11 patients in each arm.

On September 17, 2007, the Division requested that Sanofi-Aventis update the safety information in the labeling following the January 2006 Guidance to Industry regarding the presentation of information in the Adverse Reactions section. The request provided information from the guidance, requested updating labeling, and recommended a discussion to finalize the information to be included in this section.

Comments:

Sanofi Aventis did not address the request from September 17, 2007 to update section 6.2 Adverse Reactions and Table 1. However, Sanofi-Aventis, like other applicants, needs to provide updated labeling for this section consistent with the January 2006 Guidance to Industry document on Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format, dated January 2006.

The review team, after completing a thorough review of Study 22 and summarizing information to be included in labeling regarding the efficacy and safety findings from Study 22, sent that proposed labeling to Sanofi-Aventis. The updated information in the draft labeling is consistent with the current guidance, and can be approved. I agree with the team's recommendation for approval of the new information, and am aware that the previous safety information has not been addressed by the applicant. Given that Study 8 information was included in the original approval from 1998, it is understandable that the information should not be removed; however, it should be made consistent with current guidance.

Therefore, an approvable letter will be issued asking the company to provide updated information for the Adverse Reactions section consistent with requests made of other applicants. The guidance on Adverse Reactions was posted in January 2006 (previously available guidance was from May 2000) and the Physician Labeling Rule was implemented in June 2006.

Orphan Designation:

Rifapentine was granted Orphan Designation in June 1995. Therefore, this application is exempt from the Pediatric Research Equity Act (PREA) requirements that pediatric studies be conducted.

Pediatric Studies:

Rifapentine was issued a written request on June 19, 1998 and asked to conduct a clinical pharmacology study and an efficacy study in pediatric patients. The reports were due “on or before five years from the date of this letter.” The applicant did not conduct/submit these studies. No pediatric studies are required because the product has orphan designation. However, given that both the number of pediatric patients who would use this drug is not a “substantial number”¹ and this product does not “provide a meaningful therapeutic benefit over existing therapies” in the treatment of pediatric patients, a recommendation would be made that such studies can be waived. In adult studies, although sterilization at 2 months was similar to the control regimen, relapse rates at 2 years were higher in the rifapentine arm.

REVIEW OF CURRENT SUBMISSION:

Chemistry: Priftin is marketed as a 150 mg tablet. There is no new information submitted.

Pharmacology /Toxicology: There are no new studies submitted. The following labeling is added based on the previously submitted rat carcinogenicity study:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility,

Hepatocellular carcinomas were increased in male NMRI mice (Harlan Winkleman) which were treated orally with rifapentine for two years at or above doses of 5 mg/kg/day (equivalent to a human dose of 0.4 mg/kg/day or 1/5 th of the recommended human dose, in the intensive phase, based on body surface area conversions). In a two

¹ Although PREA does not define “substantial number,” FDA guidance on “How to comply with Pediatric Research Equity Act” suggest a number of 50,000.

year rat study, there was an increase in nasal cavity adenomas in Wistar rats treated orally with rifapentine at 40 mg/kg/day (equivalent to a human dose of 6.5 mg/kg/day or 3 times the recommended human dose in the intensive phase, based on body surface area conversions).

Clinical Pharmacology/Pharmacometrics:

Study 22 had a pharmacokinetic substudy published.² The abstract reports that patients on the rifapentine/INH arm who relapsed/failed had significantly lower INH AUC compared to patients who did not relapse/fail. However, it should also be noted that patients in the rifapentine arm received rifapentine/INH once weekly, while the control arm received rifampin/INH twice weekly.

To understand why once-weekly isoniazid/rifapentine therapy for tuberculosis was less effective than twice-weekly isoniazid/rifampin, we studied human immunodeficiency virus-seronegative patients with either failure (n = 4), relapse (n = 35), or cure (n = 94), recruited from a comparative treatment trial. In multivariate analyses that were adjusted for severity of disease, low plasma concentrations of isoniazid were associated with failure/relapse with once-weekly isoniazid/rifapentine (median isoniazid area under the concentration-time curve for 12 hours after the dose [AUC₀₋₁₂] was 36 µg · hour/ml in failure/relapse versus 56 µg · hour/ml in control cases p = 0.005), but not with twice-weekly isoniazid/rifampin. Furthermore, two patients who relapsed with *Mycobacterium tuberculosis* mono-resistant to rifampin had very low concentrations of isoniazid. Finally, isoniazid acetylase status determined by N-acetyltransferase type 2 genotype was associated with outcome with once-weekly isoniazid/rifapentine (p = 0.03) but not twice-weekly isoniazid/rifampin. No rifampin pharmacokinetic parameter was consistently and significantly associated with outcome (p > 0.10). Because low isoniazid concentrations were associated with failure/relapse, a drug with consistently greater area under the concentration-time curve than isoniazid may be needed to achieve highly active once-weekly therapy with rifapentine.

Clinical:

The following information is a summary of excerpts from the Medical Officer Review and proposed labeling:

Results of Study 22, conducted by CDC, were submitted and reviewed in this submission. The study involved 1004 HIV seronegative and 71 HIV seropositive patients with drug-susceptible pulmonary tuberculosis. These patients were randomized to rifapentine/INH or rifampin/INH after they completed the initial 2 months treatment period with 4 drugs (rifampin, isoniazid, pyrazinamide, and either ethambutol or streptomycin). At time of randomization, there were somewhat more patients in the rifapentine arm who had cavitary disease, bilateral disease, positive sputum smear and positive sputum culture, these differences were significant at p<0.05. Treatment was given under direct observation and consisted of rifapentine 600 mg and isoniazid 15mg/kg (max 900 mg) once weekly or rifampin 10 mg/kg (max 600 mg) and isoniazid 15 mg/kg (max 900 mg) twice weekly for the 4 month continuation phase. Enrollment of HIV seropositive patients was stopped when 4 of 36 patients in the rifapentine combination group developed rifampin mono-resistance.

The table below provides information on outcome, and the reviewers noted that failure and relapse rates could be underestimated because the majority of patients only had one sputum sample collected at each visit, and a positive culture was defined as > 10 organisms. As shown in the table below, a treatment response was achieved in a higher number of patients in the rifapentine arm, but the relapse rate at 24 months was higher in the rifapentine arm. Mortality was comparable at the end of treatment but numerically higher at 24 months in the rifampin arm, these were not statistically significant.

² Weiner M et al. Low isoniazid concentrations and outcome of tuberculosis treatment with once-weekly isoniazid and rifapentine. Am J Respir Crit Care Med 2003;167:1341-7.

Clinical Outcome in HIV Negative Patients with Pulmonary Tuberculosis		
	Rifapentine Combination Treatment % (n/N)	Rifampin Combination Treatment % (n/N)
Status at End of 4 Months Continuation Phase		
Treatment Response *	93.8% (471/502)	91.0% (457/502)
Not Converted	1.0% (5/502)	1.2% (6/502)
Did Not Complete Treatment**	4.2% (21/502)	7.0% (35/502)
Deaths	1.0 % (5/502)	0.8% (4/502)
Status Through 24 Month Follow-up:		
Relapsed	8.7% (41/471)	4.8% (22/457)
Sputum Negative	79.4% (374/471)	80.1% (366/457)
Lost to Follow-up	7.9% (37/471)	9.8% (45/457)
Deaths	4.0% (19/471)	5.3% (24/457)

* Treatment response was defined as subjects who responded successfully after 16 doses of rifampin and isoniazid or after 8 doses of rifapentine and isoniazid, but before the end of continuation phase therapy.

**due to drug toxic effects, non-adherence, withdrawal of consent, receipt of nonstudy regimen, other.

Higher relapse rates in HIV seronegative patients were seen in patients with a positive sputum culture at 2 months (i.e., at the time of study randomization), cavitation on chest x-ray, and bilateral pulmonary involvement. The labeling will reflect the findings in the seronegative patients.

Seventy-one HIV seropositive patients were enrolled into the study. There were no treatment failures during the study phase therapy. Sixty-one patients completed therapy and were assessed for relapse. The rates of relapse were 16.7% (5/30) in the rifapentine group and 9.7% (3/31) in the rifampin group. Risk factors that predisposed to relapse in the HIV seropositive patients included the presence of both pulmonary and extrapulmonary disease at baseline, low CD4 counts, use of azole antifungals and younger age. In HIV seropositive patients, 4 of the 5 relapses from the rifapentine combination group involved *M. tuberculosis* strains with rifampin monoresistance (RMR). No relapse strain in the twice weekly rifampin/isoniazid group had acquired drug resistance. These data are consistent with other documented acquired rifampin monoresistance in HIV seropositive adults who fail or relapse after treatment with intermittent regimens with isoniazid and other rifamycins (rifampin and rifabutin). For these reasons, the labeling will summarize this information and caution about the use of rifapentine in HIV positive patients.

Based on the Medical Officer safety analysis, there were more hepatic events in the rifampin-treated subjects (6.8%) versus the rifapentine-treated subjects (3.8%). This difference in part was due to the differences in the incidence of Grade 4 hepatotoxicity. The reason for this is not clear but may have to with the less frequent dosing of rifapentine.

Statistics: The statistical review of study one is reflected in the table of results from Study 22, above. The Statistical reviewer noted that while the relapse rate in the rifapentine arm is statistically significant, it is lower than was seen in Study 008 (submitted within the original NDA). As seen in the table below, the lack of significance may in part be due to the lower sample size in Study 008.

Failure/relapse rate	Rifapentine/ IND once weekly	Rifampin/IND twice weekly	95% CI, p value
Study 008	29/248 (12%)	15/226 (7%)	[-0.1%, 10.2%] p-value 0.06
Study 22	46/502 (9.2%)	28/502 (5.6%)	[0.4%, 6.8%], p-value 0.04

However, the statistical reviewer notes that when sensitivity analyses are done taking into consideration the overall category of death, loss to follow up, failure and relapse (and other permutations), the significance is not seen.

Sensitivity analysis	Rifapentine	Rifampin	95% CI
All failures, relapses, deaths, failures to complete treatment, losses of follow-up, consent withdrawals	133/502(26.5%)	143/502 (28.5%)	2.0 (-7.5, 3.5)

When looking at the characteristics of the TB infections, there is a slight imbalance in the two arms of the study, as shown in this table from the Statistical reviewer:

<i>Study 22</i>	Rifapentine N=502	Rifampin N=502
Cavitation on chest radiograph at induction*	278/488(57%)	246/487 (51%)
X-ray cavities within 2 wks of induction	243/472(51%)	218/468(47%)
Chest X-ray cavities at prerandomization	202/457(44%)	177/464(38%)
Bilateral disease on chest radiograph within 2 wks of induction or at prerandomization	290/498(58%)	269/498(54%)
X-ray bilateral disease within 2 wks of induction	270/493(55%)	241/292(49%)
Chest X-ray bilateral disease at prerandomization	247/481(51%)	229/484 (47%)
Sputum positive by smear*	73/480 (15%)	53/486 (11%)
Sputum positive by culture*	102/443(23%)	78/443 (18%)

* p < 0.05

Microbiology: The microbiology review of this application concurred that the information provided in the labeling initially continued to be valid and correct. Information from Study 22 were also reviewed and the following findings summarized in the review:

The failure and relapse rates reported in this study could be under estimated due to the limitation of the microbiologic methods used in the study. Positive culture was based on either one sputum sample with >10 colonies on solid media OR at least 2 positive sputum samples on liquid or solid media. However, only one sputum sample was collected at each visit in a majority of patients. In HIV seronegative patients who completed treatment, the rate of failure/relapse was 46/502 (9.2%) in those treated with isoniazid/rifapentine once a week, and 28/502 (5.6%) in those treated with isoniazid/rifampin twice a week (p=0.04). Of patients without pulmonary cavitation, rates of failure/relapse were closely similar between the rifapentine (2.9%) and rifampin (2.5%) groups (p=0.81). Rates of failure/relapse in patients with pulmonary cavitation were 15.8% and 9.5% in the rifapentine and rifampin groups, respectively. In HIV seropositive patients who completed treatment, the rate of failure/relapse was 5/30 (16.7%) in those treated with isoniazid/rifapentine once a week; and 3/31 (9.7%) in those treated with isoniazid/rifampin twice a week (p=0.47). In HIV seropositive patients, 4 of the 5 relapses from the once-weekly isoniazid/rifapentine group involved *M. tuberculosis* strains with rifamycin monoresistance (RMR). No relapse strain in the twice weekly isoniazid/rifampin group had acquired drug resistance (p=0.05). These data are consistent with other documented acquired rifamycin monoresistance in HIV seropositive adults who fail or relapse after treatment with intermittent regimens with isoniazid and other rifamycins (rifampin and rifabutin).

The Microbiology reviewer also noted that correlation between rifapentine MICs and clinical cure has not been established. Interpretive criteria/breakpoints to determine whether clinical isolates of *M. tuberculosis* are susceptible or resistant to rifapentine have not been established.

Labeling:

The labeling submitted in this supplement was presented in the Physician Labeling Rule format required of all applications submitted after June 30, 2006. It was reviewed by the Division, consulted to the SEALD team. The labeling is acceptable, with the exception as noted above for 6.2 Adverse Reactions and Table 1.

SUMMARY:

I concur with the recommendations of the review team that the current submission fulfills the second of the postmarketing required studies specified in the June 22, 1998 approval letter. Results of this study show that, as with the original Study 008, relapse rates are higher in the rifapentine arm, and may be due to the once-weekly use of rifapentine/INH. It is also noted that the number of patients with positive sputum smear and culture, and cavitory disease is higher in the rifapentine arm -- these are considered risk factors for relapse. The statistical difference in failure/relapse on the rifapentine arm is not preserved when all "nonsuccess" outcomes of failure, relapse, death, and loss-to-followup are considered as an endpoint. On the other hand, hepatic adverse events are somewhat lower, and it is noted that the INH AUC's in these failure/relapse patients in the rifapentine arm are lower than in the cures of the rifapentine arm. Therefore, the results of Study 22 are consistent with the results of Study 008.

The data on HIV positive patients is small, there were 5/35 relapses and in 4 of these rifampin-mono-resistance developed, therefore the labeling will reflect this information.

However, given that the information requested in the September 17, 2007 communication to Sanofi-Aventis has not been submitted, and specifically section 6.2 Adverse Reactions has not been updated, the applicant should be issued an approvable letter and requested to provide this information.

RECOMMENDATIONS:

This supplement should be issued an approvable letter.

The submission of Study 22 fulfills the request for postmarketing clinical studies from the approval letter dated June 22, 1998, as required under 21 CFR 314.510 Subpart H.

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/s/

Renata Albrecht
5/13/2008 07:24:28 PM
MEDICAL OFFICER

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-024/S008

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-024/S-008
Letter Date	April 23, 2009
Stamp Date	April 23, 2009
Review Completion Date	May 29, 2009
Reviewer Name	Tafadzwa Vargas-Kasambira, MD, MPH
Team Leader	Joette Meyer, PharmD
Division Director	Renata Albrecht, MD
Established Name	Rifapentine
Trade Name	Priftin®
Therapeutic Class	Rifamycin Antimycobacterial
Applicant	sanofi-aventis US LLC
Type of Submission	sNDA Resubmission
Formulation	150 mg Tablets
Dosing Regimen	600 mg twice weekly for 2 months (initial phase) followed by 600 mg once weekly for 4 months (continuation phase) in combination with other antituberculosis agents
Indication	Treatment of pulmonary tuberculosis caused by <i>Mycobacterium tuberculosis</i> in combination with one or more anti-tuberculosis drugs
Intended Population	Adult

1. Purpose Statement

This review describes the Applicant's response to the FDA's Approvable Letter of May 13, 2008 requesting submission of revised draft labeling for the rifapentine (Priftin®) package insert.

2. Recommendation

The Applicant's revised package insert is acceptable. The Applicant should be issued an approval letter for this sNDA resubmission.

3. Regulatory History

Rifapentine was approved for the treatment of pulmonary tuberculosis caused by *Mycobacterium tuberculosis* (MTB) on June 22, 1998. The drug was approved under the Accelerated Approval Regulations (21 CFR 314.5 10) Subpart H. The surrogate endpoint used for approval was the relapse rate at 6 months after completion of treatment in Study 008, in lieu of the 2 year relapse rate. The accelerated approval commitments in order to achieve full approval status included the following:

1. The final Clinical Study Report issued upon completion of Clinical Study 008 will be submitted to the Agency for review. In this final report both safety and efficacy data for the 2 years of follow-up will be included.
2. Hoechst Marion Roussel [currently sanofi-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-positive subjects who relapsed in the rifapentine treatment arm. It was agreed, since this study was being conducted by CDC under a separate IND that CDC would submit study results upon completion of the study.

The applicant submitted the 2-year follow-up data from Study 008 on December 17, 1999 (NDA 21-024/S-005), thus meeting one part of the accelerated approval requirements, and received an Approval letter on October 20, 2000.

The complete report for USPHS Study 22, required for conversion to full approval of the application, was submitted as an Efficacy Supplement on July 12, 2007. The Medical Officer recommended approval of the application (see review by Regina Alivisatos, M.D. dated April 23, 2008 in DFS). During the review cycle the rifapentine labeling was converted to PLR format by the review team. However, on May 13, 2008 the Agency issued an Approvable Letter to the Applicant. The cited deficiency concerned the fact that the table of adverse reactions (ARs) included in the package insert did not conform to the format described in the January 2006 *Guidance For Industry: Labeling for Human Prescription Drug and Biological Products — Implementing the New Content and*

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Format Requirements. The AR table from Study 008 contained only treatment-related ARs, rather than treatment-emergent ARs (i.e., all ARs which were reported during the study period rather than only those attributed to study drug by the investigators). In addition in the Approvable letter, the Applicant was asked to submit a safety update as described at 21CFR 314.50(d)(5)(vi)(b) that included data from all non-clinical and clinical studies of the drug under consideration, regardless of indication, dosage form, or dose level.

4. Review

The Applicant submitted their complete response to the May 13, 2008 Approvable Letter on April 23, 2009. In summary, the submission contained, as requested, the revised AE table containing common treatment-emergent AEs that occurred in $\geq 1\%$ of patients in Study 008, as well as a listing following the table, of less common AEs that occurred in $< 1\%$ of the rifapentine combination therapy patients.

The applicant did not sponsor any other clinical trials for rifapentine since NDA approval on June 22, 1998. As such, no additional clinical trial safety data have been collected by sanofi-aventis for rifapentine. The applicant therefore did not submit any safety update.

During the review cycle, the reviewer requested minor changes to the proposed package insert for rifapentine. On May 18, 2009 and again on May 22, 2009, requests for minor changes to the package insert were sent to the Applicant. These requests were incorporated into the package insert that the Applicant resubmitted on May 20, 2009 and May 29, 2009.

Of note, the Applicant included in the new table of treatment emergent adverse reactions, two preferred terms of (b) (4) and (b) (4) under the System Organ Class of “Body as a Whole – General” as follows:

System Organ Class Preferred Term	Initial Phase ¹		Continuation Phase ²		Total ³	
	Rifapentine Combination (N=361) N(%)	Rifampin Combination (N=361) N(%)	Rifapentine Combination (N=304) N(%)	Rifampin Combination (N=317) N(%)	Rifapentine Combination (N=361) N(%)	Rifampin Combination (N=361) N(%)
BODY AS A WHOLE - GENERAL						
Back Pain	15 (4.2)	11 (3.0)	11 (3.5)	4 (1.3)	25 (6.9)	15 (4.2)
Pain	14 (3.9)	17 (4.7)	8 (2.5)	5 (1.6)	22 (6.1)	22 (6.1)
Chest Pain	10 (2.8)	11 (3.0)	10 (3.2)	5 (1.6)	20 (5.5)	16 (4.4)
Injury Accident	5 (1.4)	5 (1.4)	12 (3.8)	14 (4.6)	17 (4.7)	17 (4.7)
Abdominal Pain	3 (0.8)	3 (0.8)	4 (1.3)	4 (1.3)	7 (1.9)	7 (1.9)
Fever	5 (1.4)	7 (1.9)	1 (0.3)	1 (0.3)	5 (1.4)	7 (1.9)

The reviewer requested clarification on these two preferred terms. The Applicant responded on May 20, 2009 that

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patients who experienced an overdose that resulted in an adverse reaction were coded to (b) (4) if no adverse reaction occurred they were coded to (b) (4). Overdoses involved either too frequent administration (daily doses instead of 2 doses per week for rifapentine during the Initial Phase, or the 1-2 doses per week for rifapentine, rifampin, and isoniazid during the Continuation Phase) or incorrect weight-based doses (rifampin, pyrazinamide, and ethambutol during the Initial Phase, or isoniazid and rifampin during the Continuation Phase). Seven patients had adverse reactions, (b) (4) associated with an overdose. In the rifampin combination group these reactions included hematuria, anorexia, back pain, arthralgia, and myalgia. In the rifapentine combination group these reactions included hematuria, neutropenia, hyperglycemia, ALT increased, hyperuricemia, pruritus, and arthritis.

In response, the MO reviewer requested that both preferred terms be removed from the table. A description of the number of patients who overdosed without an AR was added to the CLINICAL STUDIES section as follows:

Despite observed therapy, 65/361 (18%) of patients in the in the rifapentine arm and 34/361 (9%) in the rifampin arm received overdoses of one or more of the administered study medications during the initial or continuation phase of treatment. Only seven of these patients had adverse events reported with the overdose (5 in the rifapentine group and 2 in the rifampin group).

In the ARs table, the preferred term of (b) (4) was removed and the associated ARs in the rifapentine and rifampin groups were incorporated into other parts of the table (e.g., reports of hematuria were added to the preferred term of hematuria under the system organ class of Renal and Urinary).

5. Conclusions and Recommendations

The applicant has appropriately replaced the treatment-related adverse reactions with treatment-emergent adverse reactions for Study 008 in the package insert. The labeling was found to be acceptable.

This submission completes the accelerated approval commitments required by the Agency (21 CFR 3.14 subpart H) in the June 22, 1998 Approval letter. Full approval is recommended.

The final agreed-upon revisions to the Section 6 ADVERSE REACTIONS/6.2 Clinical Trial Experience subsection of the revised label are included below:

Tafadzwa Vargas-Kasambira, M.D., M.P.H.
MO, OND/OAP/DSPTP

Joette M. Meyer, Pharm.D.
Clinical Team Leader, DSPTP

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6 ADVERSE REACTIONS

6.2 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to PRIFTIN in a randomized, open label, active-controlled trial of patients with pulmonary tuberculosis, excluding those with HIV-infection. The population consisted of primarily of male subjects with a mean age of 37 ± 11 years. In the initial 2 month phase of treatment (60 days), 361 patients received rifapentine 600 mg twice a week in combination with daily isoniazid, pyrazinamide, and ethambutol and 361 subjects received rifampin in combination with isoniazid, pyrazinamide and ethambutol all administered daily. Ethambutol was discontinued when drug susceptibility testing was completed. During the 4 month continuation phase, 321 patients in the rifapentine group continued to receive rifapentine 600 mg dosed once weekly with isoniazid and 307 patients in the rifampin arm received twice weekly rifampin and isoniazid. Both treatment groups received pyridoxine (Vitamin B6) over the 6 month treatment period.

Twenty-two deaths occurred in the study (eleven in the rifampin combination therapy group and eleven in the rifapentine combination therapy group).

In the study, 18/361 (5.0%) rifampin combination therapy patients discontinued the study due to an adverse reaction compared to 11/361 (3.0%) rifapentine combination therapy patients. Three patients (two rifampin combination therapy patients and one rifapentine combination therapy patient) were discontinued in the Initial Phase as a result of hepatitis with increased liver function tests (ALT, AST, LDH, and bilirubin). Concomitant medications for all three patients included isoniazid, pyrazinamide, ethambutol, and pyridoxine. The two rifampin patients and one rifapentine patient recovered without sequelae.

As shown in Table 1, hyperuricemia was the most frequently reported reaction and was most likely related to the pyrazinamide since only two cases were reported in the Continuation Phase when this drug was no longer included in the treatment regimen.

Seven patients had adverse reactions associated with an overdose. In the rifampin combination group these reactions included hematuria, anorexia, back pain, arthralgia, and myalgia. In the rifapentine combination group these reactions included hematuria, neutropenia, hyperglycemia, ALT increased, hyperuricemia, pruritus, and arthritis.

The following table (Table 1) presents treatment-emergent adverse reactions associated with the use of any of the four drugs in the regimens (rifapentine/rifampin, isoniazid, pyrazinamide, or ethambutol) which occurred in ≥1% of patients during treatment and post-treatment through the first three months of follow-up.

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Table 1. Treatment-Emergent Adverse Reactions Occurring in ≥1% of Patients						
System Organ Class Preferred Term	Initial Phase¹		Continuation Phase²		Total³	
	<i>Rifapentine Combination (N=361) N(%)</i>	<i>Rifampin Combination (N=361) N(%)</i>	<i>Rifapentine Combination (N=304) N(%)</i>	<i>Rifampin Combination (N=317) N(%)</i>	<i>Rifapentine Combination (N=361) N(%)</i>	<i>Rifampin Combination (N=361) N(%)</i>
RENAL & URINARY						
Pyuria	39 (10.8)	56 (15.5)	47 (14.8)	36 (11.8)	78 (21.6)	83 (23.0)
Proteinuria	36 (10.0)	53 (14.7)	14 (4.4)	27 (8.9)	47 (13.0)	71 (19.7)
Hematuria	39 (10.8)	38 (10.5)	32 (10.1)	27 (8.9)	64 (17.7)	61 (16.9)
Urinary Tract Infection	32 (8.9)	24 (6.6)	23 (7.3)	10 (3.3)	48 (13.3)	32 (8.9)
Urinary Casts	20 (5.5)	22 (6.1)	11 (3.5)	7 (2.3)	29 (8.0)	28 (7.8)
Cystitis	5 (1.4)	6 (1.7)	1 (0.3)	1 (0.3)	6 (1.7)	7 (1.9)
METABOLIC & NUTRITIONAL						
Hyperuricemia	115 (31.9)	83 (23.0)	0 (0.0)	2 (0.7)	115 (31.9)	83 (23.0)
Hyperkalemia	14 (3.9)	22 (6.1)	20 (6.3)	21 (6.9)	33 (9.1)	41 (11.4)
Hypoglycemia	22 (6.1)	27 (7.5)	15 (4.7)	11 (3.6)	36 (10.0)	35 (9.7)
Nonprotein Nitrogen Increased	4 (1.1)	3 (0.8)	10 (3.2)	15 (4.9)	14 (3.9)	17 (4.7)
Hyperglycemia	10 (2.8)	8 (2.2)	4 (1.3)	2 (0.7)	13 (3.6)	9 (2.5)
LDH Increased	5 (1.4)	7 (1.9)	0 (0.0)	2 (0.7)	5 (1.4)	9 (2.5)
Hyperphosphatemia	2 (0.6)	1 (0.3)	3 (0.9)	5 (1.6)	5 (1.4)	6 (1.7)
HEMATOLOGIC						
Anemia	41 (11.4)	41 (11.4)	5 (1.6)	10 (3.3)	44 (12.2)	51 (14.1)
Lymphopenia	38 (10.5)	37 (10.2)	10 (3.2)	9 (3.0)	46 (12.7)	45 (12.5)
Neutropenia	22 (6.1)	21 (5.8)	27 (8.5)	24 (7.9)	45 (12.5)	41 (11.4)
Leukopenia	16 (4.4)	11 (3.0)	11 (3.5)	9 (3.0)	24 (6.6)	17 (4.7)
Leukocytosis	6 (1.7)	13 (3.6)	5 (1.6)	2 (0.7)	11 (3.0)	15 (4.2)
Neutrophilia	5 (1.4)	11 (3.0)	4 (1.3)	2 (0.7)	9 (2.5)	13 (3.6)
Thrombocytosis	20 (5.5)	13 (3.6)	1 (0.3)	0 (0.0)	20 (5.5)	13 (3.6)
Thrombocytopenia	6 (1.7)	6 (1.7)	4 (1.3)	6 (2.0)	9 (2.5)	11 (3.0)
Polycythemia	3 (0.8)	2 (0.6)	5 (1.6)	3 (1.0)	8 (2.2)	5 (1.4)
Lymphadenopathy	4 (1.1)	2 (0.6)	0 (0.0)	2 (0.7)	4 (1.1)	4 (1.1)
BODY AS A WHOLE - GENERAL						
Back Pain	15 (4.2)	11 (3.0)	11 (3.5)	4 (1.3)	25 (6.9)	15 (4.2)
Pain	14 (3.9)	17 (4.7)	8 (2.5)	5 (1.6)	22 (6.1)	22 (6.1)
Chest Pain	10 (2.8)	11 (3.0)	10 (3.2)	5 (1.6)	20 (5.5)	16 (4.4)
Injury Accident	5 (1.4)	5 (1.4)	12 (3.8)	14 (4.6)	17 (4.7)	17 (4.7)
Abdominal Pain	3 (0.8)	3 (0.8)	4 (1.3)	4 (1.3)	7 (1.9)	7 (1.9)
Fever	5 (1.4)	7 (1.9)	1 (0.3)	1 (0.3)	5 (1.4)	7 (1.9)
Fatigue	3 (0.8)	1 (0.3)	1 (0.3)	3 (1.0)	4 (1.1)	4 (1.1)
Edema Dependent	4 (1.1)	1 (0.3)	0 (0.0)	1 (0.3)	4 (1.1)	2 (0.6)
DERMATOLOGIC						
Rash	15 (4.2)	26 (7.2)	8 (2.5)	8 (2.6)	22 (6.1)	33 (9.1)
Sweating Increased	19 (5.3)	18 (5.0)	5 (1.6)	4 (1.3)	23 (6.4)	22 (6.1)
Pruritus	10 (2.8)	16 (4.4)	3 (0.9)	0 (0.0)	13 (3.6)	16 (4.4)
Acne	9 (2.5)	5 (1.4)	0 (0.0)	3 (1.0)	9 (2.5)	8 (2.2)
Skin Disorder	2 (0.6)	3 (0.8)	3 (0.9)	5 (1.6)	5 (1.4)	8 (2.2)
Rash Maculopapular	6 (1.7)	3 (0.8)	0 (0.0)	1 (0.3)	6 (1.7)	4 (1.1)
Eczema	2 (0.6)	2 (0.6)	3 (0.9)	2 (0.7)	4 (1.1)	3 (0.8)
RESPIRATORY						
Hemoptysis	27 (7.5)	20 (5.5)	6 (1.9)	6 (2.0)	30 (8.3)	25 (6.9)
Coughing	21 (5.8)	8 (2.2)	9 (2.8)	11 (3.6)	29 (8.0)	17 (4.7)
Upper Respiratory Tract Infection	5 (1.4)	9 (2.5)	12 (3.8)	15 (4.9)	17 (4.7)	22 (6.1)
Bronchitis	1 (0.3)	1 (0.3)	8 (2.5)	1 (0.3)	9 (2.5)	2 (0.6)
Pharyngitis	5 (1.4)	0 (0.0)	2 (0.6)	5 (1.6)	7 (1.9)	5 (1.4)
Epistaxis	2 (0.6)	2 (0.6)	3 (0.9)	1 (0.3)	5 (1.4)	3 (0.8)
Pleuritis	4 (1.1)	1 (0.3)	0 (0.0)	1 (0.3)	4 (1.1)	2 (0.6)
GASTROINTESTINAL						
Dyspepsia	6 (1.7)	11 (3.0)	4 (1.3)	6 (2.0)	10 (2.8)	17 (4.7)
Vomiting	6 (1.7)	14 (3.9)	3 (0.9)	3 (1.0)	9 (2.5)	17 (4.7)

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Nausea	7 (1.9)	3 (0.8)	2 (0.6)	1 (0.3)	9 (2.5)	4 (1.1)
Constipation	6 (1.7)	1 (0.3)	2 (0.6)	1 (0.3)	7 (1.9)	2 (0.6)
Diarrhea	5 (1.4)	2 (0.6)	2 (0.6)	0 (0.0)	7 (1.9)	2 (0.6)
Hemorrhoids	4 (1.1)	0 (0.0)	1 (0.3)	0 (0.0)	5 (1.4)	0 (0.0)
INFECTIOUS DISEASE						
Influenza	9 (2.5)	8 (2.2)	22 (6.9)	12 (3.9)	28 (7.8)	20 (5.5)
Infection Tuberculosis	0 (0.0)	5 (1.4)	9 (2.8)	4 (1.3)	9 (2.5)	9 (2.5)
Infection	1 (0.3)	2 (0.6)	4 (1.3)	4 (1.3)	5 (1.4)	6 (1.7)
Herpes Zoster	2 (0.6)	0 (0.0)	2 (0.6)	3 (1.0)	4 (1.1)	3 (0.8)
HEPATIC & BILIARY						
ALT Increased	18 (5.0)	23 (6.4)	7 (2.2)	10 (3.3)	25 (6.9)	32 (8.9)
AST Increased	15 (4.2)	18 (5.0)	7 (2.2)	8 (2.6)	21 (5.8)	26 (7.2)
NEUROLOGIC						
Headache	11 (3.0)	13 (3.6)	3 (0.9)	7 (2.3)	14 (3.9)	20 (5.5)
Dizziness	5 (1.4)	5 (1.4)	1 (0.3)	1 (0.3)	6 (1.7)	6 (1.7)
Tremor	3 (0.8)	1 (0.3)	2 (0.6)	0 (0.0)	5 (1.4)	1 (0.3)
PSYCHIATRIC						
Anorexia	14 (3.9)	18 (5.0)	8 (2.5)	6 (2.0)	21 (5.8)	22 (6.1)
Insomnia	2 (0.6)	2 (0.6)	2 (0.6)	2 (0.7)	4 (1.1)	4 (1.1)
MUSCULOSKELETAL						
Arthralgia	13 (3.6)	13 (3.6)	3 (0.9)	5 (1.6)	16 (4.4)	18 (5.0)
Arthritis	4 (1.1)	5 (1.4)	1 (0.3)	0 (0.0)	4 (1.1)	5 (1.4)
Arthrosis	4 (1.1)	1 (0.3)	0 (0.0)	1 (0.3)	4 (1.1)	2 (0.6)
Gout	3 (0.8)	1 (0.3)	1 (0.3)	0 (0.0)	4 (1.1)	1 (0.3)
CARDIOVASCULAR						
Hypertension	3 (0.8)	5 (1.4)	3 (0.9)	2 (0.7)	6 (1.7)	7 (1.9)
OPHTHALMOLOGIC						
Conjunctivitis	8 (2.2)	2 (0.6)	1 (0.3)	1 (0.3)	9 (2.5)	3 (0.8)

Note: $\geq 1\%$ refers to rifapentine in the TOTAL column.

- 1 Initial Phase consisted of therapy with either rifapentine or rifampin combined with isoniazid, pyrazinamide, and ethambutol administered daily (rifapentine twice weekly) for 60 days.
- 2 Continuation Phase consisted of therapy with either rifapentine or rifampin combined with isoniazid for 120 days. Rifapentine patients were dosed once weekly; rifampin patients were dosed twice weekly.
- 3 A patient may have experienced the same adverse reaction more than once during the course of the study, therefore, patient counts across the columns may not equal the patient counts in the TOTAL column.

In addition to the adverse reactions reported in Table 1, adverse reactions were reported post-treatment during the 3 month through 24 month follow-up period. Although the protocol for this study specified collection of serious adverse reactions during this period, some non-serious adverse reactions were reported as well. For the rifapentine combination group these included the following: hematuria, infection tuberculosis, proteinuria, urinary casts, hyperkalemia, hypoglycemia, injury accident, skin disorder, respiratory disorder, stupor, prostatic disorder.

Treatment-emergent adverse reactions reported during treatment and post-treatment through the first three months of follow-up in $<1\%$ of the rifapentine combination therapy patients are presented below by body system in order of frequency.

Renal & Urinary: urethral disorder, dysuria, pyelonephritis, urinary incontinence, urination disorder.

NDA 21-024/S-008

Priftin® (rifapentine) Tablets

Metabolic & Nutritional: weight decrease, BUN increased, diabetes mellitus, alkaline phosphatase increased, hypophosphatemia, hypercalcemia, hypovolemia, weight increase.

Hematologic: lymphocytosis, hematoma, purpura, anemia hypochromic, anemia normocytic, thrombosis.

Body as a Whole - General: laboratory test abnormal, edema legs, asthenia, edema face, abscess, edema peripheral, malaise.

Dermatologic: skin ulceration, urticaria, dry skin, furunculosis, skin discoloration, dermatitis fungal, nail disorder, alopecia, rash erythematous.

Respiratory: abnormal breath sounds, pneumothorax, pneumonia, pleural effusion, rhinitis, dyspnea, pneumonitis, sinusitis, sputum increased, pulmonary fibrosis, upper respiratory congestion, asthma, chest x-ray abnormal, bronchospasm, laryngeal edema, laryngitis, respiratory disorder,

Gastrointestinal: tooth disorder, gastroenteritis, gastritis, esophagitis, cheilitis, dry mouth, pancreatitis, proctitis, salivary gland enlargement, tenesmus, gastrointestinal disorder not specified.

Infectious Disease: infection fungal, infection parasitic, infection protozoan.

Hepatic & Biliary: bilirubinemia, hepatomegaly, jaundice.

Neurologic: somnolence, seizure not specified, dysphonia, hypoesthesia, torticollis, hypertonia, hyporeflexia, meningitis, migraine headache, stupor.

Psychiatric: anxiety, confusion, drug abuse, aggressive reaction, agitation.

Musculoskeletal: myalgia, myositis, bone fracture, muscle weakness, muscle spasm.

Cardiovascular: syncope, tachycardia, palpitation, hypotension orthostatic, pericarditis.

Reproductive Disorders: penis disorder, vaginitis, vaginal hemorrhage, cervical smear test positive, leukorrhea, mastitis male, prostatic disorder.

Hearing & Vestibular: ear disorder not specified, otitis media, earache, otitis externa, tympanic membrane perforation.

Ophthalmologic: eye pain, eye abnormality.

Neoplasms: pulmonary carcinoma, neoplasm not specified, carcinoma, lipoma.

Vascular (Extracardiac): thrombophlebitis deep, vascular disorder, vasodilation.

Special Senses Other: taste loss.

Pregnancy, puerperium and perinatal conditions: abortion

In another randomized, open-label trial in 1075 HIV seronegative and seropositive patients with pulmonary tuberculosis the overall adverse event rate did not differ substantially from the previous trial. Patients who had completed an initial 2 month phase of treatment with 4 drugs were randomly assigned to receive either rifapentine 600 mg and isoniazid once weekly or rifampin and isoniazid twice weekly for the 4 month continuation phase.

In the rifapentine arm, 502 HIV seronegative and 36 HIV seropositive patients were randomized and in the rifampin arm 502 HIV seronegative and 35 HIV seropositive patients were randomized to treatment.

The death rate among all study participants was 71/1075 (6.6%) and did not differ between the two treatment groups (6.5% for the rifapentine combination regimen compared to 6.7% for the rifampin combination regimen; $P = 0.87$).

There were 526 treatment-emergent adverse events regardless of causality reported from 251 patients treated with the rifapentine combination regimen and 513 adverse events reported from 248 patients treated with the rifampin combination regimen. On both study arms the most frequently reported adverse events were hyperglycemia, pneumonia, liver toxicity, and death and were consistent with concurrent underlying conditions that included alcohol abuse, pancreatitis and HIV.

There was a greater percentage of patients in the rifampin combination arm who developed hepatic adverse events (35/513; 6.8 %) compared to 20/526 (3.8%) in the rifapentine combination arm. The types of other adverse events were similar between the treatment arms.

Hyperuricemia was not reported as an adverse reaction in this study of continuation phase therapy. In the previous study which evaluated initial therapy containing pyrazinamide, hyperuricemia was reported in 32% of rifapentine and 23% of rifampin combination treated patients (see Table 1).

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CLINICAL REVIEW

Application Type	Efficacy Supplement
Submission Number	21-024/SE7-008
Letter Date	July 12, 2007
Stamp Date	July 12, 2007
PDUFA Goal Date	May 13, 2008
Reviewer Name	Regina Alivisatos, MD
Team Leader	Joette Meyer, PharmD.
Established Name	Rifapentine
Trade Name	Priftin®
Therapeutic Class	Rifamycin Antimycobacterial
Applicant	Sanofi-Aventis Pharmaceuticals
Priority Designation	S
Formulation	150 mg Tablets
Dosing Regimen	600 mg ^{(b) (4)} week
Indication	Treatment of Pulmonary Tuberculosis caused by <i>Mycobacterium tuberculosis</i> in combination with one or more anti-tuberculosis drugs
Intended Population	Adult

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1 Executive Summary

Rifapentine (Priftin®) was approved for the treatment of pulmonary tuberculosis caused by *Mycobacterium tuberculosis* (MTB) on June 22, 1998. This approval was based upon the accelerated approval regulations (21 CFR 314 Subpart H) where the 6-month relapse rate was used as a surrogate for the 2-year relapse rate.

The original NDA submission included interim efficacy results based on data collected from an ongoing open label, randomized, active-controlled clinical trial (Protocol 0047PR0008) for the treatment of tuberculosis. This study was entitled “Efficacy and Safety of Rifapentine Combination Therapy Compared to Standard Therapy in the Treatment of Previously Untreated Pulmonary Tuberculosis” and was conducted in South Africa, the United States, and Canada. Patients were randomized to receive one of two treatment regimens:

- Treatment A (control): 2 months daily isoniazid (INH)/rifampin R/pyrazinamide (PZA)/ethambutol (EMB) followed by 4 months twice weekly INH/R
- Treatment B: 2 months daily INH/PZA/EMB and twice weekly rifapentine (Rpt) followed by 4 months once weekly INH/Rpt.

The endpoints included sputum conversion at the end of treatment and tuberculosis relapse at 6 months and 2 years after the end of therapy. The results showed that the rifapentine regimen was similar to the rifampin regimen in converting sputum cultures to negative at the end of treatment (6 months). However, there were approximately twice as many relapses in the rifapentine arm than the rifampin arm 6 months after treatment. Exploratory analyses by the applicant suggested that lack of compliance with the companion drugs was a possible reason for the higher relapse rate. The development of resistance to rifamycins in subjects treated with rifapentine was not seen in this pivotal clinical trial.

