CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-024/S-005

MICROBIOLOGY REVIEW

HFD-590
D. Willard

OCT 11 2000

Microbiology Review

Division of Special Pathogen and Immunologic Drug Products

(HFD-590)

NDA# 21-024

Reviewer : Linda Gosey
Correspondence Date : 12-22-99
CDER Receipt Date : 12-24-99
Review Assigned Date: 12-29-99
Review Complete Date: 08-26-00

Sponsor: Hoechst Marion Roussel
PO Box 9627
Kansas City, Missouri 64134

Submission Reviewed: SLR

Drug Category: Anti-tuberculous

Indication: Treatment of pulmonary tuberculosis

Dosage Form: Oral tablets: 150 mg

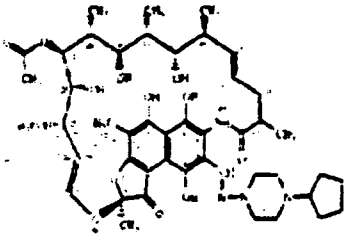
Product Names:

a. Proprietary: Priftin

b. Nonproprietary: Rifapentine, MDL 473, DL473-IT

c. Chemical: (3-{{(4-cyclopentyl-1-piperazinyl)imino}methyl}-rifamycin)

Structural Formula:



NDA 21024.SLR
Rifapentine/TB
Hoechst Marion Roussel

Supporting Documents: [redacted]

Background:

In support of NDA 21-024 the sponsor conducted a single phase III open label, randomized, multi-center, comparative clinical trial. The study was designed to evaluate the safety and efficacy of rifapentine combination therapy compared to standard therapy containing rifampin in the treatment of previously untreated pulmonary tuberculosis. Efficacy was measured as the time to sterilization of sputum cultures, as well as the rate of relapse post-therapy. In the review of the original clinical data treatment cure was assessed at the end of therapy (week 24). Because the follow-up period was for a total of 24 months the sponsor proposed to evaluate the relapse rate at 6 months post therapy as a surrogate marker for long term efficacy. The FDA deemed this acceptable. In 1998 the FDA granted accelerated approval for rifapentine to be used in combination with INH and [redacted] for the treatment of pulmonary tuberculosis. To obtain full approval the sponsor was required to submit to the FDA the 24 month follow-up data. This NDA supplement contains the 2 year follow-up data and will be the topic of discussion of this review.

Summary:

Summary of the Original Study Design - Protocol 473PR0008:

Clinical study 473PR0008 was conducted in South Africa, Canada and North America. Patients were randomized 1:1 to receive therapeutic regimen A or B.

Treatment A

Intensive phase (60 days)

Isoniazid - 300 mg/day
Rifampin - 450 - 600 mg/day
[redacted]
Pyridoxine - 50 mg/day

Continuation phase (120 days)

Isoniazid - 600-900 mg twice a week
Rifampin - 450 - 600 mg twice a week
Pyridoxine - 50 mg/day

Treatment B

Intensive phase (60 days)

Isoniazid - 300 mg/day
Rifapentine - 600 mg/twice a week
[redacted]
Pyridoxine - 50 mg/day

Continuation phase (120 days)

Isoniazid - 600-900 mg twice a week
Rifapentine - 600 mg once a week
Pyridoxine - 50 mg/day

The primary endpoint in this study was microbiologic, i.e., the eradication of *M. tuberculosis* organisms from the sputum of infected subjects. Activity was measured as the time to sterilization of sputum cultures, as well as the rate of relapse post-therapy. For the purpose of accelerated approval the therapeutic response at the end of 6 months follow-up was used as the surrogate marker to demonstrate drug activity in each treatment arm provided 24 month post-therapy data would be submitted for review.

In the intensive treatment phase of the study isoniazid (INH), [redacted] and rifampin or rifapentine were administered. A fourth drug, [redacted] was administered until susceptibility test results were available in the event that a multi-drug resistant strain (MDRTB) was present. If the *M. tuberculosis* (MTB) isolate was susceptible to isoniazid, rifapentine, rifampin and [redacted] was dropped from the treatment regimens. For patients to be evaluable their baseline *M. tuberculosis* isolate had to be susceptible to isoniazid, rifapentine, rifampin[redacted]

At various time points during the study 1-3 sputum samples were collected for microbiologic assessment. Three sputum samples were collected at baseline. During the treatment phase of the study two sputum samples were collected at days 15, 30, 60, 90, 120, 150 and 180. During the follow up period a single sputum sample was collected at months 3, 6, 12, 18 and 24. At each time point early morning sputum samples were collected and shipped to the reference laboratories where they were processed for mycobacterial culture and smear. Specimens of poor quality were to be replaced with sputum samples of better quality. Susceptibility testing was to be conducted on the baseline MTB isolates as well as organisms recovered from the sputum at day 30 and on every sputum culture positive for *M. tuberculosis* thereafter.

