CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-024/S-005

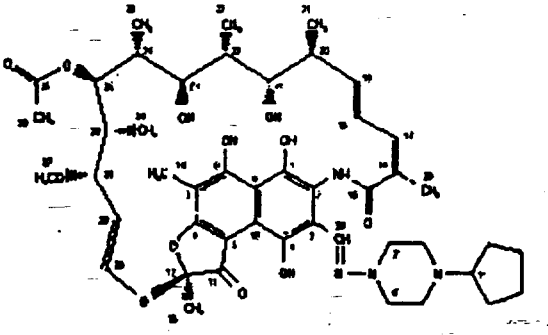
MEDICAL REVIEW

Medical Officer Review of NDA 21-024/SE7-005: Rifapentine (Priftin ™)

Date Submitted: December 17, 1999
Date Received : December 21, 1999
Date Assigned: December 23, 1999
Date Completed: September 11, 2000

Applicant: Adventis Pharmaceuticals

Drug: Proprietary name - Priftin ®
Generic name - rifapentine
Chemical name - rifamycin, 3-[[(4-cyclopentyl-1-piper-azinyl) 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-l-piperazinyl)-formimidoyl]-2,7-(epoxypentadeca[1,11,13]trienimino)naphtho[2,1-b]furan-1,11(2H)dione 21-acetate.
Molecular formula - C_{47} H_{64} N_4 O_{12}
Molecular weight - 877.04
Molecular structure -



Drug Class: rifamycin antibiotic

Formulation: 150 mg tablets
Route of administration: oral

Related IND: [redacted]

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1 Rifapentine (Priftin ®) 24 month update

This review discusses the Rifapentine study report 008 (24 month follow-up data on TB relapse) and proposed labeling changes (SE7-005). The applicant submitted the final study report on June 29, 1999. This was in compliance with one of the accelerated approval commitments required by the FDA. Follow-up data for TB relapse is to confirm the use of the 6-month relapse rate as a surrogate endpoint for efficacy. The applicant submitted proposed labeling changes based upon the final study report. Recommendations regarding the proposed labeling changes are made in this review.

1.1 Background

Rifapentine (Priftin) was approved for the treatment of tuberculosis on June 22, 1998. The approval was based upon the accelerated approval regulations (21CRF 314 subpart H). In this case, the 6-month relapse rate is being used as a surrogate for the 2-year relapse rate.

Hoechst Marion Roussel, Inc. submitted New Drug Application 21-024 for rifapentine to the FDA December 1997. This submission included interim efficacy results based on data collected through November 8, 1996 from a 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 patients would have been treated and followed to the 6-month post therapy visit.

Rifapentine was granted orphan drug designation for the treatment of tuberculosis in June of 1995. The current submission is based upon the accelerated approval regulations (21CRF 314 subpart H). In this case, the 6-month relapse rate is being used as a surrogate for the 2-year relapse rate.

An Anti-Viral Advisory Committee Hearing (May 5, 1998) was held to discuss the efficacy and safety of Rifapentine. During the advisory committee meeting a closed session was held, during which CDC made a presentation to the advisory committee, the topic of which is confidential.

The committee voted to recommend approval of rifapentine for the treatment of pulmonary tuberculosis, with only one dissenting vote. The committee was concerned that rifapentine be used with extreme caution, if at all in HIV positive patients. This was due to both the information from a study presented by the CDC where rifamycin resistance developed in the HIV-positive patients, and the potential for rifapentine to significantly reduce the AUC (area under the curve) of the protease inhibitor, Indinavir. It was felt that experts in the field of HIV and TB may need to utilize the agent, and given current knowledge of pharmacokinetics and the management of TB, more frequent dosing in the intensive phase may prevent resistance. This was speculation not based upon clinical study information. In addition, it was felt that in HIV-infected patients, the continuation phase should be biweekly, until further studies can future clarify these issues.

In general the committee believed that rifampin and rifapentine would be comparable agents, however, currently the optimal therapeutic regimen has not been determined for rifapentine. It was pointed out that clinicians utilize rifampin differently than they did 25 years ago when it was approved.