The safety profile of rifapentine in study 008 was similar to that of rifampin with one exception. There was a greater incidence of hyperuricemia during the first two months of therapy (intensive phase) for the rifapentine arm compared to the rifampin arm.

The accelerated approval commitments in order to achieve full approval status included the following:

1. The final Clinical Study Report issued upon completion of Clinical Study 008 will be submitted to the Agency for review. In this final report both safety and efficacy data for the 2 years of follow-up will be included.
2. Hoechst Marion Roussel 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-positive subjects who relapsed in the rifapentine treatment arm. It was agreed, since this study was being conducted by CDC under a separate IND that CDC would submit study results upon completion of the study.

The Applicant submitted the final report of study 008 in December 1999 thus meeting part 1 of the accelerated approval requirements. The final study report provided data on the tuberculosis (TB) relapse rate at 24 months after completion of 6 months of study treatment. The majority of relapses (where relapse was defined as a positive sputum culture occurring after conversion to negative and after completion of therapy) were reported during the 6 months following the last dose of study drug.

The current submission contains the results of study USPHS 22 and represents the final accelerated approval commitment for rifapentine. This study addresses the issue of efficacy and relapse in subjects in whom rifapentine was utilized as a component of the continuation phase of anti-tuberculous treatment during last 4 months of therapy at a weekly dose with INH as compared to the standard continuation regimen of rifampin and INH twice a week for 4 months. This open label, comparative study, which is the topic of this review, demonstrated in the FDA analysis relapse/failure rates in HIV-negative subjects 24 months after the end of continuation therapy (following a total of 6 months of treatment) of 7% (41/471) for the rifapentine-treated subjects compared to 4.8% (22/457) for rifampin-treated subjects. These results were consistent with the failure/relapse rates from study 008 at the same timepoint (12% (29/248) for rifapentine-treated subjects as compared to 7% (15/226) for rifampin-treated subjects.

Unlike study 008, study 22 also included HIV-positive subjects. However, enrollment of HIV seropositive patients was stopped when 4/36 patients in the rifapentine combination group developed rifamycin monoresistance. Sixty-one HIV-positive patients completed therapy and were assessed for relapse. The rates of relapse were 16.7% (5/30) in the rifapentine group and 9.7% (3/31) in the rifampin group.

1.1 Recommendation on Regulatory Action

This submission was made in compliance with the second and final accelerated approval commitment required by the Agency (21 CFR 3.14 subpart H) in the June 1998 approval letter. The applicant has satisfied all the accelerated approval commitments required by the Agency in the 1998 approval letter under subpart H. Full approval is recommended.

A Pediatric Written Request was issued on June 19, 1998 to study the pharmacokinetics and clinical efficacy of rifapentine in children under 12 years of age, however, studies were never conducted by the Applicant. Therefore, it is recommended that pediatric studies should be waived in children < 12 years of age because of the low incidence of reported tuberculosis cases amongst children < 15 years of age (2006 Total # reported TB cases US: 13,779, pediatric N= 807 (5.9%): data from CDC) and because there is little therapeutic advantage to the use of rifapentine in children because of the relative risk of higher relapse rates associated with rifapentine and the possibility of the development of resistant Mycobacteria without any obvious safety benefit relative to traditional rifamycin therapies.

The label has been converted to Physician Labeling Rule (PLR) format and should be revised to include information from study 22 and to change the INDICATIONS and USAGE section to reflect full approval of the indication.

1.2 Recommendation on Postmarketing Actions

None

1.3 Summary of Clinical Findings

Study USPHS 22 was a prospective, open-label, comparative study of two continuation phase antituberculosis treatment regimens. After completing the 8 week induction (initial) phase therapy, eligible subjects were randomized to receive study (continuation) phase therapy for an additional 16 weeks with a regimen consisting of either once-weekly rifapentine and isoniazid (INH) or twice-weekly rifampin and INH. Randomized subjects were followed for 2 years after the scheduled completion of study phase therapy, until death, or for those with relapse, for one year after the diagnosis of relapse.

There were 3 study phases:

- Induction (initial) phase therapy (any pre-randomization therapy)
- Study phase therapy (post-randomization therapy, Study Weeks 0 to 16-22)
- Follow-up phase therapy (Study Weeks 16-22 to 118).

Eligible subjects were randomized to one of two study regimens and were stratified by site and by subject HIV status.

The study phase therapy started a maximum of 7 days after randomization, lasted a minimum of 16 weeks, and consisted of either 32 doses of rifampin 600 mg and INH 900 mg administered twice weekly or 16 doses of rifapentine 600 mg and INH 900 mg administered once a week. Adequate study phase therapy consisted of receipt of 100% of the prescribed doses within 22 weeks.

After completion of study phase therapy, subjects were seen four times during the first year of follow-up (Study Weeks 28 ± 2 weeks, 40 ± 2 weeks, 52 ± 2 weeks and 64 ± 2 weeks) and twice during the second year of follow-up (Study Weeks 92 ± 4 weeks and 116 ± 4 weeks).

In addition, during the follow-up phase, subjects were seen and evaluated if at any time they developed signs and symptoms associated with tuberculosis.

The primary objective/endpoint of study 22 was a comparison of the failure/relapse rate between the 2 treatment arms at the completion of the continuation phase of treatment for MTB (i.e., failure during treatment or relapse after treatment). Failure/relapse included both bacteriologic (culture) and clinical (signs and symptoms) criteria. Secondary objectives included an assessment of failure and relapse rates of the 2 regimens, to compare the development of drug resistant tuberculosis in subjects classified as failure/relapses, to compare efficacy and safety in a subset of HIV-positive subjects, and to compare the safety including mortality rates of the two regimens

A total of 1004 HIV-negative subjects were enrolled, 502 to each treatment arm at 29 sites. No site enrolled more than 15% of the subjects. In addition, seventy-one HIV-positive subjects were also enrolled. Enrollment started in 1995 and follow-up was completed in 2001. Subjects were stratified by HIV status and were assessed separately although cumulative efficacy was also calculated. The initial intent was to enroll 80 HIV-positive subjects but the enrollment of this group was terminated early due to an increased number of failures as well as the development of resistance in 4 subjects.

HIV negative subjects were primarily males, non-Hispanic black and of low socioeconomic status. The groups were similar with regards to initial treatment but more rifapentine treated subjects had evidence of cavitory disease, bilateral disease, and were culture or smear positive at study baseline. It is possible, that the increased number of subjects with these risk factors on the rifapentine arm influenced the greater relapse rate seen on this arm.

Of the subjects treated with the rifapentine regimen, 6% (31/502) did not complete treatment compared to 9% (45/502) of the subjects treated with the rifampin standard regimen. The reasons for treatment discontinuation did not differ significantly between the groups and included death, non-compliance, and toxicity. Four hundred seventy one (471) rifapentine-treated subjects (471) completed treatment as compared to 457 rifampin-treated subjects. The mean duration of follow-up after completion of treatment was similar between the arms (20.4 months in the rifapentine arm, 20.3 months in the rifampin arm).

Of the 71 HIV-positive subjects enrolled (36 subjects in the rifapentine arm and 35 in the rifampin arm), 61 (86%) completed treatment and were assessed for relapse. Enrollment of HIV-positive subjects was stopped when 4 of 36 rifapentine-treated subjects developed rifamycin monoresistance.

Both HIV-positive treatment groups were similar in terms of disease severity with approximately one third of the subjects in each group having evidence of cavitation at the time of enrollment. Of note, none of the rifapentine-treated subjects had a positive sputum smear or culture at the time of enrollment as compared to 12–19% in the rifampin group.

1.3.2 Efficacy

Efficacy in HIV-negative Subjects: In the CDC ITT analysis, failure/relapse occurred in 46 (9.2%) of 502 subjects in the rifapentine group and in 28 (5.6%) of 502 in the rifampin group ($p=0.04$). The difference in crude event rates between treatment groups was 3.6% (95% CI 0.004–0.068). Life-table rates of failure/relapse were 10.3% (SD 1.5) in the rifapentine group and 5.9% (1.1) in the rifampin group ($p=0.035$).

On multivariate Cox proportional-hazards analysis, five factors were identified as being independently associated with failure/relapse: non-Hispanic white race, being underweight, bilateral pulmonary involvement, cavitation on chest radiograph, and positive sputum culture at 2 months. These results were confirmed via independent analyses of the submitted datasets. The following table generated by the Agency Statistical Review Team, contains assessments of sputum conversion at the end of treatment (6 months total: 2 months of initial and 4 months of randomized continuation treatment) and relapse rates at the end of follow-up (24 months) in all

HIV seronegative patients randomized to treatment. The failure and relapse rates reported in this study could be underestimated due to the limitation of the microbiologic methods used in the study. Positive culture was based on either one sputum sample with >10 colonies on solid media OR at least 2 positive sputum samples on liquid or solid media. However, only one sputum sample was collected at each visit in a majority of patients.

Clinical Outcome in HIV Negative Patients with Pulmonary Tuberculosis

Clinical Outcome in HIV Negative Patients with Pulmonary Tuberculosis

	Rifapentine Combination Treatment % (n/N)	Rifampin Combination Treatment % (n/N)
Status at End of 4 Months Continuation Phase		
Treatment Response *	93.8% (471/502)	91.0% (457/502)
Not Converted	1.0% (5/502)	1.2% (6/502)
Did Not Complete Treatment**	4.2% (21/502)	7.0% (35/502)
Deaths	1.0 % (5/502)	0.8% (4/502)
Status Through 24 Month Follow-up:		
Relapsed	8.7% (41/471)	4.8% (22/457)
Sputum Negative	79.4% (374/471)	80.1% (366/457)
Lost to Follow-up	7.9% (37/471)	9.8% (45/457)
Deaths	4.0% (19/471)	5.3% (24/457)

* Treatment response was defined as subjects who responded successfully after 16 doses of rifampin and isoniazid or after 8 doses of rifapentine and isoniazid, but before the end of continuation phase therapy.

**due to drug toxic effects, non-adherence, withdrawal of consent, receipt of nonstudy regimen, other.

Efficacy in HIV-positive Subjects: There were no treatment failures during the induction/initial treatment phase or during the study treatment phase in the HIV-positive subjects. In the PP analysis there were 5 relapses (5/31) in the rifapentine treated subjects (16.6%) versus 3/31 (9.6%) in the rifampin treated subjects (Applicant p value = 0.47). In an Agency ITT analysis where all dropouts were considered failures the difference between the treatment arms remained similar (30.6% failures in the rifapentine arm versus (20% in the rifampin arm).

Relapses occurred from 9 – 34 weeks after the EOT (median 19) in the Rifapentine subjects and from 11- 24 (median 14 weeks) in the standard rifampin subjects. The relapse rates for the 2 year endpoint calculated by Kaplan Meier were 17.8% in the rifapentine group versus 10% in the rifampin group (p = 0.41). Four of the relapses in the rifapentine group involved MTB strains with rifamycin monoresistance as compared to none of the strains from relapses on the standard treatment arm.

Risk factors for relapse in the HIV-positive subset included the presence of both pulmonary and extrapulmonary disease at baseline, low CD4 counts, use of azole antifungals and age (younger).

Conclusion: The findings of the CDC efficacy analyses of study 22 demonstrated relapse/failure rates in HIV-negative subjects at 24 months following the end of continuation therapy of 9.2% (46/502) for the rifapentine group compared to 5.5% (28/502) for the rifampin group and were consistent with those from study 008 where overall relapse rates at 24 months were 12% (29/248) for rifapentine-treated subjects as compared to 7% (15/226) for rifampin-treated subjects. Agency analyses generated similar results (24 month rifapentine relapse rate 41/471 (8.7%) versus rifampin 22/457 (4.8%).

Further, the study delineates via risk factor analyses, which populations can safely receive rifapentine as part of their anti-tuberculosis treatment regimen. Due to the risk of rifamycin monoresistance, HIV-positive subjects should not receive rifapentine treatment. In HIV-negative subjects, higher relapse rates were seen in subjects with evidence of cavitory disease or bilateral pulmonary involvement on chest- x-ray and those who did not convert their sputum cultures to negative after the initial 2 month phase of treatment. These subjects should not receive rifapentine treatment at all or with extreme caution.

It should be clarified that although the relapse rates at 24 months following the end of treatment seen in subjects treated with once weekly rifapentine in conjunction with INH during the continuation phase of anti-tuberculous treatment were statistically significantly greater than the rates seen in subjects treated with rifampin and INH, these results were no different than those seen in study 008 which formed the original basis for accelerated approval. Further, in study 22 the applicant was able to clearly delineate subgroups of subjects at risk of relapse, including those with cavitory lesions, bilateral pulmonary disease and/or positive sputum cultures at the end of the initial treatment phase. This information allows prescribers to better identify subjects who are more likely to respond to rifapentine treatment. Other factors that should be taken into account when assessing the risk-benefit of rifapentine treatment include the improved compliance with a once weekly dosing regimen and thus the increased feasibility of DOT and the somewhat better tolerability of rifapentine compared to rifampin containing regimens. It remains true, however, that the optimal therapeutic regimen for rifapentine has not yet been defined and clinical trials are continuing with this goal.

1.3.3 Safety

The adverse events reported from study 022 do not differ substantially from the AEs in the label for study 008. There were 526 treatment-emergent adverse events regardless of causality reported from 251 subjects treated with the rifapentine combination regimen and 513 adverse events reported from 248 subjects treated with the rifampin combination regimen. On both study arms the most frequently reported adverse events were hyperglycemia, pneumonia, liver toxicity, and death and were consistent with concurrent underlying conditions that included alcohol abuse, pancreatitis, and HIV.

There was a greater percentage of subjects in the rifampin combination arm who developed hepatic adverse events (35/513 (6.8 %) compared to 20/526 (3.8%) in the rifapentine combination arm). The types of other adverse events were similar between the treatment arms.

Hyperuricemia was not reported as an adverse event in this study where pyrazinamide was not used as opposed to the previous study as indicated in product labeling.

Overall AEs in HIV-positive subjects were proportionally more serious than in HIV-negative. However the events that occurred were primarily associated with the underlying HIV disease rather than with study treatment. As expected most events were from the liver although not disproportionately so.

The overall crude mortality rate among all study participants was 71/1075 (6.6%) and did not differ between the two treatment groups (6.5% for the rifapentine group compared to 6.7% for the rifampin group, $P = 0.87$).

Mortality rates were substantially higher in HIV-positive than HIV-negative subjects (15/71; 21.1% vs. 56/1004; 5.6%; $P < 0.001$). The mortality rate was 10.5% among the 19 subjects who received HAART during the study compared to 29.6% among the 27 subjects who received no HAART ($P = 0.16$).

No deaths were attributed to anti-tuberculosis drug toxicity. Among the 71 participants who died, the last sputum culture prior to death was negative in 58, missing in 1, positive for non-tuberculous mycobacteria in 8, and positive for *M. tuberculosis* in 4. Of these 4, 1 died of trauma, 1 of central nervous system toxoplasmosis, and 1 of metastatic lung cancer. Only one death (1/71; 1.4%) death was attributed to TB (pulmonary hemorrhage before treatment started).

Among HIV-negative subjects, 18/56 (32%) deaths were associated with malignancy, and 13 (23%) were attributed to injuries, accidents, drug overdose, or unknown cause. Other causes of death in HIV-negative subjects included cardiac disease (6), chronic obstructive pulmonary disease (2), bacterial pneumonia (2), and cerebrovascular accident (2).

Of the 16 deaths (9 rifapentine, 7 rifampin) in HIV-positive subjects, 11 were due to AIDS, two to malignancy, and two to drug overdose and one was unknown and occurred during late follow-up.

Deaths occurred throughout the study, during both the study and follow-up phases. There was a suggestion of increased mortality among HIV-positive subjects near the end of the follow-up period. The rate of death among HIV-negative subjects appeared stable over time. In a multivariate Cox proportional hazards model, factors independently associated with death were (in decreasing order of magnitude of hazard ratio) malignancy, HIV infection, alcohol use, unemployment, and age (per 1-year increase).

addition the label has been converted to PLR format and has sustained numerous formatting and content changes in order to be in compliance with the Physician Labeling Rule (PLR)

Regulatory History:

Rifapentine (Priftin®) was approved for the treatment of tuberculosis on June 22, 1998. This approval was based upon the accelerated approval regulations (21 CFR 314 subpart H) where the 6-month relapse rate was used as a surrogate for the 2-year relapse rate. Rifapentine was granted orphan drug designation for the treatment of tuberculosis in June of 1995.

Hoechst Marion Roussel Inc., the original applicant, submitted New Drug Application 21-024 for rifapentine to the FDA in December 1997. The original submission included interim efficacy results based on data collected through November 8, 1996 from an ongoing open label, randomized, active-controlled clinical trial (Protocol 0047PR0008) for the treatment of tuberculosis. To better understand the incidence of relapse, the applicant with prior FDA agreement, submitted a clinical update on March 4, 1998 that summarized follow-up data through a July 1997 cut-off date. By this date, all of the subjects had been treated and followed to the 6 month post therapy visit.

In study 008, the rifapentine regimen was similar to the rifampin regimen in converting sputum cultures to negative at the end of treatment (6 months). However, there were approximately twice as many relapses in the rifapentine arm than the rifampin arm 6 months after treatment. Exploratory analysis by the applicant suggested that lack of compliance with the companion drugs was a possible reason for the higher relapse rate. Thus, the importance of adherence to the regimen is stressed in the label. The development of resistance to rifampin was not seen in this clinical trial.

The safety profile of rifapentine in study 008 was similar to that of rifampin with one exception. There was a greater incidence of hyperuricemia during the first two months of therapy (intensive phase) for the rifapentine arm compared to the rifampin arm.

A closed Anti-Viral Advisory Committee Hearing (May 5, 1998) was held to discuss the efficacy and safety of rifapentine during which CDC made a presentation to the advisory committee of the preliminary results of Study 22, including details regarding the use of rifapentine in subjects with HIV infection.

The committee voted to recommend approval of rifapentine for the treatment of pulmonary tuberculosis with only one dissenting vote. The committee cautioned that rifapentine should be used with extreme caution, if at all, in HIV-positive subjects. This was due to the development of rifamycin resistance in 4 HIV-positive subjects, and the potential for rifapentine to significantly reduce the AUC (area under the curve) of the protease inhibitor, indinavir. It should be noted that this AC was convened at a time when few protease inhibitors were available. Since that time there are many more therapeutic options for the treatment of HIV infection.

It was the AC's general belief that rifampin and rifapentine were comparable agents, but that the optimal therapeutic regimen had not yet been determined for rifapentine. The committee also discussed extensively the issues associated with the higher relapse rates in the rifapentine group. Issues discussed included adherence (compliance) to treatment and the differences in the PK profiles of rifapentine plus INH compared to rifampin plus INH. Due to the long half-life of rifapentine there could be a period of time each week in which the subject has measurable blood levels of rifapentine, but not INH, leaving the subject essentially being treated with rifapentine monotherapy. However, neither INH nor rifampin resistance was seen in the 008 study. The committee recommended not to restrict the use of rifapentine to specialty groups, but that clear explanation of study dosing and results be placed in the label for the clinician to use in decision making.

The committee recommended further studies, including the completion of the CDC study USPHS 22, which utilized rifapentine in the last 4 months of therapy once weekly with INH, and standard rifampin therapy in the first two months of intensive (initial) therapy. This study is the topic of this review.

The accelerated approval commitments in order to achieve full approval status from the June 22, 1998 Approval letter included the following:

1. The final Clinical Study Report issued upon completion of Clinical Study 008 will be submitted to the Agency for review. In this final report both safety and efficacy data for the 2 years of follow-up will be included.
2. HMR 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-positive subjects who relapsed in the rifapentine treatment arm. It was agreed, since this study was being conducted by CDC under a separate IND that CDC would submit study results upon completion of the study.

The Applicant submitted the final report of study 008 in December 1999 thus meeting a part of the accelerated approval requirement. That study provided data on the TB relapse rate at 24 months after enrollment in study 008, which was added to the CLINICAL STUDIES section of the label.

The following table shows the cumulative relapse rate through 12 months of follow-up (after the last dose of study drug). The majority of relapses (where relapse was defined as a positive sputum occurring after conversion to negative and after completion of therapy) were reported during the first 6 month follow-up period.

Cumulative Relapse Rate for Intent to Treat Patients in Study 0008

Interval from Last Dose of Study Drug to Relapse	Rifampin Combination (N= 232)	Rifapentine Combination (N=252)	Total (N= 484)
3 months	5 (2.2%)	17 (6.7%)	22 (4.5%)
6 months	10 (4.3%)	22 (8.7%)	32 (6.6%)
12 months	11 (4.7%)	27 (10.7%)	38 (7.9%)

NDA Table 8-64, S8-V1.127-p38

Overall relapse rates were 4.7% (11/232) for rifampin and 10.7% (27/252) for rifapentine in the intent to treat analysis.

A substantial number of subjects in this cohort were lost to follow-up at the 24 month date (approximately 1/3). The 24-month rates of relapse are 12% (29/248) for rifapentine and 7% (15/226) for rifampin subjects; $p=0.08$ using Fisher's exact test; 95% CI for the difference in rates, rifapentine minus rifampin, of (-0.5%, 10.6%); Odds Ratio corresponding to the difference is 1.86, 95% CI of (0.06, 3.12) demonstrating that the rates of relapse for rifapentine were similar to those for rifampin.

The rates of relapse at 24-months did not substantially differ from those at 6 months. It was suggested that the risk for relapse was greater in certain subjects such as those with a failure to convert at the end of treatment and those with non-compliance to the INH continuation regimens. The FDA AC which originally recommended approval felt that the higher rate of relapse in the rifapentine group compared to the rifampin group was acceptable given that additional pharmacokinetic and phase 3 studies were underway to further define a more effective regimen and subject characteristics which would predict relapse.

3. Data Sources, Review Strategy, and Data Integrity

3.1 Sources of Clinical Data

- Electronic submissions from the CDC of study 22 (efficacy and safety datasets, 5 publications) dated:
 - January 23, 2007 \\CDSESUB1\NONECTD (b) (4) \N 030\2007-01-23
 - March 23, 2007 \\CDSESUB1\NONECTD (b) (4) \N 031\2007-03-23
- MOR of NDA 21-024 (06/98)
- Approval letter of NDA 21-024 (06/98)
- MOR of SE7-005 (09/00)
- Current Priftin® label
- SE7-008 NDA application from Sanofi Aventis dated July 12, 2007
\\CDSESUB1\NONECTD\N21024\S 008\2007-07-12
- March 11, 2008 electronic submission including revised labeling

3.2 Tables of Clinical Studies

Study No.	Indication (Rifapentine dosage)	Comparator (treatment duration)	Treated Subjects (n)	Geographic Regions
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22	Adult TB Continuation Phase RFP 600 mg + INH 900 mg q week x 4 months	RIF 600 mg +900 mg INH twice a week x 4 months	1004 HIV (-) 71 HIV (+)	US
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3.3 Review Strategy

The primary source of data emphasized in this review was the controlled, phase 3 study 22 in adult TB. A review of safety is also provided. Please see the ISS review for further details.

3.4 Data Quality and Integrity

As rifapentine is an approved product, no sites were recommended for DSI inspection.

3.5 Compliance with Good Clinical Practices

The clinical trial was conducted in accordance with good clinical practices. The investigators agreed to comply with requirements concerning written informed consent and the rights of human subjects, as outlined in 21 CFR Part 50 and the ethical principles contained in the Declaration of Helsinki. Prior to study initiation, the protocol and written informed consent were reviewed by an institutional review board or ethical committee, as outlined in 21 CFR Part 56 and the ethical principles contained in the Declaration of Helsinki. There were no identified cases of investigator fraud associated with this indication.

3.6 Financial Disclosures

FDA form 3454 certifying to the financial interests of the investigators was submitted on March 11, 2008. This form was signed by the VP and CFO of Sanofi-Aventis, the applicant, and certified that all efforts were made to obtain the financial disclosure 1572 forms from the investigators of study 22 but that these efforts were unsuccessful because approximately 10 years have passed since the study was performed. This is well beyond the time required for retention of trial records.

4. Clinical Pharmacology

A brief summary of the pharmacokinetics of rifapentine in healthy volunteers and in HIV-positive subjects follows. Although rifapentine has a 15 hour half-life, pharmacokinetic studies did not demonstrate accumulation of rifapentine. Please see original BioPharm review of 1998 for further details.

4.1 Pharmacokinetics

Healthy Volunteers (Single dose (150-1200 mg) and multiple dose (150-500 mg q 24 hours and 600 mg q 72 hours)).

- Rifapentine is well absorbed
- Peak plasma concentrations 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.
- Metabolized to an active metabolite, 25-desacetyl rifapentine (mean peak plasma concentrations of approximately 30-40% of those observed for rifapentine).
- Hepatically metabolized, and induces liver enzymes; thus the potential for drug interactions exists.

HIV-positive subjects:

- Mean C_{max} and AUC (0-∞) values of rifapentine 20% and 20% to 25% lower, in asymptomatic HIV-positive subjects (17 subjects) as compared to healthy, young male volunteers.
- C_{max} and AUC (0-∞) values of 25-desacetyl rifapentine metabolite in asymptomatic HIV-positive subjects were 6% to 10% and 9% to 18% higher, respectively, as compared to healthy subjects.
- Mean CL_{po} value of rifapentine was 29% to 30% higher in asymptomatic HIV-positive subjects as compared to healthy, young male volunteers.
- Rifapentine was well-tolerated in asymptomatic HIV-positive subjects.

In a drug-drug interaction study between indinavir and rifapentine, 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). The indinavir C_{max} decreased by 55% while the AUC decreased by 70%. Indinavir did not affect the pharmacokinetics of rifapentine.

***Comment:** Rifapentine achieves lower systemic exposure in HIV-positive subjects, which may account for the reduced efficacy seen in these subjects. Rifapentine also substantially reduces the systemic exposure to concomitant HIV therapies like indinavir. The study 008 excluded HIV-positive subjects but study 22 included HIV-positive subjects and 5 of 30 relapsed. Of the 5 relapses, 4 developed rifampin mono-resistant strains of TB. This study was subsequently modified to exclude HIV-positive subjects.*

4.2 Study 22 Pharmacokinetic Substudy

As part of the accelerate approval commitment #2, the Applicant was asked to report the results of a pharmacokinetic sub-study undertaken in Study 22. This sub-study was added because of the occurrence of rifampin monoresistance in four HIV-infected subjects who relapsed in the rifapentine treatment arm.

The results of the sub-study were published in the following article:

Weiner M, Burman W, Vernon A, et al. Low isoniazid concentrations and outcome of tuberculosis treatment with once-weekly isoniazid and rifapentine. Am J Respir Crit Care Med 2003;167:1341-7.

The abstract discussing the results is reproduced below. See the Clinical Pharmacology Review of the current sNDA submission for a complete discussion of the results.

To understand why once-weekly isoniazid/rifapentine therapy for tuberculosis was less effective than twice-weekly isoniazid/rifampin, we studied human immunodeficiency virus–seronegative patients with either failure (n=4), relapse (n= 35), or cure (n= 94), recruited from a comparative treatment trial. In multivariate analyses that were adjusted for severity of disease, low plasma concentrations of isoniazid were associated with failure/relapse with once- weekly isoniazid/rifapentine (median isoniazid area under the concentration–time curve for 12 hours after the dose [AUC_{0–12}] was 36 µg · hour/ml in failure/relapse versus 56 µg · hour/ml in control cases p= 0.005), but not with twice-weekly isoniazid/rifampin. Furthermore, two patients who relapsed with Mycobacterium tuberculosis mono-resistant to rifamycin had very low concentrations of isoniazid. Finally, isoniazid acetylase status determined by N-acetyltransferase type 2 genotype was associated with outcome with once-weekly isoniazid/rifapentine (p=0.03) but not twice-weekly isoniazid/rifampin. No rifamycin pharmacokinetic parameter was consistently and significantly associated with outcome (p= 0.10). Because low isoniazid concentrations were associated with failure/ relapse, a drug with consistently greater area under the concentration-time curve than isoniazid may be needed to achieve highly active once-weekly therapy with rifapentine.

5 Integrated Review of Efficacy

5.1.1 Methods

The clinical protocol for study USPHS 22 and publications submitted by the CDC describing the trials and the efficacy conclusions were reviewed. In addition, confirmatory efficacy analyses were performed utilizing the datasets

5.1.2 General Discussion of Endpoints

The primary objective/endpoint of study 22 was a comparison of the failure/relapse rate between the 2 treatment arms 24 months after the completion of the follow-up phase of treatment for MTB (failure during treatment or relapse after treatment).

Other objectives included the following:

1. To compare the clinical and bacteriologic failure rates of the two study regimens at the completion of the study phase therapy.
2. To compare the clinical and bacteriologic response rates for the two study regimens among subjects who began study phase therapy with signs and symptoms of tuberculosis or cultures positive for *M. tuberculosis*.
3. To compare the toxicity associated with the two study regimens by comparing discontinuation rates due to adverse events and occurrence rates of signs and symptoms associated with adverse events during study phase therapy.
4. To compare mortality rates of the two study regimens.
5. To compare the rates of completion of therapy within 22 weeks for the two study regimens.

6. To compare the rate of development of drug-resistant tuberculosis in the two study regimens among study subjects classified as treatment failures or relapses.
7. To compare all of the above performance characteristics for the two study regimens in a small subset of HIV positive subjects.
8. To compare attitudes and beliefs about participation in this study between subjects who complete study therapy and those who fail to complete study therapy.

Medical Officer's Comment: *As per the original protocol the primary endpoints of failure or relapse could have been either bacteriologic (i.e., with culture confirmation) or clinical (i.e., based upon compatible clinical signs and symptoms, but without culture confirmation). The bacteriologic criteria were based largely on the prior experience (using solid culture media) of the British Medical Research Council. As per the CDC MO at the time this protocol was developed several standard TB laboratory practices were undergoing significant change including:*

- *Standardizing culture on liquid media as part of their routine. Liquid media cultures for TB are both more sensitive and yield more rapid positive results than do solid media cultures.*
- *Instituting DNA fingerprinting of TB isolates to establish or deny the relatedness of individual strains. RFLP (for restriction fragment length polymorphism) was used to confirm failure/relapse but was not universally applied.*

*As per the CDC "These two changes influenced the classification of endpoints. One straightforward effect was the decision to combine failure during treatment and relapse after treatment into a single category, called "failure/relapse," which became the **ultimate primary** endpoint for the study. This change was driven by the fact that liquid culture is able occasionally to detect (as positive) cultures obtained near the end of treatment, in asymptomatic subjects destined to relapse with symptoms and positive cultures shortly after the end of treatment."*

5.1.3 Study Design

Study 22 was a prospective, open-label, comparative study of two antituberculosis treatment regimens. After completing the 8 week induction (initial) phase therapy, eligible subjects were randomized to receive study phase therapy for an additional 16 weeks with a regimen consisting of either once-weekly rifapentine 600 mg and INH 900 mg or twice-weekly rifampin 600 mg and INH 900 mg. Randomized subjects were followed for 2 years after the scheduled completion of study phase therapy, until death, or for those with relapse, for one year after the diagnosis of relapse.

There were 3 study phases:

- Induction (initial) phase therapy (any pre-randomization therapy)
- Study phase therapy (post-randomization therapy, Study Weeks 0 to 16-22)
- Follow-up phase therapy (Study Weeks 16-22 to 118).

Eligible subjects were randomized to one of two study regimens and were stratified by site and by subject HIV status.

Inclusion Criteria:

1. Drug-susceptible pulmonary tuberculosis.
Only subjects with culture results positive for *M. tuberculosis* within 2 weeks after the start of the induction phase were included.
2. Documentation of completion of adequate induction phase therapy (8 weeks).
Adequate induction phase therapy included one of the following:
 - a. Alternative 1: Daily DOT administration of INH, rifampin, and pyrazinamide (PZA) and either streptomycin or ethambutol for 8 weeks. In areas where the INH resistance rate was documented to be less than 4% or when susceptibility to INH and rifampin was demonstrated, ethambutol or streptomycin were dropped from this induction phase regimen.
 - b. Alternative 2: Daily administration of INH, rifampin, PZA, and either streptomycin or ethambutol for at least 14 consecutive doses (with at least 10 of every 14 doses directly observed) followed by twice-weekly or thrice-weekly doses (all directly observed) with the same drugs to complete induction phase.
3. Age: ≥ 18 years.
4. Documentation of human immunodeficiency virus (HIV) infection status.
Addendum: as of 05 March 1997, HIV positive subjects were no longer enrolled in this trial. Thus, subjects must be HIV-negative to satisfy inclusion criteria.
5. Documentation of study baseline laboratory parameters.
6. Karnofsky score of at least 60.
7. Women with child-bearing potential must agree to practice an adequate (preferably barrier) method of birth control.
8. Informed consent signed by subject and investigator is required, in accordance with state law and local IRB requirements.

Exclusion Criteria:

1. Subjects with known treatment-limiting reaction to INH or rifamycins.
2. Subjects with concomitant disorders or conditions for which INH or rifamycins are contraindicated.
3. Subjects with a history of more than 70 days of continuous anti-tuberculous therapy immediately prior to randomization. Subjects are eligible if they have received any duration of anti-tuberculous preventive therapy prior to randomization.
4. Women who are pregnant or who have an infant they are breast-feeding.
5. Subjects with only extrapulmonary TB. Subjects with both pulmonary and extrapulmonary disease are eligible.
6. Subjects with silico-tuberculosis.
7. Subjects with skeletal tuberculosis.

8. Subjects with concomitant disorders or conditions for which treatment with other drugs with antituberculosis activity (e.g., rifabutin for MAC prophylaxis) is anticipated during the course of the study.
9. As of March 5, 1997, subjects who were HIV- positive.

The study phase therapy started a maximum of 7 days after randomization, lasted a minimum of 16 weeks, and consisted of either 32 doses of rifampin and INH administered twice weekly or 16 doses of rifapentine and INH administered once a week. Adequate study phase therapy consisted of receipt of 100% of the prescribed doses within 22 weeks.

After completion of study phase therapy, subjects were seen four times during the first year of follow-up (Study Weeks 28 ± 2 weeks, 40 ± 2 weeks, 52 ± 2 weeks and 64 ± 2 weeks) and twice during the second year of follow-up (Study Weeks 92 ± 4 weeks and 116 ± 4 weeks). The following information was obtained and recorded at each visit:

- a. Signs and symptoms associated with tuberculosis (e.g. cough, fever, sweats) by interview and clinical examination.
- b. Use, including length of treatment, of antimicrobials with known antituberculosis activity.
- c. Any new medical diagnosis.
- d. Respiratory secretion specimen for AFB smear and culture. For subjects without a cough, this means collecting naturally produced sputum during Study Weeks 28, 52, 92 and 116 only.

In addition, during the follow-up phase, subjects were seen and evaluated as described above if at any time they developed signs and symptoms associated with tuberculosis.

Definitions:

Bacteriologic failure: After receiving 16 doses twice weekly or 8 doses once weekly of study phase therapy, but before the end of study phase therapy, a single respiratory secretion culture that is positive for *M. tuberculosis* with greater than 10 colonies on solid media, OR 2 or more respiratory secretion cultures with any colony count on solid media, OR 2 or more respiratory secretion cultures obtained in liquid media that are positive for *M. tuberculosis* using radiometric techniques, OR any culture that is positive for *M. tuberculosis* from an extrapulmonary site.

Bacteriologic response: No evidence of bacteriologic failure and, by the end of study phase therapy, two or more consecutive respiratory secretion cultures that are negative for *M. tuberculosis*. For the purposes of this definition, one negative respiratory secretion culture, followed by documented failure to produce sputum, will be considered a bacteriologic response. Subjects without a respiratory secretion culture that is positive for *M. tuberculosis* at randomization will not be evaluated for bacteriologic response to study phase therapy.

Bacteriologic relapse: After completion of study phase therapy and before the end of the follow-up phase, a single respiratory secretion culture that is positive for *M. tuberculosis* with greater than 10 colonies on solid media, OR 2 or more respiratory secretion cultures with any colony count on solid media, OR 2 or more respiratory secretion cultures obtained in liquid media that

are positive for *M. tuberculosis* using radiometric techniques, OR any culture that is positive for *M. tuberculosis* from an extrapulmonary site.

Clinical failure: After receiving 16 doses twice weekly or 8 doses once weekly of study phase therapy, but before the end of study phase therapy, the occurrence of signs and symptoms of tuberculosis (fever, sweats, productive cough, documented weight loss) with or without a chest radiograph that is worsening (compared to either the pre-randomization or induction phase chest radiograph), OR a chest radiograph that is worsening without another underlying cause (other than tuberculosis), OR histopathologic evidence of tuberculosis at an extrapulmonary site which results in a change in anti-tuberculous therapy and removal of the subject from study regimen.

Clinical response: A subject who is not a clinical failure and who has resolution, by the end of study phase therapy, of fever, sweats, and/or productive cough, with stable or increasing weight. Subjects without symptoms at the beginning of study phase therapy, e.g., fever, sweats, and/or productive cough, will not be assessed for clinical response.

Clinical relapse: After completion of study phase therapy but before the end of the follow-up phase, the occurrence of signs and symptoms of tuberculosis (fever, sweats, productive cough, documented weight loss, abnormal chest radiograph), OR histopathologic evidence of tuberculosis at an extrapulmonary site, in a subject who does not have another underlying cause (other than tuberculosis) and who has response to anti-tuberculous therapy used for the treatment of relapse.

5.1.4. Efficacy Findings

NOTE: All tables and figures below have been reproduced from the published report of this study (Lancet 2002;360:528-534), unless otherwise noted.

Efficacy in HIV-negative Subjects

A total of 1004 HIV-negative subjects were enrolled, 502 to each treatment arm at 29 sites. No site enrolled more than 15% of the subjects. In addition 71 HIV-positive subjects were also enrolled. Enrollment started in 1995 and follow-up was completed in 2001.

Medical Officer's Comment: As subjects were stratified by HIV status, the results of these 2 groups will be presented separately. It should also be noted that although the initial intent was to enroll 80 HIV-positive subjects, the enrollment of this group was terminated early due to an increased number of failures as well as the development of resistance in 4. All HIV-positive subjects were enrolled early in the trial (1995).

The characteristics of the randomized HIV-negative subjects can be seen in the following table (Table 1). Subjects were primarily males, non Hispanic black, and of low socioeconomic status. The groups were similar with regards to early treatment but more rifapentine-treated subjects than rifampin-treated subjects had evidence of cavitary disease (57% vs. 51%), bilateral disease (52% vs. 48%), and had a positive sputum by smear (15% vs. 11%) or culture (23% vs. 8%). NOTE: Denominators in the table copied from the applicant's submitted publications are less than the number of enrolled subjects in each arm and vary depending on how many subjects had the data collected for each parameter.

Comment: It would appear that subjects in the rifapentine group were more severely ill as compared to subjects in the rifampin group and, although this difference was not significant, it definitely influenced the greater relapse rates seen on the rifapentine treatment arm.

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Table 1: **Characteristics of patients after randomisation**

The study schematic for the HIV-negative subjects can be seen in Figure 1. Of note, 6% (31/502) of the subjects randomized to the rifapentine arm and 9% (45/502) of subjects randomized to the rifampin arm did not complete treatment. The reasons for treatment discontinuation did not differ significantly between the groups.

Slightly more rifapentine treated subjects completed rifapentine treatment (N=471) as compared to the rifampin treatment (N=457). Of the subjects who completed treatment, 97% (455/471) in the rifapentine group and 96% (440/457) in the rifampin group had 12 months of follow-up.

Of the subjects enrolled, 82.6% (415/502) in the rifapentine group and 77.2% (388/502) in the rifampin group were followed up to 24 months. There were a slightly greater number of deaths and lost to follow-up/withdrawals on the rifampin arm that led to this difference. The mean duration of follow-up after completion of treatment was 20.4 months for the rifapentine group and 20.3 months in the rifampin group.

It should be noted that only 1 death in the entire study was attributable to TB.

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Figure 1: Trial profile

In the CDC ITT analysis of the primary outcome (Table 2), failure/relapse occurred in 46 (9.2%) of 502 subjects in the once a week rifapentine group and in 28 (5.6%) of 502 in the twice a week rifampin group ($p=0.04$). The difference in crude event rates between treatment groups was 3.6%

(95% CI 0.004, 0.068). Life-table rates of failure/relapse were 10.3% (SD 1.5) in the rifapentine group and 5.9% (1.1) in the rifampin group ($p=0.035$).

On multivariate Cox proportional-hazards analysis, five factors were identified as being independently associated with failure/relapse: non-Hispanic white race, being underweight, bilateral pulmonary involvement, cavitation on chest radiograph, and positive sputum culture at 2 months. In a Cox regression model, which included only treatment group and outcome, the hazard ratio for failure/relapse between treatment groups was 1.6 (95% CI 1.0–2.6; $p=0.04$). If positive sputum culture at 2 months and cavitations were added to this model, the hazard ratio fell to 1.34 (0.83–2.18; $p=0.23$).

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Table 2: **Primary outcome**

The CDC provided numerous analyses of risk factors for failure (Table 4). Events of relapse were high in subjects with cavitation on CXR (14.4%; 40/278 in the rifapentine group and 8.9%; 22/246) in the rifampin group), bilateral infiltrates (11.7%; 34/290 versus 8.2%; 22/269), and those with culture-positive (23.5%; 24/102 versus 16.7%; 13/78) or smear-positive (17.8%; 13/73 versus 13.2%; 7/53) sputum results at 2 months.

Relapse rates increased in subjects with both cavitation and positive sputum culture at 2 months (22/82, 26.8% versus 12/55, 21.8%). (*data not shown in Table 4*).