Susceptibility testing was conducted at the U.S. and South African reference laboratories using the agar proportion and the radiometric broth methods proposed by the National Committee for Clinical Laboratory Standards (NCCLS). Both rifampin and rifapentine minimum inhibitory concentrations (MICs) were determined using the radiometric broth method. Rifampin, but not rifapentine MICs were determined using the agar proportion method.

Listed below were the proposed definitions for patient outcome used in the original NDA review.

> Treatment success: 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.
>
> Treatment failure: patients who either failed to achieve negative sputum culture, patients who achieved negative cultures through 6 months of post treatment follow-up (and for the remainder of the 2 year follow-up period), or patients who failed to remain on study due to death, adverse event, loss to follow-up regardless of the last available culture result.
>
> Relapse: a positive sputum that occurs after the patient's sputum culture has converted to negative and has completed therapy. Bacteriologically confirmed relapse consists of a single culture with a colony count of >10 and/or 2 or more cultures with a colony count <10CFU. The investigator should obtain at least 2 additional confirmatory cultures (i.e. a total of 3 specimens collected on 3 separate days).

Comments regarding Relapse at 24 months post-therapy:

During the review of the original clinical trial data the above described definitions were used to classify patient responses. At that time it was agreed that patients that had only a single [redacted] bottle positive for MTB or <10 colony forming units (CFUs) of MTB on solid medium with additional negative cultures were to be defined as a "Success".

These same definitions were used in the analysis of the 24 month post therapy data submitted in this NDA supplement. At 24 months post therapy there were 12 and 4 patients in the rifapentine and rifampin arms, respectively, that had single random positive MTB events with additional negative follow-up cultures. This reviewer considered these subjects a "Success".

One scenario that was not taken into account when developing the efficacy definitions in the original review was a situation where the patient's last culture was positive for MTB with no additional culture results. If a second culture result were to be positive for MTB the patient would be considered a relapse. However, if there were a negative MTB culture after the random positive event that patient would be considered a success.

In discussions with the reviewing medical officer, Dr. Joyce Korvick, it was decided that patients in this scenario should be analyzed both ways (i.e., success and relapse). In the rifapentine and rifampin arms there were 6 and 4 subjects, respectively, who fell into this category (i.e., last culture positive for MTB with no additional follow-up data). Listed in tables 1 and 2 are the individuals that had bacteriologic confirmed relapses or random positive MTB events.

NDA 21024.SLR
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Table 1

SPUTUM CULTURE STATUS: RIFAPENTINE ARM (24 MONTH FOLLOW-UP)

PID	Baseline MICs (µg/ml)	Day180 Result	Month Follow-up Culture Result	Additional Follow-up	FDA Outcome
Patients with no additional follow-up data					
22-015	<.5/<.125	-	18-;24(B+)	No	?
22-231	<.5/<.125	-	3,6,12 -; 18(B+)	No	?
24-069*	<.5/<.125	-	6+, 18+	Relapse	Relapse
26-021	<.5/<.126	-	12,18-; 24+	No	?
28-033*	<.5/<.125	-	3,6-; 12+(B+x2)	Relapse	Relapse
46-203	<.5/<.125	-	6,12,18-; 24(B+)	No	?
46-214*	<.5/<.125	-	6-;12+X4	Relapse 18	Relapse
46-605#	<.5/<.125	-	6;12;18-; 24(B+,L4)	No	?
48-002#	<.5/.125	-	6,12,18-;24(B+) MDRTB	No	?
39-009*	<.5/<.125	-	3;5+x4	Relapse	Relapse
30-037*	<.5/<.125	-	3+?ID; 6+x2,12(B+)	Relapse	Relapse
Patients with additional negative follow-up data					
21-006	<.5/<.125	-	3,6 -; 12(L12)	18,24	No Relapse
26-210	<.5/<.125	-	6-; 12(B+)	18,24	No Relapse
26-215	<.5/<.125	-	6,12,18-;24(B+)	26	No Relapse
26-219	<.5/<.125	-	6-; 12(B+)	18,24	No Relapse
27-209	<.5/<.125	-	6,12,18-;24(B+)	24	No Relapse
28-016	<.5/<.125	-	6,12-; 18(B+)	24	No Relapse
29-009	<.5/<.125	-	3,6-;12(L12)	24	No Relapse
30-027	<.5/<.125	-	3(B+)	12,18,24	No Relapse
30-033#	<.5/<.125	-	3+TB (B+,L1)	6,12,18,24	?
30-301	<.5/<.125	-	6(B+)	18,24	No Relapse
33-004	<.5/<.125	-	6-;15(B+)	24	No Relapse
48-007	<.5/<.125	-	3(L8)	6,12,18,24	No Relapse

