

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21024

MICROBIOLOGY REVIEW(S)

Microbiology Review

Division of Special Pathogens and Immunologic Drug Products

(HFD-590)

NDA# 21-024

Reviewer : Linda Gosey
Correspondence Date : 12-22-97
CDER Receipt Date : 12-24-97
Review Assigned Date: 12-29-97
Review Complete Date: 06-12-98

Sponsor: Hoechst Marion Roussel
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Submission Reviewed: Original NDA, Supplement BI,

APPROVED FOR
ON 06/12/98

Drug Category: Anti-tuberculous

Indication: Treatment of pulmonary tuberculosis

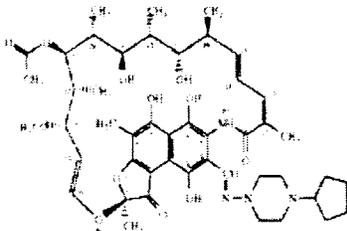
Dosage Form: Oral tablets: 150 mg

Product Names:

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- Proprietary: Priftin
- Nonproprietary: Rifapentine, MDL 473, DL473-IT
- Chemical: (3-(((4-cyclopentyl-1-piperazinyl)imino)methyl)-rifamycin)

Structural Formula:



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Background:

Every year approximately 3 million people die from tuberculosis. Treatment of pulmonary tuberculosis requires multiple drug therapy for a period of 6 to 12 months depending upon the therapeutic regimen. Most therapeutic regimens contain isoniazid (INH), rifampin (RIF) and pyrazinamide (PZA) in conjunction with either ethambutol (EM) or streptomycin (S). Even with multiple drug regimens as the standard of care drug resistance to INH and RIF is an emerging problem. In many cases drug resistance development is due to non-compliance. As a consequence, directly observed therapy (DOT) is recommended.

In this NDA the sponsor is seeking approval of rifapentine for the treatment of pulmonary tuberculosis. In support of this indication the sponsor has compiled data from a single phase III open label, randomized, multi-center, comparative clinical trial where a rifapentine containing therapeutic regimen was compared to a rifampin-based drug regimen. In addition, the sponsor has submitted pre-clinical articles describing the anti-tuberculous activity of rifapentine. Some of these articles were submitted earlier in the IND and were reviewed at that time. Preclinical studies that have not been previously reviewed are discussed in an addendum to this review.

It should be noted that the references cited in this review are numbered as they appear in the NDA submission. As a consequence, they may not appear in numerical order in this review.

Summary:

Preclinical Microbiology Review:

Metabolism of Rifapentine:

Rifapentine is metabolized into several byproducts. The 25-desacetyl metabolite is readily found in humans after oral administration and appears to be the only metabolite that has activity against tubercle bacilli. Rifapentine and the 25-desacetyl metabolite demonstrated comparable in vitro activity

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when tested against *M. tuberculosis* organisms. Both rifapentine and the 25-desacetyl metabolite accumulate in human macrophages with intracellular/extracellular ratios of approximately 24.0:1 and 7.2:1, respectively (58).

Mechanism of Action and Resistance:

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The rifamycin class of antibiotics includes several well characterized 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.

The mechanism of rifamycin action and potential mechanisms of drug resistance development in *M. tuberculosis* strains have been characterized most extensively with rifampin. As such, observations made with this drug serve as the basis for characterization of other rifamycins, including rifapentine.

The mechanism of action of rifampin was determined using *E. coli* strains(5), then subsequently confirmed in susceptible strains of *M. tuberculosis* organisms. RNA polymerase mediates the transcription of DNA to RNA. Rifampin binds to the B subunit portion of the RNA polymerase enzyme and blocks the initiation of transcription and RNA elongation. The overall inhibition of RNA synthesis by rifampin is caused by a destabilizing effect on the binding of the intermediate oligonucleotides to the active enzyme-DNA complex.

Resistance to rifampin involves the gene that encodes the RNA polymerase subunit B (rpoB). Previous studies have identified mutations in a 23 amino acid region in the 411 bp rpoB fragment in rifampin resistant strains of *M. tuberculosis*. Investigators Telenti et. al.(2) cloned this region of the RNA polymerase and subsequently compared the sequence in rifampin susceptible and resistant strains of *M. tuberculosis*. Susceptible strains did not have mutations within this conserved region of the RNA polymerase and the rpoB sequence was identical to that of the H37Rv strain. In the 66 rifampin resistant strains of *M. tuberculosis* studied fifteen different mutations were observed. The majority had a single nucleotide mutation. Only 5 isolates exhibited multiple mutations.