Finally, although the adherence to companion drugs was an issue of interest to the committee, there was speculation regarding other reasons for the higher relapse rates in the rifapentine group. These include the dosing of INH during the continuation phase and the difference in pharmacokinetic profile, ie. the longer half-life of rifapentine would essentially place the patient on mono-therapy with rifapentine for a period of time each week. However, neither INH nor rifampin resistance was seen in the submitted study.

It was 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 US CDC Study 22, which utilizes rifapentine in the last 4 months of therapy at a weekly dose with INH, and standard rifampin therapy in the first two months of intensive therapy. Many in the group felt that perhaps the optimal use would be 6 months of thrice weekly therapy, however, no data exist upon which to base that recommendation. The committee recommended further study into these types of regimens.

The efficacy of rifapentine was demonstrated in a single, open-label, randomized, active controlled trial. 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 one possible reason for the higher relapse rate. Compliance with the companion drugs in the rifapentine arm was a risk factor for relapse. While this may explain some of the difference, additional factors which were unable to be tested in this study may have had an influence on the higher relapse rate. It was felt by many on the advisory committee that a thrice-weekly dose of rifapentine may be the optimal dose, however, there is not data available upon which to make this recommendation. Thus, the importance of adherence to the regimen is stressed in the label. The development of resistance to rifampin was not seen in the pivotal clinical trial.

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

Six pregnancies occurred on the rifapentine arm; two had normal deliveries, two had first trimester spontaneous abortions, one had an elective abortion and one patient was lost to follow-up. Of the two patients who spontaneously aborted, co-morbid conditions of ethanol abuse in one and HIV infection in the other were noted.

Finally, experience in the treatment of TB in the context of HIV infection was discussed. Limited data are available for the use of rifapentine in HIV positive patients. The CDC study demonstrated a possible risk for the development of rifapentine resistant TB

isolates. Drug-drug interaction studies with Crixivan demonstrated an effect similar to that of rifampin, that is, significant decrease in AUC of Crixivan. It was recommended that this information be placed in the label and further studies be considered in HIV positive patients. Extreme caution should be taken if rifapentine is administered to HIV positive patients.

Labeling concerns at the time of the original approval were:

1. Clearly stated primary efficacy outcomes: comparable conversion rates with greater relapse rates at 6 month follow-up for rifapentine.

2. Potential drug-drug interactions, especially with protease inhibitors. The concomitant use of rifampin with protease inhibitors is contraindicated. The advisory committee did not recommend an absolute contraindication, but rather strong wording describing the interaction for practitioners in the label.

3. Inclusion of information regarding HIV positive patients and the development of rifapentine resistance in the CDC study.

4. Clear use instructions especially in the first two months of therapy: companion medications are given DAILY while rifapentine is given twice per week.

5. Increased absorption of rifapentine with food.

6. Information regarding human pregnancy outcomes was described in the label.

The accelerated approval commitments include the following two clinical trials:

1. The final Clinical Study Report issued upon completion of Clinical Study 008 will be submitted to the Agency for review. The projected timing is June 1999. In this final report both safety and efficacy data for the 2 years of follow-up will be included.

2. 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-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 study results upon completion of the study.

In order to achieve full approval status, the applicant must at a minimum complete 2 year follow-up on study 0008, and support completion of the US CDC Study 22 .

FDA Recommendations for the original NDA are described in the following paragraph.

The single controlled study submitted in support of accelerated approval of Rifapentine (Priftin®) for the treatment of pulmonary tuberculosis meetings regulatory requirements for approval for this indication. Pursuant to 21 CFR 314 Sub-part H (accelerated approval) the study performed meets the need for new agents in regimens which require fewer directly observed therapy visits potentially decreasing non-compliance thus

contributing to a public health need to reduce the number of tuberculosis cases in the United States. As required in subpart H, the surrogate marker utilized in this study was the 6-month follow-up relapse rate. This endpoint will be reviewed at completion of the study, i.e. at the 2-year follow-up point. It is believed that the 6-month relapse rate is an adequate surrogate for the 2-year relapse rate.