PID=patient identification number; <.5/<.125 µg/ml = minimum inhibitory concentrations (MICs) for rifampin and rifapentine; B+ = [redacted] positive medium; L6=six colonies of MTB isolated on [redacted] (-)= negative MTB culture; ?=unable to definitively determine patient outcome, patient to be assessed as a relapse and success; (#)= patients with inadequate follow-up at the time of the original NDA approval that are suspected of a potential relapse; (*)= patients that were considered a true relapse at the time of the original NDA approval; MDRTB= multi-drug resistant *M. tuberculosis*.

Table 2

SPUTUM CULTURE STATUS: RIFAMPIN ARM (24 MONTH FOLLOW-UP)

PID	Baseline MICs(µg/ml)	Day180 Result	Month Follow-up Culture Result	Additional Follow-up	FDA Outcome
Patients with no additional follow-up data					
22-230	<.5/<.125	-	6,12-;18(B+)	No	?
24-44	<.5/<.125	-	3,6-;12 6/6+;24(B+)	No	?
24-66	<.5/<.125	-	3,6,12-;18(B+)	No	?
30-34*	<.5/<.125	-	3,6,12-;18+X3	Relapse	Relapse
30-216*	<.5/<.125	-	3,6,12-;18+x2	Relapse	Relapse
30-38*	<.5/<.125	-	12,18-;24+X4	Relapse	Relapse
33-59#	<.5/<.125	-	3-;6(B+,L6)	12	No Relapse
46-610	<.5/<.125	-	6,12,18-; 24(B+)	No	?
46-13*	<.5/<.125	-	3,6-;12(B+,L1) 18(B+,L8)	Relapse	Relapse
Patients with additional negative follow-up data					
28-017	<.5/0.125	-	6,12-; 18(B+,L4)	24	No Relapse
30-004	<.5/0.125	-	3,6-;12(B+)	18,24	No Relapse
31-011	<.5/0.125	-	3+(L3)strep R	6,12,24	No Relapse
33-059	<.5/0.125	-	3-;6(B+,L6)	12	No Relapse
26-016	<.5/0.125	-	3+,no sens/RFLP	?	Dropped

PID=patient identification number; <.5/<.125µg/ml= minimum inhibitory concentration (MICs) for rifampin and rifapentine; B+ = [redacted] positive medium; L6=six colonies of MTB isolated on [redacted] (-)= negative MTB culture; RFLP = restriction fragment length polymorphism; strep R = streptomycin resistant strain of MTB; ?= unable to definitively determine patient outcome, patient to be assessed as a relapse and success; (#)= patients with inadequate follow-up at the time of the original NDA approval that are suspected of a potential relapse; (*)= patients that were considered a true relapse at the time of the original NDA approval; RFLP= restriction fragment length polymorphism.

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Table 3 shows the number of intent-to-treat subjects in the rifapentine and rifampin arms that fell into the various relapse categories during follow-up.

Table 3

Number of Tuberculosis Relapse Patients who Received Rifampin or Rifapentine Therapeutic Regimens

Response/#patients	Rifampin	Rifapentine
ITT patients	226	248
Relapses at 6 mo follow-up	11	24*
Relapses at 24 mo follow-up	15	29
Random Positive Events with no additional follow-up	4	6

ITT, Intent to treat patient population; mo - month
* - one patient was dropped due to loss to follow-up

At the end of 24 months of follow-up there were 4 and 5 additional culture confirmed cases of MTB relapse in the rifampin and rifapentine arms, respectively. This brought the total number of relapse subjects to 15/226 (6.6%) in the rifampin arm and 29/248 (11.7%) in the rifapentine arm.