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Miller *et. al.*(6) confirmed this mechanism of drug resistance development by identifying and sequencing the *rpoB* gene of MTB strain H37Rv and comparing it to the same gene for *M. leprae* and *E. coli*. They found that in *E. coli* strains, rifampin resistance was associated with a total of 17 different mutations within the *rpoB* gene. These mutations included 14 point mutations, 2 deletions, and 1 insertion. To confirm that these mutations were responsible for rifampin resistance, allelic exchanges to a plasmid expressing mutant *rpoBs* took place. Rifampin susceptibility testing was then conducted to demonstrate that the plasmid conferred a rifampin resistant phenotype to rifampin susceptible *E. coli* organisms.

In the evaluation of rifampin resistance in MTB isolates 15 different mutations were found which altered 8 codons. These mutations corresponded to the same mutated regions identified in *E. coli* strains. To confirm that these altered regions of the *rpoB* gene produced rifampin resistance the investigators transformed *M. smegmatis* organisms which were initially rifampin susceptible to rifampin resistant phenotypes through the introduction of a rifampin resistant allele on the *rpoB* gene.

Like rifampin, rifapentine inhibits DNA-dependent RNA polymerase in susceptible strains of bacteria (i.e. *Escherichia coli*) and *M. tuberculosis* but not in mammalian cells. 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.

Bodmer *et. al.*(74) used the radiometric broth susceptibility method to determine the MIC patterns of rifampin, rifabutin and rifapentine against both rifampin susceptible and resistant strains of MTB. Rifapentine MICs ranged from <0.015 to 0.125 ug/ml for rifampin susceptible strains of MTB. Mutations at amino acid positions 513, 526 and 531 of the *rpoB* regions were associated with high levels of cross resistance to all three rifamycins. Mutations at positions 511, 516, 518 and 522 were associated with rifabutin MICs of 0.25 to 1.0 ug/ml and high MIC values (4 - >8 ug/ml) for rifampin and rifapentine (See table 1). When tyrosine was substituted for aspartate at position 516 moderate susceptibility to rifampin and rifapentine was observed; MICs of 2.0 and 0.5 ug/ml, respectively. Moghazeh *et al.*(75) provided additional confirmatory evidence that high

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levels of cross-resistance exist between rifampin and rifapentine. These data show that the majority of the *rpoB* gene mutations studied produced rifampin and rifapentine MIC values of >32 ug/ml (See table 2).

Table 1

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Rifamycins in rifampicin-resistant *M. tuberculosis*

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Table. Comparison of *rpoB* genotype and antimicrobial susceptibility test results for 36 isolates of *M. tuberculosis*.

mutation position ^a	Genotype amino acid substitution	isolates (n)	Phenotype MIC (mg/L)		
			rifampicin	rifabutin	rifapentin
Wild type	wild type	10	0.25-0.5	<0.015-0.125	<0.015-0.125
Leu 511	Pro	1	>8.0	0.5	>8.0
Gln 513	Leu	1	>8.0	>8.0	>8.0
Asp 516	Tyr	2	2.0	0.25	0.5
Asp 516	Val	3	≥8.0	0.25-0.5	4.0->8.0
Asn 518	deletion	1	>8.0	1.0	4.0
Ser 522	Leu	1	>8.0	0.5	8.0
His 526	Arg	2	>8.0	>8.0	>8.0
His 526	Asp	3	>8.0	>8.0	>8.0
His 526	Pro	2	>8.0	>8.0	>8.0
His 526	Tyr	3	>8.0	>8.0	>8.0
His 526; Val 498	Gln; Ala	2	>8.0	8.0	>8.0
Ser 531	Leu	3	>8.0	4.0->8.0	>8.0
Ser 531	Trp	1	>8.0	8.0	>8.0
Ser 531	Tyr	1	>8.0	>8.0	>8.0

^aNumbers correspond to *E. coli* RNA polymerase amino acid positions.