Rifapentine (Priftin®) was approved on June 22, 1998 for the treatment of pulmonary tuberculosis.

1.2 REVIEW OF STUDY 008: 24 MONTH UPDATED DATA.

1.2.1 EFFICACY:

This study presents data on the TB relapse rate in the collect follow up data (24 months after enrolling into the study) for patients in study #008. In the original study 640 patients were to be evenly randomized to one of two treatment regimens (see below).

Treatment Regimens Proposed for Study

	Treatment A	Treatment B
Intensive Phase (60 days)	Isoniazid 300 mg/day	Isoniazid 300 mg/day
	Rifampin 450 or 600 mg daily*	Rifapentine 600 mg twice a week
	[redacted]	
	[redacted]	
	Pyridoxine 50 mg/day	Pyridoxine 50 mg/day
Continuation Phase (120 days)	Isoniazid 600 or 900 mg twice a week*	Isoniazid 600 or 900 mg once a week*
	Rifampin 450 or 600 mg* twice a week	Rifapentine 600 mg once a week
	Pyridoxine 50 mg/day	Pyridoxine 50 mg/day

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

*note: [redacted] was administered daily until susceptibility tests returned. If M. tuberculosis isolated was susceptible to I/Rpt/R/P, then [redacted] was discontinued from the treatment regimen. If M. tuberculosis was resistant to I/Rpt/R/P, the patient was discontinued from the study and treated appropriately.

1.2.1.1 Clinical studies section of proposed labeling

The applicant submitted the final study report for study #008 on June 29, 1999. The proposed labeling changes in the Clinical Study Section of the label are based upon the data collected through 24 months. Initial review of the final study report did not support the relapse rate changes that were listed in the proposed label. The applicant was queried in this regard and provided a detailed explanation regarding the differences in a memo

dated January 17, 2000. The explanation involved the differences in analysis that the applicant performed for the study and those that the FDA requested to be included in the label. This difference revolved around definitions for endpoints of interest. The memo served to clarify and resolved the differences to the FDA's satisfaction. Additional review and verification of the final list of relapses based upon agreed upon endpoints follows in the next section.

1.2.1.2 Relapses:

The definition of relapse was dependent upon the status at the end of TB treatment. The definitions for relapse as well as conversion at the end of treatment used to construct Table 2.2 in the proposed label are as follows:

Sputum Conversion at the end of treatment: " will be measured by determining the percentage of all patients in each treatment group with 2 consecutive negative sputum cultures which remain negative through the end of 180 days of treatment."

"**Treatment Success** is defined as achievement of negative sputum cultures in the active treatment period which is sustained through 6 months of post treatment follow-up (and for the remainder of the 2 year follow-up period). Patients who remain on study, but for who a culture result is unavailable (e.g., due to missed study visit or culture contamination) may be categorized as a treatment success if and only if they present with negative culture results from scheduled visits both prior to and following the missing data point."

"**Treatment failure** is defined as those patients who either failed to achieve negative sputum culture, patients who achieved negative cultures, but failed to sustain such negative cultures through 6 months of post-treatment follow up (and for the remainder of the two year follow up period) or patients who failed to remain on study (e.g., due to death, adverse event, or loss to follow up) regardless of last available culture result."

"**Relapse** is defined as a positive sputum(s) which occurs after the patient's sputum culture has converted to negative and he or she has completed therapy. Bacteriologically confirmed relapse consists of a single culture with a colony count of $\geq$ 10 and/or 2 or more cultures with a colony count < 10. The investigator should obtain at least two additional confirmatory cultures (i.e., a total of three specimens collected on 3 separate days)."