A second analysis was performed where the subjects that had a random positive MTB event with no additional follow-up data were classified as relapses. In this worse case scenario, there were 19/226 (8.4%) and 35/248 (14.1%) subjects who relapsed in the rifampin and rifapentine arms, respectively.

In both analyses the incidence of tuberculosis relapse in the rifapentine arm versus the rifampin arm was approximately 1.8:1. The 48 month follow-up relapse data are consistent with the efficacy findings at 6 months post therapy. The data demonstrate that the potential for relapse is approximately twice as great when a therapeutic regimen contains rifapentine versus rifampin. The few

additional cases of MTB relapse between 6 and 24 months post therapy suggest that the 6 month post therapy time assessment point is a good surrogate marker to measure the activity of rifamycin containing therapeutic regimens against pulmonary tuberculosis.

Comments regarding Restriction Fragment Length Polymorphism:

The sponsor conducted Restriction Fragment Length Polymorphism (RFLP) on all relapse *M. tuberculosis* isolates and baseline MTB isolates recovered from the same patient. RFLP is a DNA fingerprinting tool used to identify specific strains of *M. tuberculosis*. *M. tuberculosis* DNA fragments are separated by the *pvu*II endonuclease. These fragments are then tagged by the insertion of numerous copies of the DNA probe IS*6110* and separated by electrophoresis. The distinct number and location of the DNA probe IS*6110* produces a unique RFLP pattern (bands) specific to that MTB strain.

In the NDA submission the sponsor only describes the number of RFLP bands that are common between the baseline MTB isolate and the MTB isolate recovered from the patient at the time of relapse. The RFLP patterns were not available to the reviewing microbiologist for an independent assessment. Of the pairs of MTB isolates tested (baseline isolate and follow-up isolate from the same patient) the majority of them had the same RFLP pattern with most of the pairs having >10 bands in common.

Of the 29 patients in the rifapentine arm that relapsed, 22 had the same RFLP pattern suggesting a true relapse. RFLP patterns were not available for 3 subjects. Four patients, 22-214, 22-229, 46-214 and 46-202 had different RFLP patterns for the MTB isolates recovered during follow-up suggesting that they had become infected with a new strain of MTB and were not true relapses.

Of the 15 rifampin subjects that relapsed, the sponsor stated that 10 had the same RFLP pattern suggesting true relapse of the initial MTB disease. The RFLP patterns could not be determined for three rifampin relapse subjects. Two patients 26-014 and 29-024 appear to have become infected with a different strain of MTB after completion of initial therapy (i.e. a different RFLP pattern on the relapse strain compared to the baseline isolate).

While the RFLP data are of interest it should be reiterated that the raw data were not provided in the NDA, thus the reviewing

microbiologist could not make an independent assessment of these findings. If in fact the RFLP data are accurate and the subjects with no RFLPs are not counted then there would be 22/248 (8.9%) true relapses in the rifapentine arm and 10/226 (4.4%) true relapses in the rifampin arm. The incidence of true relapse is again 2:1 for subjects enrolled in the rifapentine arm versus the rifampin arm.

Comments regarding Susceptibility Data:

In this clinical trial the agar proportion method and the radiometric broth method were utilized to determine the susceptibility of MTB isolates to various agents. The agar proportion method [redacted] was used to differentiate susceptible and resistant strains of MTB against INH, [redacted] rifampin, streptomycin, ethionamide, capreomycin and [redacted] It should be noted that the sponsor did not determine rifapentine MICs using the agar proportion method.

The radiometric broth method (BACTEC) employing [redacted] 7H12 broth, pH 6.8, (NCCLS procedure M24-T) was used to compare rifampin and rifapentine MIC values. Rifampin was tested at 0.5, 2.0, and 8.0 ug/ml and rifapentine at 0.125, 0.5, 2.0 and 8.0 ug/ml. The MTB isolate H37Rv was used as the control organism, yielding rifampin and rifapentine MICs of 0.5 ug/ml. It should be noted that rifapentine susceptibility testing should have been tested in serial 2 fold dilutions to more accurately measure the activity of rifapentine against MTB isolates.