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Table 2

Clinical isolates of *M. tuberculosis* with *rpoB* gene mutations tested against rifampin, rifapentine and KRM-6148

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Strain	FP*	No. of tests	Culture date ^b	Amino acid position	Base change(s)	Amino acid change(s) ^c	MIC (µg/ml) of:		
							RMP	RPE	KRM
TN801	001	14	8/93	511, 512	CTG to CCG, AGC to AOC	Leu to Arg, Ser to Thr	2	1	<1
TN794	AH	4	8/93	511, 516	CTG to CCG, GAC to TAC	Leu to Arg, Asp to Tyr	>32	>32	<1
TN715	AB	11	4/93	513	CAA to AAA	Gln to Lys	>32	>32	16
TN806	CP	7	7/93	513	CAA to CTA	Gln to Leu	>32	>32	16
TN1733	AF3	12	5/93	513, 514	Deletion of CAA, TTC	Deletion of Gln, Phe	>32	>32	8
TN728	001	14	4/93	513-516	Deletion of AA-TTC-ATG-G	Gln-Phe-Met-Asp to His	>32	>32	<1
TN804	AR1	12	8/93	516, 517	Deletion of GAC, CAG	Deletion of Asp, Gln	>32	>32	8
TN1916	C	3	8/92	517, 518	Deletion of CAG, AAC	Deletion of Gln, Asn	>32	>32	16
TN877	C	3	8/92	517, 518	Deletion of CAG, AAC	Deletion of Gln, Asn	>32	>32	16
TN865	W	16	7/92	526	CAC to TAC	His to Tyr	>32	>32	32
TN635	W1	17	7/93	526	CAC to TAC	His to Tyr	>32	>32	>32
TN3806	W1	17	8/94	526	CAC to TAC	His to Tyr	>32	>32	>32
TN800	L	3	8/93	526	CAC to TAC	His to Tyr	>32	>32	16
TN994	T	12	9/92	526	CAC to AAC	His to Asn	16	16	4
TN644	A	8	1/93	526	CAC to GAC	His to Asp	>32	>32	16
TN981	AC	7	7/92	526	CAC to GAC	His to Asp	>32	>32	16
TN659	CM	19	12/92	526	CAC to CTC	His to Leu	8	8	8
TN792	001	12	8/93	526	CAC to CTC	His to Leu	8	8	<1
TN640	AT	7	1/93	531	TCG to TTG	Ser to Leu	>32	>32	>32
TN1811	W12	16	2/94	531	TCG to TTG	Ser to Leu	>32	>32	>32
TN807	001	14	7/93	531	TCG to TGG	Ser to Trp	>32	>32	2
TN798	001	11	8/93	531, 514	TCG to TTG, TTC to TTT	Ser to Leu, Phe to Phe	>32	>32	16
TN805	H	2	8/93	531, 528	TCG to TTG, CGC to CGT	Ser to Leu, Arg to Arg	>32	>32	>32
TN1595	N2	15	10/93	533	CTG to CCG	Leu to Pro	>32	>32	4
TN657	H	2	2/93		Wild type	Wild type	1	1	1

* FP, IS6110 DNA fingerprint code (letter assignment described previously [10]). Unique (not previously identified) fingerprints were assigned code 001.
^b Month/year.
^c Amino acid abbreviations: Arg, arginine; Asn, asparagine; Asp, aspartic acid; Gln, glutamine; His, histidine; Leu, leucine; Lys, lysine; Met, methionine; Phe, phenylalanine; Pro, proline; Ser, serine; Thr, threonine; Trp, tryptophan; Tyr, tyrosine.
^d RMP, rifampin; RPE, rifapentine; KRM, KRM-6148.

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References cited:

Reference 2: Telenti, et al., 1993. Detection of rifampicin resistance mutations of *Mycobacterium tuberculosis*. Lancet. 341:647-650.

Reference 5: Wehrli. 1983. Rifampin: mechanism of action and resistance. Rev. Infect. Dis. 5:S407-411.

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Reference 6: Miller, et al., 1994. The *rpoB* gene of *Mycobacterium tuberculosis*. Antimicrob. Agents Chemother. 38: 805-811.

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Reference 58: Mor, et al., 1995. Comparison of activities of rifapentine and rifampin against *Mycobacterium tuberculosis* residing in human macrophages. *Antimicrob. Agents Chemother.* 39:2073-77.

Reference 74: Bodmer, et al., 1995. Mutation position and type of substitution in the B-subunit of the RNA polymerase influence in vitro activity of rifamycins in rifampin-resistant *Mycobacterium tuberculosis*. *J. Antimicrob. Chemother.* 35:345-48.