The remainder of this section will focus on an analysis of the efficacy section of the proposed clinical label (Table 2.2). It is important to reconcile the differences between the current label and the proposed label based upon the results of the complete 24-month follow-up data. It was postulated that the majority of relapses would occur in the first 6 months of follow up. Thus, it is critical in the evaluation of relapse to ensure correct categorization of outcome. This is especially so due to the small numbers of events that are occurring in this study.

The following represents the current approved label.

Table 2-2 presents clinical outcome in Study 008.

Table 2-2. Clinical Outcome in Study 008 *		
	Rifapentine Combination	**Rifampin Combination**
Status at End of Treatment		
Converted	**87% (249/286)**	**81% (229/284)**
Not Converted	**1% (4/286)**	**3% (8/284)**
Lost to Follow-up	**12% (33/286)**	**17% (47/284)**
Status in Follow-up:		
Relapsed	**10% (25/249)**	**5% (11/229)**
Sputum negative, Still being followed	**81% (201/249)**	**90% (205/229)**
Lost to Follow-up	**9% (23/249)**	**6% (13/229)**
*All data through 8 July 1997 for patients with confirmed susceptible MTB (rifapentine combination, n=286; rifampin combination, n=284).		

The following table represents the proposed labeling change.

Table 2-2. Clinical Outcome in Study 008*

	Rifapentine Combination	Rifampin Combination
Status at 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)

* All data for patients with confirmed susceptible MTB (rifapentine combination, n=286; rifampin combination, n=283).

FDA review of culture status from the June '99 study report was in general agreement with the applicant's results as reported in the proposed table. However, there were some patients with data whose outcome classification was further analyzed by the FDA.

The definition of relapse was based upon a culture being positive with ~~10~~ or more colony forming units. This definition did not take into account the possibility of sputum culture

being positive by the [redacted] test alone. The following tables represent culture results for patients, who converted at the end of treatment and subsequently were found to have a positive culture, which were not previously counted as relapses.

Sputum Culture Status: Rifapentine arm (24-month follow up report)

PID	Baseline Sensitivity	Day 180 Culture Result	Culture result Mo. Follow-up	Additional Follow up?	Applicant Outcome	FDA Outcome
PATIENTS WITH NO F/U AFTER + SPUTUM						
22-215	s/s	Neg	18 -; 24+TB (B)	No	No relapse	?
22-231	s/s	Neg	3; 6; 12-; 18+TB (B)	No	Lost to FU	?
24-69	s/s	Neg	6+TB; 18+TB	**Relapse**	**Relapse**	Agree
26-021	s/s	Neg	12; 18-; 24+TB (B)	NO	No relapse	?
28-33*	s/s	Neg	3; 6-; 12+TB (Bx2)	**Relapse**	**Relapse**	Agree
46-203	s/s	Neg	6,12,18-; 24+TB(B)	NO	No relapse	?
46-214*	s/s	Neg	6-; 12+TB (X4)	--	**Relapse**	Agree
46-605#	s/s	Neg	6,12,18-; 24+TB (B, 4col)	NO	No relapse	?
48-002#	s/s	Neg	6,12,18-; 24+TB (B) MDRTB	NO	No relapse	?
39-009*	s/s	Neg	3, 5+TB (x4)	**Relapse**	**Relapse**	Agree
30-37*	s/s	Neg	3+?ID, 6x2+, 12 (B)	**Relapse**	**Relapse**	Agree
PATIENTS WITH F/U						
21-0006	s/s	Neg	3, 6-; 12+TB (L-12)	18, 24 -	No relapse	Agree
26-210	s/s	Neg	6 -, 12+TB (B)	18, 24 -	No relapse	Agree
26-215	s/s	Neg	6, 12, 18 -; 24+TB (B)	26 -	No relapse	Agree
26-219	s/s	Neg	6-; 12+TB (B)	18, 24 -	No relapse	Agree
27-209	s/s	Neg	6,12,18-; 24+TB (B)	27 -	No relapse	Agree
28-16	s/s	Neg	6, 12-; 18+TB (B)	24 -	No relapse	Agree
29-09	s/s	Neg	3, 6-; 12+TB (12)	24 -	No relapse	Agree
30-27	s/s	Neg	3+TB (B)	12, 18, 24 -	No relapse	Agree
30-301	s/s	Neg	6+TB (B)	18 24 -	No relapse	Agree
30-33#	s/s	Neg	3+TB (B,1); 6,12,18, 24 -	--	No relapse	Agree
33-04	s/s	Neg	6-; 15+TB (B)	24	No relapse	Agree
48-007	s/s	Neg	3+TB (8)	6, 12, 18, 24 -	No relapse	Agree