NOTE: (1) Not all patients enrolled were included in each analysis because of missing data
(2) The relapse rates in subjects with both cavitation and positive sputum cultures at 2 months were independently confirmed by the Agency statisticians. (NOT sure about this yet)

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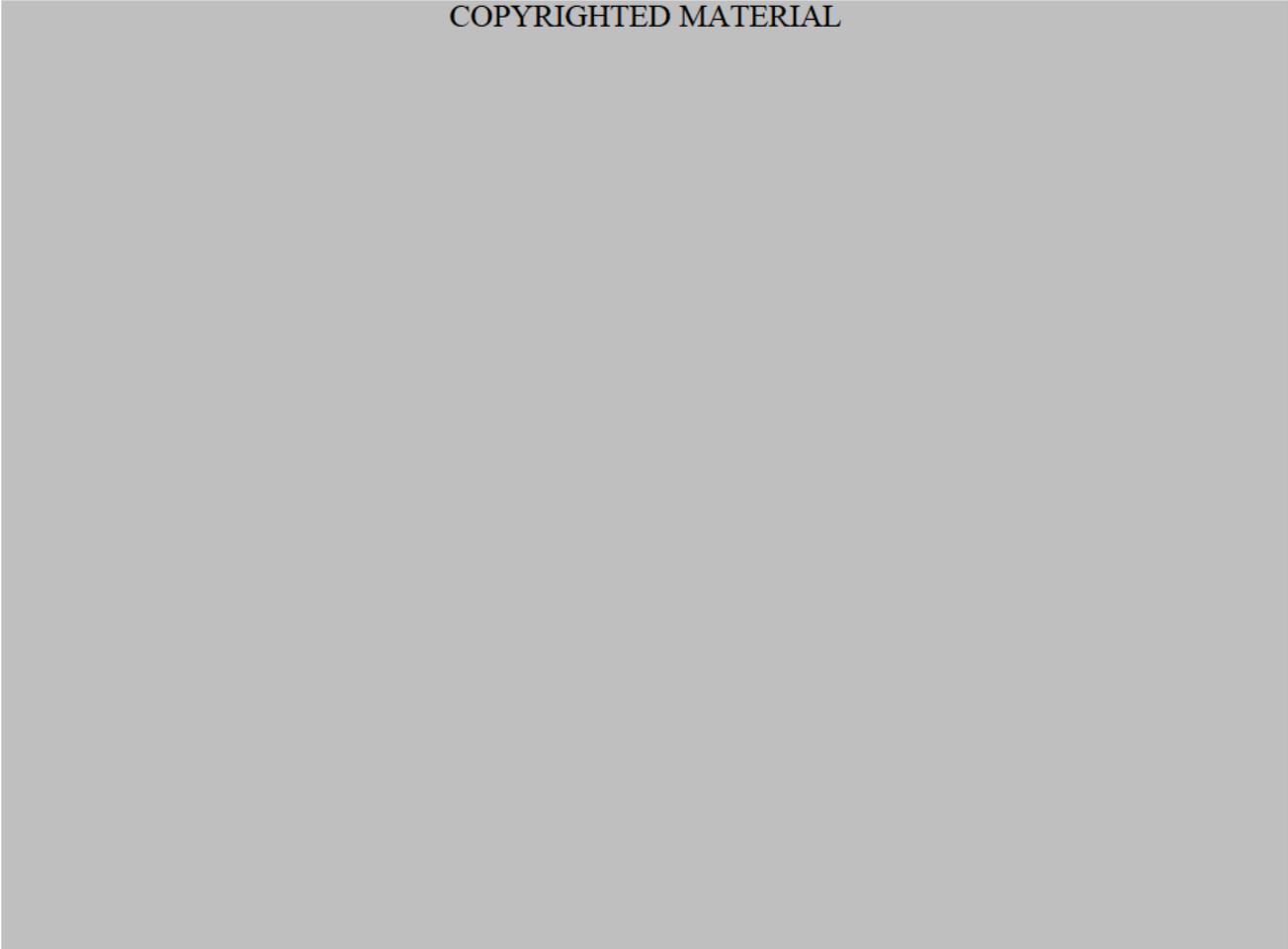


Table 4: Rate of treatment failure or relapse by presence of specified risk factor

As can be seen in Figure 2, life-table rates of failure/relapse in patients with cavitation were 15.8% and 9.5% in patients on rifapentine and rifampin, respectively.

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Figure 2: Cumulative percentage failure or relapse by treatment group stratified by presence or absence of cavitation

As per the Lancet publication, the effect of daily treatment (5 days a week) as compared to treatment 3 x week during the initial phase of therapy (first 2 months) was also assessed and it was found that subjects that received daily treatment had a lower relapse rate (31/503) 6.2% versus the three times a week group (43/501, 8.6%, $p = 0.18$).

Note: This analysis appeared to have been performed on the entire dataset and was confirmed by the Agency statisticians.

Additional Confirmatory MO analyses (data generated from SAS datasets):

The MO performed a confirmatory analysis of the primary endpoint (rate of failure/relapse) at 24 months following the end of treatment in the ITT population for both HIV-negative and HIV-positive subjects using the electronic datasets provided by the Applicant. The results in HIV-negative subjects are consistent with those in the Lancet publication, as shown in the table created by the MO below. The results in HIV-positive subjects where the inclusion of the CDC censored subjects (N = 6 rifapentine and N = 4 rifampin) were included as failures reaffirmed the study conclusions that there was a greater number of failure/relapses on the rifapentine treatment arm as compared to the rifampin treatment arm.

NOTE: PP Relapse rates in HIV-positive subjects were 16.7% (5/30) in the rifapentine group and 9.7% (3/31) in the rifampin group versus and ITT analysis of 11/36 (30.6%) in the rifapentine treated group and 7/35 (20%) in the rifampin-treated group.

ITT Study 22

HIV (-)		
	Rifapentine N = 502	Rifampin N = 502

Failure/Relapse	46 (9.2%)	28 (5.5%)
Cure	456 (90.8%)	474 (94.5%)
HIV (+)		
	Rifapentine N = 36	Rifampin N = 35
Failure/Relapse	11 (30.6%)	7 (20%)
Cure	25 (69.4%)	28 (80%)

The following table generated by the Agency Statistical Review Team, contains assessments of sputum conversion at the end of treatment (6 months total: 2 months of initial and 4 months of randomized continuation treatment) and relapse rates at the end of follow-up (24 months) in all HIV seronegative patients randomized to treatment. The failure and relapse rates reported in this study could be underestimated due to the limitation of the microbiologic methods used in the study. Positive culture was based on either one sputum sample with >10 colonies on solid media OR at least 2 positive sputum samples on liquid or solid media. However, only one sputum sample was collected at each visit in a majority of patients.

Clinical Outcome in HIV Negative Patients with Pulmonary Tuberculosis

Clinical Outcome in HIV Negative Patients with Pulmonary Tuberculosis

	Rifapentine Combination Treatment % (n/N)	Rifampin Combination Treatment % (n/N)
Status at End of 4 Months Continuation Phase		
Treatment Response *	93.8% (471/502)	91.0% (457/502)
Not Converted	1.0% (5/502)	1.2% (6/502)
Did Not Complete Treatment**	4.2% (21/502)	7.0% (35/502)
Deaths	1.0% (5/502)	0.8% (4/502)
Status Through 24 Month Follow-up:		
Relapsed	8.7% (41/471)	4.8% (22/457)
Sputum Negative	79.4% (374/471)	80.1% (366/457)
Lost to Follow-up	7.9% (37/471)	9.8% (45/457)
Deaths	4.0% (19/471)	5.3% (24/457)

* Treatment response was defined as subjects who responded successfully after 16 doses of rifampin and isoniazid or after 8 doses of rifapentine and isoniazid, but before the end of continuation phase therapy.

**due to drug toxic effects, non-adherence, withdrawal of consent, receipt of nonstudy regimen, other.

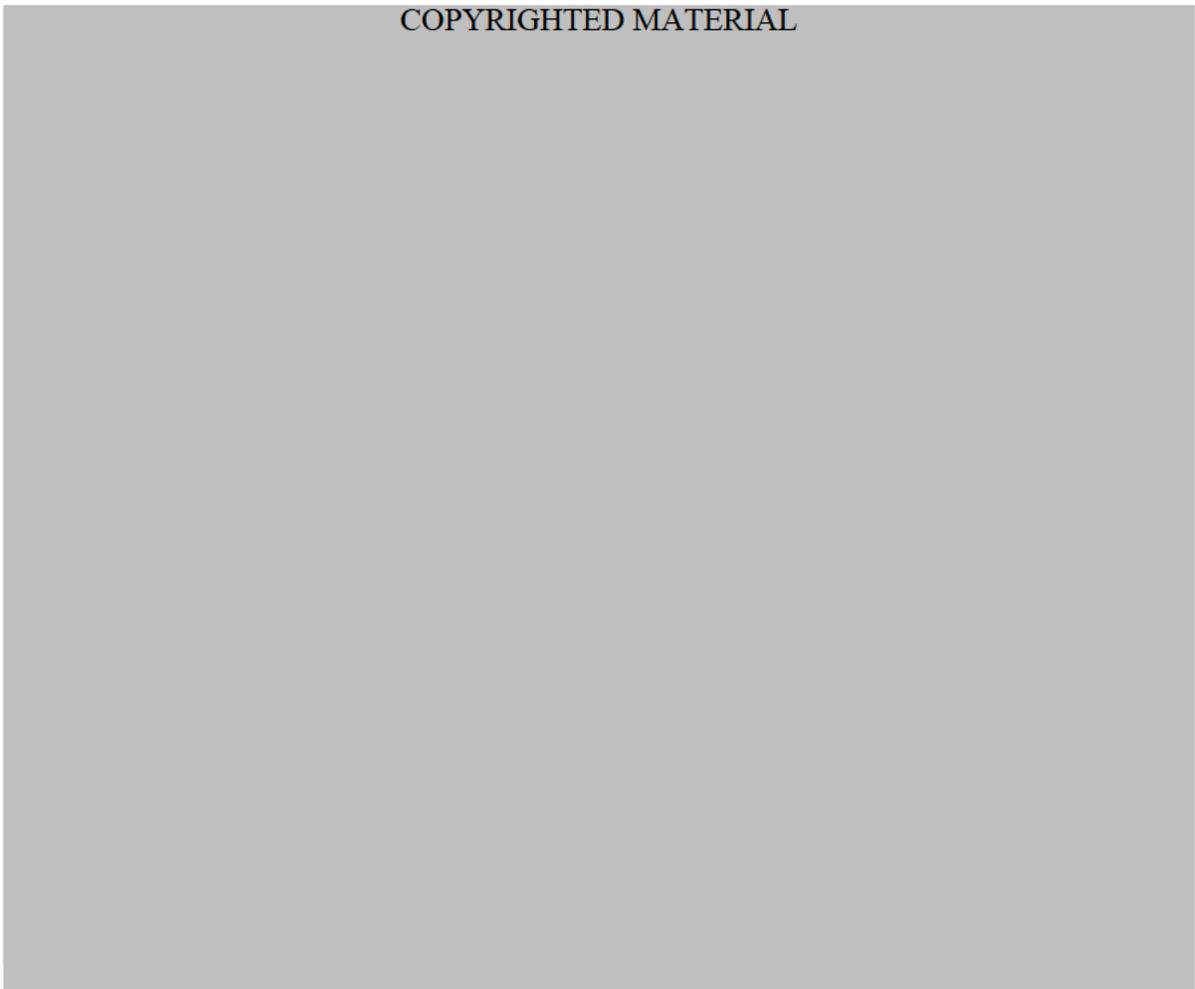
Efficacy Conclusions in HIV-negative subjects:

The findings of the efficacy analyses of study 22 demonstrated relapse/failure rates in HIV-negative subjects at 24 months following the end of continuation therapy of 9.2% (46/502) for the rifapentine group compared to 5.5% (28/502) for the rifampin group and were consistent

with those from study 008 where overall relapse rates at 24 months were 12% (29/248) for rifapentine-treated subjects as compared to 7% (15/226) for rifampin-treated subjects. Therefore the results from study 22 confirm the results of trial 008 that led to the original accelerated approval for rifapentine. Further, the current submission delineates via risk factor analyses, which populations are at higher risk of relapse and may not be suitable candidates for rifapentine therapy. HIV-negative subjects with a higher risk of relapse include those with evidence of cavitory disease or bilateral pulmonary involvement on CxR and those who have not converted their sputum cultures to negative after the initial 2 month phase of treatment. These subjects should not receive rifapentine treatment at all or only with extreme caution.

Efficacy in HIV-positive subjects:

Seventy-one HIV-positive subjects were enrolled in this trial (36 subjects randomized to rifapentine plus INH and 35 to rifampin plus INH) and 61 (86%) completed treatment and were assessed for relapse as shown in the schematic below. Enrollment of HIV-positive subjects was stopped when 4 of 36 rifapentine treated subjects developed rifamycin monoresistance.



Medical Officer's Comment: Similar numbers of subjects on each arm (6 rifapentine and 4 rifampin) did not complete the study. One subject on each arm developed drug-related hepatitis and were discontinued because of an AE. Of the remaining 3 subjects on the

rifampin arm that did not complete treatment, one subject had a mycobacterium other than MTB and 2 did not follow the protocol defined regimen. On the rifapentine arm, 5 subjects who did not complete the study treatment were switched to rifampin standard treatment when the study was terminated. The applicant did not provide an ITT analysis and the data on these subjects was censored in the CDC analyses. Sixty-one subjects were included in the CDC analysis and the median time at risk for relapse was 86 weeks.

Baseline characteristics for the 61 HIV-positive subjects included in the applicant's analysis are shown in Table 1. The 2 treatment groups were similar with approximately one third of the subjects in each group with evidence of cavitation at the time of enrollment. Of note, none of the subjects in the rifapentine arm had a positive sputum smear or culture at the time of enrollment as compared to 12 –19% of subjects the rifampin arm.

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Table 1: Baseline characteristics of HIV-seropositive participants for whom relapse data are available, by treatment group

There were no treatment failures during the induction phase or during the study treatment phase. There were 5 relapses (5/30) in the rifapentine group (16.6%) versus 3/31 (9.6%) in the rifampin group (Applicant p value = 0.47). Four of the 5 relapses in the rifapentine group involved *M. tuberculosis* strains with rifamycin monoresistance; no relapse strain in the rifampin group had acquired drug resistance (p=0.05). The eight relapses occurred at seven different clinic sites.

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Table 2: Univariate analysis of rifampin mono-resistant relapse among HIV-seropositive participants assessed for relapse

Relapses occurred from 9 – 34 weeks after the EOT (median 19 weeks) in the rifapentine group and from 11- 24 (median 14 weeks) in the rifampin group. The relapse rates for the 2 year endpoint calculated by Kaplan Meier were 17.8% in the rifapentine group versus 10% in the rifampin group ($p = 0.41$).

The applicant also compared time to relapse for resistant and sensitive strains and found that time to relapse was similar (16 versus 19 weeks post EOT).

Table 3 shows the results of a univariate analysis of the risk factors for relapse among HIV-positive subjects. Risk factors for relapse included the presence of both pulmonary and extrapulmonary disease at baseline, low CD4 counts, use of azole antifungals and age (younger).

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Of the subjects who were censored from the CDC analysis, one additional rifapentine subject who did not complete the study relapsed as compared to 2 additional rifampin subjects who did not complete the study. As shown in the table above created by the MOR, the inclusion of the CDC censored subjects as failures in the analysis had no effect on the study conclusions.

5.1.5 Clinical Microbiology

For an in depth review see Agency Clinical Microbiology Review. The CDC performed analyses on MTB isolates from all subjects. Of the 8 relapses in the HIV-positive subgroup, 5 rifapentine and 3 rifampin, the baseline isolate was not available from one subject. Seven pairs of baseline and relapse isolates had identical DNA fingerprints by *IS6110*. Analysis of the *rpob*

gene for the four rifamycin monoresistant relapse isolates identified four distinct mutations (His526Tyr, Ser531Leu, Ser522Leu, 6-base deletion 516-517).

5.1.6. Efficacy Conclusions

Efficacy Conclusions in HIV-negative subjects:

The findings of the CDC efficacy analyses of study 22 demonstrated relapse/failure rates at 24 months following the end of continuation therapy of 9.2% (46/502) for the rifapentine group compared to 5.5% (28/502) for the rifampin group and were consistent with those from study 008 where overall relapse rates at 24 months were 12% (29/248) for rifapentine-treated subjects as compared to 7% (15/226) for rifampin-treated subjects. Agency analyses generated similar results (24 month rifapentine relapse rate 41/471 (8.7%) versus rifampin 22/457 (4.8%).

Further the current submission delineates via risk factor analyses, which populations can safely receive rifapentine as part of their tuberculosis treatment regimen. The optimal population that should receive rifapentine are HIV-negative subjects without evidence of cavitory disease on CxR. In addition subjects, who have not converted their sputum cultures to negative after the initial 2 month phase of treatment and/or who have evidence of bilateral pulmonary involvement, should not receive rifapentine.

It should be clarified that although the relapse rates seen in subjects treated with once weekly rifapentine in conjunction with INH during the continuation phase of anti-tuberculous treatment were statistically significantly greater than the rates seen with a rifampin containing regimen. These results were no different than those that formed the original basis for an approval. Further with this study the applicant was able to clearly delineate those subgroups of subjects in whom there is a high expectation of relapse including those with cavitory lesions, bilateral pulmonary disease and/or positive sputum cultures at the end of the initial treatment phase. This information allows for more accurate and safe labeling of Rifapentine. Other factors that need to be taken into account when making a recommendation for a regulatory action include the once weekly dosing regimen and thus the increased feasibility of DOT and compliance and the somewhat better tolerability of rifapentine compared to rifampin containing regimens. It remains true however that the optimal therapeutic regimen for rifapentine has not yet been defined and clinical trials continue with this goal.

Efficacy Conclusions in HIV-positive subjects: Once weekly rifapentine in combination with INH cannot be used safely in HIV-positive subjects as part of a continuation phase anti-TB regimen because of concerns regarding the development of relapse caused by rifamycin monoresistant strains of TB as evidenced by 4 of 31 subjects that received a full course of rifapentine in study 22. The reason for the development of this selective monoresistance is not clear but it has been hypothesized that functional monotherapy can develop despite supervised therapy. Possible causes include an inadequate rifapentine dose because it is highly protein bound, inadequate INH levels either because of faster metabolism in rapid acetylation phenotypes or because of its shorter half life both of which lead to increased periods of exposure to rifapentine alone. Another cause could be increased serum concentrations of rifapentine but not INH in subjects concurrently treated with azole antifungals that inhibit the P450 enzyme system.

6. Integrated Review of Safety

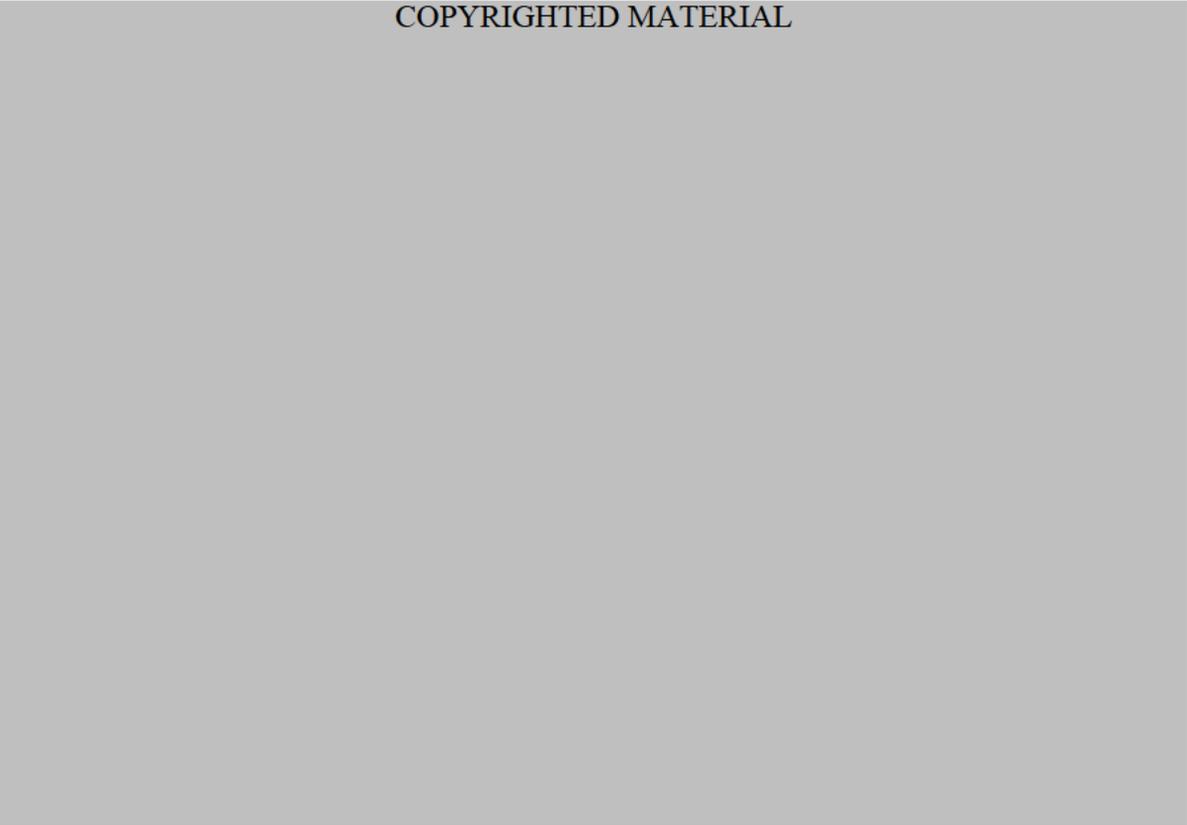
6.1. Methods and Findings

The CDC provided an AE dataset that included 1075 treated subjects; 71 were HIV-positive and 1004 HIV-negative; 537 were treated with rifapentine and 538 with rifampin.

As per the following demographic table (Table 1) subjects randomized to receive once-weekly INH plus rifapentine were more likely to have a cavity on CXR and a positive sputum smear, and were more likely to have treatment failure/relapse. There were no other significant differences by treatment arm.

Compared with HIV-negative participants, HIV-positive subjects were more likely to be black, have been born in the US or Canada, lack a high school degree, be homeless, use illicit drugs, have a history of unemployment or incarceration, and have treatment failure/relapse; they were less likely to have a cavity on CXR.

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The publications submitted for review by the applicant were reviewed for safety and confirmatory analyses were performed utilizing the SAS datasets provided.

6.1.1. Deaths

The following publication provided the primary analyses of mortality:

T. R. Sterling et al. Mortality in a large tuberculosis treatment trial: Modifiable and Non-modifiable risk factors; INT J TUBERC LUNG DIS 10(5):542–549

The overall crude mortality rate among all study participants was 71/1075 (6.6%). Crude mortality rates did not differ between the two treatment groups (6.5% for the rifapentine group compared to 6.7% for the rifampin group, $P = 0.87$). No deaths were attributed to anti-tuberculosis drug toxicity. Among the 71 subjects who died, the last sputum culture prior to death was negative in 58, missing in 1, positive for non-tuberculous mycobacteria in 8, and positive for *M. tuberculosis* in 4. Of these 4, 1 died of trauma, 1 of central nervous system toxoplasmosis, and 1 of metastatic lung cancer. Only 1/71 (1.4%) death was attributed to TB (pulmonary hemorrhage before treatment started).

Mortality rates were substantially higher in HIV-positive than HIV-negative subjects (15/71; 21.1% vs. 56/1004; 5.6%; $P < 0.001$). Of the HIV-positive subjects, four received concomitant HAART during anti-tuberculosis therapy, and 15 more received HAART during the follow-up phase. The mortality rate was 10.5% among the 19 subjects who received HAART during the study compared to 29.6% among the 27 subjects who received no HAART ($P = 0.16$).

Deaths occurred throughout the study, during both the study and follow-up phases. As shown in the figure below, there was a suggestion of increased mortality among HIV-positive subjects near the end of the follow-up period. The rate of death among HIV-negative subjects appeared stable over time.

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Figure Kaplan-Meier survival distribution plot, by HIV serostatus and month after enrollment. Log rank $\chi^2 = 25.70$; $P < 0.0001$. HIV = human immunodeficiency virus.

HIV-Negative Subjects

Among HIV-negative subjects, 18/56 (32%) deaths were associated with malignancy, and 13 (23%) were attributed to injuries, accidents, drug overdose, or unknown cause. The most types of malignancies were: cancer of the lung (4), prostate (4), larynx (3), and pancreas (3). Of the alcohol-related deaths: 2 were related to intoxication, 2 to gastrointestinal bleeding, and 2 due to cirrhosis. Other causes of death in HIV-negative subjects included cardiac disease (6), chronic obstructive pulmonary disease (2), bacterial pneumonia (2), and cerebrovascular accident (2).

HIV-Positive Subjects

Of the 15 deaths in HIV-positive subjects, 11 were due to AIDS, two to malignancy, and two to drug overdose.

NOTE: Review of the datasets revealed 73 deaths in total including 16 in HIV-infected subjects. The Applicant was queried on Sept. 11, 2007 as to the discrepancy in numbers of deaths. The most likely explanation was the addition of 2 late deaths, one each in the HIV-negative and -positive populations. Further information was not provided; however, it seems unlikely that this discrepancy would radically change the conclusions drawn from these analyses. Nine of the 16 deaths were in subjects treated with INH/Rifapentine and 7 in subjects treated with INH/Rifampin.

Because there was no difference in mortality by treatment arm, all study subjects were combined for analyses that assessed predictors of mortality. In univariate analyses, 12 factors were significantly associated with an increased risk of death: age, male sex, white race, lack of a high school degree, unemployment, illicit drug use, daily alcohol use, Karnofsky score < 80, birth in North America, homelessness, malignancy, and HIV infection. The presence of a cavity on CXR and Asian race/ethnicity were associated with a reduced risk of death ($P = 0.065$ and 0.035 , respectively).

In a multivariate Cox proportional hazards model, factors independently associated with death were (in decreasing order of magnitude of hazard ratio) malignancy, HIV infection, alcohol use, unemployment, and age (per 1-year increase), as shown in Table 3.

Table 3 Multivariate Cox proportional hazards model for mortality in TBTC Study 22

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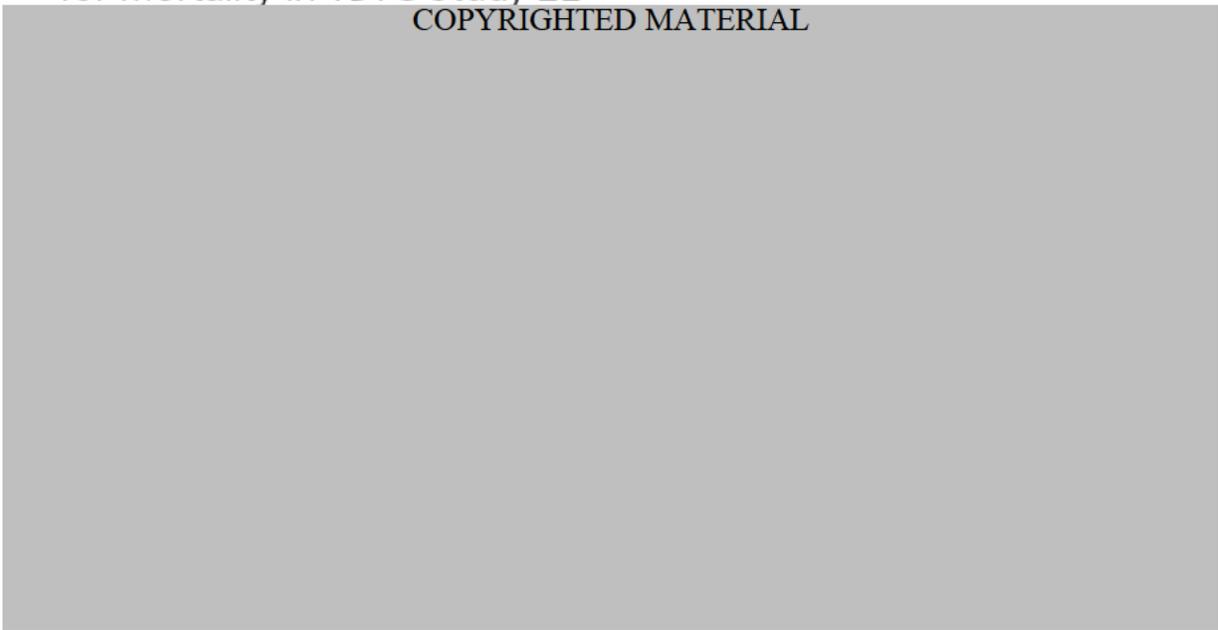


Table 4 shows that the risk of death increases with the number of cumulative risk factors identified in Table 3.

Table 4 Risk of death according to cumulative number of risk factors

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Comment: The mortality results of study 22 in HIV-negative subjects (5.6%) are higher, but consistent with those of study 008 (crude mortality 3.6%). As expected the mortality rate was higher in the HIV-positive subjects (21.1%) and reflected the limited general use of HAART at the time of study initiation. As expected as HAART usage became more prevalent, mortality in HIV positive subjects decreased. However, the overall mortality rate was similar between the treatment arms (6.5% for the rifapentine group compared to 6.7% for the rifampin group).

6.1.2. Other Serious Adverse Events

Adverse events were categorized by toxicity grade and by treatment group, as shown in the table below, created by the MOR using the electronic datasets. A breakdown of these events is provided in the text after the table. Generally the number of reported Grade 4 and 5 events was greater in the rifampin-treated subjects as compared to the rifapentine-treated subjects but similar types of events were reported from both treatment arms and in most cases were attributable to underlying diseases such as alcoholism and cancer.

Toxicity Grades III - V	Rifapentine N* = 251	Rifampin N = 248
3	90	73
4	45	62
5	23	28

*N= subjects reporting

Toxicity Grades: Grade 3 -4 = Grades III – IV, Grade 5 = death

Grade 5 Toxicities

23/251 of the rifapentine-treated subjects had a Grade 5 AE. Reported events included 16 deaths, one GI bleed, one fall, one suicide, one diarrhea, one PE, one unresponsive and one cancer.

Similarly 28/248 rifampin-treated subjects developed an AE classified as Grade 5. Reported Grade 5 events included 26 deaths, 1 hospitalization due to pneumonia, one mass and one CA prostate. Of the deaths, 9 were not associated with a cause and the remainder were associated with trauma in 3, respiratory in 5, malignancy in 2, bleeding in 6, arrhythmia or MI in 2, and sudden in one.

Grade 4 Toxicities

Forty-five events in the rifapentine group were classified as Grade 4 including 14 events of hospitalization for alcohol use and complications including one case of pancreatitis and hepatitis. Three of the Grade 4 events were reports of liver toxicity. The remaining Grade 4 events included seizures and hospitalizations either for other infections or for other acute events such as cardiac arrest, etc.

There were 62 Grade 4 events in the rifampin group which included (events in more than 1 subject) diabetes hyperglycemia in 5 subjects, Grade 4 liver toxicity in 7, 2 each of DKA, pneumothorax, seizure, and alcoholic seizure.

Grade 3 Toxicities: Of the Grade 3 events 12 rifapentine-treated subjects had Grade 3 liver toxicity. 2 subjects had relapse, and 2 had hypertension; all other events were reported in one subject each.

There were 3 reported Grade 3 events in rifampin-treated subjects that included 11 reports of Grade 3 liver toxicity, 7 reports of hyperglycemia associated with diabetes mellitus, 6 reports of hypertension, 3 of Grade 3 liver toxicity/alcohol use and 2 each of diabetes and pneumothorax. All other events occurred in only once each.

6.1.3. All Adverse Events

There were 526 AEs (all severity) reported from 251 rifapentine-treated subjects. All events that occurred in more than one subject are listed in the table created by the MOR using electronic datasets below. Generally the reported AEs are consistent with concurrent illnesses that the subjects enrolled in this study would be expected to have such as complications from alcohol use, etc. The AE profile for rifapentine in this study is consistent with that reported in the original 1998 NDA and 2000 supplement for study 008.

Of note, hyperuricemia was not reported as an AE in study 22. In study 008 hyperuricemia was the most frequently reported reaction that was assessed as treatment related and was most likely related to use of pyrazinamide (PZA). Cases of hyperuricemia in study 008 were reported during the initial phase when PZA was being used, but no cases were reported in the Continuation Phase when PZA was no longer included in the treatment regimen. In study 22 PZA was also not used as part of the Continuation Phase, and no cases of hyperuricemia were reported, supporting the conclusion that rifapentine does not cause hyperuricemia.

There were 513 AEs reported from 248 rifampin treated subjects. As in the rifapentine-treated group the common AEs were consistent with the demographic of the population studied and were similar to the AEs on the rifapentine arm.

On both study arms the most frequently reported AEs were hyperglycemia, pneumonia, liver toxicity, and death.

Common AEs occurring in ≥ 2 subjects

	Rifapentine N = 526	Rifampin N = 513
DM, HYPERGLYCEMIA	12	13
HOSP: PNEUMONIA	13	11
GRADE 3 LIVER TOXICITY	10	11
DEATH	8	10
R/O RELAPSE	8	3
PREGNANCY	7	11
URI	7	9
BRONCHITIS	7	10
DEPRESSION	0	6
PNEUMONIA	6	2
HYPERTENSION	6	8
HOSP. ETOH	6	0
HOSP: PNEUMOTHORAX	0	5
SINUSITIS	0	4
HOSP: SEIZURE, ETOH	4	3
HOSP: HEMOPTYSIS	4	0
DIZZINESS	4	0
RASH	4	0
RASH ACNEIFORM	0	2
LOW BACK PAIN	3	0
HOSP: RELAPSE 3	3	0
HOSP: ETOH PANCREATITIS	3	0
HOSP: CHEST PAIN	3	0
HEMOPTYSIS	3	0
HBP	3	0
HERPES ZOSTER	0	3
COUGH, FEVER	2	0
GRADE 4 LIVER TOXICITY	2	7
GRADE 2 LIVER TOXICITY	0	5
HEADACHE	2	0
HOSP: ASTHMA	2	5
HOSP: CA LARYNX, CHEMO_RX	2	0
HOSP: CHEST PAIN	2	0
HOSP: CHF	2	0
HOSP: CRYPTO MENINGITIS	2	0
HOSP: DETOX	2	0
HOSP: DM, HYPERGLYCEMIA, DKA	2	2
HOSP: CVA	0	2
HOSP: ETOH, PANCREATITIS	2	2
HOSP: GI BLEED (U), ETOH	2	3
HOSP: HERNIA REPAIR	2	0
HOSP: R/O MI	0	2
HOSP: HYSTERECTOMY	0	2
HOSP: PNEUMOCOCCAL PNEUMONIA	2	0
HOSP: PNEUMONIA ?RELAPSE	2	0

HOSP: R/O FAILURE	2	0
HOSP: R/O RELAPSE	2	3
HOSP: SEIZURE	0	2
HOSP: PCP	0	2
INCREASED HEMOGLOBIN	2	0
LEUCOPENIA	0	3
PANCREATITIS	2	2
PHARYNGITIS	2	0
PLEURAL EFFUSION	2	0
UTI	2	0
THROMBOCYTOPENIA	0	2
TONSILITIS	0	2
HOSP: TB NONCOMLIANCE	0	2
DIARRHEA	0	2
DIABETES	0	2
ANKLE SPRAIN	0	2

6.1.4 Adverse Events by HIV status.

On the rifapentine arm 459 events were reported in HIV-negative subjects and 67 from HIV-positive subjects as compared to 456 events reported in the rifampin arm from 513 HIV-negative subjects and 57 events from HIV-positive subjects.

Adverse Events in HIV-Negative Subjects

Generally the frequency of reported events was similar between the treatments arms. As per the following table reproduced from the CDC Lancet publication, from the 1004 HIV-negative subjects no deaths were attributable to complications of treatment. The only death from tuberculosis was associated with massive hemoptysis, arising between enrollment and first dose of study treatment. There were no differences between treatment groups in frequency of grade 4 adverse events, grade 4 events attributable to study treatment, grade 3 or 4 hepatotoxicity, or severe thrombocytopenia. A closely similar proportion of patients in each treatment group permanently discontinued treatment because of an adverse event. There were no cases of rifamycin 'flu-like syndrome. (NOTE: Any numeric differences between the CDC publications and the Agency generated numbers are caused by changes made to the datasets over time by the CDC primarily because of the addition of data to this trial that was NOT performed for registration purposes).

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**Table 5: Number of adverse events by treatment group
Adverse Events in HIV-Positive Subjects**

On the rifapentine arm of the 67 events in HIV-positive subjects, 3 were Grade 5 toxicity and included death in 2 subjects and hospitalization from pneumonia in one; 6 events were Grade 4 and included liver toxicity in 2 and hospitalization for pneumonia or respiratory problems in an additional 4 (one report for each event).

There were a total of 4 events of liver toxicity, non-alcohol related, of which 2 were Grade 3 and there was one event each of Grades 2 and 4.

On the rifampin arm of 57 subject/events, 7 had Grades 2 - 4 liver toxicity that included (N=3 Grade 2, N=3 Grade 3, and N=2 Grade 4). In addition there were 4 Grade 5 events (all deaths), and 3 Grade 4 events (N=1 cryptococcal meningitis and 2 Grade 4 liver toxicities).

Common AEs occurring in at least 2 HIV-positive subjects are shown in the table created by the MOR using the electronic SAS datasets below.

Common AEs occurring in ≥ 2 HIV subjects

	Rifapentine N = 67	Rifampin N = 57

HOSP: PNEUMONIA	6	4
GRADE 3 LIVER TOXICITY	2	3
DEATH	1	3
HOSP PCP	0	2
HOSP CRYPTO MENINGITS	2	0
GRADE 4 LIVER TOXICITY	1	2

Overall AEs in HIV-positive subjects were proportionally more serious than in HIV-negative subjects. However, the events that occurred were primarily associated with the subject's underlying HIV disease rather than with study treatment. As expected most events were from the liver although not disproportionately so.

6.1.5 Hepatic Adverse Events:

Generally most SAEs reported in Section 6.1.3 above appeared to be from the liver in both HIV-negative and HIV-positive subjects. The electronic datasets were assessed by the MOR specifically for all liver events including those related to alcohol use. As shown in the following table created by the MOR, there were more hepatic events in the rifampin-treated subjects (6.8%) versus the rifapentine-treated subjects (3.8%). This difference in part was due to the differences in the incidence of Grade 4 hepatotoxicity. The reason for this is not clear but may have to do with the less frequent dosing of rifapentine.

Hepatic Adverse Events in All Subjects by Toxicity Grade and Treatment Arm

	Rifapentine N = 526	Rifampin N = 513
GRADE 2 BILIRUBIN	1	0
GRADE 2 HEP/HEMAT TOXCITY	0	1
GRADE 2 HEPATIC TOXCITY	0	1
GRADE 2 LIVER TOX	0	1
GRADE 2 LIVER TOXICITY	4	5
GRADE 3 HEPATIC TOXICITY	1	1
GRADE 3 LIVER TOX ETOH	0	1
GRADE 3 LIVERTOX HEPC	0	1
GRADE 3 LIVER TOXICITY	10	11
GRADE 3 LIVER TOXICITY ANEMIA	1	0
GRADE 3 LIVER TOXICITY ETOH	0	3
GRADE 3 LIVER TOXICITY VOMITING	0	1
GRADE 4 HEPATIC TOXICITY	0	1
GRADE 4 LIVER TOXICITY	2	7
GRADE 4 LIVER TOXICITY ETOH	1	0
GRADE 4 HEPATIC TOXICITY ETOH	0	1
TOTAL REPORTED HEPATIC AEs	20	35

6.1.6 Summary of Safety

The adverse events reported from study 022 do not differ substantially from the AEs reported in the label for study 008. There were 526 AEs (all severity) reported from 251 rifapentine-treated subjects and 513

AEs reported from 248 rifampin-treated subjects. Generally the reported AEs were consistent with concurrent illnesses that the subjects enrolled in this study would be expected to have such as complications from alcohol use, etc. The events were similar between the treatment arms although there was a greater percentage of rifampin-treated subjects with hepatic AEs (6.8%) compared to rifapentine-treated subjects (3.8%). Of note, hyperuricemia was not reported as an AE in study 22, as it was in study 008. On both study arms the most frequently reported AEs were hyperglycemia, pneumonia, liver toxicity, and death.

Overall AES in HIV-positive subjects were proportionally more serious than in HIV-negative subjects. However the events that occurred were primarily associated with the subject's underlying HIV disease rather than with study treatment. As expected most events were from the liver although not disproportionately so.

The overall crude mortality rate among all study participants was 71/1075 (6.6%). Crude mortality rates did not differ between the two treatment groups (6.5% for the rifapentine group and compared to 6.7% for the rifampin group, $P = 0.87$). No deaths were attributed to anti-tuberculosis drug toxicity. Among the 71 participants who died, the last sputum culture prior to death was negative in 58, missing in 1, positive for non-tuberculous mycobacteria in 8, and positive for *M. tuberculosis* in 4. Of these 4, 1 died of trauma, 1 of central nervous system toxoplasmosis, and 1 of metastatic lung cancer. Only 1/71 (1.4%) death was attributed to TB (pulmonary hemorrhage before treatment started).

Mortality rates were substantially higher in HIV-positive than HIV-negative subjects (15/71; 21.1% vs. 56/1004; 5.6%; $P < 0.001$). The mortality rate was 10.5% among the 19 subjects who received HAART during the study compared to 29.6% among the 27 subjects who received no HAART ($P = 0.16$).

Deaths occurred throughout the study, during both the study and follow-up phases. There was a suggestion of increased mortality among HIV-positive subjects near the end of the follow-up period. The rate of death among HIV-negative subjects appeared stable over time. In a multivariate Cox proportional hazards model, factors independently associated with death were (in decreasing order of magnitude of hazard ratio) malignancy, HIV infection, alcohol use, unemployment, and age (per 1-year increase).

Among HIV-negative subjects, 18/56 (32%) deaths were associated with malignancy, and 13 (23%) were attributed to injuries, accidents, drug overdose, or unknown cause. Other causes of death in HIV-negative subjects included cardiac disease (6), chronic obstructive pulmonary disease (2), bacterial pneumonia (2), and cerebrovascular accident (2).