Antimycobacterial susceptibility testing was conducted against all baseline MTB isolates and all MTB isolates recovered from patients either who failed therapy or relapsed. A total of 241 and 259 subjects in the rifampin and rifapentine arms, respectively, had baseline MTB isolates sent for susceptibility testing. In the rifampin and rifapentine arms there were 15 and 11 subjects, respectively, that had drug resistant MTB isolates at baseline. These subjects were dropped from the study. There were 226 and 248 baseline MTB isolates in the rifampin and rifapentine arms, respectively, that had rifampin MICs <0.5 ug/ml and rifapentine MICs <0.125 ug/ml. These data suggest that rifapentine MICs are 4 fold lower than rifampin MICs for susceptible strains of MTB.

Susceptibility patterns were evaluated on all MTB isolates recovered from relapse patients. Relapse rates after 24 months of follow-up were 11.7% (29/248) in the rifapentine arm and 6.6% (15/226) in the rifampin arm. Of the subjects in the rifampin arm, 13/15 (86.7%) remained pan-sensitive at the time of relapse. One subject, 22-0335 had a pan sensitive strain at baseline however, at month 6 of follow-up the MTB isolate recovered was streptomycin resistant. Patient 50-001 was considered a treatment cure after 24 weeks of therapy. At the 3 month follow-up visit there were no signs or symptoms of TB. However, at the 6 month follow-up visit the patient was symptomatic and *M. tuberculosis* was recovered from the sputum. Susceptibility testing was conducted showing the isolate to be resistant to INH, streptomycin, rifampin (MIC >8.0 ug/ml), rifapentine (MIC >8.0 ug/ml), [redacted] and ofloxacin. The RFLP pattern demonstrated that the two MTB isolates were the same suggesting relapse was due to the same MTB strain and that multi-drug resistance had occurred.

Twenty six of the 29 (89.6%) MTB relapse patients enrolled in the rifapentine arm had pan-sensitive MTB isolates both at baseline and at the time of relapse. One patient 22-225 developed INH resistance at the 3 month follow-up visit. A second subject 46-202, had a pan-sensitive strain of MTB at the time of enrollment. However, on day 120 of therapy, the MTB isolate recovered was multi-drug resistant. The RFLP patterns suggested that the multi-drug resistant tuberculosis (MDRTB) isolate was a new strain thus causing new disease. Lastly, subject 48-002, had a random positive MTB event at the 12 month follow-up visit with an MDRTB strain. There were two subsequent negative cultures, thus this patient was considered a success. These data suggest that relapse was not consistently associated with discernable drug resistance to either rifampin or rifapentine.

A total of eight rifampin resistant MTB isolates were recovered during this study. Four were baseline MTB isolates and 3 isolates were recovered during treatment or follow-up. One patient had a negative baseline culture and a positive culture at day 30. All eight MTB isolates were associated with multidrug resistance. Rifampin or rifapentine mono-resistance was not seen in either the rifampin or rifapentine containing arms. All 8 MDRTB isolates had a rifampin MIC of >8.0 ug/ml and a rifapentine MIC of >8.0 ug/ml using the BACTEC method. These data suggest that for *M. tuberculosis* organisms, there is total cross resistance between

rifampin and rifapentine. Additional MTB isolates must be tested to confirm these observations after appropriate validation and standardization susceptibility studies have been conducted. Due to the low number of patients, three, which developed rifamycin resistance during follow-up it is impossible to discuss the correlation between relapse of disease and the various rifamycin therapies. A significant number of MTB isolates recovered from patients who relapse will have to be evaluated before it can be determined if relapse of disease due to the same RFLP strain of MTB occurs when a particular rifamycin containing therapeutic regimen is used.

Lastly, it should be reiterated, as was stated in the original microbiology review of the rifapentine NDA that breakpoints for rifapentine have not been established. Rifapentine breakpoints for MTB strains will be determined after the sponsor has conducted appropriate validation and standardization susceptibility studies using both the agar proportion method, as well as the radiometric broth method.

Rifapentine Label:

In this NDA supplement the sponsor is proposing to change several sections of the rifapentine label. At this time the sponsor does not intend to change the microbiology section of the label. However, they have proposed new wording to the last paragraph of the clinical trials section describing the microbiologic results from study 189. Below is the sponsor's version of this paragraph followed by the FDA's recommended wording.

Sponsor's proposed new wording of the last paragraph of the Clinical Trials section:

In vitro susceptibility testing was conducted against [redacted] *M. tuberculosis* isolates recovered from 62 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 [redacted] (MIC ≤0.5 ug/ml) [redacted] The remaining eight patients [redacted] (MIC >8.0 ug/ml) *M. tuberculosis* isolates had rifapentine MICs of >8.0 ug/ml. [redacted]

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

FDA's recommended wording of the last paragraph of the Clinical Trials section:

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 rifampin susceptible (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 ug/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 >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.