Reference 75: Moghazeh, et al., 1996. Comparative antimycobacterial activities of rifampin, rifapentine, and KRM-1648 against a collection of rifampin-resistant *Mycobacterium tuberculosis* isolates with known rpoB mutations. *Antimicrob. Agents Chemother.* 40:2655-57.

Clinical Studies:

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Protocol 000473PR0008:

In support of the NDA 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. The study was conducted in South Africa, Canada and North America.

Patients were randomized 1:1 to receive therapeutic regimen A or B (shown on the following page).

Treatment A

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Intensive phase (60 days)

Isoniazid - 300 mg/day
Rifampin - 450 - 600 mg/day
Pyrazinamide - 1500 or 2000 mg/day
Ethambutol - 800 or 1200 mg/day
Pyridoxine - 50 mg/day

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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
Pyrazinamide - 1500 or 2000 mg/day
Ethambutol - 800 or 1200 mg/day
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

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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 sponsor proposed to use the therapeutic response at the end of therapy (day 180) as a surrogate marker to demonstrate drug activity in each treatment arm. This proposal was deemed to be acceptable. For full approval data on relapse rates up to 48 months post-therapy are required.

The secondary objectives of this study were to evaluate the pharmacokinetics of rifapentine as they relate to patient demographics, concomitant medications and disease state.

In the intensive treatment phase of the study isoniazid (INH), pyrazinamide (PZA) and rifampin or rifapentine were administered. A fourth drug, ethambutol, was administered until susceptibility test results were available in the event that a multi-drug resistant strain was present. If the *M. tuberculosis* (MTB) isolate was susceptible to isoniazid, rifapentine,

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rifampin and pyrazinamide, then ethambutol was dropped from the treatment regimens. Patients with baseline *M. tuberculosis* isolates resistant to isoniazid, rifapentine, rifampin or pyrazinamide were discontinued from the study and treated with alternative therapy.

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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.

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The proposed definitions for patient outcome were as follows: successful treatment, probable successful treatment, relapse or treatment failure. Patients that met one of the two "successful" definitions had to have two consecutive months of negative sputum cultures after 60 to 180 days of treatment which remained negative throughout the 2 year follow-up or through the last available follow-up visit. The proposed definition for relapse, was the presence of at least 10 colonies of *M. tuberculosis* in two or more sputum samples after at least two consecutive sputa had been negative for MTB.

Given that the primary endpoints in this multi-center clinical trial were microbiologic and the trial was conducted in multiple countries it was imperative that steps be taken to ensure that the microbiologic data derived from the study be consistent and comparable to the extent possible. For this study clinical samples collected in Canada and the United States were shipped to Dr. Heifets' laboratory in Denver for culture and susceptibility testing. Samples collected in South Africa were processed at the University of Natal Medical Microbiology Laboratory, Republic of South Africa, headed by Professor A. W. Sturm.

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The procedures used for isolation and identification of *M. tuberculosis* were as follows. Sputum samples were processed using the sodium hydroxide/N-acetyl L-cysteine digestion decontamination procedure. The staining procedures employed in this study included the auramine-O and Ziehl-Neelsen techniques. Clinical samples processed in the United States for mycobacteria were identified to the species level using the Accuprobe system. At the South African reference laboratory the following biochemical tests results were used to confirm the identification of the infectious organisms as MTB: colonial morphology, growth at only niacin positive, nitrate positive and negative 68°C catalase test. Thiophene-2-carboxylic acid hydrazide (TCH) and PZase tests were conducted only on the initial baseline mycobacterial isolates. Four biochemical tests were used at both laboratories to differentiate between *M. bovis* and *M. tuberculosis*. MTB isolates recovered from patients suspected of disease relapse were evaluated by restriction fragment length polymorphism (RFLP) analysis. RFLP results were available on 14 patients at the time of the filing of this NDA.

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. During the clinical trial Dr. Heifets conducted additional (proficiency) testing procedures to ensure that the two laboratories were producing reproducible data and that susceptibility test results were comparable.