Of the 15 deaths in HIV-positive subjects, 11 were due to AIDS, two to malignancy, and two to drug overdose.

7. Overall Assessment

7.1 Conclusions

The findings of the CDC efficacy analyses of study 22 demonstrated relapse/failure rates in HIV-negative subjects at 24 months following the end of continuation therapy of 9.2% (46/502) for the rifapentine group compared to 5.5% (28/502) for the rifampin group; and were consistent with those from study 008 where overall relapse rates at 24 months were 12% (29/248) for rifapentine-treated subjects as compared to 7% (15/226) for rifampin-treated subjects. Agency analyses generated similar results (24 month rifapentine relapse rate 41/471 (8.7%) versus rifampin 22/457 (4.8%).

Further, the study delineates via risk factor analyses, which populations can safely receive rifapentine as part of their anti-tuberculosis treatment regimen. Due to the risk of rifamycin monoresistance, HIV-positive subjects should not receive rifapentine treatment. In HIV-negative subjects, higher relapse rates were seen in subjects with evidence of cavitory disease or bilateral pulmonary involvement on chest- x-ray and those who did not convert their sputum cultures to negative after the initial 2 month phase of treatment. These subjects should not receive rifapentine treatment at all or with extreme caution.

It should be clarified that although the relapse rates at 24 months following the end of treatment seen in subjects treated with once weekly rifapentine in conjunction with INH during the continuation phase of anti-tuberculous treatment were statistically significantly greater than the rates seen in subjects treated with rifampin and INH, these results were no different than those seen in study 008 which formed the original basis for accelerated approval. Further, in study 22 the applicant was able to clearly delineate subgroups of subjects at risk of relapse, including those with cavitory lesions, bilateral pulmonary disease and/or positive sputum cultures at the end of the initial treatment phase. This information allows prescribers to better identify subjects who are more likely to respond to rifapentine treatment. Other factors that should be taken into account when assessing the risk-benefit of rifapentine treatment include the improved compliance with a once weekly dosing regimen and thus the increased feasibility of DOT and the somewhat better tolerability of rifapentine compared to rifampin containing regimens. It remains true, however, that the optimal therapeutic regimen for rifapentine has not yet been defined and clinical trials are continuing with this goal.

7.2 Recommendation on Regulatory Action

This submission was made in compliance with the second and final accelerated approval commitment required by the Agency (21 CFR 3.14 subpart H) in the June 1998 approval letter. The applicant has satisfied all the accelerated approval commitments required by the Agency in the 1998 approval letter under subpart H. Full approval is recommended.

A Pediatric Written Request was issued on June 19, 1998 to study the pharmacokinetics and clinical efficacy of rifapentine in children under 12 years of age, however, studies were never conducted by the Applicant. Therefore, it is recommended that pediatric studies should be waived in children < 12 years of age because of the low incidence of reported tuberculosis cases amongst children < 15 years of age (2006 Total # reported TB cases US: 13,779, pediatric N= 807 (5.9%): data from CDC) and because there is little therapeutic advantage to the use of rifapentine in children because of the relative risk of higher relapse rates associated with rifapentine and the possibility of the development of resistant Mycobacteria without any obvious safety benefit relative to traditional rifamycin therapies.

The label has been converted to Physician Labeling Rule (PLR) format and should be revised to include information from study 22 and to change the INDICATIONS and USAGE section to reflect full approval of the indication.

7.3 Labeling Review

The label was revised to include results of study 22 in the CLINICAL STUDIES section and also to change the INDICATIONS AND USAGE section to reflect full approval of the indication. In addition, the label was revised for structure and content to fit the PLR format.

Below is a summary of the significant changes to the various sections of the label (indicated using the PLR section numbers). The entire proposed label can be found in the APPENDIX.

1 INDICATIONS AND USAGE

- Deleted general information regarding the treatment of pulmonary tuberculosis.
- Specified the limitations of use:

(b) (4)

PRIFTIN[®] should not be used as monotherapy in either the initial or the continuation phases of antituberculous treatment.

2 DOSAGE AND ADMINISTRATION

- Added a general statement regarding the treatment options for Initial Phase and Continuation Phase.

(b) (4)

(b) (4)

5 WARNINGS AND PRECAUTIONS

- Reordered section based upon public health impact, as per the Guidance on labeling. Added statement that rifapentine should not be used in the Continuation Phase in HIV-positive subjects, based upon the results of study 22:
- PRIFTIN should not be used as a once weekly Continuation Phase regimen in combination with isoniazid in HIV seropositive patients with pulmonary tuberculosis because of an unacceptable rate of failure/relapse documented with the presence of rifamycin-resistant organisms* Specified that the patients receiving rifapentine concomitantly with protease inhibitors and non-nucleoside reverse transcriptase inhibitors will have substantially decreased plasma concentrations of PIs and NNRTIs.
- Changed the wording in the section on (b) (4) to reflect the standard wording found in the labels of other antimicrobial products for “*Clostridium difficile*-Associated Diarrhea”

6 ADVERSE REACTIONS

- Added a section on serious and otherwise important adverse reactions which refers to the adverse reactions discussed in the WARNINGS AND PRECAUTIONS section.
- Added information regarding the safety database.
- Added a summary of the safety information from study 22, but did not add another table of adverse events, since the safety profile in study 22 was similar to study 008.

7 DRUG INTERACTIONS

- Created subsections for important drug interactions (protease inhibitors, non-nucleoside reverse transcriptase inhibitors, and hormonal) at the beginning of the section.
- Modified the table of other drug interactions for completeness and ease of reading.

12 CLINICAL PHARMACOLOGY

- Added information the Microbiology subsection (12.4) to provide specific direction regarding susceptibility testing for determining development of drug resistance.

13 NONCLINICAL TOXICOLOGY

- Added results from the completed carcinogenicity study

14 CLINICAL TRIALS

- Added additional details regarding the study design of Study 008
- Incorporated data from Study 22

8 References:

TBTC Study 22 Data\Published Papers

- Vernon A, Burman W, Benator D, Khan A, Bozeman L. Acquired rifamycin resistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. *Lancet* 1999;353:1843-1847.
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- Jasmer RM, Bozeman L, Schwartzman K, Cave MD, Saukkonen KK, Metchock B, Khan A, Burman WJ & TBTC. Recurrent tuberculosis in the United States and Canada. *Am J Respir Crit Care Med* 2004;170:1360-1366.
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- Khan A, Sterling TR, Reves R, Vernon A, Horsburgh CR & TBTC. Lack of weight gain and relapse risk in a large tuberculosis treatment trial. *Am J Respir Crit Care Med* 2006;174:344-348.
- Sterling TR, Zhao Z, Khan A, Chaisson RE, Schluger N, Mangura B, Weiner M, Vernon A. Mortality in a large tuberculosis treatment trial: modifiable and non-modifiable risk factors. *Int J Tuberc Lung Dis* 2006;10(5):542-549.

9. APPENDIX

Proposed Label:

23 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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this page is the manifestation of the electronic signature.**

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4/23/2008 03:29:12 PM
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4/23/2008 04:28:14 PM
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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-024/S008

PHARMACOLOGY REVIEW(S)



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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 21-024
SERIAL NUMBER: 008
DATE RECEIVED BY CENTER: 7/12/2007
PRODUCT: PRIFTIN
INTENDED CLINICAL POPULATION: Patients with tuberculosis
SPONSOR: sanofi-aventis
DOCUMENTS REVIEWED: Efficacy supplement SE7/4F
REVIEW DIVISION: Division of Special Pathogen and Transplant Drug
Products (HFD-590)
PHARM/TOX REVIEWER: Owen McMaster, Ph.D.
PHARM/TOX SUPERVISOR: William Taylor, Ph.D.
DIVISION DIRECTOR: Renata Albrecht, M.D.
PROJECT MANAGER: Hyun Son

Date of review submission to Division File System (DFS):

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

There are no data presented in this NDA that would preclude approval of this drug.

B. Recommendation for nonclinical studies

There are no additional nonclinical studies being recommended at this time.

C. Recommendations on labeling

The following wording is being proposed for the Carcinogenesis, Mutagenesis, Impairment of Fertility section of the label.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility



II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Rifapentine has been studied extensively in rats, mice, dogs, guinea pigs, rabbits and monkeys for up to two years. C_{max} is achieved 2-8 hours after oral dosing in the tested species. The drug is eliminated mainly in the feces and the primary metabolite in the plasma is the 25-desacetyl rifapentine. Adverse effects of rifapentine were detected in the liver, spleen, bone marrow, lymphatics, adrenals, kidneys, testes, body weight, stomach, red blood cells, leukocytes and cholesterol. Rifapentine has been marketed for 10 years and substantial safety data are available.

B. Pharmacologic activity

Rifapentine inhibits DNA-dependent RNA polymerase in susceptible strains of *Mycobacterium tuberculosis*. Rifapentine and its 25-desacetyl metabolite have been shown to be active against rifamycin-susceptible strains of *Mycobacterium tuberculosis*. Rifapentine is bactericidal against intracellular and extracellular *Mycobacterium tuberculosis* and accumulates in human monocyte-derived macrophages.

C. Nonclinical safety issues relevant to clinical use

There are no nonclinical safety issues that would preclude the approval of rifapentine for the treatment patients with tuberculosis.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-024

Review number: 1

Sequence number: 008

Date: 7/12/2007

Type of submission: Efficacy supplement

Information to sponsor: Yes

Sponsor : sanofi-aventis U.S. LLC, 55 Corporate Drive, P.O. Box 5925, Bridgewater, NJ 08807-5925

Manufacturer for drug substance: Gruppo Lepetit S.p.A., 20020 Lainate, Italy

Reviewer name: Owen McMaster

Division name: Division of Special Pathogen and Transplant Products

HFD 590

Review completion date: April 17, 2008

Drug:

Trade name: PRIFTIN[®]

Generic name: rifapentine

Code name: MDL 473

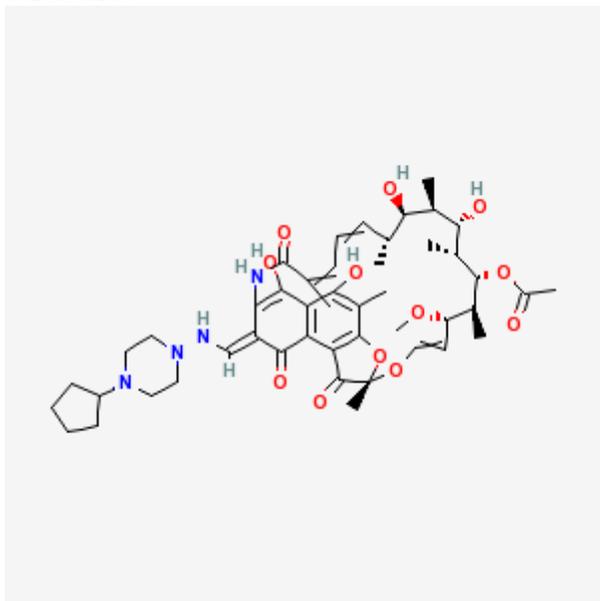
Chemical name: rifamycin, 3-[[[4-cyclopentyl-1-piperazinyl]imino]methyl]- or 3-[N-(4-Cyclopentyl - 1-piperazinyl)formimidoyl] rifamycin or 5,6,9,17,19,21-hexahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-8-[N-(4-cyclopentyl-1-piperazinyl)-formimidoyl]-2,7-(epoxy)pentadeca[1,11,13]trienimino)naphtho[2,1-b]furan-1,11(2H)-dione 21-acetate.

CAS registry number: 61379-65-5

Molecular formula: C₄₇H₆₄N₄O₁₂

Molecular weight: 877.04

Structure:



Relevant IND: 45,138

Relevant NDAs: None

Relevant DMF's: (b) (4)

Drug class: Anti-tuberculosis agent

Intended clinical population: Patients with pulmonary tuberculosis.

Clinical formulation:

PRIFTIN[®] (rifapentine) for oral administration contains 150 mg of the active ingredient rifapentine per tablet. The 150 mg tablets also contain, as inactive ingredients: calcium stearate, disodium EDTA, FD&C Blue No. 2 aluminum lake, hydroxypropyl cellulose, hypromellose USP, microcrystalline cellulose, polyethylene glycol, pregelatinized starch, propylene glycol, sodium ascorbate, sodium lauryl sulfate, sodium starch glycolate, synthetic red iron oxide, and titanium dioxide.

Route of administration: Oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Background

In 1998, PRIFTIN was approved for the treatment of pulmonary tuberculosis via an accelerated approval. The current submission is an efficacy supplement and contains the results of study USPHS 22, which addresses efficacy and relapse in patients receiving PRIFTIN. This represents the final accelerated approval commitment for rifapentine.

Studies reviewed within this submission:

No Pharmacology or Toxicology studies were submitted with this NDA. Previously submitted rat and mouse carcinogenicity data are being added to the PRIFTIN label at this time.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Rifapentine inhibits DNA-dependent RNA polymerase in susceptible strains of *Mycobacterium tuberculosis*. It accumulates in macrophages and is active against both intracellular and extracellular *M. tuberculosis* organisms. Intraperitoneal injections of rifapentine, at doses about 3 times the average daily recommended dose in the intensive phase, based on body surface area conversions, resulted in slight decreases in spontaneous activity and muscle tone, slight motor incoordination, mild tremors, and slight mydriasis in mice. Rifapentine was associated with minimal effects on the heart rate when given to dogs.

2.6.2.2 Primary pharmacodynamics

Mechanism of action:

Rifapentine inhibits DNA-dependent RNA polymerase in susceptible strains of *Mycobacterium tuberculosis*.

Drug activity related to proposed indication:

Rifapentine and its 25-desacetyl metabolite have been shown to be active against some strains of *Mycobacterium tuberculosis*. Rifapentine is bactericidal against intracellular and extracellular *Mycobacterium tuberculosis* and accumulates in human monocyte-derived macrophages. In one clinical trial (Study 008), sputum culture conversion rates (87 %) were slightly higher for patients treated with a drug combination (isoniazid, pyrazinamide and ethambutol) containing rifapentine compared to patients treated with a combination containing rifampin (80 %).

2.6.2.4 Safety pharmacology

Neurological effects:

Intraperitoneal (i.p.) dosing of rifapentine (75 mg/kg) provided no protection against pentylenetetrazole-induced convulsive death in male CF-1 mice. Conditioned behavior was not affected by 25 mg/kg i.p. injections in the rat. In mice, i.p. injections of 100 mg/kg (equivalent to 8 mg/kg, almost 3 times the average daily oral intensive phase dose based on body surface area comparisons) resulted in slight decreases in spontaneous activity and muscle tone, slight motor incoordination, mild tremors, and slight mydriasis. At 300 and 600 mg/kg mice showed marked decreases in spontaneous activity and muscle tone, marked motor incoordination, mild mydriasis and exophthalmos and death.

Cardiovascular effects:

Rifapentine did not affect systolic pressure in spontaneously hypertensive rats at doses up to 100 mg/kg (equivalent to a human dose of 16 mg/kg, or 6 times the average daily recommended dose in the intensive phase, based on body surface area conversions). Only slight, transient increases in heart rate were detected in dogs given oral doses equivalent to 11 times the average daily oral intensive phase dose. I.p. rifapentine (10 mg/kg) did not affect blood pressure or heart rate inhibited by vagal stimulation or carotid occlusion in dogs. Responses to norepinephrine, acetylcholine, isopropylnorepinephrine, histamine or angiotensin were also unaffected by 10 mg/kg intraperitoneal doses of rifapentine in dogs.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Rifapentine is quickly absorbed after oral dosing (T_{\max} 2-8 hours) and extensively distributed, with apparent volume of distribution of 0.5 to 1 L/kg in rats. Distribution is highest to the adrenals, liver, pancreas, submaxillary glands, kidneys, fat, heart, thymus, spleen and lungs. In the plasma, it is mainly converted to 25-desacetyl rifapentine. Rifapentine is primarily eliminated via the feces, which accounted for 92 % of the drug-related radioactivity in the rat, with urine accounting for 6 %.

2.6.4.2 Methods of Analysis

Rifapentine was measured by one of three general methods: (1) microbiological assay (agar diffusion microbiological assay utilizing *Sarcina lutea*), (2) reverse phase high-performance liquid chromatography or (3) liquid scintillation counting of radiolabeled drug.

2.6.4.3 Absorption

Rifapentine is rapidly absorbed after oral administration with C_{\max} values of 2 hours for the mouse, 6 hours for the monkey 8 hours for the rat and 9 hours in man.

2.6.4.4 Distribution

Rifapentine was extensively distributed with an apparent volume of distribution between 0.5 and 1 L/kg in rats. Distribution studies in mice and rats showed that the highest concentrations were detected in the adrenals, liver, pancreas, submaxillary glands, kidneys, fat, heart, thymus, spleen and lungs.

2.6.4.5 Metabolism

Rifapentine is partially hydrolyzed by an esterase to form 25-desacetyl rifapentine, its primary metabolite. In rats, the ratio of the parent to metabolite in bile decreased from 33 in the first hour to 3 at 48 hours. In man, 99% of the drug-related radioactivity in plasma was associated with rifapentine and 25-desacetyl rifapentine. Bioaccumulation was observed in rats with repeated dosing up to three months, but this was not observed with monkeys. Metabolic induction appears to occur with chronic dosing, balancing the effects of rifapentine accumulation such that there is no evidence of accumulation in rats dosed for one year.

2.6.4.6 Excretion

Rifapentine is excreted unmetabolized in the bile. In rats, feces and urine accounted for 92 % and 6 % of the rifapentine respectively. In man, 70 % of drug-related radioactivity

was recovered from the feces and 17 % from the urine. Elimination half-life was between 13-20 hours in animals (rats, mice and monkeys) and 12 hours in man.

Discussion and Conclusions

Rifapentine is quickly absorbed after oral dosing with distribution highest to the adrenals, liver, pancreas, submaxillary glands, kidneys, fat, heart, thymus, spleen and lungs. In the plasma, it is mainly converted to 25-desacetyl rifapentine. Rifapentine is primarily eliminated via the feces, which accounted for 92 % of the drug-related radioactivity in the rat, with urine accounting for 6 %. Although these studies provided a solid basis from which to design the clinical trials, many of the studies are very old (1980's) and did not rely on HPLC for quantification. Current HPLC techniques provide a more reliable representation of rifapentine pharmacokinetics.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:

Rifapentine was subjected to extensive toxicology evaluation involving rats, mice, dogs, guinea pigs, rabbits and monkeys with 2 year carcinogenicity studies in rats and mice.

Single dose toxicity

In acute oral studies, LD₅₀ values were calculated to be as low as 1700 mg/kg in rats (equivalent to a dose of 275 mg/kg, or 110 times the average daily recommended dose in the intensive phase, based on body surface area conversions) and as low as 2000 mg/kg in mice (equivalent to a dose of 162 mg/kg or 65 times the average daily recommended dose in the intensive phase, based on body surface area conversions). These animals showed mild sedation/depression, rough coats, slight encrustations around the eyes, red colorations of the extremities and fecal pellets. In dogs, high doses (up to 3000 mg/kg, equivalent to a human dose of 623 mg/kg or 250 times the average daily recommended dose in the intensive phase, based on body surface area conversions) resulted no deaths, but sedation, ataxia, dyspnea, salivation, vomiting, reddish coloration of the mucosa, skin and feces were observed.

Repeat dose toxicity

Repeat dose general toxicology studies ranged from three-week dietary studies in mice to one-year studies in rats and monkeys.

Clinical signs included decreased spontaneous activity, rough coats, ataxia, decreases in body weight gains and food consumption. Rifapentine-dosed animals showed red or

yellow coloration of the ears, extremities and tissues, a finding likely due to the color of the test material.

Target organs included the liver (hepatocellular hypertrophy, pale hepatic foci, accentuated lobular liver patterns, hepatocellular vacuolation, steatosis, bilirubinemia, increased AST, ALP and alkaline phosphatase, absolute and relative liver weights), lymphatics (dilatation of small intestinal lacteals and mesenteric lymph node), testes, (decreased spermatogenesis and/or testicular degeneration) bone marrow, (prominent adipose tissue in bone marrow, decreased bone marrow cellularity) kidney, (increased BUN, renal steatosis), spleen, (hyperplasia and hypertrophy of splenic histiocytes), pancreas, (pancreatic acinar cell degeneration), leukocytes (decreased), adrenals (swelling of the adrenal fasciculata), body weight, (decreased) stomach, (dilatation), cholesterol, (decreased) red blood cell parameters, (decreased mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin, and hemoglobin concentration) and serum proteins (decreased). Hepatocellular carcinoma and fibrosarcoma in the head were also observed in one rat in the one year study. Other neoplasms observed in that study included pituitary adenoma and adenoma of the adrenal cortex. Monkeys showed similar effects to the other species treated with rifapentine, but results were confounded by changes that the sponsor ascribed to parasitic infections. The NOAEL for the one year monkey study was determined to be 80 mg/kg/day, a dose equivalent to a human dose of 26 mg/kg/day or 10 times the average daily recommended dose in the intensive phase, based on body surface area conversions). No NOAEL could be determined for the one year rat study since bilirubinemia and multifocal pale hepatic foci were observed even at 10 mg/kg/day (a dose equivalent to about 2 mg/kg/day which is slightly less than the average daily recommended dose in the intensive phase, based on body surface area conversions).

Genetic toxicology:

25-desacetyl rifapentine, the primary metabolite of rifapentine, was positive in the *in vitro* mammalian chromosome aberration test in V79 Chinese Hamster cells. Rifapentine was negative in the *in vitro* gene mutation assay in bacteria (Ames test); *in vitro* point mutation test in *Aspergillus nidulans*; *in vitro* gene conversion assay in *Saccharomyces cerevisiae*; host-mediated (mouse) gene conversion assay with *Saccharomyces cerevisiae*; *in vitro* Chinese hamster ovary cell/hypoxanthine-guanine-phosphoribosyl transferase (CHO/HGPRT) forward mutation assay; *in vitro* chromosomal aberration assay utilizing rat lymphocytes; and *in vivo* mouse bone marrow micronucleus assay.

Carcinogenicity:

Rifapentine was studied in two year carcinogenicity studies in rats and mice. Hepatocellular carcinomas were increased in male NMRI mice (Harlan Winkleman) which were treated orally with rifapentine for two years at or above doses of 5 mg/kg/day (equivalent to a human dose of 0.4 mg/kg/day or 1/5 th of the recommended human dose, in the intensive phase, based on body surface area conversions).

Table 1. Numbers of mice* with hepatocellular carcinoma after two years of treatment with rifapentine.

	Males	Females
Control 1	8/50	0/50
Control 2	10/50	0/50
5 mg/kg	19/50	0/50
20 mg/kg	25/50	3/50
80 mg/kg	20/50	1/50

*Between 12 and 24 animals (out of 50) survived to terminal sacrifice, but all animals were evaluated.

Comment: The sponsor has proposed that the label state that these tumors were found ^(b)₍₄₎

In a study of 12 control groups of NMRI mice, Bombhard et al. (Spontaneous tumors in NMRI mice from carcinogenicity studies, Exp. Pathol. 1989;129-145) illustrates that male NMRI mice had 36 of the 38 spontaneous liver tumors recorded over 12 studies. While male mice are clearly more prone to develop these tumors than females, the rifapentine-dosed animals showed twice as many tumors as control animals. The tumors are therefore clearly related to rifapentine dosing.

In a two year rat study, there was an increase in nasal cavity adenomas in Wistar rats treated orally with rifapentine at 40 mg/kg/day, (equivalent to a human dose of 6.5 mg/kg/day or 3 times the recommended human dose in the intensive phase, based on body surface area conversions).

Table 2. Incidences (%) of nasal cavity neoplasia in Wistar rats treated with rifapentine for two years*

	Males	Females
Control 1	0/50	0/50
Control 2	2/50	0/50
2.5 mg/kg	0/49	0/49
10 mg/kg	2/49	2/49
40 mg/kg	22/50	8/50

* Between 32 and 43 animals (out of 49 or 50) survived to terminal sacrifice, but all animals were evaluated.

These data should be added to the Carcinogenicity, Mutagenesis, Impairment of Fertility section of the label. See proposed wording in “Recommendations on labeling” above.

Reproductive toxicology:

Reproductive toxicology studies were conducted in rats and rabbits at doses up to 40 mg/kg/day. In rats, rifapentine administration at 40 mg/kg/day (a dose equivalent to 6.5 mg/kg/day or 3 times the recommended dose in the intensive phase, based on body surface area conversions) was associated with increased resorption and post implantation loss, decreased mean fetus weight, increased number of stillborn pups and slightly increased mortality during lactation. Rabbits given 6 times the recommended dose (based on body surface area comparisons) showed higher post-implantation losses and an increased incidence of stillborn pups.

When rifapentine was administered at 40 mg/kg/day (3 times the average daily recommended dose in the intensive phase based on body surface area comparisons) to mated female rats late in gestation (from day 15 of gestation to day 21 postpartum), pup weights and gestational survival (live pups born/pups born) were reduced compared to controls.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

There are no data that would preclude the approval of rifapentine for the treatment of tuberculosis.

Recommendations:

No additional studies are being recommended at this time.

Owen McMaster, Ph.D.

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/s/

Owen McMaster
4/29/2008 09:38:35 AM
PHARMACOLOGIST

William Taylor
4/29/2008 10:15:51 AM
PHARMACOLOGIST

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-024/S008

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDY

NDA/Serial Number: NDA 21-024/S-008
(referenced information submitted to IND [REDACTED] (b) (4))

Drug Name: Priftin (rifapentine)

Indication(s): Pulmonary tuberculosis

Applicant: Sanofi Aventis.

Date(s): Submission date: July 12, 2007
PDUFA due date: May 13, 2008

Review Priority: Standard Review

Biometrics Division: Division of Biometrics IV

Statistical Reviewer: Xianbin Li, Ph.D.

Concurring Reviewers: Karen Higgins, Sc.D.

Medical Division: Division of Special Pathogen and Transplant Products

Clinical Team: Regina Alivisatos, M.D.; Joette Meyer, Pharm.D. (acting TL)

Project Manager: Hyun Son, Pharm.D.

Keywords: Clinical studies, NDA review, superiority

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1 EXECUTIVE SUMMARY

1.1 *Conclusions and Recommendations*

Rifapentine was approved in the treatment of pulmonary tuberculosis under the Accelerated Approval Regulation (21 CFR 314.510) based on 6-month follow-up results from Study 008. Final (two-year follow-up) results of this study, reviewed in July, 2000, indicated that the conversion rates at the end of treatment were somewhat higher among rifapentine patients and relapse rates through 2-year follow-up also appeared to be higher among rifapentine patients (approximately double), however, which still supported continued approval of this NDA. As an accelerated approval commitment, the sponsor submitted the results of Study 22, in which the clinical efficacy of rifapentine once a week, compared with the standard twice a week rifampicin-based treatment, in the last 4 months (continuation phase) of a 6-month regimen for the treatment of drug-susceptible pulmonary tuberculosis in HIV-seronegative and HIV-seropositive patients was evaluated.

In Study 22, among HIV-seronegative patients, although the difference in 2-year failure/relapse rates between the two groups was statistically significant, this difference and the failure-relapse rates of the two treatment groups were lower than those reported in Study 008. The efficacy results of this study support the results seen in the previous study.

Among HIV-seropositive patients, the sponsor stated that failure/relapse rates in both treatment groups were much higher than the currently acceptable level (3.5%). These two regimens are not recommended for HIV-seropositive population.

1.2 *Brief Overview of Clinical Studies*

This submission contains the results of Study 22, entitled “Efficacy and Safety of Once-Weekly Rifapentine and Isoniazid Compared to Twice-Weekly Rifampin and Isoniazid in the Continuation Phase of Therapy for Pulmonary Tuberculosis”. This study, conducted by the CDC, was required for full approval of rifapentine.

Rifapentine was approved under the Accelerated Approval Regulations (21 CFR 314.510) Sub-part H on June 22, 1998. The sponsor, Sanofi Aventis, in NDA 21,204 S008, submitted on July 12, 2007, referenced information submitted to IND [REDACTED] (b) (4) [REDACTED]. This NDA submission contains data from Study 22, the protocol for Study 22 as well as 7 published papers [1-7].

Study 22 was a prospective, open-label, comparative study of two anti-tuberculosis treatment regimens. After completing 2-month induction phase therapy, eligible patients were randomized to receive 16 weeks of continuation study phase therapy with a regimen consisting of either once-weekly 600 mg rifapentine and 900 mg isoniazid (INH) or

twice-weekly 600 mg rifampin (rifampicin) and 900 mg INH (standard regimen). Randomized patients were followed for 2 years after the scheduled completion of study phase therapy, until death, or for those with relapse, for one year after the diagnosis of relapse. The primary objective was to compare the clinical and bacteriologic relapse rates associated with the two study regimens.

1.3 Statistical Issues and Findings

The statistical review is based on the sponsor submitted published papers on this study, since there is no complete study report submitted.

A total of 1075 (1004 HIV-seronegative and 71 HIV-seropositive) subjects were enrolled in the USA and Canada. The primary endpoint was failure/relapse at the completion of 2 year follow-up in the intent-to-treat population by HIV status. Among HIV-seronegative subjects, failure/relapse occurred in 46 (9.2%) of 502 patients in the rifapentine group and in 28 (5.6%) of 502 in the rifampicin group. The difference in failure/relapse rates between the two treatment groups was 3.6% (95% CI [0.4%, 6.8%], p-value 0.04). Although the difference in failure/relapse rates between the two groups was statistically significant, the difference and failure/relapse rates were lower than those in Study 008 (11.7% (29/248) in the rifapentine group, 6.6% (15/226) in the rifampicin group, difference 5.1% (95% CI: [-0.1%, 10.2%], p-value 0.06), which was the study supporting the accelerated approval.

Among HIV-seropositive subjects, there were no treatment failures during study phase therapy. The 2-year relapse rates were 16.7% and 9.7% in the rifapentine and rifampicin groups, respectively and the difference in relapse rates was 7.0% with a 95% CI [-9.9%, 23.9%], p-value 0.47. The relapse rates observed were much higher than the currently acceptable rate of 3.5%. Therefore, the appropriate use of rifapentine in HIV-seropositive patients with tuberculosis remains unclear.

The overall crude mortality rate among all participants was 71/1075 (6.6%). Crude mortality rates did not differ between the two treatment groups (6.5% for the rifapentine group versus 6.7% for the rifampicin group, difference -0.2%, 95% CI [-3.1%, 2.8%], p-value 0.87). Mortality rates were substantially higher in HIV-seropositive subjects than in HIV-seronegative subjects (21.1% (15/71) versus 5.6% (56/1004), difference 15.5%, 95% CI [5.9%, 25.1%], p-value<0.001). Among HIV-seronegative subjects, the proportion of subjects with grade 4 adverse event(s) was lower in the rifapentine group than in the rifampicin group.

2 INTRODUCTION

2.1 Overview

Rifapentine (Priftin) has a long half-life in serum, which suggests a possible treatment once a week for tuberculosis.

Priftin was approved under the Accelerated Approval Regulation (21 CFR 314.510) on June 22, 1998, based on the 6-month results from ongoing Study 008 as a surrogate for 2-year follow-up results. Final results with 2-year follow-up of this study were submitted on December 17, 1999 (S-005) and approved on October 20, 2000. The approval letter dated on Jun 22, 1998 required further adequate and well-conducted studies to verify and describe clinical benefit and it was agreed that the CDC would submit study results from Study 22 upon completion of the study.

In Study 22, the sponsor planned to conduct a randomized, multi-center, open-label trial from 29 tuberculosis clinics across the U.S. and Canada.

2.2 Data Sources

The data sets for this study were submitted electronically at the following location: \\fdswa150\nonectd\ (b)(4)\TBTC Study 22 Data\Datasets. This reviewer found the data sets to be well organized and of good quality. The following data sets were used in the review process: HIVneg, HIVpos, trt_fail, trt_rel, death, and perm_dep.

3 STATISTICAL EVALUATION

The TB Trials Consortium (TBTC) Study 22 will be reviewed in this section.

3.1 Evaluation of Efficacy

3.1.1 Study Objectives

The primary objective was to compare the clinical and bacteriological relapse rates at the completion of the follow-up phase.

Secondary objectives included the following:

1. To compare the clinical and bacteriologic failure rates of the two study regimens at the completion of the study phase therapy.
2. To compare the clinical and bacteriologic response rates for the two study regimens among patients who began study phase therapy with signs and symptoms of tuberculosis or cultures positive for *M. tuberculosis*.
3. To compare the toxicity associated with the two study regimens by comparing discontinuation rates due to adverse events and occurrence rates of signs and symptoms associated with adverse events during study phase therapy.
4. To compare mortality rates of the two study regimens.
5. To compare the rates of completion of therapy within 22 weeks for the two study regimens.
6. To compare the rate of development of drug-resistant tuberculosis in the two study regimens among study patients classified as treatment failures or relapses.
7. To compare all of the above performance characteristics for the two study regimens in a small subset of HIV seropositive patients.
8. To compare attitudes and beliefs about participation in this study between patients who complete study therapy and those who fail to complete study therapy.

3.1.2 Study Design

This was a prospective, open-label, multicenter comparative study of two anti-tuberculosis treatment regimens. The study contained induction phase therapy (8 to 10 weeks), study phase therapy (Study Week 0 to 16-22), and follow-up phase (Study Weeks 16-22 to 118).

The induction phase therapy included: 1) daily directly-observed therapy (DOT) administration of isoniazid (INH), rifampin, and pyrazinamide (PZA) and either streptomycin or ethambutol for 8 weeks, or 2) daily administration of INH, rifampin, PZA, and either streptomycin or ethambutol for at least 14 consecutive doses (with at least 10 of every 14 doses directly observed) followed by twice-weekly or thrice-weekly doses (all directly observed) with the same drugs to complete induction phase. The induction therapy had to include a minimum of 40 observed daily doses (or equivalent intermittent doses), and had to be completed within 70 days.

After completing the induction phase therapy, eligible patients who met the inclusion criterion (including culture-positive drug-susceptible pulmonary tuberculosis on specimen collected no later than 2 weeks after the start of the induction phase of therapy) and none of the exclusion criteria were randomized to receive study phase therapy. Randomization was stratified by site and patient HIV status, with a random block of 2, 4, or 6 patients to ensure approximate equal numbers of patients in each treatment group, for both HIV-negative and HIV-positive subjects.

The study phase therapy included either 32 doses of twice weekly INH/rifampicin or 16 doses once weekly INH/rifapentine. The doses were 15 mg/kg (maximum: 900 mg) INH plus 10 mg/kg (maximum: 600 mg) of rifampicin twice weekly, or 15 mg/kg (maximum: 900) INH plus 600 mg rifapentine once weekly, administered orally.

Randomized patients were planned to be followed for 2 years after the scheduled completion of study phase therapy, until death, or for those with relapse, for one year after the diagnosis of relapse. Patients were seen at Study Weeks 4, 8, 12 and 16 during study phase therapy; four times during the first year of follow-up (Study Weeks 28±2, 40±2, 52±2, and 64±2), and twice during the second year of follow-up (Study Weeks 92±4 and 116±4).

3.1.3 Statistical Considerations

3.1.3.1 Primary Endpoint

Relapse, defined in the protocol as the occurrence of tuberculosis after the completion of study phase therapy and before the end of the follow-up phase, was the primary outcome. Relapse was classified as bacteriologic and/or clinical. Relapse may include either reactivation of disease or re-infection.

Comment: Though relapse was not explicitly stated in the protocol to be the primary endpoint, the primary objective was to compare relapse rates and the power of the study was calculated based on relapse rates. So this reviewer concludes that relapse is the primary endpoint as defined in the protocol.

The medical division received a letter dated 1/22/07 from Dr. Andrew Vernon of the CDC and former Study 22 Project Officer regarding the primary endpoint of this study. In that letter he states that there was a decision to combine failure during treatment with relapse after treatment into a primary endpoint for the study, called “failure/relapse.” This was discussed with the Data and Safety Monitoring Board and was driven by the ability to detect positive cultures near the end of treatment.

Comment: This review will report both a combined endpoint of failure/relapse as well as the endpoint of relapse and failure as defined in the protocol.

3.1.3.2 Primary Analysis

According to the protocol, analysis of primary and secondary endpoints would be done both on an intention-to-treat basis and by sub-analysis of patients who complete the protocol.

Comment: There is no definition for subjects who completed protocol in the protocol. However, complete therapy was defined in the protocol.

Time-to-event analyses were planned to be used to compare relapse rates. Considering that the observed data were interval censored, methods which include appropriate modifications to the Kaplan Meier methodology and the Cox proportional hazards model were planned to be used.

Comment: Though the above analysis method was stated in the protocol as the method used “to evaluate the efficacy of the experimental arm”, it does not appear to be the analysis used in the journal articles which describe the results of the studies. It is stated that life table survival was analyzed using the log-rank test in statistical method sections in the published papers. However the failure/relapse rates were compared using the comparison of two binomial variables. In this review, we will report analyses based on comparison of failure/relapse rates by Fisher’s exact test or the normal approximation to the binominal distribution.

3.1.3.3 Separate Analyses by HIV Status

In the protocol, separate analyses for HIV-positive and HIV-negative subjects were not mentioned. However, the sample size calculations were performed separately for HIV+ and HIV-negative subjects. Therefore, separate analyses by HIV status are acceptable.

3.1.3.4 Sample Size Calculation

The sample size calculation assumed the relapse rate of the standard therapy was 3.5%, and the experimental was 8.5%. This would lead the study to have 80% power to detect a difference in relapse rates between the two arms at a 0.05 two-sided level. The sample size calculated was 691 HIV-negative patients. The total number of HIV-negative patients planned to enroll for randomization was 1,000, based on a retention rate of 70%.

Comment: This sample size calculation is for determining that the experimental arm has more relapses. It is not clear how success would be claimed for the experimental arm.

The protocol stated that though HIV-seropositive patients were eligible for enrollment into the study, it expected to enroll only about 80 such patients. Assuming that 40 HIV-positive persons were in each treatment arm, and that the relapse rate for HIV-seropositive persons was the same as the one assumed for HIV-seronegative persons in the control arm (3.5%), the study would have a power of 0.80 to detect a relapse rate of 25.8% or greater in the rifapentine group.

Comment: It appears that the focus of the study was in HIV-seronegative subjects. Note that the relapse rate in the rifapentine groups for HIV-positive patients to be detected was much higher than that for HIV-negative patients, while the rates were the same in the rifampicin group for both HIV-positive and HIV-negative patients. A larger sample size was indicated to detect a smaller difference in relapse rates in HIV-negative subjects.

3.1.4 Sponsor's Analysis Results

The results of Study 22 were not summarized in a single detailed study report, but instead were published in 7 articles [1-7]. This section will summarize relevant information as contained in these articles. The sponsor's analysis was performed by HIV Status.

3.1.4.1 Patient Disposition, Demographic and Baseline Characteristics

3.1.4.1.1 HIV-seronegative Subjects

In this study, a total of 1004 HIV-seronegative patients were enrolled between 1995 and 1998.

Table 1 shows characteristics of HIV-seronegative patients at randomization. Demographic features were similar between the two groups. Similar induction (or intensive) regimens were used. However, subjects in the rifapentine group were more likely to have cavitory disease, bilateral disease, and positive sputum smear or sputum culture results at randomization.

Table 1: Characteristics of HIV-seronegative patients

	Rifapentine N=502	Rifampicin N=502
<i>Demographic feature</i>		
Age (years, mean[SD])	45(15)	45(15)
Men	372(74%)	380 (76%)
Ethnic origin		
Non-Hispanic white	88 (18%)	89 (18%)
Non-Hispanic black	206 (41%)	193 (38%)
Hispanic	123 (25%)	129 (26%)
Asian/Pacific Islander	67 (13%)	72 (14%)
Native American	18 (4%)	19 (4%)
<i>Clinical feature</i>		
Reported diabetes	75 (15%)	80 (16%)
Underweight at diagnosis of tuberculosis	151 (30%)	138/501 (28%)
Bodyweight (kg, mean [SD])	64 (13)	64 (13)
<i>Haemological features</i>		
Haemoglobin (g/dL, mean [SD])	13(2)	13(2)
White blood cell count ($\times 10^9/L$, mean [SD])	7 (3)	7 (2)
Platelet count ($\times 10^9/L$, mean [SD])	299 (105)	291 (107)
<i>Intensive therapy</i>		
Days of intensive therapy (mean [SD])	63 (5)	63 (5)
Total intensive phase dose (mean [SD])	54 (9)	54 (8)
Treatment two times a week during the intensive phase	253 (50%)	248 (49%)
Use of streptomycin during intensive phase	37 (7%)	39 (7%)
<i>Physical signs</i>		
Cavitation on chest radiograph ^{1*}	278/488(57%)	246/487 (51%)
Cavities at diagnosis	243/472(51%)	218/468(47%)
Cavities at randomization (within 2 weeks)	202/457(44%)	177/464(38%)
Bilateral disease on chest radiograph ¹	290/498(58%)	269/498(54%)
Bilateral disease at diagnosis	270/493(55%)	241/492(49%)
Bilateral disease at randomization (within 2 weeks)	247/481(51%)	229/484 (47%)
Sputum positive by smear at randomization*	73/480 (15%)	53/486 (11%)
Sputum positive by culture at randomization*	102/443(23%)	78/443 (18%)

* $p < 0.05$

¹Patients were classified as having cavitation or bilateral disease if signs were present on chest radiograph obtained at diagnosis (within 2 weeks of the start of induction) or within 2 weeks prior to randomization (at the end of the induction phase)

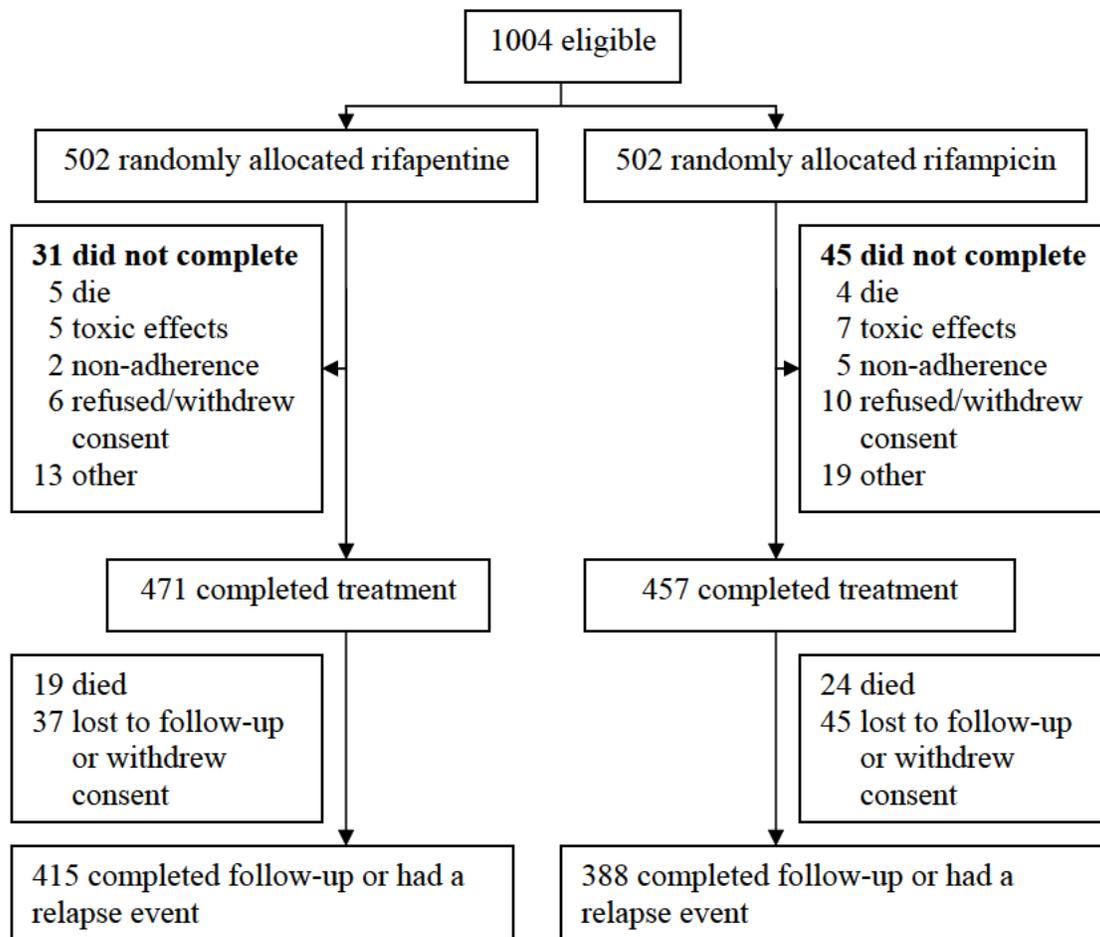
Adapted from Table 1 in The Tuberculosis Trials Consortium (2002).