B = Bactec culture positive

Review of the table above reveals that for patients with single [redacted] positive cultures or single culture positivity with low colony forming unit counts, subsequent sputum cultures were negative. FDA is in agreement with the applicant's classification for these patients. Also, additional patients whom the applicant classified as relapses did meet the bacteriologic definition, which was verified by the FDA. Finally, 6 patients with only [redacted] positive cultures and no additional follow up remain to be considered. Since there

is no agreement in the clinical community as to how to count these types of patients, they could be counted as relapses or successes, albeit, without further documentation. The argument for counting them as successes comes from that evidence in the bottom section of the table. Patients where follow up was collected had negative sputum cultures subsequently. However, additional analyses were under taken in order to understand the effect on the relapse outcome. A sensitivity analysis was conducted where these patients were added to the total patients reported by the applicant as relapses (see below).

By similar reasoning, review of the following table reveals 4 patients who were [redacted] culture positive without additional follow up.

Sputum Culture Status: Rifampin arm (24 month follow up report)

PID	Baseline Sensitivity	Day 180 Culture Result	Culture result Mo. Follow-up	Additional Follow up?	Applicant Outcome	FDA Outcome
PATIENTS WITH NO F/U AFTER + SPUTUM						
22-230	s/s	Neg	6, 12 -; 18+TB (B)	NO	LTF	?
24-44	s/s	Neg	3, 6 -;6+(x2,6col); 24 +TB (B)	NO	No relapse	?
24-66	s/s	Neg	3, 6, 12 -; 18+TB (B)	NO	LTF	?
30-34*	s/s	Neg	3, 6, 12 -; 18+TB (x3)	NO	Relapse	Agree
30-216*	s/s	Neg	3, 6, 12 -; 18+TB (x2)	NO	Relapse	Agree
30-38*	s/s	Neg	12, 18 -; 6 MOTT, 24+TBx4	NO	Relapse	Agree
46-610	s/s	Neg	6, 12, 18 -; 24+TB (B)	No	No relapse	?
46-13*	s/s	Neg	3, 6 -; 12+TB (B,1), 18+(B,8)	NO	Relapse	Agree
PATIENTS WITH F/U						
28-17	s/s	Neg	6, 12 -; 18+TB (B,4)	24-	No relapse	
30-04	s/s	Neg	3,6 -; 12+TB (B)	18, 24 -	No relapse	
31-11	s/s	Neg	3+TB (3)strepR	6,12,24 -	No relapse	
33-59#	s/s	Neg	3-; 6+TB (B,6)	12 -	LTF	
26-16	s/s	Neg	M3+TB (B)	6-	No relapse	

The sensitivity analysis of the following relapse rates was performed:
rifapentine relapse (add 6 patients to the 29 in the proposed label) **35/248 (14.1%)**
VS
rifampin relapse (add 4 patients to the 15 in the proposed label) **19/226 (8.4%).**

The resulting Confidence Interval for the difference (rifapentine – rifampin) is (-0.9%, 12.7%).