Clinical Trial Study Results:

Incidence of MTB:

In study 473PR0008 a total of 283 and 284 patients were treated with multi-drug regimens containing rifampin and rifapentine, respectively. All of these patients were included in the intent to treat (ITT) analysis. To be considered "evaluatable", per the protocol design, patients could not be pregnant or HIV positive at baseline, had to have received study drugs and had a

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positive MTB culture at baseline with an organism susceptible to isoniazid (INH), rifampin, pyrazinamide (PZA) and ethambutol (EM). The sponsor also eliminated subjects from the evaluable population who did not complete the intensive or continuation phases of therapy or did not return for evaluation during the follow-up period. As a result, a total 218 and 227 patients were considered microbiologically evaluable in the rifampin and rifapentine treatment arms, respectively (See table 3).

Table 3

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**CRITERIA FOR EXCLUDING PATIENTS FROM THE
 EVALUABLE PATIENT POPULATION FOR MICROBIOLOGIC
 EVALUATION OF RIFAPENTINE ACTIVITY**

Criteria/#patients	Rifampin	Rifapentine
ITT patients	283	284
1° Exclusion criteria		
Baseline culture negative	1	1
HIV positive	9	4
Not treated	1	2
Baseline MTB resistant	2	3
2° Exclusion criteria		
Incomplete therapy	43	31
No follow up cultures	9	16
Modified ITT patients	218	227

ITT, intent to treat; MTB, *M. tuberculosis*;

M. tuberculosis failures and relapses:

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. To accomplish this the definitions described below were used to classify therapeutic responses in the evaluable population. To be considered a microbiologic cure

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patients had to have a positive baseline MTB culture that become negative during therapy. Also, once sputum cultures became negative for MTB they had to remain negative for the entire treatment period with at least two consecutive negative sputum cultures prior to the end of therapy (day 180) and at least one negative follow-up sputum culture. Patients who were considered a failure had to have completed therapy, had positive MTB cultures throughout the treatment period or have intermittent negative sputum cultures during therapy with positive cultures before and after the negative sputum cultures. 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.

The FDA's intent to treat microbiologic analysis was designed to obtain greater information regarding rifapentine's activity against pulmonary tuberculosis (Table 4). In this analysis the microbiologic results from each patient were evaluated. Because this assessment takes into account only the microbiologic data and is dependent upon interpretation of the microbiologic definitions, the number of patients placed in each category may vary from those described by the sponsor or the figures discussed in the medical officer review.

Table 4

**MICROBIOLOGIC RESPONSES FOR THE
 MODIFIED INTENT TO TREAT PATIENTS**

Response/#patients	Rifampin	Rifapentine

MITT patients	218	227

Failures	6	4
Relapses	11	25
Random Positive Cultures		
M. tuberculosis	7	13
MOTTS	21	16
MAC	1	0
No Identification	12	8
Cures	160	161

MITT, modified intent to treat; MOTTS, Mycobacterium other than tuberculosis;
 MAC, Mycobacterium avium complex;

In this study the number of patients who failed therapy in the rifapentine arm was greater in the FDA microbiology analysis compared to that provided by the sponsor (4 versus 1, respectively). The larger number of rifapentine failures in the FDA analysis is due to a more strict interpretation of the definition for failure. The FDA counted patients as a failure if: 1) they had a positive sputum culture for MTB on day 180 followed by subsequent positive cultures or 2) they had positive cultures up to or on day 150, a negative culture at day 180 and then subsequent positive cultures during follow-up (starting at month 3). Based on this definition 6 (2.8%) and 4 (1.8%) treatment failures were identified in the rifampin and rifapentine arms, respectively. With respect to drug resistance development, 2/6 (33%) of the patients in the rifampin arm developed INH resistance (0/4 in the rifapentine arm). None of the patients in either treatment arm developed mono-resistance to rifampin while on study drugs. Rifapentine resistance could

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not be determined as susceptibility breakpoints have not yet been established.

An in depth evaluation of patients that relapsed following the completion of both the intensive and continuation phases of therapy was also performed. Both the sponsor and the FDA agreed that 11 (5.0%) of the patients in the rifampin arm and 25 (11.0%) in the rifapentine arm relapsed. Of the patients in the rifampin arm, one relapsed with an MDRTB strain, 1 developed resistance to streptomycin and 8 were sensitive to all of the study drugs (i.e., "pan-sensitive"). In the rifapentine arm, one patient developed multi-drug resistance on day 150 of therapy, one developed INH resistance and 23 had pan-sensitive strains of MTB at the time of relapse.