Figure 1 shows the trial profile. There were 502 patients in each group. A total of 76 (7.6%) patients did not complete the assigned treatment (31 (6.1%) in the rifapentine group and 45 (8.9%) in the rifampicin group). Non-completion of treatment was due to death, drug toxic effects, non-adherence, refusal or withdrawal of consent, physician judgment, treatment failure, pregnancy, receipt of non-study regimen, or others. There were no significant differences in these reasons between the treatment groups.

This leaves a slight imbalance in the number of subjects who completed therapy, 471 in the rifapentine arm and 457 in the rifampicin arm. Of these subjects, 56 and 69 subjects did not complete follow-up or have a failure/relapse event. Overall the number of patients who completed follow-up or who had an event was 415 in the rifapentine arm and 388 in the rifampicin. This makes up 83% of those enrolled in the rifapentine arm compared to 77% of those enrolled in the rifampicin arm (p-value 0.03).

Comment: This significant imbalance in the number of subjects not completing follow-up or having an event should be considered in the interpretation of the study results. This will be discussed further in section 3.1.5.

Figure 1: Trial profile for HIV-seronegative subjects



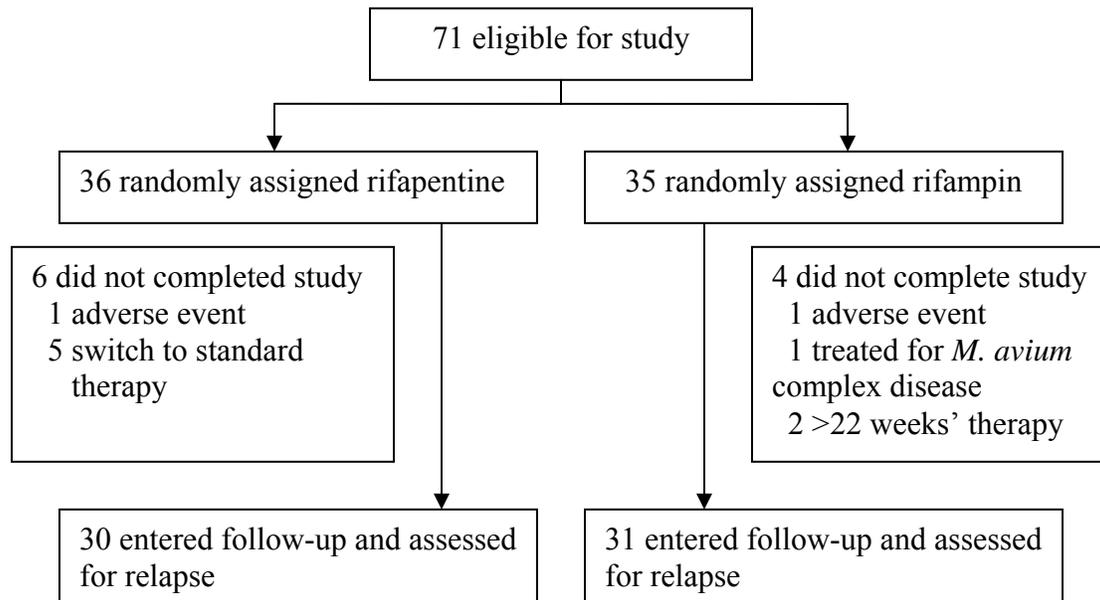
Adapted from Figure 1 in The Tuberculosis Trials Consortium (2002).

3.1.4.1.2 HIV-seropositive Subjects

Enrolment began in April, 1995. After four rifamycin mono-resistant relapses occurred among HIV-seropositive patients in the rifapentine group, the enrolment of HIV-seropositive patients was stopped by the Data and Safety Monitoring Board, CDC, and the investigators. Of 71 enrolled HIV-seropositive patients (Figure 2), 10 did not

complete treatment because of use of other anti-tuberculosis drugs to treat *M. avium* complex disease (1 patient), drug discontinuation due to presumed drug-related hepatitis adverse events (2), defaulting from therapy duration (2), and the switch to standard therapy when the HIV-seropositive group was closed (5).

Figure 2: Trial profile for HIV-seropositive patients



Adapted from Trial profile in Vernon et al (1999).

Baseline characteristics at enrolment showed a number of imbalances between the two groups, for example, sex, bilateral infiltrates, positive sputum culture at enrolment, median haemoglobin, median white-blood-cell count and CD4 cell counts (Table 2). However, the numbers of subjects were small.

3.1.4.2 Efficacy Analysis Results

3.1.4.2.1 HIV-seronegative Subjects

There were 46 (9.2%) failure/relapses in the rifapentine group and 28 (5.6%) in the rifampicin group (Table 3). There was a statistically significant difference in failure/relapse rates between the two groups (3.6%, 95% CI [0.4%, 6.8%], p-value 0.04).

Comment: Although the difference in relapse rates between the two groups was statistically significant, the difference and rates were lower than those in Study 008 (11.7% (29/248) in the rifapentine group, 6.6% (15/226) in the rifampicin group, with a difference 5.1%, 95% CI [-0.1%, 10.2%], p-value 0.06).

Table 2: Baseline characteristics of HIV-seropositive patients with relapse data

	Rifapentine N=30	Rifampicin N=31
<i>Demographic feature</i>		
Media age (years)	39	44
Men	23(77%)	28 (90%)
White/black/Hispanic (%)	13/73/13	10/74/16
<i>Clinical</i>		
History illicit drugs (%)	50	52
History alcohol abuse (%)	47	51
Mean Karnofsky status	89	94
Previous tuberculosis (%)	13	16
Extrapulmonary disease (%)	23	19
Given streptomycin (%)	3	3
Cavitation on chest radiography (%)	33	32
Bilateral infiltrates (%)	43	61
Positive sputum smear at enrolment (%)	0	12
Positive sputum culture at enrolment (%)*	0	19
Mean induction DOT doses	53	51
Mean days for induction	64	65
Median haemoglobin (g/L)†	11.4	12.3
Median white-blood-cell count (per mL)†	3400	4500
Median (IQR) CD4 cell count (per mL)	118 (52–315)	137 (65–301)

*p=0.05. †p=0.03. Adapted from Table 1 in Vernon et al (1999).

Table 3: Primary endpoints from HIV-seronegative patients

	Rifapentine (N=502) n(%)	Rifampicin (N=502) n(%)	Relative risk (95% CI)
<i>Failure after 8 weeks of treatment</i>			
Culture-positive failure	5 (1.0)	3(0.6)	1.67(0.40-6.94)
Clinical failure	0	0	
Failure after non-adherence*	0	3(0.6)	
All failures	5(1.0)	6(1.2)	0.83(0.26-2.71)
<i>Relapses at 24 months</i>			
Culture-positive relapse	39(7.8)	22(4.4)	1.77(1.07-2.95)
Clinical relapse	2	0	
All relapses	41(8.2)	22(4.4)	1.86(1.13-3.08)
<i>Relapses and Failures</i>			
All failures and relapses	46(9.2)	28(5.6)	1.64(1.04-2.58)

*Culture-positive failures

Adopted from sponsor's Table 2 in The Tuberculosis Trials Consortium (2002).

Comment: As stated above, there were significantly more missing data in the rifampicin arm than in the rifapentine arm. These missing data were ignored in the sponsor's analysis and these patients were essentially considered as having not failed or relapsed.

Additional methods for handling missing data will be used in the reviewer's analysis, section 3.1.4.

3.1.4.2.2 HIV-seropositive Subjects

No treatment failures occurred during study phase therapy. There were 5 of 30 and 3 of 31 relapses after treatment in the rifapentine and rifampicin groups. The relapse rates for the 2-year endpoint were 17.8% (95% CI [3.6%, 31.9%], p-value 0.47) and 10% (95% CI [0, 20.7%], p-value 0.41), calculated by Kaplan-Meier methods, in the rifapentine and rifampicin groups, respectively. Four of the relapses in the rifapentine group involved *M. tuberculosis* strains with rifamycin mono-resistance; no drug resistance occurred in the relapsed subjects in the rifapentine group (4/30 vs. 0/31, p-value 0.05) [sic].

Comment: Only those relapsed were at the risk of having mono-resistance. Therefore, the mono-resistance rates should be 4/5, and 0/3, and the difference in mono-resistance rates was 80%, with a 95% CI [44.9%, 1] and p-value 0.14.

A sponsor's concern was the high relapse rate after therapy (10%) even among HIV-infected subjects receiving standard twice-weekly therapy. Although the 95% CI for relapse rate did not exclude currently acceptable level of 3.5%, the rate observed was three times higher than the acceptable level. The sponsor concluded that this once-weekly continuation-phase regimen should not be used in HIV-seropositive patients.

3.1.5 Reviewer's Analysis Results

3.1.5.1 HIV-seronegative Subjects

3.1.5.1.1 Discrepancies in Submitted Data Sets

There were 3 failure/relapse events (1 in the rifapentine group and 2 in the rifampicin group) excluded from the sponsor defined fail_rel variable in HIVneg data set but available in separate datasets trt_fail and trt_rel. The failure/relapse rates calculated by including these 3 additional events in the efficacy analysis were similar to the sponsor reported results (9.4% (47/502) versus 6.0% (30/502), with a difference of 3.4% (95% CI [0.1%, 6.7%]). Since the discrepancy in the numbers of events was minimal, in the following analysis we did not change the sponsor defined failure/relapse variable fail_rel.

3.1.5.1.2 Outcomes at the end of 6 month and 2-year follow-up in HIV-seronegative subjects

Based on the Figure 1 (trial profile) and Table 2 (primary outcome) in the Lancet paper by The Tuberculosis Trials Consortium (2002), we created a table (Table 4) for the outcomes at the end of 6 months of treatment (2 months of intensive treatment and 4 months of randomized continuation treatment) and relapse rates at the end of follow-up (24 months) in all HIV seronegative patients randomized to treatment. The treatment responses at the end of 6 months were similar between the two treatment groups. At the

24-month follow-up, the sputum negative rates were similar among these converted, although the relapse rate was higher in the rifapentine group.

Table 4: Clinical outcome in HIV-seronegative subjects

	Rifapentine n/N(%)	Rifampin n/N(%)
<i>Status at the end of 4-month continuation phase</i>		
Treatment Response *	471/502 (93.8)	457/502 (91.0)
Not Converted	5/502 (1.0)	6/502 (1.2)
Did Not Complete Treatment**	21/502 (4.2)	35/502 (7.0)
Deaths	5/502 (1.0)	4/502 (0.8)
<i>Status through 24-month follow-up</i>		
Relapsed	41/471 (8.7)	22/457 (4.8)
Sputum Negative	374/471 (79.4)	366/457 (80.1)
Lost to Follow-up	37/471 (7.9)	45/457 (9.8)
Deaths	19/471 (4.0)	24/457 (5.3)

* Treatment response was defined as subjects who responded successfully after 16 doses of rifampin and isoniazid or after 8 doses of rifapentine and isoniazid, but before the end of continuation phase therapy.

**due to drug toxic effects, non-adherence, withdrawal of consent, receipt of non-study regimen, other.

3.1.5.1.3 Missing Data – Sensitivity Analyses

As stated in section 3.1.4.1.1 there was a significant difference between treatment arms in the number of subjects with missing data (87/502 [17.3%] vs. 114/502 [22.7%]), and therefore a difference in the number of subjects who completed follow-up or had an event (415/502 [82.7%] vs. 388/502 [77.3%]). Since the percent of subjects with missing data were even larger than the percent of subjects with an event, it is difficult to come to any firm conclusions regarding the results of the study. This is even more problematic since the number of subjects with missing data was so imbalanced between treatment arms. In this section, additional analyses on the failure/relapse endpoints are conducted as sensitivity analyses to attempt to account for missing data in various ways. None of the sensitivity analyses led to a significant difference between the treatment arms.

There were 26 and 31 deaths in the rifapentine and rifampin groups, respectively, during study treatment or follow-up phase, 2 and 3 of whom had treatment failure/relapse outcomes before death. Twenty four and 28 deaths were included as treatment successes in the sponsor’s analysis. We conducted a sensitivity analysis in which all subjects who did not complete the treatment or died, or were lost to follow-up or withdrew consent in the follow-up phase were treated as treatment failures/relapses (Table 5). The results show that there was no statistical difference in the failure/relapse rates between the two groups in two sensitivity analyses. The failure/relapse rates including deaths as failures (Table 5 (a)) were 13.9%, and 11.1% in the rifapentine and rifampin groups, respectively, with no statistically significant difference in failure/relapse rates between the two groups (p-value 0.18). The failure/relapse rates were much more similar when deaths and failures

to complete treatment, losses of follow-up, and consent withdrawals (Table 5(b)) were treated as treatment failures (p-value 0.48). Two additional analyses were conducted where all subjects with missing data (including deaths) were excluded (Table 5 (c)) and where all subjects with missing data were excluded though deaths were included as failures (Table 5 (d)). Neither of these analyses led to significant differences between the two groups.

Table 5: Reviewer’s analysis of primary endpoints including different events in HIV-seronegative subjects

Event	Rifapentine (N=502) n(%)	Rifampicin (N=502) n(%)	Difference (in percentage) (95% CI)
(a) All failures, relapses, and deaths	70 (13.9)	56 (11.1)	2.8 (-1.3, 6.9)
(b) All failures, relapses, deaths, failures to complete treatment, losses of follow-up, consent withdrawals	133 (26.5)	143 (28.5)	2.0 (-7.5, 3.5)
(c) Failures/relapse – excluding missing	46/415 (11.1)	28/388 (7.2)	3.9 (-0.1, 7.8)
(d) Failures/relapse/Death – excluding missing	70/439 (15.9)	56/416 (13.5)	2.5 (-2.3, 7.2)

3.1.5.1.4 Analysis by Cavitation, Bilateral Disease, and Positive Sputum

Since at randomization subjects in the rifapentine group were more likely to have cavitation on chest radiograph, bilateral disease on chest radiograph, and positive sputum results (Table 1), the reviewer tabulated failure/relapse events by these potential risk factors and conducted a logistic regression to examine the effect of treatment on sponsor defined failure/relapse endpoint after adjusting for these potential risk factors, where positive sputum was defined if either sputum by smear or by culture was positive. It appeared that these risk factors were associated with failure/relapse outcomes (Table 6).

Table 6: Primary endpoint by treatment and cavities, bilateral disease and sputum culture

	Rifapentine n/N (%)	Rifampicin n/N (%)
<i>Cavities</i>		
Yes	40/278 (14.4)	22/246 (8.9)
No	6/210 (2.9)	6/241 (2.5)
<i>Bilateral disease</i>		
Yes	34/290 (11.7)	22/269 (8.2)
No	12/212 (5.7)	6/233 (2.6)
<i>Sputum culture</i>		
Positive	26/124 (21.0)	15/100 (15)
Negative	20/378 (5.3)	13/402 (3.2)

As Table 7 shows, after adjusting for these factors, the odds ratio of failure/relapse of rifapentine versus rifampicin was not statistically significant. In addition, there were no significant two-way interaction terms between the treatment variable and these factors to be included in the model. These potential risk factors appeared to be associated with failure/relapse and partially attributable for the higher failure/relapse rate in the rifapentine group.

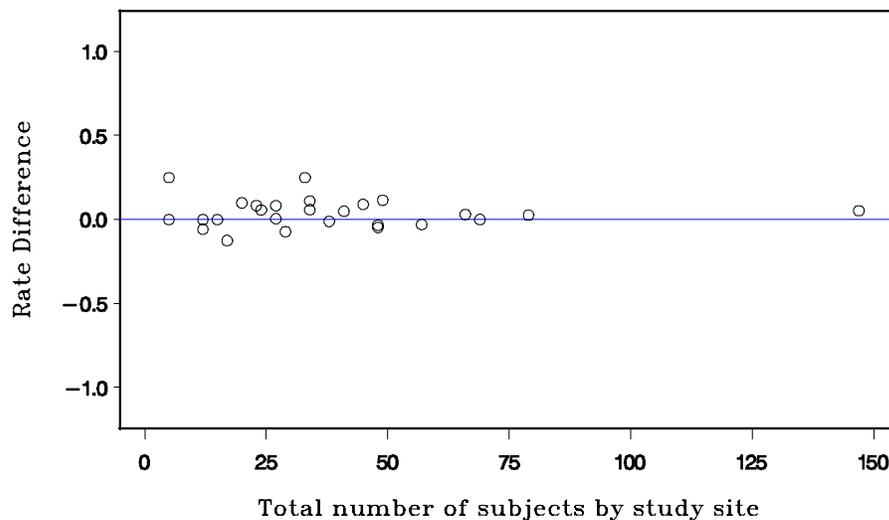
Table 7: Results of logistic regression of failure/relapse on cavitation, bilateral disease, sputum positive culture, and therapy

	Odds ratio	95% CI	p-value
Cavitation	3.40	1.77, 6.52	0.0002
Bilateral disease	1.88	1.07, 3.32	0.029
Positive sputum	3.50	2.11, 5.81	<0.0001
Rifapentine	1.45	0.88, 2.41	0.149

3.1.5.1.5 Treatment Effect by Study Site

There were 26 participating study sites, with the total number of patients per site ranging from 5 to 147 with a mean of 39. Figure 3 shows the difference in failure/relapse rates in HIV-seronegative subjects versus the total number of patients by study site. Sites with more than 50 subjects showed less variability in the differences in failure/relapse rates and rate differences were closer to 0, compared with study sites with fewer than 50 subjects.

Figure 3: Difference in failure/relapse rates in HIV-seronegative subjects by study site



3.1.5.2 HIV-seropositive Subjects

There were 5 relapses out of 30 subjects in the rifapentine group and 3 out of 31 in the rifampicin group. The sponsor used Kaplan-Meier method to analyze the relapse rates for the 2-year endpoint for the two groups separately. Since a comparison of two proportions was used for HIV-seronegative subjects, the reviewer used this method for consistency. The difference in relapse rates was 7.0% with a 95% CI [-9.9%, 23.9%], p-value 0.47.

3.2 Evaluation of Safety

3.2.1 Sponsor's Adverse Events and Mortality Analysis

3.2.1.1 HIV-seronegative Subjects

Grade 4 adverse events occurred less frequently in the rifapentine group than in the rifampicin group (Table 8). Numbers of death were similar between the two groups. Malignancy was accountable for 32% (18) of all 56 deaths (8 and 9 were in the rifapentine and rifampicin groups, respectively; one-death difference due to discrepancy between the published papers and datasets) and 23% (13) were attributed to injuries, accidents, drug overdose, or unknown causes. Other causes of death included cardiac disease (6), chronic obstructive pulmonary disease (2), bacterial pneumonia (2), and cerebrovascular accident (2).

Table 8: Number of adverse events by treatment group in HIV-seronegative subjects

	Rifapentine (N=502)	Rifampicin (N=502)
Death	26 (5%)	30 (6%)
Death during study treatment	5 (1%)	4 (1%)
Death during follow-up	21 (4%)	26 (5%)
Any grade 4 adverse event, number of patients with events *	44 events, 29 (6%)	72 events, 51 (10%)

*p-value=0.01 for difference in numbers of patients with events.

Adapted from Table 5 in The Tuberculosis Trials Consortium (2002).

3.2.1.2 HIV-seropositive Subjects

There were no serious unexpected toxic effects associated with rifapentine and no significant differences in adverse events between the two groups. None of the 16 deaths (9 and 7 deaths in the rifapentine and rifampicin groups) were attributable to tuberculosis. Of the 15 deaths in HIV-seropositive subjects, 11 were due to AIDS, 2 to malignancy, and 2 to drug overdose. The mortality rate was 10.5% among the 19 patients who received HAART (4 during the anti-tuberculosis, and 15 during the follow-up phase) compared to 29.6% among the 27 patients who received no antiretroviral therapy.

Note: There was a discrepancy in the number of deaths among HIV-seropositive subjects: 16 deaths in Vernon et al (1999) and in the submitted data set and 15 deaths in Sterling et al (2005).

3.2.1.3 All Subjects

In addition, the overall mortality rate among all HIV-seronegative and HIV-seropositive participants was 71/1075 (6.6%). There was no statistically significant difference in crude mortality rates between the two treatment groups (6.5% for the rifapentine group vs. 6.7% for rifampicin group, difference -0.2%, 95% CI [-3.1%, 2.8%], p-value 0.87). However, as expected, the mortality rate in HIV-seropositive subjects was statistically higher than in HIV-seronegative subjects (21.1% (15/71) versus 5.6% (56/1004), difference 15.5%, 95% CI [5.9%, 25.1%], p-value<0.001). Malignancy was the most common cause of death, such as, cancer of the lung (4), prostate (4), larynx (3), and pancreas (3). There were 7 alcohol-related deaths. No deaths were attributed to anti-tuberculosis drug toxicity and only one death to tuberculosis. Among all subjects who died, the last sputum culture prior to death was negative in 58, missing in 1, positive for *M. tuberculosis* in 4. Three of these 4 deaths were attributable to trauma, central nervous system toxoplasmosis and metastatic lung cancer.

4 Findings in Special/Subgroup Populations

4.1 Gender, Race and Age

4.1.1 Efficacy Analyses by Gender, Race and Age for HIV-negative Subjects

Analyses for subgroup populations, by gender, race and age, were conducted by the reviewer to evaluate the consistency of efficacy across different subgroups.

Table 9: Primary endpoints from HIV-seronegative patients by age, sex and race

	Rifapentine Failure or relapse /n (%)	Rifampicin Failure or relapse /n (%)
<i>Gender</i>		
Male	36/372 (9.68)	26/380(6.84)
Female	10/130 (7.69)	2/122 (1.64)
<i>Race</i>		
White	14/88 (15.91)	10/89 (11.24)
Black	18/206 (8.74)	11/193 (5.70)
Hispanic	9/123 (7.32)	4/129 (3.10)
Other	5/85 (5.9)	3/91 (3.30)
<i>Age</i>		
18 to 39	24/194 (12.37)	11/214(5.14)
40 to 64	21/263 (7.98)	15/236 (6.36)
65 or more	1/45 (2.22)	2/52 (3.85)

Table 9 shows that subjects between age 18 and 39 in the rifapentine group were more likely to have failure/relapse than those in the same age group in the rifampicin group (difference 7.2%, 95% CI [1.7%, 12.7%], p-value 0.012). Female subjects in the rifapentine group were more likely to have failure/relapse than female subjects in the

rifampicin group (difference 6.1%, 95% CI [0.9%, 11.2%], p-value 0.035). There were no statistical differences in failure/relapse rates by race between the two treatment groups.

As Table 10 shows, including deaths as failures, subjects younger than 65 years old or females were more likely to have failure or relapse in the rifapentine group than in the rifampicin group, but the differences were not statistically significant (p-value 0.053, and 0.786, respectively). There were no statistically significant differences in failure/relapse rates between the two treatment groups by gender and race.

Table 10: Primary endpoints including deaths as failures from HIV-seronegative patients by age, sex and race

	Rifapentine Failure or relapse / n (%)	Rifampicin Failure or relapse /n (%)
<i>Gender</i>		
Male	57/372 (15.32)	50/380(13.16)
Female	13/130 (10.00)	6/122 (4.92)
<i>Race</i>		
White	21/88 (23.86)	18/89 (20.22)
Black	28/206 (13.59)	20/193 (10.36)
Hispanic	13/123 (10.57)	12/129 (9.30)
Other	8/85 (9.41)	6/91 (6.60)
<i>Age</i>		
18 to 39	26/194 (13.40)	16/214 (7.48)
40 to 64	34/263 (12.93)	28/236 (6.36)
65 or more	10/45 (22.22)	12/52 (23.08)

Table 11: Primary endpoints including deaths, failures to complete treatment, losses of follow-up, consent withdrawals as failures from HIV-seronegative patients by age, sex and race

	Rifapentine Failure or relapse /n (%)	Rifampicin Failure or relapse /n (%)
<i>Gender</i>		
Male	73/372 (19.62)	73/380(19.21)
Female	17/130 (13.08)	16/122 (13.11)
<i>Race</i>		
White	26/88 (29.55)	21/89 (23.60)
Black	36/206 (17.48)	32/193 (16.58)
Hispanic	17/123 (13.82)	27/129 (20.93)
Other	11/85 (9.41)	9/91 (6.60)
<i>Age</i>		
18 to 39	35/194 (18.04)	33/214 (15.42)
40 to 64	45/263 (17.11)	40/236 (16.95)
65 or more	10/45 (22.22)	16/52 (30.77)

Table 11 displays the failure/relapse rates with deaths, failures to complete treatment, losses of follow-up, and consent withdrawals as failures. The differences in failure/relapse rates by gender, race and age between the two treatment groups were not statistically significant.

4.1.2 Efficacy Analyses by Gender, Race and Age for HIV-seropositive Subjects

The following table shows the relapse events by gender, race and age. However, due to the small sample sizes, the relapse rates were difficult to compare.

Table 12: Primary endpoints from HIV-seronegative patients by gender, race, and age

	Rifapentine Relapse /n (%)	Rifampicin Relapse /n (%)
<i>Gender</i>		
Male	4/27 (14.81)	3/31 (9.68)
Female	1/9 (11.11)	0/4 (0)
<i>Race</i>		
White	1/4 (25.00)	0/3 (0)
Black	3/28 (10.71)	3/25 (12.00)
Hispanic	1/4 (25.00)	0/6 (0)
Other	0	0/1 (0)
<i>Age</i>		
18 to 39	4/20 (20.00)	1/14 (7.14)
40 to 64	1/14 (7.14)	2/21 (9.52)
65 or more	0/2 (0)	0

4.2 Other Special/Subgroup Populations

None

5 Conclusions and Recommendation

5.1 Statistical Issues and Collective Evidence

The following statistical issues were found among HIV-seronegative subjects:

- Among HIV-seronegative patients, the difference in failure/relapse rates between the two treatment groups was statistically significant. However, this difference and the failure/relapse rates in the two treatment groups were lower than those reported in Study 008. Furthermore, after considering deaths, losses to follow up, and consent withdrawals as treatment failure/relapse events, there were no difference in failure/relapse rates.
- The difference in failure/relapse rates between treatment arms seemed to be mainly driven by results in younger HIV negative subjects and in HIV negative females where significant differences were found within these subgroups.

However, differences were no longer significant once missing data was accounted for.

- At randomization, HIV-seronegative subjects in the rifapentine group appeared to have higher proportions of cavitation, and positive sputum culture, which, were associated with a higher probability of treatment failure/relapse. These imbalances may have been driving much of the difference seen between treatment arms.

It is difficult to know how to interpret the results of the study for HIV negative subjects. The sponsor has submitted articles which state that there was a significant increase in failure/relapse in the rifapentine arm; however, our sensitivity analyses show that this conclusion was not robust in the face of the large amount of missing data. One might consider the conclusions of the article as the “worse case” scenario and that these “worse case” results are supportive of the results seen in the previous study, 008.

5.2 Conclusions and Recommendations

Among HIV-seronegative patients, although the difference in failure/relapse rates between the two groups was statistically significant, this difference and the two rates were lower than those in Study 008. After considering deaths, losses to follow up, and consent withdrawals as treatment failures, there were no differences in failure/relapse rates. The efficacy results of this study support the results seen in the previous study.

Among HIV-seropositive patients the relapse rates in both groups were higher than the currently acceptable level (3.5%) as indicated by the sponsor. The appropriate use of rifapentine in HIV-seropositive patients with tuberculosis remains unclear.

Crude mortality rates did not differ between the two treatment groups. Among HIV-seronegative subjects, the proportion of subjects with grade 4 adverse event(s) in the rifapentine group was lower than in the rifampicin group.

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-024/S008

MICROBIOLOGY REVIEW(S)

MICROBIOLOGY REVIEW
DIVISION OF SPECIAL PATHOGEN AND TRANSPLANT PRODUCTS

NDA #: 21-024

REVIEWER: Maureen K. Davidson
CORRESPONDENCE DATE: 12-July-2007; 23-Feb 2008;
12-Mar-2008; 31-Mar-2008
CDER RECEIPT DATE: 13-July-2007; 25-Feb-2008
14-Mar-2008; 31-Mar-2008
REVIEW ASSIGN DATE: 30-July-2007; 25-Feb-2008
14-Mar-2008; 31-Mar-2008
REVIEW COMPLETE DATE: 08-May-2008

SPONSOR: Sanofi-Aventis US LLC
55 Corporate Drive
Bridgewater, NJ 0887

SUBMISSION REVIEWED: SE7 / S-008

DRUG CATEGORY: Antimycobacterial

INDICATION: Treatment of pulmonary tuberculosis

DOSAGE FORM: 150 mg tablet

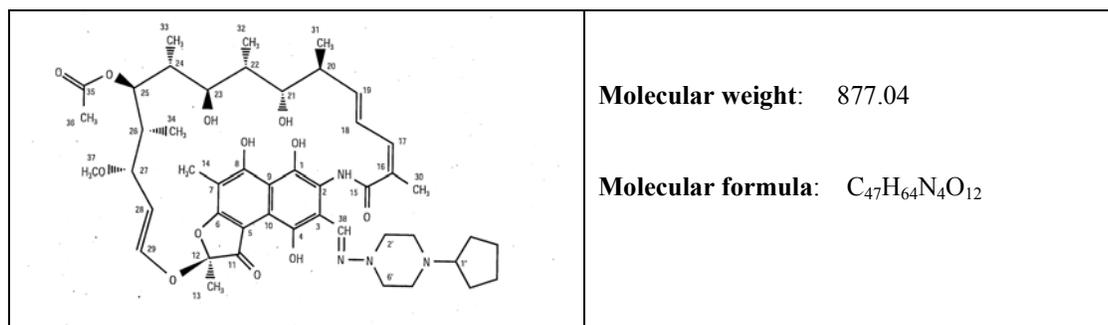
PRODUCT NAMES:

a. **PROPRIETARY:** Priftin

b. **NONPROPRIETARY:** Rifapentine

c. **CHEMICAL:** rifamycin, 3-[[[(4-cyclopentyl-1-piperazinyl)imino]methyl]- or 3-[N-(4-Cyclopentyl - 1-piperazinyl)formimidoyl] rifamycin or 5,6,9,17,19,21-hexahydroxy-23-methoxy 2,4,12,16,18,20,22-heptamethyl-8-[N-(4-cyclopentyl-1-piperazinyl)-formimidoyl]-2,7-(epoxypentadeca[1,11,13]trienimino) naphtho[2,1-b]furan-1,11(2H)-dione 21-acetate

STRUCTURAL FORMULA:



SUPPORTING DOCUMENTS: IND [REDACTED] (b) (4) NDA 24-024; IND 45, 138

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1. EXECUTIVE SUMMARY

The sponsor has proposed to include results of the Centers for Disease Control and Prevention Study 22 in human immunodeficiency virus (HIV) seronegative and seropositive patients in the package insert.

The activity of rifapentine was reviewed previously (for details see microbiology NDA reviews dated 6/12/1998 and 8/26/2000). Additional testing against 95 patient isolates by the radiometric and agar proportion methods showed that rifapentine MICs ranged from 0.03 to 0.25 µg/ml. In another study rifapentine was tested against laboratory strains (n=9) and clinical isolates (n=33) by radiometric and agar dilution methods as recommended by the Clinical and Laboratory Standards Institute document M24A. The rifapentine MIC values (0.06 µg/ml) were 2 to 4 fold less than those for rifampin. These observations are similar to the studies reviewed previously. Overall, the results suggest that (b) (4) µg/ml of rifapentine could be considered a breakpoint for *in vitro* susceptibility tests.

Some studies done in response to fulfillment of Phase 4 commitments included standardizing *in vitro* susceptibility testing. For this, efforts were made to test the stability of rifapentine in broth medium with *Bacillus subtilis* as the indicator organism under conditions used for *in vitro* susceptibility assays. The results showed a reduction in the drug concentration by seven days incubation at 35° C. Whether this will impact interpretation of 2 to 3 week susceptibility tests, especially for slow-growing mycobacteria, is not known. However, it is noteworthy that rifapentine MICs are 2 to 4 fold lower than rifampin MICs.

The agar proportion method is more accurate than the radiometric method in detecting low levels of resistance even though it takes 3 to 4 weeks. Studies indicate that there is a high level of cross resistance between rifapentine and rifampin and that most strains (51/97; 53%) of rifampin resistant *M. tuberculosis* were also resistant to rifapentine, rifabutin, and rifalazil. About 36% (35/97) of the strains were only resistant to rifampin and rifapentine and 9% (9/97) were resistant to rifampin only. Mutations in the *rpoB* gene that induce resistance to rifampin induce cross resistance to rifapentine in 88/97 (91%) of the isolates. Of the 97 strains/isolates tested, no isolate with resistance to rifapentine alone was observed thereby suggesting that resistance to rifapentine alone is very unlikely to occur. These findings confirm the studies reviewed earlier for approval of rifapentine (for details see microbiology reviews dated 6/12/98 and 8/26/2000).

Study 22 was performed at 29 geographical sites in the USA and Canada and there was no attempt to standardize the microbiological methods used at the participating laboratories. During this time, microbiological cultural procedures were evolving. However, results of repeat testing of isolates at the CDC laboratory for organism identification, *in vitro* susceptibility testing against rifampin, and genotyping by restriction fragment length polymorphisms were used for all analyses. Given the fact that only one sputum specimen was collected from the majority of patients at each assessment visit, and that a positive culture was based on either one culture with > 10 colonies or at least two positive sputum samples on liquid or solid media, it is likely the number of microbiologically positive specimens, and thus the numbers of failures and relapses, is probably underestimated in this study, regardless of treatment regimen.

Study 22 included both HIV positive and HIV negative subjects. In the HIV negative patient population the failure rate (1%) was the same in both treatment groups regardless of whether the clinical response or bacteriological response was used. The clinical relapse rate was 8.4% in the rifapentine treatment group and 5% in the rifampin treatment group. The bacteriological relapse rate was 8.3% for the rifapentine treatment group and 5.1% for the rifampin treatment group. There were no treatment failures in the HIV positive patient population. The clinical relapse rates between the two treatment regimens appear to be similar in the HIV positive patients with a relapse rate of 16.6% in the rifapentine treatment group and 14.3% in the rifampin treatment group. The bacteriological responses are also similar, with the relapse rate of 17.1% in the rifapentine treatment group and 12.8% in the rifampin treatment group.

In vitro susceptibility testing of patients' isolates included only rifampin. Rifapentine was not tested. The number of isolates was too small to evaluate any correlation between failure/relapse and *in vitro* susceptibility. No correlation was observed between *in vitro* susceptibility results and RFLP analyses. Three of the 4 paired baseline and relapse isolates from HIV positive patients were identical by RFLP analyses. One of the individuals with a resistant strain of *M. tuberculosis* had two separate organisms identified by RFLP analysis. However, the data suggest that development of resistance to rifampin is more common in HIV positive compared to HIV negative patients and in those treated with rifapentine than in with rifampin.

The frequent presence of *Mycobacterium* sp. other than *M. tuberculosis* in the individuals in Study 22 was unexpected. Although colonization or co-infection with these organisms may have affected clinical parameters, the evaluation of patients for possible failure/relapse required the isolation and identification of any *Mycobacterium* sp. and did not rely solely upon clinical parameters. Therefore, the presence of these non-tuberculosis mycobacteria in the study patients does not affect the overall results of the study.

2. INTRODUCTION AND BACKGROUND

The subject of this submission is rifapentine/Priftin[®] which is a long-acting derivative of rifamycin and is approved (6/22/1998) for treatment of pulmonary tuberculosis. This submission is an efficacy supplement submitted in support of proposed labeling changes to include results from the Centers for Disease Control and Prevention (CDC) study 22 in human immunodeficiency virus (HIV) seropositive and seronegative patients. The submission also includes published reports (1-7) resulting from that study. The use of rifapentine has been incorporated into current guidelines recommended by the American Thoracic Society, Centers for Disease Control and Prevention, and Infectious Disease Society of America for the treatment of tuberculosis (8). The proposed labeling revisions include the recommendations in these guidelines.

Both rifapentine and the active metabolite 25-desacetyl rifapentine are highly bound to plasma proteins (rifapentine 97.7% ; 25-desacetyl rifapentine 93.2%) with most of rifapentine bound to albumin. Sirgel *et. al.* (9), demonstrated that only the free moieties were active in lesions. The time to maximum concentration (T_{max}) of rifapentine is 4.83 ± 1.80 hours. The half life ($T_{1/2}$) of rifapentine and 25-desacetyl rifapentine is similar (13.19 ± 1.38 and 13.35 ± 2.67 hours, respectively). After a 600 mg oral dose of rifapentine, the maximum concentration (C_{max}) of

rifapentine is 15.05 ± 4.62 $\mu\text{g/mL}$ and the C_{max} for 25-desacetyl rifapentine is 6.26 ± 2.06 $\mu\text{g/mL}$. The area under the curve for 0 to 72 hours [$\text{AUC}_{(0-72\text{h})}$] is 319.54 ± 91.52 $\mu\text{g}\cdot\text{h/mL}$ for rifapentine and 215.88 ± 85.96 $\mu\text{g}\cdot\text{h/mL}$ for 25-desacetyl rifapentine. When rifapentine is administered daily, steady-state conditions are achieved after 10 days.

Tuberculosis

Pathogenesis: Pulmonary tuberculosis (TB) is a chronic, progressive infection with *Mycobacterium tuberculosis* that occurs almost exclusively from inhalation of droplet nuclei containing the organism (10). Airborne droplet nuclei lodge in subpleural terminal airspaces, predominantly in the lower lung, usually in only one site. Tubercle bacilli replicate inside macrophages, ultimately killing them; inflammatory cells are attracted to the area, causing a tubercle and sometimes pneumonitis. In the early weeks of infection, some infected macrophages migrate to regional lymph nodes (e.g., hilar, mediastinal). In 95% of cases, after about 3 weeks of uninhibited growth, the immune system suppresses bacillary replication before symptoms or signs develop. Foci of infection in the lung or other sites resolve into granulomas which may have necrotic centers. *M. tuberculosis* can survive in these granulomas for years. Ultimately, the host's resistance determines whether the infection resolves without treatment, remains dormant, or becomes active.

In about 10% of patients overall, latent infection develops into active disease, although the percentage varies significantly by age and other risk factors. In 50 to 80 % of those who develop active disease, TB reactivates within 2 years of infection, but it can occur decades later. Since hematogenous spread of *M. tuberculosis* can occur during the initial infection, any organ can be seeded with the organism but reactivation occurs most often in the lung apices, where O_2 tension is highest. One of the major risk factors for progression of the disease is impaired immunity, including use of corticosteroids, diabetes, advanced age, cancer, and infection with HIV. Rarely, the primary focus immediately progresses, causing acute illness with pneumonia (sometimes cavitory), pleural effusion, and marked mediastinal or hilar lymph node enlargement. Tissue damage is due to delayed hypersensitivity typically producing granulomatous necrosis. Lung lesions are cavitory. The course of the disease varies greatly, depending on the virulence of the organism and the state of host defenses (10).