1.2.1.3 Resistance and RFLP (restriction fragment length polymorphism) issues

Overall, the development of resistance to rifapentine was not seen.
The applicant attempted to perform sensitivity and RFLP on all relapse isolates; however, this did not occur for all patients (for more detail see FDA's Microbiologist's Review). Of those isolates studied, there were three patients with documented MDRTB isolates who were originally sensitive to rifampin upon admission into the study. Of these three patients, one was a rifapentine relapse patient, another was a rifampin relapse patient while the third was a rifapentine treatment success patient with a single follow-up isolate with <10 colonies. Restriction fragment length polymorphism RFLP studies showed the follow-up isolates from the two rifapentine patients to be genetically different from the baseline strain while RFLP data on the rifampin patient indicated strain consistency between the baseline and relapse isolates. These results of the genotyping are unclear due to the lack of standardization in the interpretation of RFLP. For example, one isolate only had two bands that were similar and yet it was noted to be the original isolate that had developed resistance. It appears that resistance to the rifamycins was rarely seen in this study, however, general statements regarding the development of resistance vs. reinfection with separate isolate cannot be made. These data are inconclusive regarding the development of resistance due to the low numbers of patients with documented relapse. In addition, there was a significant number of patients who were lost to follow up in the post treatment period.

1.2.1.4 Summary of Efficacy

The majority of relapses were reported during the first 6 month follow-up period. A substantial number of patients in this cohort were lost to follow-up at the 24 month date (approximately 1/3). Assuming that the patients who were lost to follow up did not relapse the confidence intervals on the difference are similar to those found in the original NDA. The 24-month rates of relapse are 12% (29/248) for rifapentine and 7% (15/226) for rifampin patients; p=0.08 using Fisher's exact test; 95% confidence intervals 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). These statistics demonstrate that the rates of relapse for rifapentine are similar to those for rifampin, although the relapse rates are numerically higher than those for rifapentine compared to rifampin, these statistics support that they are reasonably similar since the 95%confidence interval of the difference includes zero. Sensitivity testing which counted the lost to follow-up patients as relapses gives wider 95% confidence intervals of the difference (-2.5%. 16.1%; Odds Ratio 1.34 [0.95, 1.49]).
(Please refer to statistical review for additional detail.)
The rates of relapse at 24-months do not appear substantially different than those at 6 months. However, as is typical in most clinical studies in tuberculosis, there was a lost-to follow-up rate of approximately 1/3 in each group. This weakens conclusions which may be drawn from the data. When these data are placed in a larger framework, they are similar to preliminary data the CDC reported at the 2000 American Thoracic Society Meetings in Toronto Canada. The Odds Ratio appears to approach 2 for the difference in rates (rifapentine-rifampin) for both the Adventis trial (Study 008) and the CDC study. It is suggested that the relapse rates may be lowered in practice by identifying patients at

risk for relapse (failure to convert at the end of treatment, and compliance with INH regimens). Currently, rifapentine is not widely used in the U.S.. The relatively high rates of relapse in both treatment groups may signify the lower efficacy of a six-month induction regimen given intermittently. The FDA Advisory Committee which originally recommended approval felt that the difference in relapse rates was acceptable, given that additional pharmacokinetic and phase III studies were underway to further define a more effective regimen and/or patient characteristics which would predict relapse. Regarding the latter, these are described in the label, especially adherence to regimens and status of sputum at the end of the induction phase.

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1.2.2 SAFETY

1.2.2.1 Treatment Related Adverse Events:

The proposed labeling changes involve small numbers (one or two patients) that do not affect the overall summary of safety regarding the adverse event profile. The following table highlights the changes, where the differences between the original label and the proposed label are bolded.

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Table 2-3. Treatment-Related Adverse Events Occurring in ≥1% of the Patients in Study 0008