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In the protocol it was stated that an analysis of restriction fragment length polymorphism (RFLP) would to be conducted on MTB isolates obtained from patients that relapsed following antituberculous therapy. At the time of this review, RFLP results were available on 7/11 (64%) and 11/25 (44%) of the relapse MTB isolates from the rifampin and rifapentine arms, respectively. In the rifampin and rifapentine arms 5/7 and 9/11 of these MTB isolates had the same RFLP pattern indicating that these patient relapses were due to the same strain of MTB. However, for the remaining 2/7 (rifampin) and 2/11 (rifapentine) patients the RFLP patterns were different, suggesting that these patients did not relapse, but instead, became infected with a different strain of MTB. The MDRTB strain recovered from a patient in the rifapentine arm had a different RFLP pattern. Unfortunately, RFLP testing was not performed on the MDRTB strain isolated from a relapse patient in the rifampin arm. The sponsor's interpretation of the RFLP results cannot be verified until the individual RFLP patterns are submitted to the Division for an independent assessment.

Another factor assessed was the time it took to clear MTB from sputum cultures and the rate of relapse. At the end of the intensive phase of therapy (day 60) sputum cultures were negative for MTB in 8/11 (73%) and 12/25 (48%) of the patients that ultimately relapsed in the rifampin and rifapentine arms, respectively. These data suggest that patients who do not clear MTB organisms from their lungs on or before day 60 were at a higher risk for relapsing if they were taking a rifapentine containing therapeutic regimen versus a rifampin therapeutic

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regimen. The exact cause for the longer clearance time and the higher rate of relapse in the rifapentine arm is unclear. However, the microbiologic data suggest that the rifapentine dose and/or schedule used in this clinical trial may not represent the optimal treatment regimen.

The ability to accurately interpret the microbiologic endpoints observed in this trial is confounded by the number and types of randomly occurring positive mycobacterial cultures. Isolates causing these random events were identified and categorized as MTB, *M. avium* complex (MAC), mycobacterium other than tuberculosis (MOTT) and "no identification". These random events occurred in 41/218 (18.8%) and 37/227 (16.3%) of the evaluable patients enrolled in the rifampin and rifapentine arms, respectively.

In this study random MTB positive cultures occurred in 7 (3.2%) and 13 (5.7%) patients in the rifampin and rifapentine arms, respectively. The majority of these patients had only one negative follow-up culture after the random event. In the rifampin and rifapentine arms, 4/7 and 3/13 of the random positives occurred at day 180 of treatment. The remaining positives occurred during the follow-up period.

With the currently available data it is not possible to determine if patients with random positive MTB cultures eventually relapsed at a later date. While these numbers are small it should be noted that the incidence of random positive cultures for MTB in the rifapentine arm was approximately twice that found in the rifampin arm. This incidence rate (1.86) approximates the ratio of relapses (i.e. 2.27:1) seen in the rifapentine and rifampin arms. Pending receipt of the follow-up data it is unknown whether these random events constitute true relapses.

A review of the culture results revealed a substantial number of positive cultures due to MOTT organisms. In the rifampin and rifapentine arms there were 21 (9.6%) and 16 (7.0%) MOTT events, respectively. The cause for this unusually high incidence of potential contamination is unknown. With the data submitted in the original NDA it is impossible to determine whether these isolates were actually a mycobacterial species other than tuberculosis or an *M. tuberculosis* isolate that was identified incorrectly. Additional information has been

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requested from the sponsor and will be addressed in an addendum to this review.

In some instances there were positive mycobacterial cultures where the isolate was not identified; 12 in the rifampin arm and 8 in the rifapentine arm. Fifty percent and 62.5% of these events occurred while patients were receiving the rifampin and rifapentine treatment regimens, respectively. Again, it is unknown what organism(s) produced these positive events. Additional information has been requested from the company and will be discussed in an addendum to this review.

Assessment of Susceptibility Data:

In this study the agar proportion method and the broth method were utilized to determine the susceptibility of the MTB isolates to various agents. The agar proportion method (middlebrook 7H10 agar containing 10% oleic acid, albumin, dextrose and catalase (OADC)) was used to differentiate susceptible and resistant strains of MTB against 0.2 and 1.0 ug/ml INH, 7.5 ug/ml ethambutol, 1.0 ug/ml rifampin, 2.0 and 10.0 ug/ml streptomycin, 10.0 ug/ml ethionamide and 10.0 ug/ml capreomycin. Susceptibility to PZA was also tested with this method using concentrations of 100, 300 and 900 ug/ml. It should be noted that the sponsor did not determine rifapentine MICs using the agar proportion method.