Diagnosis: Diagnosis of pulmonary tuberculosis is based on skin tests, chest radiographs, clinical signs and symptoms, and microbiological assays, primarily sputum cultures and smears. The standard recommendation for microbiological assessment of tuberculosis is an early morning sputum collected on three consecutive days (11). The Clinical and Laboratory Standards Institute (CLSI) recommends three samples collected at 8-24 hour intervals (12). Both specimen collection recommendations note that the sensitivity of detection of *M. tuberculosis* by cultural methods is diminished by having only one sample to be cultured. Sputum can be expectorated or induced by inhaling aerosolized saline. More invasive procedures, such as bronchial washings, gastric washings, and transbronchial biopsies are reserved for special cases. Sputum smears are prepared with Ziehl-Neelsen or Kinyoun stains for conventional light microscopy or fluorochrome stains for fluorescent microscopy. The finding of acid-fast bacilli (AFB) in a sputum smear is strong presumptive evidence of TB, but definitive diagnosis requires a positive

sputum culture or a positive rapid molecular test. For optimal detection of *M. tuberculosis* by cultural methods, culture of sputum should be performed both in broth and on solid (agar based) media and there are several FDA and CLSI approved methods for performing cultures (12). Culture results may take more than three weeks, and *in vitro* susceptibility testing can take up to eight weeks by conventional bacteriologic methods. Both growth in liquid media and detection of growth by radiometric methods are more sensitive, and more rapid, than growth and detection of mycobacteria on agar. Higher rates of isolation of *M. tuberculosis* have been reported from patients on anti-tuberculosis treatment when their specimens are cultured in liquid media (11,12). Please note that detection of *M. tuberculosis* by radiometric broth culture is significantly faster and more sensitive than growth on solid media. The average time of growth by radiometric methods is 5 to 14 days for *M. tuberculosis* as compared to 10 to 12 days on agar based media (i.e., Middlebrook 7H11) or 18 to 24 days on egg based medium (i.e., Lowenstein- Jensen). (11,12)

Treatment: Treatment of tuberculosis is complex (10) and this is reflected in the study design for CDC Study 22. All patients with new, previously untreated TB should receive a two month initial phase of treatment (also referred to as the induction or intensive phase) followed by a four or seven month continuation phase of treatment. For both initial and continuation phases, the total number of doses (calculated by doses/week times number of weeks) must be administered; thus if any doses are missed, treatment is extended and not stopped at the end of the time period. Initial-phase therapy is with four antibiotics for the first two months: isoniazid (INH), rifampin, pyrazinamide, and ethambutol. These can be given daily throughout (for all regimens, 5 days/week is considered equivalent to daily), or daily for 2 weeks followed by doses 2 or 3 times/week for 6 weeks. At the end of the initial phase of therapy (about 2 months), pyrazinamide is stopped, and cultures and smears are obtained. Continuation phase treatment depends on the results of the sputum cultures and smears and presence or absence of a cavitary lesion on the initial chest x-ray. If both culture and smear are negative, but the chest x-ray still shows lesions or cavitations, or the culture or smear is positive but x-ray showed no cavitation, INH and rifampin are continued for four more months (total of 6 months treatment). If the x-ray showed cavitation and the culture or smear is positive, INH and rifampin are continued for seven more months (total of 9 months treatment). In either regimen, ethambutol is stopped if the isolate shows no resistance to any drug. Continuation-phase drugs can be given daily, twice weekly, or 3 times weekly. Verification of efficacy of treatment is based on clinical response to therapy and culture and smear results during and after treatment. The follow-up period after treatment is usually about 1.5 to 2 years, during which time samples for smears and/or culture may be collected. These treatment guidelines were used in the design of Study 22. At the time Study 22 was conducted, the role of rifapentine in treatment of tuberculosis was unclear, but current treatment guidelines include an option of treatment with rifapentine in HIV-negative patients with negative sputum cultures and smears at the end of the 2 month initial treatment phase and no cavitation on chest x-ray (10).

Development of Resistance. *In vitro* susceptibility testing, using a standardized method such as that recommended by the CLSI, is considered to be an acceptable method for evaluating drug resistance. Efforts are also being made to evaluate drug resistance by the use of molecular

methods. These methods have been shown to be useful for epidemiology studies but their usefulness in differentiating relapse from new infection remains unclear.

***In vitro* susceptibility testing.** *In vitro* susceptibility testing should be performed on the initial isolate from all patients and repeated if the patient is culture-positive after three months of appropriate therapy or shows clinical evidence of failure to respond to therapy (10). Methods for *in vitro* susceptibility testing of *M. tuberculosis* are based on proportion methods and rely on a bacteriological definition of drug resistance that was developed in recognition of the difficulties in defining clinical resistance for mycobacteria. Resistance is defined as "a decrease in sensitivity of sufficient degree to be reasonably certain that the strain concerned is different from a sample of wild strains of human type that have never come into contact with the drug" (12,13).

There are two methods (agar and radiometric) of performing *in vitro* susceptibility testing of *M. tuberculosis* which are approved by the FDA and CLSI (12,13), and both are proportion methods. Briefly, the agar proportion method is performed by inoculating equal quantities of several dilutions of a standardized inoculum onto Middlebrook 7H10 agar medium with and without the test drug. The number of colony forming units (CFU) growing on the drug-containing medium is compared with the number growing on the drug-free medium and expressed as a percentage. For several decades the agar proportion method using Middlebrook 7H10 agar has been considered the standard method in the USA. The radiometric method is a variation of the proportion method in which the drug is placed in broth rather than in an agar medium and is designed to give results equivalent to the agar proportion method. The agar proportion and radiometric methods both define resistance as growth of greater than 1% of an inoculum of bacterial cells in the presence of a "critical" concentration of antituberculous drug. The critical concentrations of antituberculous drugs were adopted by international convention and represent the lowest concentration of drugs that inhibit 95% of 'wild strains' of *M. tuberculosis* that have never been exposed to the drugs, while at the same time not inhibiting strains of *M. tuberculosis* that have been isolated from patients who are not responding to therapy, and that are considered resistant. When greater than 1% of the tested bacterial population in a clinical isolate becomes resistant to the critical concentration of a drug, that drug is not useful for antituberculous therapy. The results of *in vitro* susceptibility testing using the critical concentrations of primary antituberculous drugs (i.e., INH, rifampin, ethambutol, and pyrazinamide) correlate well with clinical effectiveness in patients with tuberculosis (12,13). Please note that although the radiometric broth culture method is used for *in vitro* sensitivity testing, it is not as sensitive as agar based methods for detecting low numbers of resistant organisms (11,13). For this reason, the agar proportion method remains the standard *in vitro* susceptibility testing method. The more rapid radiometric broth based test is often used in conjunction with the agar proportion method to provide more rapid results.

Molecular Methods. Molecular methods such as IS6110-based restriction fragment length polymorphism (RFLP) analysis, spoligotyping, and mycobacterial interspersed repetitive units (MIRU) analysis have been used for genotyping in epidemiological studies to establish or deny the relatedness of individual strains of *M. tuberculosis* (14-18). There is no FDA approved method of genotyping *M. tuberculosis*. In 2004, the CDC Tuberculosis Genotyping Program was initiated to enable rapid genotyping of isolates from every patient in the USA with culture-

positive tuberculosis. Spoligotyping and MIRU analyses are based on polymerase chain reaction (PCR) methods, do not require viable organisms, and are superior for those strains of *M. tuberculosis* which contain no or few copies of the IS6110 sequence which is required for RFLP analyses. RFLP analysis using the 1,355 base pair, mobile, repetitive, insertional sequence IS6110 is considered the 'gold standard' for genotyping strains of *M. tuberculosis* for epidemiologic purposes (11, 18-22). Briefly, RFLP analysis is based on polymorphisms generated by variability in both the copy numbers and the chromosomal positions of IS6110 in isolates of *M. tuberculosis*. IS6110-based RFLPs can usually discriminate between *M. tuberculosis* strains with identical results by PCR-based methods, reinforcing the value of this technique (14).

RFLP analyses are done on DNA extracted from isolates grown in broth and are done according to an internationally recognized, standardized protocol (19). Briefly, RFLP analysis is based on polymorphisms generated by variability in both the copy numbers and the chromosomal positions of IS6110 in isolates of *M. tuberculosis*. Studies with multiple isolates from the same patients over long time periods have shown that the position and number of copies per strain of *M. tuberculosis*, and thus the RFLP patterns, have a half life of about 4.5 years (14, 20, 22). Therefore, the stability of the RFLP pattern is sufficient to allow use of this technique in epidemiological studies, and to assess relatedness among strains of *M. tuberculosis* (14). However, its usefulness in differentiating relapse from new infection is unclear.

Mechanism of Drug Resistance. The rifamycin class of antibiotics includes several well characterized, FDA approved agents: rifampicin, rifampin, rifabutin, and rifapentine. Rifampicin is a product of *Nocardia mediterranei* whereas rifampin and rifapentine are semisynthetic derivatives. Rifapentine is a cyclopentyl derivative of rifampin. Rifamycins bind to the β subunit of the DNA dependent RNA polymerase encoded by the gene *rpoB* and block the transition from transcription initiation to transcription elongation (21). Resistance to rifamycins in *M. tuberculosis* strains is principally due to one of several single point mutations that occur in an 81 base pair (bp) region (27 codons) of the *rpoB* gene (23). There is a high level of cross resistance among rifamycins. However, not all mutations within the 81 bp region exhibit the same level of resistance (23). For example, alterations in codons 511, 516, 518, and 522 result in organisms that have low-level resistance to rifampin and rifapentine, but remain susceptible to rifabutin and rifalazil (23). Please note that in the previous microbiology review in which the cross resistance of rifapentine and rifampin was evaluated (6/12/1998), several studies were reviewed that indicated that the level of cross reactivity was very high (essentially 100%) between rifapentine and rifampin. There have been no reports of sensitivity to rifapentine without sensitivity to rifampin. More than 96% of the rifampin-resistant strains of *M. tuberculosis* contain a mutation in the 81 bp region of the *rpoB* gene. The most common mutations (65–86%) alter either codon 526 or codon 531, and result in high-level resistance to rifampin and rifapentine (MIC > 32 μ g/ml). Rare mutations associated with rifampin resistance have also been found in the amino-terminal region of *rpoB* gene (23).

3. PRECLINICAL/NONCLINICAL MICROBIOLOGY

No new information is presented in the submission. For details of *in vitro* and *in vivo* activity of rifapentine, please see microbiology reviews for NDA 24-024 (6/12/1998 and 8/26/2000) and

IND 45,138 (1/30/95). There have been a few papers published since the FDA approval of rifapentine which directly relate to the activity of the drug and the sponsor submitted a small study related to the stability of rifapentine under conditions used for *in vitro* susceptibility testing.

3.1 *In Vitro* Sensitivity Testing

Heifets *et al.* (24) followed the CLSI guidelines (M-24-A: Susceptibility testing of Mycobacteria, Nocardiae, and Other Actinomycetes) to develop agar dilution and radiometric methods of rifapentine *in vitro* susceptibility tests. Rifampin was used as a comparator because both radiometric and agar proportion assays had already been established. Three susceptible strains of *Mycobacterium tuberculosis* (strains H37Rv, Atencio, and Erdman) were tested on Middlebrook-Cohn 7H10 and 7H11 agars and in BACTEC 7H12 broth. The H37Rv strain is the FDA and CLSI recommended quality control strain for both the radiometric and agar proportion methods. The baseline minimum inhibitory concentration (MIC) values for rifapentine and rifampin were determined in three experiments. The results in Table 1 show comparable results by both methods. This experiment also illustrated the reproducibility of the methods since there was no variation in the MIC values obtained in the three experiments.

Strain	Rifapentine MIC (µg/ml)		Rifampin MIC (µg/ml) (Comparator)	
	Radiometric method	Agar Dilution method	Radiometric method	Agar Dilution method
H37Rv ^b	0.03	0.06	0.06	0.06
Atencio	0.03	0.06	0.06	0.12
Erdman	0.03	0.06	0.06	0.12

^a 3 experiments were done with each strain of *M. tuberculosis*. There was no variability in the results, so no standard deviations are shown.
^b This strain is recommended by the FDA and CLSI[®] as the quality control strain for both the radiometric and agar proportion methods.
Adapted from (24)

The MICs of rifapentine against five additional laboratory strains of *M. tuberculosis* showed similar results (Table 2). Please note that the values obtained with the H37Rv, Atencio, and Erdman strains are no more than 2 fold different from the results shown in Table 1.

Strain	Radiometric Method (µg/ml)	Agar Proportion Method (µg/ml)
H37Rv ^a	0.06	≤ 0.03
Erdman	0.06	≤ 0.03
Atencio	0.03	≤ 0.03
12067	0.06	≤ 0.03
12060	0.12	0.06
12066	0.12	≤ 0.03
12064	0.06	≤ 0.03
12058	0.12	0.25

^a This strain is recommended by the FDA and CLSI[®] as the quality control strain for both the radiometric and agar proportion methods. Adapted from (24)

The rifapentine MICs against 93 of 95 patient isolates by the radiometric broth method were also in the range of 0.03 to 0.12 µg/ml; 2 isolates had MICs of 0.25 µg/ml.

These data suggest that ^{(b) (4)} µg/ml of rifapentine could be considered a breakpoint for *in vitro* susceptibility tests. Please note that this is only one doubling dilution less than the breakpoint listed for rifampin in the currently approved labeling and in the CLSI standardized methods for *in vitro* susceptibility testing of mycobacteria (9).

In response to the request from the FDA to develop an *in vitro* susceptibility assay for rifapentine the sponsor used standardized CLSI methodology (Document M23-A). The data provided include the stability of rifapentine at different temperatures using a bioassay. Briefly, rifapentine was initially dissolved in methanol and then diluted in test medium consisting of Middlebrook 7H9 medium supplemented with OADC enrichment and 0.76 gm ascorbic acid (final concentration 10⁻³ M) to prevent oxidation of rifapentine to its microbiologically-inactive state. The bioactivity was determined using an ATCC strain (6633) of *Bacillus subtilis*, because it is a fast growing bacterium. The bioassay was designed to determine the concentration of the drug remaining after incubation at various times and temperatures. Growth of the *B. subtilis* in the test solutions was compared to a standard curve developed using standard concentrations of rifapentine. Results indicated that stock solutions of rifapentine were stable for at least 6 months at -60°C and MIC plates were stable for at least 6 weeks at -60°C. The results of triplicate testing show about 60% reduction in antibiotic concentration by seven days at 35° C. These findings may impact interpretation of 2 to 3 week susceptibility tests for slow-growing mycobacteria, especially if it is assumed that constant exposure to antibiotic is required for antimicrobial efficacy. Please note that *M. tuberculosis* was not used for such testing. The experiment does suggest that rifapentine MICs should be interpreted with caution. The results may vary with duration of incubation of the *M. tuberculosis*.

3.2 Drug Resistance

Heifets *et al.* (24) used mutant strains of *M. tuberculosis* induced by growing the parent strains on agar containing 8 µg of rifapentine or rifampin and subculturing any colonies which grew on

these agars. The resulting strains were resistant to both rifapentine and rifampin at concentrations above 8.0 µg/ml, which was the concentration of both drugs used in experiments. The actual MIC for both rifapentine and rifampin as determined by the agar proportion method was 32 µg/ml. The sensitive strain (H37Rv) and the H37RPT-R resistant strain, derived from the parent strain, were used for reproducibility studies (Table 3). Based on replicate testing of the sensitive strains of *M. tuberculosis* in 10 experiments, there was about a 4-fold variation in the MIC values for both rifampin and rifapentine when tested by the agar proportion method. However, by the radiometric method, no variability in the MIC values was reported for either rifapentine or rifampin. When the resistant strain was tested in 10 replicate experiments, the MICs for both rifapentine and rifampin was > 8 µg/ml for both methods.

Table 3. Reproducibility of Rifampin and Rifapentine MIC determinations

Strain	Number of Experiments	Radiometric Method MIC (µg/ml)		Agar Proportion Method MIC(µg/ml)	
		Rifampin (Comparator)	Rifapentine	Rifampin (Comparator)	Rifapentine
H37Rv	7	0.12	≤ 0.03	0.12	≤ 0.03
H37Rv	2	0.12	≤ 0.03	0.12	0.12
H37Rv	1	0.12	≤ 0.03	0.5	0.12
H37RPT-R	10	> 8	> 8	> 8	> 8

H37Rv is a susceptible strain of *M. tuberculosis* and is recommended by the FDA and CLSI as the quality control strain for both the radiometric and agar proportion methods. H37RPT-R is a resistant strain derived from H37Rv; the H37RPT-R MIC for both rifapentine and rifampin is 32 µg/ml. Adapted from (24)

In another experiment using 33 clinical isolates that were resistant to rifampin, the MICs of rifampin and rifapentine were determined by both agar dilution and radiometric methods (Table 4). There was no more than a 2-fold variability in the rifapentine and rifampin MICs by either of the methods. This experiment also illustrates the high cross resistance between rifampin and rifapentine.

Table 4. Distribution of Rifapentine MICs of 33 Rifampin Resistant <i>M. tuberculosis</i> Clinical Isolates					
Rifampin MIC (µg/ml)	Rifapentine MIC (µg/ml)				Totals
	2.0	4.0	8.0	> 8.0	
Agar Proportion Method					
2.0	0	0	0	0	0
4.0	0	0	1	2	3
8.0	0	1	0	1	2
> 8.0	0	0	3	25	28
Total	0	1	4	28	33
Radiometric Method					
4.0	0	0	0	0	0
8.0	0	0	6	0	6
> 8.0	0	0	5	22	27
Total	0	0	11	22	33

In another experiment, Heifets *et al.* (24) evaluated the sensitivity of the radiometric method to detect low level resistance to rifampin and rifapentine (Table 5). The H37RPT-R resistant mutant of *M. tuberculosis* was used to create artificial mixtures of organisms containing 1, 10, and 50% of the rifapentine and rifampin resistant mutants and the susceptible parent strains. These mixtures were tested by radiometric (BACTEC) and agar methods. Controls consisted of fully susceptible strains and 100% resistant mutants. These experiments showed that resistance to either rifampin or rifapentine was not detected by the radiometric method if the culture contained less than 10% resistant bacteria. The lack of sensitivity in detecting organisms resistant to rifapentine by the radiometric method was deemed unacceptable in previous microbiology reviews (6/12/1998). Even though the agar proportion method for *in vitro* sensitivity testing takes 3 to 4 weeks, it is more accurate in detecting low levels of resistance and it provides data on the actual proportion of resistant bacteria. The radiometric method takes an average of 5-14 days (11-13).

Table 5. Sensitivity of Radiometric Method for Detection of Resistance to Rifampin and Rifapentine in Mixtures of Sensitive and Resistant Strains of *M. tuberculosis*

Strain and % resistant bacteria incorporated into inoculum	% Resistant bacteria actually found on agar plates containing drug at the following concn (µg/ml):					RMP MIC (µg/ml)		RPT MIC (µg/ml)	
	0.25	0.5	2.0	4.0	8.0	Agar method	BACTEC method	Agar method	BACTEC method
H37Rv									
1	4	2	2	4	4	>8.0	0.12		
10	16	14	9	10	6	>8.0	4.0		
50	100	60	39	84	71	>8.0	>8.0		
100	100	100	100	100	100	>8.0	>8.0		
Atencio									
1	8	3	4	2	1	>8.0	0.12		
10	10	18	11	14	16	>8.0	8.0		
50	42	67	43	100	83	>8.0	>8.0		
100	100	100	100	100	100	>8.0	>8.0		
Erdman									
1	3	2	2	1	2	>8.0	0.12		
10	15	20	19	19	23	>8.0	8.0		
50	92	86	57	69	74	>8.0	>8.0		
100	100	100	100	100	100	>8.0	>8.0		
H37Rv									
1	4	3	3	2	4			>8.0	0.06
10	10	10	10	17	12			>8.0	4.0
50	63	55	39	43	45			>8.0	>8.0
100	100	100	100	100	100			>8.0	>8.0
Atencio									
1	3	3	5	4	2			>8.0	0.06
10	27	30	30	22	27			>8.0	8.0
50	93	100	99	85	100			>8.0	>8.0
100	100	100	100	100	100			>8.0	>8.0
Erdman									
1	3	1	0	0.7	0			2.0	0.06
10	19	19	9	15	16			>8.0	8.0
50	83	84	96	78	70			>8.0	>8.0
100	100	100	100	100	100			>8.0	>8.0

RMP = Rifampin; RPT = Rifapentine
BACTEC = radiometric method
Adapted from (24)

3.3 Cross Resistance with Other Rifamycins

Saribas *et al.* (25), examined the relationship between *rpoB* gene mutations and cross resistance to rifapentine, rifampin, rifabutin, and rifalazil in 97 rifampin-resistant clinical isolates of *M. tuberculosis* from Turkey. The rifampin-susceptible strain H37Ra (ATCC 25177) was used as a negative control. Please note this is an avirulent, pan-susceptible, strain of *M. tuberculosis* that is recommended by CLSI for *in vitro* susceptibility testing procedures in laboratories that wish to decrease the risk of laboratory acquired infections. Twenty-one rifampin-susceptible clinical isolates were included as negative controls; all were susceptible to all four drugs. *In vitro* susceptibility testing was performed by the agar proportion method with each drug at a critical concentration of 1 µg/ml. This concentration of drug is what is recommended for *in vitro* sensitivity testing for resistance against rifampin but the data supporting the testing of rifapentine, rifabutin, and rifalazil at 1 µg/ml are unclear. As shown in Table 6, most strains (53%) of rifapentine resistant *M. tuberculosis* were also resistant to rifampin, rifabutin, and rifalazil, but there were 35 strains (36%) that were only resistant to rifapentine and rifampin. Only nine isolates (9%) were resistant to rifampin only. Mutations in the *rpoB* gene that induced

resistance to both rifampin and rifapentine were reported in 88/97 (91%) of the isolates. There were no instances of resistance to rifapentine alone. The patterns of resistance were shown to be related to specific mutations in the *rpoB* gene for 14 of the resistant clinical isolates (Table 7). These findings confirm the studies reviewed earlier that also identified development of resistance to mutations in the *rpoB* gene (for details see NDA Microbiology review dated 6/12/1998).

Table 6. Comparison of Rifamycin Drug Resistance ^a of <i>M. tuberculosis</i> Clinical Isolates from Turkey	
Drugs	Number of Strains Resistant (%)
Rifapentine + Rifampin + Rifabutin + Rifalazil	51/97 (53%)
Rifapentine + Rifampin + Rifabutin	1/97 (1%)
Rifapentine + Rifampin + Rifalazil	1/97 (1%)
Rifapentine + Rifampin	35/97 (36%)
Rifampin	9/97 (9%)
Total	97 (100%)
^a Resistance was determined by growth on media containing 1µg/ml of each drug. Adapted from (25).	

Table 7. Relationships Among Mutations in the <i>rpoB</i> Genes of 14 Clinical Isolates of <i>M. tuberculosis</i> and Resistance to Rifamycins	
Mutation	Drugs to which resistance is gained
513 Glycine →leucine	Rifampin + rifapentine + rifabutin + rifalazil
516 Aspartic acid →valine	Rifampin + rifapentine
516 Aspartic acid →tyrosine	Rifampin + rifapentine
526 Histidine →glutamic acid	Rifampin + rifapentine
526 Histidine→ leucine	Rifampin + rifapentine
526 Histidine→ tyrosine	Rifampin + rifapentine + rifabutin + rifalazil
531 Serine →leucine	Rifampin + rifapentine + rifabutin + rifalazil
Adapted from (25).	

4. CLINICAL MICROBIOLOGY

4.1 Clinical Study 22

The sponsor submitted one prospective, multisite, open-label, clinical study conducted by the CDC (CDC Protocol 1427 / TBTC/USPHS Study 22) in HIV seronegative and HIV seropositive individuals. The study was designed to compare the safety and efficacy of a once-weekly regimen of INH and rifapentine to the standard twice-weekly regimen of INH and rifampin in the 4-month continuation phase of TB treatment in HIV negative and HIV positive patients. The

main objective was to compare, at the completion of the follow-up phase of treatment, the clinical and bacteriologic relapse rates associated with the two study treatment regimens in HIV negative and HIV positive patients. Secondary objectives of the study were to compare:

- a) clinical and bacteriologic failure rates of the two study treatment regimens at the completion of the study phase therapy in HIV negative and HIV positive patients.
- b) clinical and bacteriologic response rates for the two study treatment regimens among patients who began study phase therapy with signs and symptoms of tuberculosis or cultures positive for *M. tuberculosis* in HIV negative and HIV positive patients.
- c) rate of development of drug-resistant tuberculosis in the two study treatment regimens among study patients classified as a treatment failure or relapse in HIV negative and HIV positive patients.

The study design incorporated all three phases of treatment of tuberculosis, but was designed to evaluate the efficacy of two different treatment regimens used in the continuation phase of treatment. Definitions of the three phases of the study were:

- A. **Induction phase therapy:** Treatment of tuberculosis prior to randomization, lasting 8 to 10 weeks before patients were randomized and began the continuation/study phase of therapy. The treatment regimens and doses of all drugs used were the same as those currently recommended in the CDC, American Thoracic Society, and Infectious Diseases Society of American Treatment of Tuberculosis Publications and in the current FDA approved package inserts for the drugs. Directly observed therapy (DOT) was used for all treatments. All patients had to have documentation of completion of adequate induction phase therapy, which consisted of one of the following:
 - *Alternative 1:* DOT administration of INH, rifampin, and pyrazinamide (PZA) and either streptomycin or ethambutol for 8 weeks. In areas where the INH resistance rate was documented to be less than 4% or when susceptibility to INH and rifampin was demonstrated, ethambutol or streptomycin could be dropped from this induction phase regimen. Eight weeks of continuous therapy was the desired period for induction phase but any patient who completed 45 daily doses within 10 weeks was considered to have had adequate induction phase therapy and was eligible for this study.
 - *Alternative 2:* DOT administration of INH, rifampin, PZA, and either streptomycin or ethambutol for at least 14 consecutive doses followed by twice-weekly or thrice-weekly doses with the same drugs to complete induction phase. Eight weeks of continuous therapy was the desired period for induction phase but any patient who had completed 56 "daily" doses within 10 weeks was considered to have had adequate induction phase therapy and was eligible for this study.
- B. **Continuation phase therapy (the Study phase). Study Weeks 0 to 16-22.** After completing the induction phase therapy, eligible patients were randomly assigned to receive either 32 oral doses of twice weekly INH/rifampin [15 mg/Kg of INH (maximum: 900mg) plus 10 mg/Kg of rifampin (maximum: 600mg)] or 16 doses of once weekly INH/rifapentine [15 mg/Kg of INH (maximum: 900mg) plus 600mg of rifapentine], administered within a 22-week period. DOT was used for all treatments.
- C. **Follow-up phase. Study weeks 16-22 to 118.** The follow-up phase consisted of the 24-month period (104 weeks) after the planned completion of continuation/study phase therapy if there was no relapse, or the 12-month (52 weeks) period after diagnosis of relapse.

Patients (>18 years old; 1004 HIV negative; 74 HIV positive) were enrolled and treated at 29 geographical sites in the USA and Canada. Patients were required to have documented positive culture for *M. tuberculosis* from a pulmonary site (i.e., sputum, gastric lavage, BAL, or biopsy) and the organism had to be sensitive to both INH and rifampin by the agar proportion method of *in vitro* sensitivity testing. Patients with both pulmonary and extrapulmonary disease were eligible as were patients who had received antituberculous preventive therapy prior to randomization. Documentation of HIV status was required. Exclusion criteria included patients with only extrapulmonary tuberculosis, silicotuberculosis, or skeletal tuberculosis; patients with a history of more than 70 days of continuous antituberculous therapy immediately prior to randomization; and patients with concomitant disorders or conditions for which treatment with other drugs with antituberculosis activity (e.g., rifabutin for *Mycobacterium avium* Complex prophylaxis) were anticipated during the course of the study. Please note that the HIV positive arm of the study was closed and the data analyzed separately from the data from the HIV negative patient population.

Patients were evaluated for clinical (e.g., cough, fever, sweats, weight loss) and microbiological outcome during the continuation/study phase (study weeks 4, 8, 12, and 16) of treatment and during the follow-up period done at specified times. During the follow up period, patients were examined quarterly during the first year of follow-up (at approximately study week 28, 40, 52, and 64) and twice during the second year of follow-up (at approximately study week 92 and 116). Respiratory secretion specimens for AFB smear and culture were collected and patients were evaluated for signs and symptoms associated with tuberculosis by interview and clinical examination. If a patient was unable to produce sputum naturally, sputum was induced, if possible. For patients without a cough, naturally produced sputum was collected only during the first year of follow-up. If patients had clinical signs and symptoms associated with tuberculosis, they were evaluated as possible relapse cases. It also appears from the datasets that biopsy or autopsy samples were collected on some of the patients.

Important microbiological definitions used in this study include:

- a) **Bacteriological response:** two or more consecutive respiratory secretion cultures that had no growth of *M. tuberculosis* by the end of continuation/study phase therapy. One negative respiratory secretion culture, followed by documented failure to produce sputum, was also considered a bacteriologic response.

The number of attempts to produce sputum before considering the *M. tuberculosis* to be eradicated was not specified.

- b) **Relapse:** occurrence of tuberculosis after the completion of continuation/study phase therapy and before the end of the follow-up phase. Patients were followed for the first year after relapse.
- c) **Treatment failure:** failure to respond to study therapy either clinically and/or bacteriologically after 16 doses of INH/rifampin or after 8 doses of INH/rifapentine, but before the end of continuation/study phase therapy.

- d) **Reinfection:** bacteriologic relapse with RFLP mismatch (i.e., the RFLP banding pattern of the isolate obtained during study phase of therapy did not match the baseline RFLP from the same patient) where laboratory contamination was not suspected.

Microbiological criteria used to determine bacteriologic relapse or treatment failure consisted of at least one of the following:

- (i) a single respiratory secretion culture that was positive for *M. tuberculosis* with greater than 10 colonies on solid media. Please note that the basis for using 10 colonies as a threshold value is unclear.
- (ii) 2 or more respiratory secretion cultures with any colony count on solid media
- (iii) 2 or more respiratory secretion cultures obtained in liquid media that were positive for *M. tuberculosis* using radiometric techniques
- (iv) any culture that was positive for *M. tuberculosis* from an extrapulmonary site.

Microbiological Methods

Sputum samples were cultured at the site laboratory. All isolates from all patients (baseline and any relapse or treatment failure isolates) were sent to the CDC for confirmatory identification of organisms, *in vitro* susceptibility testing, and storage. Patients suspected of relapsing or failing treatment were evaluated for drug-resistance by *in vitro* susceptibility testing and RFLP analysis using matched baseline and failure/relapse isolates. Please note that at the time Study 22 was conducted, genotyping was not universally performed on all *M. tuberculosis* isolates.

Culture:

Sputum specimens were cultured by agar or broth methods and had AFB smears prepared at the individual study sites in a Clinical Laboratory Improvement Act (CLIA)-certified laboratory using FDA-approved tests. There was no effort to standardize methods across all laboratories. However, the identification of all *Mycobacterium* species was confirmed at the CDC using standard methodology (11,12). Most study sites cultured a single sputum specimen at each study visit. Radiometric detection of mycobacterial growth in liquid media was not universally used at the time this study was completed and it is unclear when the participating laboratories began using radiometric and/or both liquid and agar based media for all *M. tuberculosis* cultures. Most sites that performed broth cultures used an FDA approved radiometric method.

***In vitro* susceptibility testing:**

Rifampin was used for all *in vitro* susceptibility testing. Rifapentine was not included for testing because there was no approved method for testing rifapentine and CDC did not have rifapentine test material for use in *in vitro* susceptibility testing. *In vitro* susceptibility testing at the individual laboratories was done by either the radiometric method or by agar proportion method, or both. Testing by the agar proportion method was repeated by CDC on all isolates and the CDC results were used for study reports and for determination of drug resistance. Definitions related to *in vitro* susceptibility testing are:

- a) *Growth on culture*: Any positive culture by the radiometric method, or greater than 1% growth on solid media by the agar proportion method.
- b) *Drug resistance*: Growth in the presence of a critical concentration of a study drug. The critical concentrations were specified as 0.2µg/mL for INH resistance and 1µg/mL for rifampin. These are the currently recommended concentrations for these drugs in the FDA package inserts and CLSI standardized *in vitro* susceptibility tests for *M. tuberculosis*.

Please note that the results from specimens collected at the test of cure visits could be affected by the methodology used at the various laboratories. Given the uncertainty of microbiological procedures used at the various laboratories, the fact that only one sputum specimen was collected at each assessment visit in the majority of patients, and that a positive culture was based on either one culture with > 10 colonies or at least two positive sputum samples on liquid or solid media it is likely the number of microbiologically positive specimens is probably underestimated in this study, which could result in falsely low number of patients with microbiologically documented failure or relapse, regardless of treatment regimen.

RFLP analysis:

RFLP analysis is based on polymorphisms generated by variability in both the copy numbers and the chromosomal positions of IS6110 in isolates of *M. tuberculosis*. Different sites within the genome, including the DR, *ipl* and DK1 loci, have been reported as hot spots for the integration of IS6110. This suggests that the integration of IS6110 is not a truly random event and the frequency of transposition is influenced by the site of insertion within the mycobacterial genome (17). The identification of IS6110 insertion hot spots complicates the interpretation of IS6110 RFLP data because strains with low copy numbers of IS6110 integration may produce “false” clusters which must be subdivided by a second typing method independent of IS6110 (14,17). This is why it is necessary to use a second probe based on the plasmid pTBN12 to determine relatedness of strains of *M. tuberculosis* with less than seven bands on RFLP analysis. (14,17).

Since the RFLP pattern depends both on the number of copies of IS1660 in the strain and the location of the copies within the genome (and thus the size of the DNA fragments after endonuclease digestion) it is highly unlikely that two unrelated isolates would have identical RFLP patterns. For this reason, organisms are grown on agar and individual colonies picked for RFLP analyses. However, the possibility of reinfection with the same strain cannot be ruled out. Please note that this method would not be able to distinguish a mixed infection with multiple strains of *M. tuberculosis* if all strains were present in the bacterial sample used for the DNA extraction. A relatively large amount of DNA is needed for RFLP analysis so it is possible that selection of multiple colonies might be necessary. Selecting multiple colonies could increase the chances of using DNA from multiple strains or species of mycobacteria that have similar colonial morphology. Therefore, one of the limitations is that the results would depend on the number of colonies which are processed for such analyses.

Three parameters are critical for a standardized IS6110-based DNA RFLP system: the specificity of the restriction enzyme, the nature of the DNA probe, and the use of appropriate molecular

mass standards (19). The restriction enzyme *PvuII* cleaves the IS6110 sequence only once, resulting in IS6110-hybridizing fragments of at least 0.90 or 0.46 kb, depending on the IS6110 probe that is used. Since *M. tuberculosis* usually contains 8 to 20 copies of IS6110, the use of a DNA probe which overlaps both sides of the *PvuII* site would result in 16 to 40 bands. This large number of bands would result in overcrowded lanes with overlapping bands. Therefore, a DNA probe to the right of the *PvuII* site on the physical map is used as the hybridizing probe. The exact DNA sequence of the probe does not matter as long as the IS sequence used is to the right of the *PvuII* cleavage site. This reduces the number of IS6110-containing bands to about half of the maximum number possible (about 8-20 bands). Studies with multiple isolates from the same patients over long time periods have shown that the position and number of copies per strain of *M. tuberculosis*, and thus the RFLP patterns, have a half life of about 4.5 years (20, 22). Therefore, the stability of the RFLP pattern is sufficient to allow use of this technique in epidemiological studies, and to assess relatedness among strains of *M. tuberculosis* (11,14). However, its usefulness in differentiating relapse from new infection is unclear.

In study 22, RFLP analyses of paired baseline and failure/relapse isolates were used to help determine whether a patient suffered a true treatment failure or relapse or was re-infected with a different strain of *M. tuberculosis*. The standardized RFLP analysis method of Van Embden and Cave (19), which is stated to be an internationally standardized method, was used for genotyping the paired isolates at the CDC. Briefly, the technique used by the CDC entailed the growth of each clinical isolate of *M. tuberculosis*, extraction of DNA from each isolate, restriction endonuclease digestion of the DNA with *PvuII*, agarose gel separation of the DNA fragments followed by Southern blotting, and hybridization of the fragments containing the IS6110 sequence with a peroxidase-labeled nucleotide probe for the IS6110 element. It is unclear how many colonies from each patient isolate collected at different visits were processed for RFLP analyses. According to the published literature, all strains of *M. tuberculosis* contain at least one copy of the IS1600 sequence, and theoretically, this is the lower limit of detection for this assay. However, the performance characteristics of the assay were not submitted, so the true lower limit of detection cannot be ascertained.

In order to compare RFLP patterns between *M. tuberculosis* isolates run on different gels the size of each IS6110-hybridizing fragment was determined. This required the use of molecular size markers which span the 10- to 0.9-kb range of most IS6110-hybridizing fragments and included a combination of external and internal standards. External molecular size markers are run in two or three lanes of each gel. As an additional control, *PvuII* digested DNA from reference strain of *M. tuberculosis* Mt14323 (which gives 10 approximately evenly spaced bands of known size) was also used. The use of external markers is adequate for comparing small numbers of similar strains but the precision of molecular size determinations can be improved by inclusion of internal standards within each sample. This procedure 'normalizes' the banding pattern obtained on different gels thus allowing comparison of banding patterns obtained in different laboratories or at different times in the same laboratory. Finally, to be able to compare RFLP patterns obtained from different laboratories, a minimal resolving power of the gels is needed. At a given

agarose concentration, the resolving power mainly depends on the electrophoresis time. The standard method recommends using conditions such that the distance between the 0.9-kb marker (the approximate size of the smallest *Pvu*II IS-containing fragment) and the 10-kb marker is at least 10 cm (19). The current guidelines for RFLP analyses use the same criteria to distinguish relatedness as those used in Study 22, *i.e.*, patterns with 7 or more bands provide more specificity in distinguishing between isolates (14). For RFLP patterns containing less than 7 bands, it is necessary to use a second probe based on the plasmid pTBN12 to determine relatedness of strains of *M. tuberculosis* (14). Please note that the performance characteristics of the assays or photographs of RFLP patterns were not submitted for review and were not included in the published papers (5).

Results

A total of 1004 HIV negative patients and 74 HIV positive patients were enrolled in Study 22. The results of USPHS Study 22 have been reported in several published papers (1-7). Please note that treatment failure was defined as failure to respond to study therapy either clinically and/or bacteriologically after 16 doses of INH/rifampin or after 8 doses of INH/rifapentine, but before the end of continuation/study phase therapy. Relapse was defined as the occurrence of tuberculosis after the patient was cured during continuation/study phase therapy and before the end of the follow-up phase. Please note that all enrolled patients are included in this review.

The results from datasets (HIVneg; HIVpos, and S22.Myco) summarized in Table 8 show that in the HIV negative patient population the clinical and bacteriological failure rates (1%) were the same in both treatment groups. The clinical relapse rate was 8.4% in the rifapentine treatment group and 5% in the rifampin treatment group; the bacteriological relapse rate was 8.3% for the rifapentine treatment group and 5.1% for the rifampin treatment group.

Microbiological outcome data were available for all 74 HIV positive subjects whereas clinical outcome was measured in 71 patients (Table 8). Please note that this analysis is based on the microbiology dataset and includes 10 more patients than were reported in the published study by Vernon *et al.* (1), and (b) (4) based on 61 patients. The reason for excluding these 10 patients from analysis was not specified. However, for the purpose of this review, all 74 HIV positive patients were included. There were no failures in the HIV positive patient population. The clinical relapse rates between the two treatment regimens was similar in the HIV positive patients with a relapse rate of 16.6% in the rifapentine treatment group and 14.3% in the rifampin treatment group. The bacteriological responses are also similar, with the relapse rate of 17.1% in the rifapentine treatment group and 12.8% in the rifampin treatment group.

The sponsor combined relapses and treatment failures into one category termed ‘failure/relapse’ for data analysis. The results of the HIV positive patient population reported by Vernon *et al.* (1), and (b) (4) included results from 61 patients. The Vernon study states that failure/relapse occurred in 5 of 30 patients (16.7%) in the once weekly INH plus

rifapentine group and in 3 of 31 (9.7%) patients in the twice weekly INH plus rifampin group but the authors noted this was not a statistically significant difference in failure/relapse rates. Addition of the additional 10 patients to the analysis does not substantially alter the failure/relapse rates in either of the treatment arms (Table 8).

Table 8. Clinical Response and Bacteriologic Response¹ in Study 22 Patients

HIV Negative							
INH / Rifapentine Once Per Week				INH / Rifampin Twice Per Week			
Clinical Response (n = 502)		Bacteriologic Response (n = 481)		Clinical Response (n = 502)		Bacteriologic Response (n = 490)	
Success	Failure/Relapse	Success	Failure/Relapse	Success	Failure/Relapse	Success	Failure/Relapse
456	5 / 41 (5 / 42) ^a	436	5 / 40	474	5 / 23 (5 / 25) ^a	462	5/25
Failure/Relapse Rate 1% / 8.2% (1% / 8.4%) ^a		Failure/Relapse Rate 1% / 8.3%		Failure/Relapse Rate 1% / 4.6% (1% / 5%) ^a		Failure/Relapse Rate 1% / 5.1%	
Combined Rate: 9.2 % (9.3%)		Combined Rate: 9.3%		Combined Rate: 5.6% (6%)		Combined Rate: 6.1%	
HIV Positive							
INH / Rifapentine Once Per Week				INH / Rifampin Twice Per Week			
Clinical Response (n = 36)		Bacteriologic Response (n = 35)		Clinical Response (n = 35)		Bacteriologic Response (n = 39^b)	
Success	Failure/Relapse	Success	Failure/Relapse	Success	Failure/Relapse	Success	Failure/Relapse
30	0/6	29	0/ 6	30	0/5	34	0/5
Relapse Rate 16.6%		Relapse Rate 17.1%		Relapse Rate 14.3%		Relapse rate 12.8%	

¹Bacteriological response based on patients with cultural data available.
^a Numbers in parentheses for HIV negative patients are results including 3 additional patients identified in the microbiology datasets and used to generate Tables 9 and 10.
^b 4 additional HIV positive patients were listed in the microbiology dataset than in the clinical datasets.
Please note that a total of 17 additional patients (3 HIV negative; 14 HIV positive) were identified in the microbiology datasets than were identified in other datasets or were included in published results.