Conclusions:

The sponsor conducted a single phase III clinical trial, 473PR0008, to compare a 6 month therapeutic regimen containing rifapentine to one containing rifampin in the treatment of pulmonary tuberculosis. In 1998 rifapentine received an accelerated approval based on 6 month follow-up data. At that time the sponsor committed to following all subjects for the entire 24 months. This NDA supplement contains the 24 month follow-up data from subjects who

completed study 473PR0008. As a consequence, the topic of discussion in this review will be the microbiologic results obtained during the 24 months of follow-up.

To characterize the microbiologic activity of the rifapentine and rifampin therapeutic regimens, an independent evaluation of the microbiologic results from patients enrolled in this study was conducted. Microbiologic relapses were defined as patients who had a positive baseline sputum culture that converted to negative, with continuous negative sputum cultures while on therapy, then a positive sputum culture for MTB during the follow-up period. For a sputum culture taken during follow-up to be considered positive there had to be ≥10 MTB CFUs per culture or two consecutive cultures with less than 10 colonies of MTB. Patients with random MTB positive events that occurred during follow-up with subsequent negative culture were considered a success. Patients that had a random positive MTB event with no additional cultures were classified two ways, a success or a relapse. Two separate analyses to assess the incidence of relapse were made. One included these random events and the second counted only the culture confirmed relapses.

At the end of 24 months of follow-up the incidence of culture confirmed relapse was 11.7% (29/248) in the rifapentine arm and 6.6% (15/226) in the rifampin arm. The relapse MTB isolates were pan-sensitive for 13/15 (86.7%) of the rifampin subjects and 26/29 (89.7%) of rifapentine relapse subjects. RFLP patterns were the same for 10/15 (66.7%) and 22/29 (75.9%) of the relapse MTB isolates from the rifampin and rifapentine arms, respectively, indicating true relapse.

The radiometric broth method [redacted] employing [redacted] 7H12 broth, pH 6.8, (NCCLS procedure M24-T) was used to compare rifampin and rifapentine MIC values. At the end of the study there were a total of 620 patients that had initial and subsequent MTB isolates. Of these isolates, 612 (98.4%) had rifampin and rifapentine MIC values of <0.5 and <0.125 ug/ml (2 isolates with rifapentine MICs of 0.25 ug/ml), respectively. All of these isolates were considered rifampin susceptible (MIC <1.0 ug/ml) using the agar proportion method. These data suggest that for rifampin susceptible MTB strains rifapentine MICs are 4-fold lower than rifampin MICs. The remaining eight patients (1.3%) were rifampin resistant with MIC values of >8.0 ug/ml and ≥1.0 ug/ml for the radiometric and agar proportion methods, respectively. The rifapentine MIC values for these rifampin resistant MTB isolates were >8.0 ug/ml (radiometric

method). The increase in rifapentine MICs seen with the rifampin resistant MTB isolates (an average increase of 128-fold compared to rifampin susceptible isolates), suggests resistance. However, this statement cannot be confirmed until the susceptibility validation studies are completed. Of note, while the number of rifampin resistant isolates recovered during this study is small the data suggest that the incidence of cross-resistance between rifapentine and rifampin is high. Cross-resistance between rifapentine or rifampin and other non-rifamycin drugs was not observed. At the present time it is not possible to compare breakpoints between rifampin and rifapentine as rifapentine breakpoints have NOT been established using either the agar proportion method or the radiometric broth susceptibility method.

In conclusion, with respect to microbiology the proposed changes to the rifapentine label are acceptable and this NDA should be taken off accelerated approval and given full approval.

Recommendations:

The sponsor should continue performing the FDA recommended validation and standardization susceptibility studies described in the original NDA review.

/S/

Linda L. Gosey
Microbiologist (HFD 590)

Concurrences:
HFD-590/Div Dir /S/ Signature 10/13/00 Date
HFD-590/Micro TL /S/ Signature 10/11/2000 Date

CC:
HFD-590/Orig.NDA#21-024
HFD-590/Division File
HFD-590/MO:Korvick
HFD-590/CSO:WillardD
HFD-590/Chem:Smith
HFD-590/Pharm:McMaster
HFD-590/Review Micro:Gosey