The broth method (BACTEC) employing middlebrook 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.

An evaluation of drug resistance development in this study found that treatment failures were not consistently associated with discernable drug resistance. The treatment relapse rates were 11% (25/227) for rifapentine and 5% (11/218) for rifampin. Treatment failures were 1.8% (4/227) in the rifapentine arm and 2.8% (6/218) in the rifampin arm. With respect to the patients who failed therapy, 2/6 in the rifampin arm developed INH resistance during the continuation phase of therapy. All of the patients in the rifapentine arm and the remaining 4/6 rifampin patients that failed therapy had pan-sensitive MTB

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strains at the end of therapy. While there were relatively few patients (n=46) that either failed or relapsed in either treatment arm, the data suggest that the development of rifampin mono-resistance is uncommon. In this study high MIC values for both rifampin and rifapentine were observed in MDRTB isolates that also displayed resistance to INH, PZA and ethambutol.

Cross-resistance between rifampin and rifapentine was also assessed. At the end of the study there were a total of 626 patients that had initial and subsequent MTB isolates. Of these isolates, 620 (99%) had rifampin and rifapentine MIC values of ≤ 0.5 and ≤ 0.125 ug/ml, respectively. All of these isolates were considered rifampin susceptible (MIC < 1.0 ug/ml) using the agar proportion method. The remaining 6 patients (1%) 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. This observation has also been confirmed in vitro by other investigators and the data are described in the "Resistance" section of this review.

Cross-resistance to the other non-rifamycin drugs was also evaluated. Of the 626 MTB isolates with susceptibility test results available 45 (7%) exhibited mono-resistance to the following: INH n=25, CAP n=14, streptomycin n=4, ethionamide n=1 and ethambutol n=1. In addition, there were 15 MTB isolates that were resistant to INH and at least one other agent. Six of these multi-drug resistant *M. tuberculosis* (MDRTB) isolates were resistant to rifampin in addition to the other agents. These data and supporting information from the published literature suggest that there is no apparent cross-resistance relationship between rifampin (and most likely other rifamycins) and the non-rifamycin anti-tuberculous agents tested in this study.

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The last issue to discuss with respect to rifapentine and rifampin susceptibility testing is the relationship between the MIC values for the two agents. In this study all MTB isolates with a rifampin MIC of ≤ 0.5 ug/ml had a rifapentine MIC of ≤ 0.125 ug/ml, using the BACTEC broth method. These data indicate that rifapentine MICs are typically about 4-fold lower than rifampin MICs for rifampin susceptible MTB strains.

At the present time is not possible to compare breakpoints for rifampin and rifapentine. Established breakpoints for rifampin using the radiometric broth method and the agar proportion method are 2.0 and 1.0 ug/ml, respectively. Rifapentine breakpoints have NOT been established as insufficient validation data are available for either susceptibility testing method. In addition, there is a problem with the interpretation of the rifapentine MICs using the radiometric broth method. Preliminary results from in vitro validation susceptibility studies conducted by the sponsor indicate that the minimum level of detection of resistant MTB organisms is approximately 10%. This inability to detect low levels of resistance with rifapentine (i.e. $< 10\%$) is unacceptable. A 1% detection level is necessary as drug resistance development and therapeutic response are closely linked. Failure to detect emerging resistance when it is between 1 and 10% of the total population could have serious implications with regard to the choice of appropriate treatment regimens and ultimately the rate of cure or relapse.

In addition, rifapentine MIC values derived from isolates recovered during the clinical trial were not provided using the established agar dilution method. This method is currently used in approximately 25% of the mycobacterial laboratories in the United States. As a consequence, rifapentine MIC values have not been established and cannot be determined until additional susceptibility validation studies are conducted. The company has agreed to conduct the appropriate studies as part of their phase IV commitment. An outline of the type of studies that should be performed to address this issue can be found in the "Recommendations" section of this review.

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Rifapentine Label:

The FDA and the sponsor have agreed to the following wording for the Microbiology sections of the rifapentine label:

1. Microbiology section:

Microbiology

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Mechanism of Action

Rifapentine, a cyclopentyl rifamycin, inhibits DNA-dependent RNA polymerase in susceptible strains of bacteria (i.e. *Escherichia coli*) and *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

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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.