Results in Table 9 show the prevalence of relapse or treatment failures during the different phases of the study. Most poor clinical outcomes during the continuation phase of therapy were categorized as treatment failures since the mycobacterial cultures were positive and the patients were still receiving rifapentine or rifampin plus INH. Please note that there were no HIV positive individuals with failure during the continuation phase of treatment and there was no difference in the numbers of individuals with relapse in the two treatment arms during the follow-up phase in HIV positive patients. However, the total number of HIV positive patients with relapses was at least 6-fold lower than observed in the HIV negative patients.

Table 9. Prevalence of Culturally Verified Relapses and Treatment Failures During Continuation and Follow-up Phases of Therapy for Tuberculosis¹

Protocol Phase	Week of Protocol	Rifapentine		Rifampin		Totals	Relapse / Treatment Failure Category
		Number of Individuals		Number of Individuals			
		HIV -	HIV +	HIV-	HIV+		
Continuation Phase ²	4	2		1		3	3 Failures
	8	1		3		4	3 Failures/ 1 Relapse
	12	1				1	1 Relapse
	16 -18			1		1	1 Failure
Totals for Continuation Phase		4	0	5	0	9	7 Failures/ 2 Relapses
Follow-Up Phase ³	19	1				1	1 Failure
	24	1				1	1 Relapse
	25			1		1	1 Relapse
	28 - 30	18	2	10	1	31	30 Relapse/ 1 Failure
	31	1				1	1 Relapse
	34	1	1			2	2 Relapse
	35	1		1		2	2 Relapse
	36			1		1	1 Relapse
	37		1			1	1 Relapse
	40 - 42	4		4	2	10	9 Relapse / 1 Failure
	45			2		2	2 Relapse
	52-54	4	1	3		8	8 Relapse
	56	1				1	1 Relapse
	58				1	1	1 Relapse
	64-66	3	1			4	4 Relapse
	68	1				1	1 Relapse
	80			1		1	1 Relapse
92 -96	2		2	1	5	5 Relapse	
116 -120	3				3	3 Relapse	
Totals for Follow-up Phase		41	6	25	5	77	3 Failures/74 Relapse
Grand Totals		45 ⁴	6	30	5	86	10 Failures/ 76 Relapse

¹ All patients completed induction phase therapy prior to beginning the Continuation Phase of therapy

² Continuation phase of therapy, after randomization to the 2 treatment protocols

³ Follow-up phase is the 2 years following completion of the study phase of treatment.

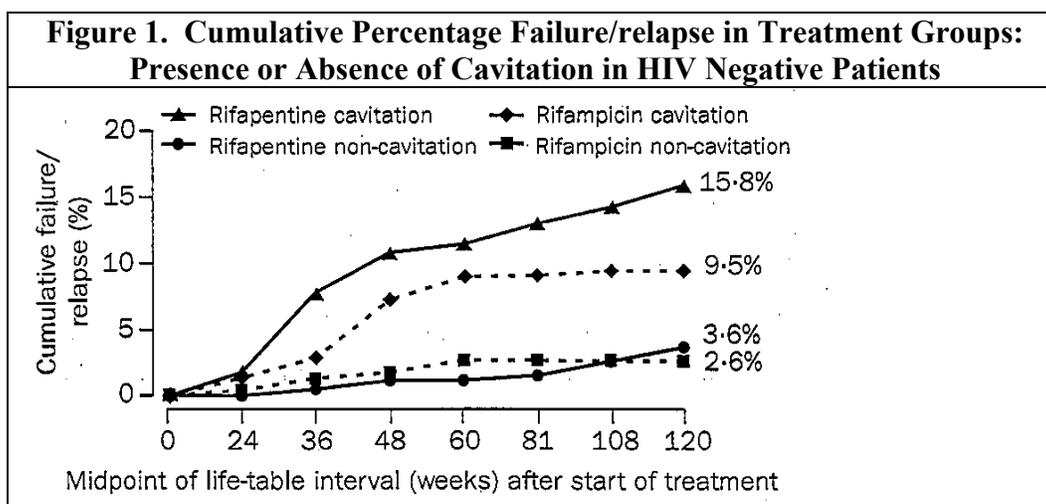
⁴ Note: In addition to these culturally verified failure/relapses, there were 2 HIV negative individuals who had negative cultures, but were considered as clinical failures/relapses. These individuals are identified in Table 10 and in parenthesis in Table 8.

Bold text in Week of Protocol column represents planned patient evaluations as per study protocol.

In the HIV negative individuals, all of the patients that had a failure or relapse had cavitory disease on chest radiograph. Cavitation was one of 5 risk factors which was statistically

associated with failure/relapse in HIV negative individuals (5). Overall, the proportion of HIV negative patients who had cavitations (462/1004) and who also suffered a failure/relapse was 63/1004 (6.3 %). Of these 63 HIV negative patients who suffered a failure/relapse, 41 were treated with rifapentine and 22 received rifampin. Thus, it appears that there is an association of failure/relapse and being treated with rifapentine. However, the association of cavitations with failure/relapse is not clear because 399/462 (86.4%) of HIV negative people with cavitations were treated successfully. In general, there was reduced overall efficacy of the rifapentine regimen, but rifapentine once a week and rifampin twice a week led to good results in HIV negative patients without cavitation (Figure 1).

The relationship between cavitory disease, rifapentine treatment, and failure/relapse was not apparent in HIV positive individuals, but the numbers of patients was small, so evaluation of these relationships could not be adequately assessed.



Although speculative because the sponsor did not provide details of the number or size of cavitations in individuals, the difference in the proportion of patients with failure/relapses in the two treatment groups at the 28 week time point could be explained by better penetration of rifampin into larger, or less numerous, cavitations because it is less bound to proteins than is rifapentine. Rifapentine is known to have a higher protein binding than does rifampicin (97% vs. 85%) and this could result in a suboptimal concentration of free active drug (26). This is supported by studies by Sirgel *et. al.* (9), in which he demonstrated that only the free drugs were active in lesions. The long replication times of the organisms would result in a ‘latent’ period in which cultures were negative but organisms were slowly growing until reaching high enough numbers to be detectable in sputa at the 28 week time period.

Table 10 summarizes the results of the analysis of the microbiology, relapse, and failure datasets (S22.Myco, S22.TRT_Rel, S22.TRT_fail). Culture results in this study were expressed as radiometric only (categorical data: positive or negative) or with categorical colony counts (< 10 colonies, > 10 colonies, or negative). The colony count data, when available, was helpful when assessing whether or not the patient suffered a failure/relapse (please see the microbiological

criteria used to determine bacteriologic relapse or treatment failure, above). Although some of these patients could have been eliminated from the analysis because they did not comply with the treatment regimen, died for reasons other than tuberculosis before completing treatment, or they had concurrent infections with other *Mycobacterium* species, the analysis included these patients to provide a conservative evaluation of the data and it appears that the sponsor also included most of these individuals in their analysis as failure/relapses. Table 11 does not include those patients who acquired infections solely with other *Mycobacterium* species during or following treatment for tuberculosis. These patients were considered treatment successes by the sponsor since the *M. tuberculosis* infection appears to have been eliminated, which is appropriate. A few patients relapsed with tuberculosis and also had infections with other mycobacteria as well, and these are noted in Table 11.

The numbers of patients with failure or relapse varied depending on which datasets were used for analyses. In Table 9, the clinical outcome data reported in the HIVneg and HIVpos datasets were used. In Tables 10 and 11, the clinical outcome data reported in the S22.TRT_Rel, S22.TRT_fail datasets were used. There were three individuals who were not identified as failure or relapses in the HIVneg or HIVpos datasets, but were listed as such in the S22.Myco, S22.TRT_Rel, S22.TRT datasets. These individuals are identified in Table 10. The changes in clinical response results if these individuals are included in the summary analyses are shown in parentheses in Table 8. Please note that the inclusion of these additional patients in the analyses did not substantially alter the results.

Table 10 . Summary Microbiology Data From Patients with Relapse or Treatment Failures in USPHS Study 22

Patient ID	Earliest Week Positive	Specimen	Culture Results	Sensitivity to Rifampin (agar proportion method)	Relapse / Failure Status	RFLP Identification Code ^a	Number of Bands for Comparison (pTBN12 results)
HIV Positive							
INH Plus Rifapentine Once Per Week (n= 6)							
13-0040	28	Expectorated sputum	Radiometric only	Resistant	Relapse	2281667	8
16-0370	37	Expectorated sputum	>10 colonies	Resistant	Relapse	2287482	4 (pTBN-12 ND)
51-0278	52	Induced Sputum	Radiometric only	Sensitive	Relapse	ND	ND
55-0059	66	Induced Sputum	Radiometric only	Sensitive	Relapse	ND	ND
60-0090	29	Blood	Radiometric only	Resistant	Relapse	2288991	4 (pTBN12=2903)
65-0356	34	Expectorated sputum	No Colony Count Done	Resistant	Relapse	2287242 2284807 2 separate pairs; mismatch	15 17 (pTBN12=2899)
INH Plus Rifampin Twice Per Week (n= 5)							
13-0022	28	Expectorated sputum	Radiometric only	Sensitive	Relapse	2287681	20
13-0472	40	Expectorated sputum	Radiometric only	Sensitive	Relapse	2287681	20
14-0302	92	Expectorated sputum	Radiometric only	Sensitive	Relapse	2280816 2281905 Mismatch	4 (pTBN-12 ND)
14-0377	40	Epididymis	Radiometric only	Sensitive	Relapse	2283358	8
62-0046 ^a	58	Hand Tenosynovium	Radiometric only	Sensitive	Relapse	1888025	10

Table 10 . Summary Microbiology Data From Patients with Relapse or Treatment Failures in USPHS Study 22

Patient ID	Earliest Week Positive	Specimen	Culture Results	Sensitivity to Rifampin (agar proportion method)	Relapse / Failure Status	RFLP Identification Code ^a	Number of Bands for Comparison (pTBN12 results)
HIV Negative							
INH Plus Rifapentine Once Per Week (n= 47)							
11-0760	52	Expectorated sputum	Radiometric only	Sensitive	Relapse	2283838	7
12-0784	116	Expectorated sputum	Radiometric only	Sensitive	Relapse	Yes NO RFLP Code	ND
12-0916	30	Induced Sputum	Radiometric only	Sensitive	Relapse	2284947	19
13-0360	28	Expectorated sputum	>10 colonies	Sensitive	Relapse	2289852	15
13-0741	29	Expectorated sputum	Radiometric only	Sensitive	Relapse	2283724	7
14-0932	40	Expectorated sputum	Radiometric only	Sensitive	Relapse	2289282	11
15-0766	40	Expectorated sputum	Radiometric only	Sensitive	Relapse	2281688	12
15-0845	28	Expectorated sputum	Radiometric only	Sensitive	Relapse	2281079	2 (pTBN-12 = H4285)
17-0274 ¹	Negative	Expectorated sputum and Induced Sputum	Negative	ND	Clinical Relapse	ND	ND
17-0365	34	Induced Sputum	>10 colonies	Sensitive	Relapse	2281645	11
17-1052	28	Expectorated sputum	Radiometric only	Sensitive	Relapse	ND	ND
18-0797	68	Expectorated sputum	< 10 colonies	Sensitive	Relapse	2281296	13
18-0879	64	Induced Sputum	>10 colonies	Sensitive	Relapse	2280786	2 (pTBN-12 ND)
18-0962 ^{2, b}	Negative	Expectorated sputum and Induced Sputum	Negative	ND	Clinical Relapse	ND	ND
18-1062 ³	12	Induced Sputum	>10 colonies	Sensitive	Clinical Relapse	2280347 2280377 Mismatch	10 15 (pTBN-12 ND)
20-0300	28	Expectorated sputum	Radiometric only	Sensitive	Relapse	2281705	3 (pTBN-12 ND)
20-0530	19	Expectorated sputum	Radiometric only	Sensitive	Treatment Failure	2283914	9
20-0563	52	Expectorated sputum	Radiometric only	Sensitive	Relapse	2281016	12
20-0642	28	Expectorated sputum	Radiometric only	Sensitive	Relapse	2287178	3 (pTBN-12 = H4288)
20-0721	31	Expectorated sputum	Radiometric only	Sensitive	Relapse	2287178	20
20-0722	28	Expectorated sputum	Radiometric only	Sensitive	Relapse	2283726	14
20-0867	52	Expectorated sputum	Radiometric only	Sensitive	Relapse	2280345	2 (pTBN-12 ND)
20-0974	28	Expectorated sputum	Radiometric only	Sensitive	Relapse	2281834	15
20-0979	92	Expectorated sputum	< 10 colonies	Sensitive	Relapse	Yes NO RFLP Code	ND
21-0008	52	Expectorated sputum	>10 colonies	Sensitive	Relapse	2284574	12
21-0130	116	Expectorated sputum	>10 colonies	Sensitive	Relapse	2281585	8

Table 10 . Summary Microbiology Data From Patients with Relapse or Treatment Failures in USPHS Study 22

Patient ID	Earliest Week Positive	Specimen	Culture Results	Sensitivity to Rifampin (agar proportion method)	Relapse / Failure Status	RFLP Identification Code ^a	Number of Bands for Comparison (pTBN12 results)
22-0169	28	Expectorated sputum	Radiometric only	Sensitive	Relapse	2284567	10
52-0382	8	Expectorated sputum	>10 colonies	Sensitive	Treatment Failure	2284795	9
53-0493	40	Expectorated sputum	Radiometric only	Sensitive	Treatment Failure	2287100	14
53-0509	29	Expectorated sputum	Radiometric only	Sensitive	Relapse	2281258	12
53-0929	28	Expectorated sputum	>10 colonies	Sensitive	Relapse	2289041	6 (pTBN-12 ND)
54-0306 ⁴	4	Expectorated sputum	Radiometric only	Sensitive	Treatment Failure	2284569	13
55-0552 ⁵	40	Expectorated sputum	Radiometric only	Sensitive	Clinical relapse	2287310	3 (pTBN-12 ND)
58-0664	35	Expectorated sputum	>10 colonies	Sensitive	Relapse	2281893	11
58-0976	56	Expectorated sputum	>10 colonies	Sensitive	Relapse	ND	ND
59-1074 ⁶	4	Expectorated sputum	Radiometric only	Resistant	Treatment Failure	2289207	8
60-0056	28	Expectorated sputum	Radiometric only	Sensitive	Relapse	2281643	14
61-0815	64	Expectorated sputum	>10 colonies	Sensitive	Relapse	2283437	8
62-0167	28	Expectorated sputum	Radiometric only	Sensitive	Relapse	ND	ND
62-0219	28	Expectorated sputum	Radiometric only	Sensitive	Relapse	2287345 2281872 2 separate pairs Mismatch	12 11
62-0354	28	Expectorated sputum	Radiometric only	Sensitive	Relapse	2287356	13
63-0820	28	Expectorated sputum	>10 colonies	Sensitive	Relapse	2281966 2283728 Mismatch	4 20 (pTBN-12 = H4280)
64-0417	28	Expectorated sputum	>10 colonies	Sensitive	Relapse	2281016	12
66-0381	92	Expectorated sputum	>10 colonies	Sensitive	Relapse	2284737 2280759 2289033 3 separate patterns, no pairs	12 12 01 (pTBN-12 ND)
68-0835	116	Expectorated sputum	Radiometric only	Sensitive	Relapse	ND	ND
68-1034	24	Expectorated sputum	Radiometric only	Sensitive	Relapse	2282786	19
70-0942 ⁷	64	Expectorated sputum	< 10 colonies	ND	Clinical Relapse	ND	ND
INH Plus Rifampin Twice Per Week (n= 30)							
11-0763	29	Expectorated sputum	Radiometric only	Sensitive	Relapse	2287847	13
13-0724 ⁸	8	Expectorated sputum	Radiometric only	Sensitive	Relapse	2283725	1 (pTBN-12 =

Table 10 . Summary Microbiology Data From Patients with Relapse or Treatment Failures in USPHS Study 22

Patient ID	Earliest Week Positive	Specimen	Culture Results	Sensitivity to Rifampin (agar proportion method)	Relapse / Failure Status	RFLP Identification Code ^a	Number of Bands for Comparison (pTBN12 results)
							H4290)
14-0094	28	Expectorated sputum	>10 colonies	Sensitive	Relapse	2284238	5 (pTBN-12 = 2895)
14-0185	52	Expectorated sputum	>10 colonies	Sensitive	Relapse	2287124	2 (pTBN-12 = 2897)
15-0833 ⁹	4	Expectorated sputum	Radiometric only	ND	Treatment Failure	2284613	2 (pTBN-12 ND)
17-0246	80	Expectorated sputum	>10 colonies	Sensitive	Relapse	2287721	9
18-0587	28	Induced Sputum	Radiometric only	Sensitive	Relapse	2287322	9
20-0201	40	Expectorated sputum	Radiometric only	Sensitive	Relapse	2284613	2 (pTBN-12 =2899)
20-0802	35	Expectorated sputum	Radiometric only	Sensitive	Relapse	2283264	10
20-0877	25	Expectorated sputum	Radiometric only	Sensitive	Relapse	2280993	10
20-0906 ^b	17	Expectorated sputum	Radiometric only	Sensitive	Treatment Failure	2280906 2286994 Mismatch	2 21 (pTBN-12 ND)
20-0955	28	Expectorated sputum	Radiometric only	Sensitive	Relapse	2281834	15
20-1000	28	Expectorated sputum	Radiometric only	Sensitive	Relapse	2280786	2 (pTBN-12 =H4278)
20-1030	28	Expectorated sputum	Radiometric only	Sensitive	Relapse	2280786	2 (pTBN-12 ND)
21-0254	28	Expectorated sputum	>10 colonies	Sensitive	Relapse	2284574	12
21-0789	52	Expectorated sputum	>10 colonies	Sensitive	Relapse	2281768	12
51-0230	42	Expectorated sputum	Radiometric only	Sensitive	Relapse	2282257	3 (pTBN-12 =H4282)
51-0691	52	Expectorated sputum	Radiometric only	Sensitive	Relapse	2281164	20
54-0434	28	Expectorated sputum	>10 colonies	Sensitive	Treatment Failure	2281766	9
58-0443	45	Expectorated sputum	>10 colonies	Sensitive	Relapse	2283439	10
60-0279	41	Expectorated sputum	Radiometric only	Sensitive	Relapse	2287258	3 (pTBN-12 =2905)
61-0031	45	Expectorated sputum	>10 colonies	Sensitive	Relapse	2284613	2 (pTBN-12 =2899)
61-0644	28	Expectorated sputum	>10 colonies	Sensitive	Relapse	2287068	10
62-0195	8	Expectorated sputum	Radiometric only	Sensitive	Treatment Failure	2284209	6 (pTBN-12 ND)
62-0463	41	Expectorated sputum	Radiometric only	Sensitive	Relapse	2287965	9
63-0252	28	Expectorated sputum	>10 colonies	Sensitive	Relapse	2287660	14
64-0553 ¹⁰	92	Expectorated sputum	>10 colonies	Sensitive	Relapse	2287266	10
64-0896	36	Induced Sputum	>10 colonies	Resistant	Relapse	2289162	11
66-0460 ^b	92	Expectorated sputum	>10 colonies	Sensitive	Relapse	2285641 2280749 Mismatch	13 10

Table 10 . Summary Microbiology Data From Patients with Relapse or Treatment Failures in USPHS Study 22

Patient ID	Earliest Week Positive	Specimen	Culture Results	Sensitivity to Rifampin (agar proportion method)	Relapse / Failure Status	RFLP Identification Code ^a	Number of Bands for Comparison (pTBN12 results)
66-0946 ¹¹	8	Expectorated sputum	>10 colonies	ND	Treatment Failure	ND	ND

^a RFLP Identification Code is a numerical code used to identify which bands are present in RFLP analysis. Identical codes for both baseline and failure/relapse isolates indicate the strain of *M. tuberculosis* isolated at failure/relapse matches the baseline strain. If < 7 bands were present, then pTBN12 analysis was required to determine relatedness of the strains.

^b Not identified as failure/relapse in analysis HIVneg or HIVpos datasets

¹ Clinical relapse; cultures negative; smears positive, died of drug overdose

² Clinical relapse; culture of biopsy material confirmed organisms in lymph nodes

³ Clinical relapse; confirmed by culture. Also had *M. gordonae* at 8 weeks.

⁴ Treatment Failure: multiple cultures positive after treatment began, especially weeks 4-16; Treatment regimen changed.

⁵ Clinical relapse; Patient self-reported relapse due to persistent cough; confirmed by culture

⁶ Treatment Failure; multiple cultures positive, and at week 9, resistant to rifampin; Weeks 12-116 had *M. chelonae* and/or *M. fortuitum*; Treatment regimen changed about week 20.

⁷ Clinical relapse; confirmed by culture

⁸ Special evaluation by medical panel; judged relapse, but patient didn't always take medication

⁹ Treatment Failure; cultures remained positive at 4, 8, 12 weeks, treatment modified

¹⁰ Patient relapsed, but didn't take medication; dropped from study

¹¹ Patient died of adenocarcinoma soon after beginning study phase of treatment

ND = Not Done

***In vitro* susceptibility testing:**

Rifampin was used for *in vitro* susceptibility testing by the agar proportion method using the CLSI reference method (13). Testing of rifapentine was not included. Only categorical results (sensitive, resistant, or not tested) were reported in the datasets. There was no association between failure or relapse and development of rifampin resistance in HIV negative individuals as there was only one resistant strain of *M. tuberculosis* in each treatment group (2/77 or 2.6 %; Table 10). However, in HIV positive patients, 4 of the 6 relapses (66.6%) from the once-weekly INH/rifapentine group involved *M. tuberculosis* strains that were resistant to rifampin. Three of the 4 paired baseline and relapse isolates were identical by RFLP analysis (Table 10). One of the individuals with a resistant strain of *M. tuberculosis* had two separate organisms identified by RFLP analysis (Table 10). None of the isolates from failure or relapse patients in the rifampin treatment group were resistant (Table 10). This strongly suggests that development of resistance to rifampin is more common in HIV positive patients treated with rifapentine than in those treated with rifampin. These data are consistent with other studies of documented acquired rifamycin monoresistance in HIV seropositive adults who fail or relapse after treatment with intermittent regimens with INH and rifamycins (27-29)

RFLP analyses

RFLP analysis was done at the CDC, but not all isolates from patients who had relapses or treatment failures were analyzed (Table 10). The RFLP patterns were expressed as numerical identification codes reflecting the RFLP pattern and recorded for the paired isolates from each patient. This allowed the RFLP patterns to be easily compared. The sponsor provided a spreadsheet containing the results of the RFLP analyses (Tables 10 and 11). Please note that 2 sets of results did not have RFLP identification codes reported and pTBN12 typing was not done

in all instances when there were less than seven bands to use for comparison between pairs of isolates, so these results are not included in Table 11. In the HIV negative patients, it is clear that failure or relapse was more common than re-infection (Tables 10 and 11).

Results	HIV Positive		HIV Negative	
	Rifapentine (n=6)	Rifampin (n=5)	Rifapentine (n=33)	Rifampin (n=26)
Treatment Failure or Relapse ¹	3/6	4/5	29/33	24/26
Possible Re-infection (Possible Mixed Infection) ² RFLP Not Done	1/6 (1/6) 2/6	1/5	4/33 (1/33)	2/26

¹ Same RFLP pattern in paired baseline and failure/relapse isolates
² Different RFLP patterns in paired baseline and failure/relapse isolates. When patients had two sets of paired isolates with different RFLP patterns, it is impossible to determine whether or not they were re-infected with a different strain of *M. tuberculosis* or if they had a mixed infection with two strains of *M. tuberculosis*. The numbers of possible mixed infections are shown in parentheses.

In a study published by Jasmer *et al.* (3), isolates collected from patients enrolled in study 22 and another study (study 23) were evaluated by RFLP analysis using the same method described above. Please note in study 23 rifabutin was used in the continuation phase of therapy instead of either rifapentine or rifampin. However, it is impossible to separate the data from the two clinical studies.

Emergence of other mycobacterial isolates:

All *Mycobacterium* species were identified as to species at the CDC using standard methodology. There were a large number of isolates of other *Mycobacterium* species besides *M. tuberculosis* from the patients in this study (Table 12). Many of the patients had multiple species recovered from one specimen. Since mycobacteria are common environmental contaminants, for most patients, these isolations are considered incidental findings not associated with disease (12). Overall, 196 of 516 (37.9 %) patients with evaluable microbiology results in the once a week INH/rifapentine treatment group and 175 of 529 (33.1 %) in the twice a week INH/rifampin treatment group had other *Mycobacterium* sp. isolated over the course of the study. The numbers of total patients in each treatment arm differs from that shown in Table 8 because all patients who had microbiology results reported in the microbiology dataset were used to generate this data rather than just those used for the clinical outcome assessment. In the rifapentine treatment group, 36 patients had multiple isolates over time (18.3%), and in the rifampin treatment group 38 patients had multiple isolates during the study (20.6%). There were 21 patients who repeatedly had the same species recovered at multiple times. The organisms which were associated with these repeated isolations are indicated in Table 10.

Table 12. Summary of Non-Tuberculosis <i>Mycobacterium</i> species Isolated from Study 22 Patients			
<i>Mycobacterium</i> species¹	Rifapentine (196 Patients)	Rifampin (175 Patients)	Totals
<i>M. gordonae</i> ²	71	67	138
<i>M. avium</i> Complex ²	31	41	72
<i>M. fortuitum</i> ²	33	25	58
<i>M. avium - intracellulare</i> ²	16	5	21
<i>M. chelonae</i>	10	5	15
<i>M. kansasii</i>	6	5	11
<i>M. terrae</i>	2	1	3
Other <i>Mycobacterium</i> species	27	30	57
¹ Some patients had more than one organism; most isolates were from sputum ² Multiple isolates from individuals over time			

The frequent presence of *Mycobacterium* sp. other than *M. tuberculosis* in these individuals is surprising and unexpected. Although all of the non-tuberculous mycobacteria listed in Table 12 have been associated with disease, they are also common environmental contaminants. The effect of colonization or co-infection with these non-tuberculous mycobacteria upon the clinical outcomes of the patients in Study 22 cannot be evaluated from the study design or from data provided by the sponsor. However, recent studies report a false positive/cross contamination rate for *M. tuberculosis* within individual laboratories of up to 3% of cultures (30). Pseudo-outbreaks of non-tuberculous mycobacteria are well documented and have been associated with such diverse sources as ice machines, community water supplies, hot tubs, nail salons, non-sterile containers, and cosmetic surgery (31). Contamination of clinical specimens can occur at the time of collection of the specimen, during specimen preparation or transportation to the laboratory, or within the laboratory. Sporadic contamination usually occurs at the time of specimen collection and is related to errors in specimen collection from the patient or transfer to an appropriate collecting device. The frequency of this type of contamination is variable. When these results are examined as a whole, there does not appear to be any relationship between isolation of non-tuberculous mycobacteria and treatment group or with the repeated isolation of a specific organism with treatment group. Since the evaluation of patients for possible failure or relapse required the isolation and identification of any *Mycobacterium* sp. and did not rely solely upon clinical parameters, the presence of these non-tuberculosis mycobacteria in the study patients does not affect the overall results of the study.

4.2 Interpretive Criteria

The FDA approved package insert for rifapentine does not include breakpoints for *in vitro* antimycobacterial susceptibility testing, and no data have been submitted to the FDA to establish breakpoints. The sponsor's small Phase 4 studies regarding stability of rifapentine in broth medium under conditions used for *in vitro* susceptibility assays showed a large reduction in antibiotic concentration by seven days incubation at 35° C using *Bacillus subtilis* as the target

organism in the testing. The relevance of this for activity against *M. tuberculosis* was not evaluated.

5 DISCUSSION

This submission is an efficacy supplement submitted in support of proposed labeling changes to include the results from HIV seropositive and seronegative patients in CDC Study 22.

Previous microbiology reviews (6/12/1998 and 8/26/2000) and data in Tables 1-3 indicate that rifapentine MIC values are usually 2 to 4 fold less than those of rifampin when tested against laboratory and clinical strains of *M. tuberculosis* and that there is a high cross resistance between rifapentine and rifampin that is directly related to specific mutations in the *rpoB* gene (Previous reviews and Tables 4-7). There are concerns about the ability of the radiometric methods to detect low numbers of rifapentine and rifampin resistant organisms. In published papers and in previous microbiology reviews it was noted that radiometric methods could not detect resistance to either rifampin or rifapentine if the culture contained less than 10% resistant bacteria. This is an unacceptable lack of sensitivity in the assays for these two drugs. Even though the agar proportion method for *in vitro* sensitivity testing takes 3 to 4 weeks, it is more accurate in detecting low levels of resistance and it provides data on the actual proportion of resistant bacteria.

Study 22 was performed at 29 geographical sites within the USA and Canada and there was no attempt to standardize the microbiological methods used at the participating laboratories. In the HIV negative patient population the failure rate (1%) was the same in both treatment groups regardless of whether the clinical response or bacteriological response was used. The clinical relapse rate was 8.4% in the rifapentine treatment group and 5% in the rifampin treatment group. When the bacteriological responses were used, the relapse rate was 8.3% for the rifapentine treatment group and 5.1% for the rifampin treatment group. There were no failures in the HIV positive patient population. The clinical relapse rates between the two treatment regimens appears to be similar in the HIV positive patients with a relapse rate of 16.6% in the rifapentine treatment group and 14.3% in the rifampin treatment group. The bacteriological responses are also similar, with the relapse rate of 17.1% in the rifapentine treatment group and 12.8% in the rifampin treatment group. Given the uncertainty of microbiological procedures used at the various laboratories, the fact that only one sputum specimen was collected at each assessment visit in the majority of patients, and that a positive culture was based on either one culture with >10 colonies or at least two positive sputum samples on liquid or solid media it is likely the number of microbiologically positive specimens is probably underestimated in this study, which could result in falsely low number of patients with microbiologically documented failure or relapse, regardless of treatment regimen.

Genotyping by IS6110 RFLP analysis of paired baseline and failure and relapse isolates of *M. tuberculosis* was done according to the international standard methodology (3;19) at the CDC for epidemiological purposes, but not all isolates from patients who had relapses or treatment failures were analyzed (Table 10). The RFLP patterns were expressed as numerical identification codes reflecting the RFLP pattern and recorded for the paired isolates from each

patient. This allowed the RFLP patterns to be easily compared. The main objective of these analyses was to determine whether the failures and relapses which occurred were true failures or relapses or were reinfections with a different strain of *M. tuberculosis* from the one each patient had prior to treatment. Rates of relapse were comparable among HIV positive and HIV negative patients but reinfection could not be assessed because of the limitations of the information available.

In vitro susceptibility was determined only by testing isolates against rifampin. Rifapentine was not tested. The number of rifampin resistant isolates was too small to establish any relationship with clinical or microbiological outcome. No correlation was observed between *in vitro* susceptibility results and RFLP analyses. Three of the 4 paired baseline and relapse isolates from HIV positive patients were identical by RFLP analysis. One of the individuals with a resistant strain of *M. tuberculosis* had two separate organisms identified by RFLP analysis.

The frequent presence of *Mycobacterium* sp. other than *M. tuberculosis* in these individuals was surprising and unexpected. Although colonization or co-infection with these organisms may have affected clinical parameters, the evaluation of patients for possible failure/relapse required the isolation and identification of any *Mycobacterium* sp. present and did not rely solely upon clinical parameters. Therefore, the presence of these non-tuberculosis mycobacteria in the study patients does not affect the overall results of the study.

6 THE LABEL

6.1 Sponsor's version of the label

The sponsor's proposed changes to the current approved label are shown below. Deletions in the current approved package insert are shown as strikeout and additions are shown as double underlined.

Microbiology

Mechanism of Action

Rifapentine, a cyclopentyl rifamycin, inhibits DNA-dependent RNA polymerase in susceptible strains of *Mycobacterium tuberculosis* but not in mammalian cells. At therapeutic levels, rifapentine exhibits bactericidal activity against both intracellular and extracellular *M. tuberculosis* organisms. Both rifapentine and the 25- desacetyl metabolite accumulate in human monocyte-derived macrophages with intracellular/extracellular ratios of approximately 24:1 and 7:1, respectively.

Resistance Development

In the treatment of tuberculosis (see INDICATIONS AND USAGE), a small number of resistant cells present within large populations of susceptible cells can rapidly become predominant. Rifapentine resistance development in *M. tuberculosis* strains is principally due to one of several single point mutations that occur in the *rpoB* portion of the gene coding for the beta subunit of the DNA-dependent RNA polymerase. The incidence of rifapentine resistant mutants in an otherwise susceptible population of *M. tuberculosis* strains is approximately one in 10^7 to 10^8 bacilli. Due to the potential for resistance development to rifapentine, appropriate susceptibility tests should be performed in the event of persistently positive cultures (b) (4)

M. tuberculosis organisms resistant to other rifamycins are likely to be resistant to rifapentine. A high level of cross-resistance between rifampin and rifapentine has been demonstrated with *M. tuberculosis* strains. Cross-resistance does not appear between rifapentine and non-rifamycin antimycobacterial agents such as isoniazid and streptomycin.

In Vitro Activity of Rifapentine against *M. tuberculosis*

Rifapentine and its 25-desacetyl metabolite have demonstrated in vitro activity against rifamycin-susceptible strains of *Mycobacterium tuberculosis* including cidal activity against phagocytized *M. tuberculosis* organisms grown in activated human macrophages.

In vitro results indicate that rifapentine MIC values for *M. tuberculosis* organisms are influenced by study conditions. Rifapentine MIC values were substantially increased employing egg-based medium compared to liquid or agar-based solid media. The addition of Tween 80 in these assays has been shown to lower MIC values for rifamycin compounds. In mouse infection studies a therapeutic effect, in terms of enhanced survival time or reduction of organ bioburden, has been observed in *M. tuberculosis*-infected animals treated with various intermittent rifapentine containing regimens. Animal studies have shown that the activity of rifapentine is influenced by dose and frequency of administration.

Susceptibility testing for *Mycobacterium tuberculosis*

Breakpoints to determine whether clinical isolates of *M. tuberculosis* are susceptible or resistant to rifapentine have not been established. The clinical relevance of rifapentine in vitro susceptibility test results for other mycobacterial species has not been determined.

6.2 Comments

1. Based on current format for PLR labeling the Microbiology information should be in section 12.4 which includes the mechanism of action.
2. In section 12.1 “Mechanism of Action” should state “Rifapentine, a cyclopentyl rifamycin, is an antimycobacterial agent” and reference be made to Clinical Pharmacology, Microbiology (12.4).
3. Some of the text in subsection “Resistance Development” is in bold. The reason for having the text in bold is unclear. It is recommended that text should not be in bold font.
4. In Resistance Development section, it is stated in paragraph 2 that “Cross-resistance does not appear between rifapentine and non-rifamycin antimycobacterial agents such as isoniazid and streptomycin”. The reason for referring to “such as isoniazid and streptomycin” is unclear and should be deleted.
5. In section: “In Vitro Activity of Rifapentine against *M. tuberculosis*”, the reason for giving experimental details such as “In vitro results indicate that rifapentine MIC values for *M. tuberculosis* organisms are influenced by study conditions. Rifapentine MIC values were substantially increased employing egg-based medium compared to liquid or agar-based solid media. The addition of Tween 80 in these assays has been shown to lower MIC values for rifamycin compounds” is unclear. This information is in the CLSI document which has been referenced. Therefore, these statements should be deleted.
6. Reference to *in vitro* susceptibility testing in Clinical Studies section from NCCLS M24-T to CLSI Method M24-A should be updated and reference be added at end of labeling.

7. There are several places in the labeling in which “rifamycin” is used when the more specific drug “rifampin” should be used because that is what was tested.
8. Given the uncertainty of microbiological procedures used at the various laboratories, the fact that only one sputum specimen was collected from the majority of patients at each assessment visit, and that a positive culture was based on either one culture with > 10 colonies or at least two positive sputum samples on liquid or solid media it is likely the number of microbiologically positive specimens is probably underestimated in the study. . This information should be added to the labeling in the Clinical Studies Section 14.
9. There are several instances in the Clinical Studies Section of the proposed labeling when the term ‘rifamycin’ is used where using the more specific drug ‘rifampin’ is more correct because only rifampin was used for *in vitro* susceptibility testing.

6.3 FDA’s Version of the Label

Based on the above comments, the package insert has been modified. The text is arranged as per PLR format and additions are double underlined and deletions are shown as strike out.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rifapentine, a cyclopentyl rifamycin, is an antimycobacterial agent [see *Clinical Pharmacology, Microbiology* (12.4)].

12.4 Microbiology

Mechanism of Action

Rifapentine, a cyclopentyl rifamycin, inhibits DNA-dependent RNA polymerase in susceptible strains of *Mycobacterium tuberculosis* but not in mammalian cells. At therapeutic levels, rifapentine exhibits bactericidal activity against both intracellular and extracellular *M. tuberculosis* organisms. Both rifapentine and the 25- desacetyl metabolite accumulate in human monocyte-derived macrophages with intracellular/extracellular ratios of approximately 24:1 and 7:1, respectively.

In Vitro Activity of Rifapentine against *M. tuberculosis*

Rifapentine and its 25-desacetyl metabolite have demonstrated *in vitro* activity against rifamycin-susceptible strains of *Mycobacterium tuberculosis* including cidal activity against phagocytized *M. tuberculosis* organisms grown in activated human macrophages. ~~In vitro results indicate that rifapentine MIC values for *M. tuberculosis* organisms are influenced by study conditions. Rifapentine MIC values were substantially increased employing egg based medium compared to liquid or agar based solid media. The addition of Tween 80 in these assays has been shown to lower MIC values for rifamycin compounds.~~

The correlation between rifapentine MICs and clinical cure has not been established. Interpretive criteria/breakpoints to determine whether clinical isolates of *M. tuberculosis* are susceptible or resistant to rifapentine have not been established.

***In Vivo* Activity**

In mouse infection studies a therapeutic effect, in terms of enhanced survival time or reduction of organ bioburden, has been observed in *M. tuberculosis*-infected animals treated with various intermittent rifapentine containing regimens. Animal studies have shown that the activity of rifapentine is influenced by dose and frequency of administration.

Drug Resistance Resistance Development

In the treatment of tuberculosis (~~see INDICATIONS AND USAGE~~), a small number of resistant cells present within large populations of susceptible cells can rapidly become predominant. Rifapentine resistance development in *M. tuberculosis* strains is principally due to one of several single point mutations that occur in the *rpoB* portion of the gene coding for the beta subunit of the DNA-dependent RNA polymerase. The incidence of rifapentine resistant mutants in an otherwise susceptible population of *M. tuberculosis* strains is approximately one in 10⁷ to 10⁸ bacilli. ~~Due to the potential for resistance development to rifapentine, appropriate susceptibility tests should be performed in the event of persistently positive cultures~~ (b) (4)

M. tuberculosis organisms resistant to other rifamycins are likely to be resistant to rifapentine. A high level of cross-resistance between rifampin and rifapentine has been demonstrated with *M. tuberculosis* strains. Cross-resistance does not appear between rifapentine and non-rifamycin antimycobacterial agents ~~such as isoniazid and streptomycin~~.

In Vitro Susceptibility testing for *Mycobacterium tuberculosis*

~~Breakpoints to determine whether clinical isolates of *M. tuberculosis* are susceptible or resistant to rifapentine have not been established. The clinical relevance of rifapentine in vitro susceptibility test results for other mycobacterial species has not been determined~~

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8 RECOMMENDATIONS

This NDA supplement is approvable with respect to microbiology pending an accepted version of the label.

Maureen K. Davidson, PhD
Microbiologist, DSPTP

CONCURRENCES:

MicroTL _____ Signature _____ Date

CC:
Project Manager\ Hyun Son

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

/s/

Maureen K Davidson
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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-024/S008

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA: 21-024	Submission Date(s): 07/12/2007
Drug	Rifapentine tablets
Trade Name	Priftin®
Reviewers	Seong H, Jang, Ph.D. (Clinical Pharmacology)
OCP Team Leader	Philip M. Colangelo, Pharm.D., Ph.D.
OCP Division	DCP4
OND Division	DSPTP
Sponsor	Sanofi-Aventis, Inc.
Submission Type; Code	Efficacy Supplement; SE7
Formulation; Strength(s)	Tablets: 150 mg
Indication	Treatment of pulmonary tuberculosis caused by <i>Mycobacterium tuberculosis</i> in combination with one or more anti-tuberculosis drugs
Dosage and Administration	Initial phase for 2 months: 600 mg twice weekly Following Initial phase: 600 mg once weekly

Rifapentine (Priftin®) was approved for the treatment of pulmonary tuberculosis caused by *Mycobacterium tuberculosis* (MTB) on June 22, 1998. This approval was based upon the accelerated approval regulations (21 CFR 314 Subpart H) where the 6-month relapse rate was used as a surrogate for the 2-year relapse rate. The accelerated approval commitments in order to achieve full approval status included the following:

1. The final Clinical Study Report issued upon completion of Clinical Study 008 will be submitted to the Agency for review. In this final report both safety and efficacy data for the 2 years of follow-up will be included.
2. Hoechst Marion Roussel 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-positive subjects who relapsed in the rifapentine treatment arm. It was agreed, since this study was being conducted by CDC under a separate IND that CDC would submit study results upon completion of the study.

The Applicant submitted the final report of Study 008 in December 1999 thus meeting the first accelerated approval requirement.

The current submission contains the results of Study USPHS 22 and represents the second accelerated approval commitment for rifapentine. Study USPHS 22 contained a PK sub-study to compare PK of isoniazid, rifapentine and rifampin between once-weekly isoniazid/rifapentine vs. twice-weekly isoniazid/rifampin in HIV-seronegative patients. The results of this PK sub-study was submitted as a published literature, entitled "Low

isoniazid concentrations and out come of tuberculosis treatment with once-weekly isoniazid and rifapetine.” The abstract of this published literature is attached at the end of this review. This PK sub-study was reviewed and found to adequately support a fulfillment of the second accelerated approval commitment from the perspective of Clinical Pharmacology.