	Intensive Phase [1]		Continuation Phase [2]		Total	
Preferred Term	Rifapentine Combination (N=361) N (%)	Rifampin Combination (N=361) N (%)	Rifapentine Combination (N=321) N (%)	Rifampin Combination (N=306) N (%)	Rifapentine Combination (N=361) N (%)	Rifampin Combination (N=361) N (%)
Hyperuricemia			0	0	**78 (21.6)**	55 (15.2)
ALT increased			**6 (1.9)**	7 (2.3)	**18 (5.0)**	24 (6.6)
AST increased			5 (1.6)	7 (2.3)	**15 (4.2)**	23 (6.4)
Neutropenia			12 (3.7)	9 (2.9)	18 (5.0)	18 (5.0)
Pyuria			6 (1.9)	**3 (1.0)**	**14 (3.9)**	12 (3.3)
Proteinuria			2 (0.6)	1 (0.3)	17 (4.7)	11 (3.0)
Hematuria			4 (1.2)	**4 (1.3)**	13 (3.6)	**15 (4.2)**
Lymphopenia			3 (0.9)	1 (0.3)	16 (4.4)	14 (3.9)
Urinary casts			4 (1.2)	0	14 (3.9)	3 (0.8)
Rash			4 (1.2)	3 (1.0)	13 (3.6)	**21 (5.8)**
Pruritus			1 (0.3)	1 (0.3)	9 (2.5)	16 (4.4)
Acne			2 (0.6)	1 (0.3)	7 (1.9)	4 (1.1)
Anorexia			3 (0.9)	4 (1.3)	8 (2.2)	10 (2.8)
Anemia			2 (0.6)	1 (0.3)	9 (2.5)	10 (2.8)
Leukopenia			3 (0.9)	5 (1.6)	7 (1.9)	8 (2.2)
Arthralgia			0	0	9 (2.5)	7 (1.9)
Pain			0	1 (0.3)	7 (1.9)	6 (1.7)
Nausea			0	1 (0.3)	7 (1.9)	3 (0.8)
Vomiting			1 (0.3)	1 (0.3)	5 (1.4)	7 (1.9)
Headache			1 (0.3)	3 (1.0)	4 (1.1)	7 (1.9)
Dyspepsia			2 (0.6)	3 (1.0)	4 (1.1)	8 (2.2)
Hypertension			1 (0.3)	1 (0.3)	4 (1.1)	1 (0.3)
Dizziness			0	1 (0.3)	4 (1.1)	1 (0.3)
Thrombocytosis			0	0	4 (1.1)	2 (0.6)
Diarrhea			0	0	4 (1.1)	0
Rash maculopapular			0	0	4 (1.1)	3 (0.8)
Hemoptysis			2 (0.6)	0	4 (1.1)	0

Note: ≥1% refers to rifapentine in the TOTAL column.

Note: A patient may have experienced the same adverse event 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.

1 Intensive Phase consisted of therapy with either rifapentine or rifampin combined with isoniazid, [redacted] 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. Events recorded in this phase includes those reported up to 3 months after Continuation Phase therapy was completed.

Medical Officer Comment: These adverse events were verified by the medical reviewer's review of the updated study report and line-listings. The proposed changes to this table in the label are acceptable.

1.2.2.2 Deaths:

Twenty-one deaths, not attributed to study medication, occurred during the trial; 11 were patients who received rifampin combination, and 10 were patients who received rifapentine combination. Five patients (three from the rifampin and two from the rifapentine combination groups) died from progression of TB, while the other 16 died from various other causes. In the rifampin combination group, these included: pulmonary embolism (three patients), AIDS progression (two patients), cardiac failure, wounds resulting from an assault, and "unknown" causes (one patient each). In the rifapentine combination group, reasons were: lung cancer (four patients), wounds resulting from an assault (two patients), "unknown" and "natural causes" (one patient each). These deaths were verified by the medical review of the study 008 report: death narratives.

Note: the death of patient 0024-0043 (rifapentine combination) due to AIDS progression was not reported until after the safety database was closed. The addition of this death brings the total number of deaths to 22.

Medical Officer Comment: The proposed changes in the label which report the number of deaths in the 24 month follow-up have been verified by review of the study 008 report. These proposed changes are acceptable.

1.2.2.3 Porphyria:

The applicant has provided several literature reports concerning the potential for exacerbation of porphyria with the use of rifampin. The following wording is proposed under the PRECAUTIONS section of the label:

"Rifampin has enzyme-inducing properties, including the 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. (Millar JW. Rifampicin-induced porphyria cutanea tarda. Br J Dis Chest, 1980; 74:405-408,: Treece GL, Magnussen CR, Patterson JR, Tschudy DP. Exacerbation of porphyria during treatment of pulmonary tuberculosis. Am Rev Respir Dis. 1976; 113:233-237.: Rifampicin Postmarketing Surveillance Report 93015387.)"