The reviewing Medical Officer (Dr. Regina Alivisatos) recommended that this submission was made in compliance with the second and final accelerated approval commitment required by the Agency (21 CFR 3.14 subpart H) in the June 1998 approval letter.

Recommendations

From the perspective of Clinical Pharmacology, the PK sub-study of Study USPHS 22 in this submission is adequate to recommend a fulfillment of the second accelerated approval commitment required by the Agency (21 CFR 3.14 subpart H) in the June 1998 approval letter.

Seong H. Jang, Ph.D.
Reviewer
Clinical Pharmacology
DCP4/OCP

Concurrence

Phil Colangelo, Pharm.D., Ph.D.
Team Leader
Clinical Pharmacology
DCP4/OCP

APPENDIX

1. PK sub-study of Study USPHS 22: Abstract of a published literature

Low Isoniazid Concentrations and Outcome of Tuberculosis Treatment with Once-Weekly Isoniazid and Rifapentine. Marc Weiner, William Burman, Andrew Vernon, Debra Benator, Charles A. Peloquin, Awal Khan, Stephen Weis, Barbara King, Nina Shah, Thomas Hodge, and the Tuberculosis Trials Consortium. *Am. J. Respir. Crit Care Med.* 167:1341-1347, 2003

To understand why once-weekly isoniazid/rifapentine therapy for tuberculosis was less effective than twice-weekly isoniazid/rifampin, we studied human immunodeficiency virus–seronegative patients with either failure (n = 4), relapse (n = 35), or cure (n = 94), recruited from a comparative treatment trial. In multivariate analyses that were adjusted for severity of disease, low plasma concentrations of isoniazid were associated with failure/relapse with once-weekly isoniazid/rifapentine (median isoniazid area under the concentration–time curve for 12 hours after the dose [AUC_{0–12}] was 36 $\mu\text{g} \cdot \text{hour}/\text{ml}$ in failure/relapse versus 56 $\mu\text{g} \cdot \text{hour}/\text{ml}$ in control $p = 0.005$), but not with twice-weekly isoniazid/rifampin. Furthermore, two patients who relapsed with *Mycobacterium tuberculosis* monoresistant to rifamycin had very low concentrations of isoniazid. Finally, isoniazid acetylator status determined by *N*-acetyl-transferase type 2 genotype was associated with outcome with once-weekly isoniazid/rifapentine ($p = 0.03$) but not twice-weekly isoniazid/rifampin. No rifamycin pharmacokinetic parameter was consistently and significantly associated with outcome ($p > 0.10$). Because low isoniazid concentrations were associated with failure/relapse, a drug with consistently greater area under the concentration–time curve than isoniazid may be needed to achieve highly active once-weekly therapy with rifapentine.

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/s/

Seong Jang
5/8/2008 03:46:40 PM
BIOPHARMACEUTICS

Phil Colangelo
5/12/2008 03:41:16 PM
BIOPHARMACEUTICS

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-024/S008

OTHER REVIEW(S)

**DIVISION OF SPECIAL PATHOGEN AND TRANSPLANT PRODUCTS
CSO LABELING REVIEW**

NDA: NDA 21-024/S-008
Drug Name: Priftin[®] (rifapentine) Tablet, 150 mg
Sponsor: Sanofi-Aventis U.S. Inc
Submission date: April 23, 2009
Receipt date: April 23, 2009
Date of Review: May 26, 2009
Reviewer: Hyun Son, Pharm.D., Regulatory Health Project Manager

Background

Priftin (rifapentine) was originally approved for the treatment of pulmonary tuberculosis on June 22, 1998 based upon the accelerated approval regulations (21 CFR 314 Subpart H).

At the time of approval, two accelerated approval commitments were outlined:

1. The final Clinical Study Report issued upon completion of Clinical Study 008 will be submitted to the Agency for review. In this final report both safety and efficacy data for the 2 years of follow-up will be included.
2. Hoechst Marion Roussel 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-positive subjects who relapsed in the rifapentine treatment arm. It was agreed, since this study was being conducted by CDC under a separate IND that CDC would submit study results upon completion of the study.

Commitment 1 was fulfilled on October 20, 2000.

On July 12, 2007, the sponsor submitted an efficacy supplement that contained the results of study USPHS 22 (#2 above) and represented the final accelerated approval commitment for rifapentine. The proposed package insert for this supplemental application was submitted, in accordance with 21 CFR 201.56 (b)(iii), conforming to the new Physician Labeling Rule (PLR) format, which became effective June 30, 2006. After review of the submission, the Division issued an Approvable letter on May 13, 2008. The approvable letter outlined revisions to the label required for approval

On April 23, 2009, Sanofi-Aventis submitted their complete response to the approvable letter with the requested revisions in the label. On May 27, 2009, a teleconference was held with the Division and Sanofi-Aventis to clarify the revisions to the label. The Division and the sponsor

were able to agree on a revised labeling which was submitted by Sanofi-Aventis on May 29, 2009.

Review

As this is the first labeling in PLR format, no side by side comparison will be performed

After review of the May 29, 2009 submission, the following was revised. These revisions were sent via email to the sponsor.

1. The 6th paragraph of section **6.2 Clinical Trials Experience** has been revised as follows:

Seven patients had adverse reactions; [REDACTED] (b) (4) associated with an overdose. In the rifampin combination group these reactions included hematuria, anorexia, back pain, arthralgia, and myalgia. In the rifapentine combination group these reactions included hematuria, neutropenia, hyperglycemia, ALT increased, hyperuricemia, pruritus, and arthritis.

2. The label should not have the lines in the left margin which denotes new information has been added to the label. These lines were deleted from the label.

Conclusions

The labeling changes are acceptable. A letter should be sent advising the applicant that this supplemental NDA application is approved. In addition, correspondence should be sent to the applicant indicating that postmarketing commitment number 2 has been fulfilled.

Hyun Son, Pharm. D.
Regulatory Project Manager

Supervisory Comment/Concurrence:

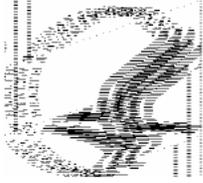
Judit Milstein
Chief, Project Management Staff

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/s/

Hyun Son
5/30/2009 10:31:58 AM
CSO

Judit Milstein
6/1/2009 07:52:56 AM
CSO
NDA 21-024/S-008 CSO Labeling review of SLR



Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

Maternal Health Team Review

Date: May 2, 2008 **Date Consulted:** April 16, 2008

From: Richardae Araojo, Pharm.D.
Regulatory Reviewer, Maternal Health Team (MHT)
Pediatric and Maternal Health Staff

Through: Karen Feibus, MD
Team Leader, Maternal Health Team (MHT)
Pediatric and Maternal Health Staff

Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

To: Division of Special Pathogen and Transplant Products (DSPTP)

Drug: Priftin (rifapentine), NDA 21-024/S-008

Subject: Pregnancy and Nursing Mothers labeling

Materials Reviewed: Pregnancy and Nursing Mothers subsections of Priftin labeling.

Consult Question: Please review the Pregnancy and Nursing Mothers subsections of labeling.

BACKGROUND

The Maternal Health Team (MHT) and the Safety Endpoints and Labeling Development (SEALD) Team have been working together to develop a more consistent and clinically useful structure for the Pregnancy and Nursing Mothers subsections of labeling. The Proposed Pregnancy and Lactation Labeling Rule is in advanced stages of the clearance process. MHT, in collaboration with SEALD, developed a framework for organizing information in the Pregnancy and Nursing Mothers subsections of labeling. This framework complies with current regulations but in the spirit of the Proposed Rule, strives to present available data in a clinically relevant and useful manner.

On April 16, 2008, the Division of Special Pathogens and Transplant Products (DSPTP) consulted the MHT and requested review of the Pregnancy and Nursing Mothers subsections of Priftin (rifapentine) labeling. Rifapentine is a rifamycin used in combination with other antituberculosis drugs for the treatment of pulmonary tuberculosis caused by mycobacterium tuberculosis.

LABELING REVIEW

This review provides revisions to the sponsors proposed Pregnancy and Nursing Mothers subsections of Priftin labeling.

Sponsors Proposed Pregnancy and Nursing Mothers Labeling

(b) (4)



MHT Recommended Labeling for Priftin

Provided below are MHT's recommended revisions to the sponsors proposed Pregnancy and Nursing Mothers subsections of labeling. Appendix A of this review provides a track changes version of labeling that highlights all changes made.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well controlled studies of Priftin use during pregnancy. In animal reproduction and developmental toxicity studies, rifapentine produced fetal harm and was teratogenic. However, because animal studies are not always predictive of human response, Priftin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Rifapentine is a rifamycin derivative that has microbiological activity similar to rifampin. When administered during the last few weeks of pregnancy, rifampin may increase the risk for maternal postpartum hemorrhage and bleeding in the exposed infant. Treatment with Vitamin K may be indicated. Pregnant women and their infants, who are exposed to rifapentine during the last few weeks of pregnancy, should have appropriate monitoring of clotting parameters.

Six patients randomized to rifapentine became pregnant during Clinical Study 008 – two delivered normal infants; two had first trimester spontaneous abortions; one had an elective abortion; and one patient was lost to follow-up. The two patients who

spontaneously aborted had co-morbid conditions (ethanol abuse in one patient and HIV infection in the other).

Animal studies in rats and rabbits revealed embryo-fetal toxicity in both species. Pregnant rats given rifapentine during organogenesis at doses 0.6 times the human dose (based on body surface area), produced pups with cleft palates, right aortic arch, increased incidence of delayed ossification, and increased numbers of ribs. When rifapentine was administered to mated female rats late in gestation, at 0.3 times the human dose (based on body surface area), pup weights and gestational survival (live pups born/pups born) were reduced compared to controls. Increased resorptions and post implantation loss, decreased mean fetal weights, increased numbers of stillborn pups, and slightly increased pup mortality during lactation were also noted. When pregnant rabbits received rifapentine at doses 0.3 to 1.3 times the human dose (based on body surface area), major fetal malformations occurred including: ovarian agenesis, pes varus, arhinia, microphthalmia and irregularities of the ossified facial tissues. At the higher dose, there were increases in post-implantation loss and the incidence of stillborn pups.

8.3 Nursing Mothers

It is not known whether rifapentine is excreted into human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother and the benefits of breastfeeding. Since rifapentine may produce a red-orange discoloration of body fluids, there is a potential for discoloration of breast milk.

When rats were given rifapentine during lactation, a slight increase in pup mortality was observed.

17.6 Pregnancy and Breastfeeding

If you are pregnant or could become pregnant, you should speak to your physician right away about using Priftin. There are no studies of Priftin in pregnancy, but Priftin caused birth defects in animals. It is important that you speak to your physician about the best way to treat your tuberculosis during pregnancy.

Women who are breastfeeding should not use Priftin. Speak to your physician about the best tuberculosis treatment and infant feeding options for you and your baby.

Appendix A – Track Changes Version of Labeling

22 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

Chardae Araojo
5/5/2008 02:36:30 PM
CSO

Karen Feibus
5/6/2008 11:36:27 PM
MEDICAL OFFICER

Lisa Mathis
6/3/2008 01:25:04 PM
MEDICAL OFFICER

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-024/S008

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 21-024

SUPPL # 008

HFD # 590

Trade Name Priftin

Generic Name rifapentine

Applicant Name Sanofi-Aventis U.S. Inc.

Approval Date, If Known May 13, 2008

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy 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 a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

SE7

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 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:

Revision fo the package insert to incorporate information from US Public Health Service (USPHS) Study 22 and CDC irfapentine IND

d) Did the applicant request exclusivity?

YES NO

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

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES NO

IF THE ANSWER TO QUESTION 2 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

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

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. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs 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.

(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:

TBTC/USPHS Study 22, Efficacy and safety of Once-weekly rifapentine and isoniazid compared to twice-weekly rifampin and isoniazid in the continuation phase of therapy for pulmonary tuberculosis.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

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

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

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

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"):

See 2c

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 # (b) (4) 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 ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! 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:

Name of person completing form: Hyun Son, Pharm.D.
Title: Regulatory Project Manager
Date: May 12, 2008

Name of Office/Division Director signing form: Renata Albrecht, M.D.
Title: Director, Division of Special Pathogen and Transplant Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Renata Albrecht
5/12/2008 06:01:15 PM

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-024 Supplement Type (e.g. SE5): SE7 Supplement Number: 008

Stamp Date: July 13, 2007 PDUFA Goal Date: May 13, 2008

HFD 590 Trade and generic names/dosage form: Priftin (rifapentine) 150 mg Tablet

Applicant: Sanofi-Aventis US, LLC Therapeutic Class: Antituberculosis

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next question.
 No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): _____

Indication #1: _____

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
 No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
 No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
 Disease/condition does not exist in children
 Too few children with disease to study
 There are safety concerns
 Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Hyun Son, Pharm.D.
Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH
STAFF at 301-796-0700**

(Revised: 10/10/2006)

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/s/

Hyun Son
4/16/2008 11:30:30 AM

Priftin (rifapentine) Tablets S-008

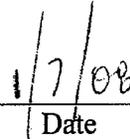
DEBARMENT CERTIFICATION

Sanofi-aventis hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



John Cook

U.S. Regulatory Affairs Marketed Products
sanofi-aventis U.S. Inc.
on behalf of sanofi-aventis U.S. LLC
Tel: (908) 243-7360 Fax: (908) 243-7377
e-mail: john.cook@sanofi-aventis.com



Date



NDA 21-024

Sanofi-Aventis U.S. LLC
Attention: John Cook
Senior Manager, U.S. Regulatory Affairs Marketed Products
55 Corporate Drive
Bridgewater, NJ 08807

Dear Mr. Cook:

We refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Priftin[®] (rifapentine) 150 mg Tablets.

We received your submission dated July 12, 2007, reporting on the following postmarketing study commitment.

2. You 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, CDC will submit results upon completion of the study.

We have reviewed your submission and conclude that the above commitment has been fulfilled.

If you have any questions, please call Christine Lincoln, RN, M.S., MBA, Regulatory Health Project Manager, at (301) 796-0752.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Renata Albrecht
6/9/2009 04:10:16 PM

From: John.Cook@sanofi-aventis.com
To: [Son, Hyun;](#)
Subject: RE: Priftin
Date: Monday, June 01, 2009 11:39:52 AM

Hello Hyun, sanofi-aventis has reviewed and approved the Agency changes listed below. Please note that the sanofi-aventis revision process required us to update our revision date to June 2009. This is located at the end of the PI.

Thanks and best regards,
John

John Cook

US Regulatory Affairs Marketed Products
Director, Base Business Products
Phone: 908-981-7532
Fax: 908-635-5839
john.cook@sanofi-aventis.com

From: Son, Hyun [<mailto:Hyun.Son@fda.hhs.gov>]
Sent: Friday, May 29, 2009 2:38 PM
To: Cook, John PH/US
Subject: Priftin
Importance: High

Hi John,

Just some minor edits:

There should not be any lines in the margin (I took it out).
Also Page 6 of the label, we deleted:

Seven patients had adverse reactions, [REDACTED] (b) (4) associated with an overdose. In the rifampin combination group these reactions included hematuria, anorexia, back pain, arthralgia, and myalgia. In the rifapentine combination group these reactions included hematuria, neutropenia, hyperglycemia, ALT increased, hyperuricemia, pruritus, and arthritis.

I will be enclosing the revised (as above) label with the action

letter, so please be mindful when you are submitting the SPL to change these items.

Thanks
Hyun

Please confirm that you received this message.

Hyun J. Son, Pharm.D.
LCDR, US Public Health Service
Senior Regulatory Management Officer
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
FDA/CDER/OND
10903 New Hampshire Ave
BLDG 22, Room 6132 (note: change in room number)
Silver Spring, MD 20993
Phone: 301-796-1939
Fax: 301-796-9881
Email: Hyun.Son@fda.hhs.gov

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/s/

Hyun Son
6/1/2009 03:33:04 PM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: May 18, 2009

To: John Cook	From: Hyun Son, Pharm.D.
Company: Sanofi-Aventis	Division of Special Pathogens and Transplant Products
Fax number: Email	Fax number: 301-796-9881
Phone number: 908-981-7532	Phone number: 301-796-1939

Subject: NDA 21-024 Priftin: PLR label

Total no. of pages including cover: 26

Concurrence:

Document to be mailed: YES NO

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NDA 21-024

Dear Mr. Cook:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Priftin[®] (rifapentine) tablets submitted April 23, 2009.

Attached is a revised version of the label. The changes affect Highlights, Adverse Reactions, and Clinical Trials. The revisions are represented by the track changes. We ask that you incorporate these revisions in your proposed label.

We are providing the above information by email for your convenience. Contact me at 301-796-1939 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Hyun Son, Pharm. D.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant
Products
FDA/CDER/OND/OAP

Enclosed: Revised Package Insert

22 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

Hyun Son
5/18/2009 11:40:08 AM
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Documents Documents and Settings sonhyNDANDA 21024 Pri ftin Correspondence NDA 21024 Label Revisi on 09May08
NDA 21-024 Pri ftin: Revised Label - sanofi -aventis response From: Son, Hyun
Sent: Friday, May 09, 2008 3:00 PM
To: 'John.Cook@sanofi -aventis.com'
Subject: NDA 21-024 Pri ftin: Revised Label

Importance: High

Attachments: proposed.5.9.08.doc

Hi John,

The team has looked over the proposed label of May 8, 2009. We have some minor revisions to the label. I have attached the word version of the label with track changes. Here are a few comments in regard to the revisions:

1. The following general statement about (b) (4) in the Highlights section is not consistent with PLR labeling and must be removed:

(b) (4)

2. The (R) symbol can only occur once in the document (top of highlights), delete in Section 1

3. Agree with additional information regarding pyridoxine and adding the complete name of the treatment guidelines, suggest removing the year (it will just become outdated)

4. Suggest unbolding "Pregnancy Category C" and adding a colon after.

Thanks

Hyun

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/s/

Hyun Son
5/12/2008 12:50:37 PM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: May 5, 2008

To: John Cook	From: Hyun Son, Pharm.D.
Company: Sanofi-Aventis	Division of Special Pathogens and Transplant Products
Fax number: Email	Fax number: 301-796-9881
Phone number: 908-981-7532	Phone number: 301-796-1939

Subject: NDA 21-024 Priftin: PLR label

Total no. of pages including cover: 28

Concurrence:

Joette Meyer, Pharm.D.	Acting Medical Team Leader
Regina Alivisatos, M.D.	Medical Reviewer
Phil Colangelo, Pharm.D., Ph.D.	Clinical Pharmacology Team Leader
Seong Jang, Ph.D.	Clinical Pharmacology Reviewer
Owen McMaster, Ph.D.	Pharmacology/Toxicology Team Leader

Document to be mailed: YES NO

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NDA 21-024

Dear Mr. Cook:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Priftin[®] (rifapentine) tablets submitted July 12, 2007.

We refer to the fax sent on April 17, 2008 which included the Agency's proposed label for Priftin. Attached is a revised version of the label since the April 17, 2008 fax which incorporates the recommendations from the maternal health team and our review team. The revisions are represented by track changes. We ask that you incorporate these formatting revisions your proposed label.

We are providing the above information by email for your convenience. Contact me at 301-796-1939 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Hyun Son, Pharm. D.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant
Products
FDA/CDER/OND/OAP

Enclosed: Revised Package Insert

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/s/

Hyun Son
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Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: April 17, 2008

To: John Cook	From: Hyun Son, Pharm.D.
Company: Sanofi-Aventis	Division of Special Pathogens and Transplant Products
Fax number: Email	Fax number: 301-796-9881
Phone number: 908-981-7532	Phone number: 301-796-1939

Subject: NDA 21-024 Priftin: PLR label

Total no. of pages including cover:

Concurrence:

Joette Meyer, Pharm.D.	Acting Medical Team Leader
Regina Alivisatos, M.D.	Medical Reviewer
Shukal Bala, Ph.D.	Microbiology Team Leader
Maureen Davidson, Ph.D.	Microbiology Reviewer
Owen McMaster, Ph.D.	Pharmacology/Toxicology Team Leader

Document to be mailed: YES NO

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NDA 21-024

Dear Mr. Cook:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Priftin[®] (rifapentine) tablets submitted July 12, 2007.

We refer to the fax sent on April 14, 2008 which included the Agency's proposed label for Priftin. Attached is a revised version of the label since the April 14, 2008 fax which incorporates the recommendations (formatting) from the Study End Point and Labeling (SEALD) team. The revisions are represented by the track changes. We ask that you incorporate these formatting revisions your proposed label.

We are providing the above information by email for your convenience. Contact me at 301-796-1939 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Hyun Son, Pharm. D.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant
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FDA/CDER/OND/OAP

Enclosed: Revised Package Insert

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/s/

Hyun Son
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REQUEST FOR CONSULTATION

TO (Office/Division):

**CDER Pediatric and Maternal Health Staff
Richardae Araujo**

FROM (Name, Office/Division, and Phone Number of Requestor):

**Hyun Son, Pharm.D.
Division of Special Pathogen and Transplant Products
301-796-1939**

DATE
April 16, 2008

IND NO.

NDA NO.
21-024

TYPE OF DOCUMENT
SE7

DATE OF DOCUMENT
July 13, 2007

NAME OF DRUG
**Priftin (rifapentine) 150 mg
tablet**

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
Tuberculosis

DESIRED COMPLETION DATE
May 2, 2008

NAME OF FIRM: **Sanofi-Aventis**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input checked="" type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review the attached label for the above NDA. This is the first PLR label for this class of drugs. If you have any questions, please contact me. Regina Alivisatos and Joette Meyer are the medical reviewer and Acting medical TL for this product, respectively. The due date for this application is May 13, 2008. Thank you.

SIGNATURE OF REQUESTOR
Hyun Son, Pharm.D.

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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Hyun Son
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Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: April 14, 2008

To: John Cook	From: Hyun Son, Pharm.D.
Company: Sanofi-Aventis	Division of Special Pathogens and Transplant Products
Fax number: Email	Fax number: 301-796-9881
Phone number: 908-981-7532	Phone number: 301-796-1939

Subject: NDA 21-024 Priftin: PLR label

Total no. of pages including cover:

Concurrence:

Joette Meyer, Pharm.D.	Acting Medical Team Leader
Regina Alivisatos, M.D.	Medical Reviewer
Shukal Bala, Ph.D.	Microbiology Team Leader
Maureen Davidson, Ph.D.	Microbiology Reviewer
Owen McMaster, Ph.D.	Pharmacology/Toxicology Team Leader

Document to be mailed: YES NO

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NDA 21-024

Dear Mr. Cook:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Priftin[®] (rifapentine) tablets submitted July 12, 2007.

We have reviewed your proposed labeling in PLR sent via email on September 6, 2007 and submission dated March 11, 2008. Our review team has extensively edited many sections of the label in order to accurately reflect the safety and efficacy of rifapentine as evidenced by the original data and the data from USPHS study 22. We have tried to be consistent with PLR formatting, but the label is undergoing review by our internal labeling group and they will have additional comments. This version of the label is subject to completion of the reviews. It may be necessary to request additional changes. If you notice any other irregularities with the formatting, you should propose the corrections. The proposed label is attached.

We are providing the above information by email for your convenience. Contact me at 301-796-1939 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Hyun Son, Pharm. D.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant
Products
FDA/CDER/OND/OAP

Enclosed: Revised Package Insert

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/s/

Hyun Son
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: March 3, 2008

To: John Cook	From: Hyun Son, Pharm.D.
Company: Sanofi-Aventis	Division of Special Pathogen and Transplant Products
Fax number: Email	Fax number: 301-796-9882
Phone number:	Phone number: 301-796-1939

Subject: NDA 21-024 Priftin: Request for clarification

Total no. of pages including cover: 2

Concurrence:

Shukal Bala, Ph.D. Microbiology Team Leader
Maureen Davidson, Ph.D. Microbiology Reviewer

Document to be mailed: YES NO

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NDA 21-024

Dear Mr. Cook:

Please refer to your supplemental New Drug Application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Priftin[®] (rifapentine) tablets submitted July 12, 2007.

We also refer to the email sent by Dr. Andrew Vernon on February 25, 2008 to Sanofi-Aventis, and CC to FDA, containing the responses to the queries from the FDA concerning the USPHS/TBTC Study 22. In the email, Dr. Vernon had included attachments. We had communicated, in an email dated February 26, 2008, that we wanted to have a teleconference with Sanofi-Aventis and CDC to request clarification of the excel spreadsheet provided in the email transmission dated February 25, 2008. In lieu of the teleconference, we are sending the information request via email.

Dr. Vernon has provided an Excel spreadsheet (CUMRFLP_228) with results of restriction fragment length polymorphism (RFLP) analyses. Please provide the following information for our review.

1. Please provide definitions of the column headings which include “DASH no”, “FP type”, “Bands”, and “other tests”
2. Within the columns, please define the data listed. For example, under the “FP type” and “pTBN-12” column headings, please clarify what the numbers in the column represent. Similarly, in the “other tests” column, please specify what “wpcr=” represents.
3. Some of the data are highlighted in different colors. Please specify what the different colors represent.
4. It would be helpful for our review if photographs or scanned images of the gels used for the RFLP analyses could be provided to accompany the spreadsheet data.

Contact me at 301-796-1939 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Hyun Son, Pharm. D.
Senior Regulatory Management Officer
Division of Special Pathogen and Transplant
Products
FDA/CDER/OND/OAP

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/s/

Hyun Son
3/3/2008 02:39:33 PM
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: November 6, 2007

To: John Cook	From: Hyun Son, Pharm.D.
Company: Sanofi-Aventis	Division of Special Pathogens and Transplant Products
Fax number: Email	Fax number: 301-796-9881
Phone number:	Phone number: 301-796-1939

Subject: NDA 21-024 Priftin: Formatting comments for the PLR label

Total no. of pages including cover: 2

Document to be mailed: YES NO

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NDA 21-024

Dear Mr. Cook:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Priftin[®] (rifapentin) tablets submitted July 12, 2007.

We have reviewed your proposed labeling in PLR sent via email on September 6, 2007 and the following formatting deficiencies have been identified:

HIGHLIGHTS

- The name of the product should be on one line if possible: Priftin[®] (rifapentine) Tablets.
- Under **ADVERSE REACTIONS** and **DRUG INTERACTIONS**, all text should be indented following each bullet.

FULL PRESCRIBING INFORMATION: CONTENTS*

- The first line, [REDACTED]^{(b) (4)} should be deleted (there are no [REDACTED]^{(b) (4)} for this product).

ADVERSE REACTIONS

- Under 6.1, the numbering of the table (Table 2-3) seems inconsistent for the section.

CLINICAL STUDIES

- Under section 14, the numbering of the tables (Table 2-1 and Table 2-2) seems inconsistent for the section.

We are providing the above information by email for your convenience. Contact me at 301-796-1939 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Hyun Son, Pharm. D.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant
Products
FDA/CDER/OND/OAP

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/s/

Hyun Son
11/6/2007 09:49:15 AM
CSO
NDA 21-024 PLR Format comments

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:

- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES NO

2. This application is an eNDA or combined paper + eNDA YES NO

This application is: All electronic Combined paper + eNDA

This application is in: NDA format CTD format

Combined NDA and CTD formats

Does the eNDA, follow the guidance?

(<http://www.fda.gov/cder/guidance/2353fnl.pdf>)

YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES

If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, _____ Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

The sponsor originally submitted this supplemental application as a labeling supplement, but because this NDA was approved as an accelerated approval with post marketing commitments, this application was considered as the last portion of the post marketing commitment to fulfill the accelerated approval and was identified as an efficacy supplement. The sponsor is working on getting this information to the agency.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as “To the best of my knowledge . . .”

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO
- PDUFA and Action Goal dates correct in tracking system? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: IND (b) (4)

- Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) _____ NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO

If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

Initially, the submission came in as a labeling supplement, however since this is a Subpart H application, the submission was coded as an efficacy supplement SE7. Hence PLR requirement came into effect. The sponsor has proposed to submit the PLR.

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
N/A YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA YES NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 5, 2007

NDA #: NDA 21-024/S-008

DRUG NAME: Priftin[®] (rifapentin) 150 mg tablet

APPLICANT: Sanofi Aventis U.S. LLC

BACKGROUND:

Priftin[®] was approved under Subpart H on June 22, 1998 for the treatment of pulmonary tuberculosis. Two accelerated approval commitments were included in the approval letter. The first commitment was completed (and acknowledged by FDA) on October 20, 1999. The second commitment is for a study that was conducted by the CDC. The CDC has completed the study and analysis and has submitted the data to IND (b)(4). The CDC has granted Sanofi-Aventis cross reference to the IND.

ATTENDEES:

Renata Albrecht, M.D.	Division Director
Joette Meyer, Pharm.D.	Acting Medical Team Leader
Regina Alivisatos, M.D.	Medical Officer
Philip Colangelo, Pharm.D., Ph.D.	Clinical Pharmacology Team Leader
Seong Jang, Ph.D.	Clinical Pharmacology Reviewer
Karen Higgins, Sc.D.	Statistics Team Leader
Xianbin Li, Ph.D.	Statistics Reviewer
Shukal Bala, Ph.D.	Microbiology Team Leader
Maureen Davidson, Ph.D.	Microbiology Reviewer
William Taylor, Ph.D.	Pharmacology/Toxicology Team Leader
Owen McMaster, Ph.D.	Pharmacology/Toxicology Reviewer
Hyun Son, Pharm.D.	Regulatory Health Project Manager

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	Regina Alivisatos
Statistical:	Xianbin Li
Pharmacology:	Owen McMaster
Clinical Pharmacology:	Seong Jang
Microbiology, clinical (for antimicrobial products only):	Maureen Davidson
Regulatory Project Management:	Hyun Son

Per reviewers, are all parts in English or English translation? YES NO

If no, explain:

CLINICAL FILE REFUSE TO FILE

• Clinical site audit(s) needed? YES NO

If no, explain:

• Advisory Committee Meeting needed? YES, date if known _____ NO

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

- Biopharm. study site audits(s) needed?
YES NO

PHARMACOLOGY/TOX N/A FILE REFUSE TO FILE

- GLP audit needed? YES NO

CHEMISTRY FILE REFUSE TO FILE

- Establishment(s) ready for inspection? YES NO
- Sterile product? YES NO
- If yes, was microbiology consulted for validation of sterilization? YES NO

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

- Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
- If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
- If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. Convey document filing issues/no filing issues to applicant by Day 74.

Hyun Son, Pharm.D.
Regulatory Project Manager

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/s/

Hyun Son
11/5/2007 10:41:45 AM
CSO
NDA 21-024/S-008 Filing Review



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: October 31, 2007

To: John Cook	From: Hyun Son, Pharm.D.
Company: Sanofi-Aventis	Division of Special Pathogens and Transplant Products
Fax number: Email	Fax number: 301-796-9882
Phone number:	Phone number: 301-796-1939

Subject: NDA 21-024 Priftin: Microbiology comments/request

Total no. of pages including cover: 3

Concurrence:

Shukal Bala, Ph.D. Microbiology Team Leader
Maureen Davidson, Ph.D. Microbiology Reviewer

Document to be mailed: YES NO

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NDA 21-024

Dear Mr. Cook:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Priftin® (rifapentin) tablets submitted July 12, 2007.

Please provide the following information for our review:

1. In the protocol on pages 41, 42, and 45 it is stated that cultures were performed at baseline and at various times throughout the study. It is unclear whether the cultures were done at different study sites participating in the clinical trial or if all isolates were shipped to the CDC for confirmation. The methods for microbiologic testing were not included in the protocol or in the papers in which the study results are described. Please provide the methods of sample collection, processing, culture, and identification of *Mycobacterium tuberculosis* and other *Mycobacterium* species for the laboratories in which these procedures were performed.
2. Presence or absence of growth from respiratory tract samples collected from patients at baseline and subsequent visits after initiation of treatment were included in the datasets. However, it is unclear how many samples were collected at each visit when sputum was the only source of the sample for microbiologic evaluation. Please clarify.
3. It appears from some of the publications (Vernon *et al.*, 1999. Lancet. 353: 1843-1847; TBTC, Lancet. 2002. 360:528-534) that *in vitro* susceptibility testing was done for some of the clinical isolates collected from patients enrolled in the study. However, the results could not be found in the datasets. Please clarify if only a subset of the isolates were chosen for *in vitro* susceptibility testing, and specify the reasons for doing so. Also, please provide the methodology used for *in vitro* susceptibility testing, specify the laboratory where such testing was done, and provide results for our review. It will be helpful for our review if the results are presented in a format as shown below (Table 1).
4. It appears from the datasets that the RFLPs were done at different laboratories. Please clarify where the actual testing was done and specify which results are from which laboratory. Please provide the details of the methods and the performance characteristics of the assay in the actual laboratory where such testing was done. It will be helpful for our review if the results are presented in a format as shown below (Table 1). Also, copies of clear gel photographs should be included for our review.

We are providing the above information by email for your convenience. Contact me at 301-796-1939 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Hyun Son, Pharm. D.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant
Products
FDA/CDER/OND/OAP

Treatment Group	HIV Status	Patient ID	Baseline Genotyping			Relapse/Failure							
			IS6110-RFLP (>5 bands)	Confirmatory pTBN12-RFLP	<i>rpoβ</i> gene mutation	Week of visit	Clinical Outcome	Culture Site	Sensitivity Testing to INH	Sensitivity Testing to Rifampin	Genotyping		
											IS6110-RFLP (>5 bands)	Confirmatory pTBN12-RFLP	<i>rpoβ</i> gene mutation
Rifapentine (Once/week)	+	11-0760	Yes	No	Not done	16	Relapse	sputum	Sensitive	Resistant	Yes	NO	His526Tyr
Rifampin (Two/week)	-	11-0561	No	Yes	Not done	64	Failure	sputum	Sensitive	Sensitive	No	Yes	Not Done
Rifapentine (Once/week)	+	11-3625	Yes**	Yes**	Not done	64	Re-infection	BAL	Sensitive	Sensitive	Yes **	Yes**	Not Done

** band pattern did not match baseline isolate.

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/s/

Hyun Son
10/31/2007 04:32:21 PM
CSO
NDA 21024 Micro Info Request



FILING COMMUNICATION

NDA 21-024/S-008

Sanofi-Aventis U.S. LLC
Attention: Mr. John Cook
Senior Manager
US Regulatory Affairs Marketed Products
55 Corporate Drive
Bridgewater, NJ 08807

Dear Mr. Cook

Please refer to your July 12, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Priftin[®] (rifapentin) tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on September 11, 2007, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Hyun Son, Pharm.D., Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Judit Milstein
Chief, Project Management Staff
Division of Special Pathogen and Transplant
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Hyun Son
9/18/2007 10:48:04 AM
NDA 21-024 Filing Sign for Judit Milstein



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: September 17, 2007

To: John Cook	From: Hyun Son, Pharm.D.
Company: Sanofi-Aventis	Division of Special Pathogens and Transplant Products
Fax number: Email	Fax number: 301-796-9882
Phone number:	Phone number: 301-796-1939

Subject: NDA 21-024 Priftin: Information request

Total no. of pages including cover: 3

Concurrence:

Joette Meyer, Pharm.D. Acting Medical Team Leader
 Regina Alivisatos, M.D. Medical Reviewer

Document to be mailed: YES NO

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NDA 21-024

Dear Mr. Cook:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Priftin[®] (rifapentin) tablets submitted July 12, 2007.

We have the following request for clarification:

1. There is an inconsistency in the number of deaths submitted in the datasets (N =73) and the number in the accompanying journal article (N = 71).¹ Please provide an explanation for this discrepancy and provide the patient IDs of the 2 subjects who were not included in the paper.
2. Please revise the Adverse Reactions section of the proposed label, submitted via email on September 6, 2007, to conform to the January 2006 Guidance Document on Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products .

This section should conform to the Guidance and should include adverse events data from both Studies 008 and 022.

As per the guidance:

"The beginning of the Adverse Reactions section should identify the most clinically significant adverse reactions and direct practitioners to more detailed information about those reactions. For example, this section should first identify and cross-reference all serious and otherwise important adverse events (AEs) described in greater detail in other labeling sections especially Warnings and Precautions. Also, adverse reactions that result in a significant rate of discontinuation or other clinical intervention (e.g., dosage adjustment, need of other therapy to treat and adverse reaction) in clinical trials) should be discussed".

"The presentation of AE information identified in clinical trials must be preceded by information necessary to interpret the AEs. This information should include a description of the overall clinical trial database from which AE data have been drawn, including a discussion of overall exposure, demographics of the exposed population, designs of the trials in which exposure occurred, and any critical exclusions from the safety database."

Presentation of "Common Adverse Reactions"

- a) Identify any treatment emergent adverse event (TEAE) in the clinical trials database which occurs in $\geq 2\%$ of rifapentine- treated patients. Please include all events, regardless of drug-relatedness as determined by the investigator. In addition, you

¹ INT J TUBERC LUNG DIS 10(5):542–549 Mortality in a large tuberculosis treatment trial: modifiable and non-modifiable risk factors T. R. Sterling,* Z. Zhao,† A. Khan,† R. E. Chaisson,‡ N. Schluger,§ B. Mangura,¶ M. Weiner,# A. Vernon† for the Tuberculosis Trials Consortium

should include events even if they occur less frequently than in the comparator arm. Do not exclude events due to lack of a causal relationship between the drug and the event (e.g., AEs considered to be biologically implausible). Table 2.3 (currently in the label) should be modified accordingly and can reflect all TEAEs (treatment emergent AEs) independent of treatment relatedness that occurred in \geq to 2% of the populations (Studies 008 and 022). In addition, you should include events even if they occur less frequently than in the comparator arm but meet the cut-off specified.

- b) Please provide a second table with treatment related AEs in \geq 2% of the population from both studies for our review. A determination of inclusion of this table will be made at a later date.
- c) Please provide AE rates (Treatment emergent and treatment related) in HIV infected subjects in a table. The inclusion of this information into labeling will also be made at a later date.

Presentation of "Less Common Adverse Reactions"

- a) Please identify any treatment emergent adverse event (TEAE) in the clinical trials database which occurs in 0.1 to 1.9% of rifapentine-treated patients. Please include all events, regardless of drug-relatedness as determined by the investigator and those which occur less frequently than in the comparator patients. Exclude TEAEs where there is no causal relationship between the drug and the event (e.g., AEs considered to be biologically implausible). Please present a separate listing of the excluded "less common" TEAEs to FDA for review.

Please note that the rates of "common" and "less common" TEAEs that are gender-specific should be determined using the appropriate denominator and that denominator should be identified in a footnote. Include a description of the data sources for the above lists which states that the rates were derived from all reported AEs not present at baseline. Include a description of the types of studies (design and study population) and note that data were pooled across studies.

Once you submit your inclusive list of TEAEs and the requested tables and upon review, we will further discuss with you which "common" TEAEs can be removed. You are welcome to propose a list of events that you feel should be excluded and the reason for exclusion.

We are providing the above information by email for your convenience. Contact me at 301-796-1939 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Hyun Son, Pharm. D.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant
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/s/

Hyun Son
9/17/2007 10:49:24 AM
CSO
NDA 21-024 Clinical Information request



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: September 7, 2007

To: John Cook	From: Hyun Son, Pharm.D.
Company: Sanofi-Aventis	Division of Special Pathogens and Transplant Products
Fax number: Email	Fax number: 301-796-9882
Phone number:	Phone number: 301-796-1939

Subject: NDA 21-024 Priftin: Microbiology comments/request

Total no. of pages including cover: 2

Concurrence:

Shukal Bala, Ph.D. Microbiology Team Leader
Maureen Davidson, Ph.D. Microbiology Reviewer

Document to be mailed: YES NO

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NDA 21-024

Dear Mr. Cook:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Priftin[®] (rifapentin) tablets submitted July 12, 2007.

In the microbiology section of the label, subheading resistance development, you have proposed to add a statement regardin (b) (4)

[REDACTED]. However, in the **Susceptibility testing for *Mycobacterium tuberculosis*** section, the approved label states that interpretive criteria/breakpoints to determine whether clinical isolates of *M. tuberculosis* are susceptible or resistant to rifapentine have not been established. Please provide for our review the protocols and data which can be used to establish interpretive criteria/breakpoints for *in vitro* susceptibility testing of clinical isolates of *M. tuberculosis* against rifapentine.

We are providing the above information by email for your convenience. Contact me at 301-796-1939 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Hyun Son, Pharm. D.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant
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/s/

Hyun Son
9/7/2007 10:40:25 AM
CSO
NDA 21-024 Micro comments



NDA 21-024/S-008

Sanofi-Aventis U.S. LLC
Attention: Mr. John Cook
Senior Manager
US Regulatory Affairs Marketed Products
55 Corporate Drive
Bridgewater, NJ 08807

Dear Mr. Cook

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Priftin [®] (rifapentin) tablets
NDA Number:	21-024
Supplement number:	008
Review Priority Classification:	Standard (S)
Date of supplement:	July 12, 2007
Date of receipt:	July 13, 2007

This supplemental application proposes the following changes:

- In the **ACTIONS/CLINICAL PHARMACOLOGY** section, addition of information providing specific direction regarding susceptibility testing for determining development of drug resistance.
- In the **CLINICAL TRIALS** section, incorporation of data from USPHS Study 22.
- In the **INDICATIONS AND USAGE** section, addition of safe and effectiveness of Priftin in HIV seropositive patients, addition of information from the 2003 ATS/CDC/IDSA treatment of TB guideline.
- In the **CONTRAINDICATION** section, addition of contraindication based on USPHS Study 22 results.
- In the **WARNINGS** section, addition of information pertaining to HIV seropositive patients based on the USPHS Study 22 results.

- In the **DOSAGE AND ADMINISTRATION** section, update information from the 2003 ATS/CDC/IDSA treatment of tuberculosis guidelines.
- Update of **HOW SUPPLIED** section.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 11, 2007, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be May 13, 2008.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and Transplant Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any question, call Hyun Son, Pharm.D., Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Judit Milstein
Chief, Project Management Staff
Division of Special Pathogen and Transplant
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Judith Milstein
8/10/2007 03:58:40 PM
NDA 21-024/S-008 Acknowledgment Letter