Medical Officer Comment: The proposed changes are acceptable.

1.2.2.4 Pregnancy:

Six patients in each treatment arm reported pregnancy through the November 8, 1996 data cutoff. In the rifampin combination arm, three patients tested positive for pregnancy during the continuation phase and three during follow-up. Three of these patients had normal deliveries, while the outcomes of the other three pregnancies were unknown.

Medical Officer Comment: the proposed label does not warrant a change as no additional pregnancies were reported in the updated study report.

1.2.2.5 Summary of Safety

The events reported in the original label have not changed substantially. The applicant provided additional information on the possibility of the exacerbation of prophyria with the use of rifampin which they which to include in the PRECAUTIONS section of the label. Review of these reports warrants the inclusion of this information because of the potential for similar rare events to within the rifamycin class of drugs.

2 Labeling Issues:

The proposed labeling changes reviewed here relate to the proposal labeled February, 2000A. The majority of changes made to the label involve the clinical study section and adverse events. FDA review of the efficacy data from the 24-month update of study #008 is in agreement with the data placed in these sections regarding efficacy and adverse events rates for this pivotal study. The applicant proposes removal of the following phrase:

"The indication for treatment of pulmonary tuberculosis with PRIFTIN is based on the 6 month follow-up treatment outcome observed in Clinical Study 008 as a surrogate for the 2 year follow-up generally accepted as evidence of efficacy in the treatment of pulmonary tuberculosis."
Medical Officer Comment: This is acceptable to the FDA due to the placement of final 24-month relapse rates in the label.

The applicant proposed to describe the microbiological results from study isolates in the clinical study section as follows:
"In vitro susceptibility testing was conducted against initial and subsequent *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 with rifampin susceptible (MIC ≤0.5 µg/ml) strains of *M. tuberculosis* had rifapentine MICs of ≤0.25 µg/ml. The remaining eight patients with rifampin resistant (MIC >8.0 µg/ml) *M. tuberculosis* isolates had rifapentine MICs of >8.0 µg/ml. Five of these patients had baseline values with multiresistant tuberculosis. Of the remaining three, one was a rifapentine relapse patient, another was a rifampin relapse patient while the third was a rifapentine treatment success patient with a single follow-up isolate with <10 colonies.

This information is provided for comparative purposes only as rifapentine breakpoints have not been established."

[redacted]

See Microbiology review for specific comments regarding MIC changes.

***Medical Officer Comment:** Changes to the proposed label in the Warnings Section, Precautions Section and Adverse Events Section are acceptable to the FDA.*

Please see final label for all changes relevant to this submission.

3 Regulatory Issues:

3.1 Accelerated Approval:

According to the original approval letter there were two clinical trials commitments the applicant agreed to. Submission of 24 month data for study #008, which had been fulfilled, and CDC study 22. As describe above in the background section, the applicant agreed to support the CDC study 22. The last patient randomized will reach the 24 month follow-up visit in March of 2001. An abstract of the interim data (6 month follow-up rates) was presented at the American Thoracic Society Meeting in Toronto in May, 2000. These rates were similar to that seen in study #008. It appears from this early report that the information from the CDC study supports the use of rifapentine for the treatment of tuberculosis. The final study report from the CDC may be expected next year and data from this study may be added to the label if felt to be appropriate at that time.

4 Recommendations:

Continuation of accelerated approval status until the CDC study 22 results are submitted and reviewed.

Medical Reviewer:
Joyce A. Korvick, M.D. /S/ 10/16/00

Concurrence:
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NDA File #21-024
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HFD-590 pharmtox: McMaster,O
HFD-590 micro: Gosey,G
HFD-590 stat: Higgins,K
HFD-590 biopharm: Kumi,K