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 medium. 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.

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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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2. The last paragraph of the Clinical Trials section:

In vitro susceptibility testing was conducted against initial and subsequent *M. tuberculosis* isolates recovered from 626 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 twenty patients with rifampin susceptible (MIC ≤ 0.5 ug/ml) strains of *M. tuberculosis* had rifapentine MICs of ≤ 0.125 ug/ml. The remaining 6 patients with rifampin resistant (MIC > 8.0 ug/ml) *M. tuberculosis* isolates had rifapentine MICs of > 8.0 ug/ml. This information is provided for comparative purposes only as rifapentine breakpoints have not been established.

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3. The second paragraph in the Indications and Usage section:

In the treatment of tuberculosis, the small number of resistant cells present within large populations of susceptible cells can rapidly become the predominant type. Consequently, clinical samples for mycobacterial culture and susceptibility testing should be obtained prior to the initiation of therapy, as well as during treatment to monitor therapeutic response. The susceptibility of *M. tuberculosis* organisms to isoniazid, rifampin, pyrazinamide, ethambutol, rifapentine and other appropriate agents should be measured. If test results show resistance to any of these drugs and the patient is not responding to therapy, the drug regimen should be modified.

Conclusions:

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Clinical:

In support of the indication proposed in the NDA the sponsor conducted a single phase III open label, randomized, multi-center, comparative clinical trial that evaluated the safety and efficacy of rifapentine combination therapy compared to standard therapy containing rifampin in the treatment of previously untreated pulmonary tuberculosis. The study was conducted in South Africa, Canada and North America. In the intensive phase of therapy (weeks 1-8) subjects received either INH, 300 mg; ethambutol, 800-1200 mg; and 1500-2000 mg PZA daily in combination with 600 mg rifapentine twice weekly or a comparable therapeutic regimen containing daily therapy with 600 mg rifampin. During the continuation phase of therapy (weeks 9-24 weeks) 600-900 mg INH was administered twice a week in combination with either 400-600 mg rifampin twice weekly or 600 mg rifapentine once a week.

The primary endpoints in this study were microbiologic and clinical. Efficacy was determined by assessing overall treatment cure and relapse rates. Data from the study show that the cure rates were comparable in both treatment arms. However, the relative risk for relapse in patients treated with the rifapentine therapeutic regimen was 2.3 times that found in the rifampin treatment arm. Clinical data also show that relapse rates were associated with the time to culture negativity. Among the patients who subsequently relapsed, at the end of the intensive phase of therapy (day 60) only 12/25 patients in the

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rifapentine arm had negative sputum cultures compared to 8/11 patients in the rifampin arm. These data suggest that patients on the rifapentine therapeutic regimen who did not clear MTB from their lungs during the intensive therapy phase were then at greater risk for possible relapse.

Of note, rifampin mono-resistance was not observed in any of the isolates recovered from either relapse group. It was not possible to directly define rifapentine resistance since breakpoints for susceptible and resistant MTB isolates have not been established. However, it should be noted that for the rifampin resistant MTB isolates rifapentine MICs increased 128-fold (from 0.125 to >8.0 ug/ml). All 6 rifampin resistant MTB isolates recovered during the clinical trial were associated with multi-drug resistance.

Information from the published literature and the microbiologic results from the clinical trial indicate that cross-resistance between rifampin and rifapentine is high. However, this cannot be confirmed until the sponsor conducts additional susceptibility studies to validate rifapentine breakpoints. Preliminary clinical results and published data do suggest that there is no apparent cross-resistance between rifampin or rifapentine and INH, pyrazinamide or ethambutol.

To better characterize the incidence of relapse, restriction fragment length polymorphism (RFLP) testing was conducted on MTB strains recovered from patients who relapsed following the completion of treatment. Currently, RFLP testing has been conducted on 64% and 44% of the relapse MTB isolates from the rifampin and rifapentine arms, respectively. The majority of these MTB isolates (71% from the rifampin arm and 82% from the rifapentine arm) had the same RFLP pattern indicating relapse (i.e. recurrence of disease with the same strain of MTB). The remaining patients had MTB isolates with different RFLP patterns suggesting that these patients became infected with a different strain of MTB after initiation of therapy.

In this study there were a substantial number of randomly occurring positive mycobacterial cultures; 18.8% and 16.3% of the evaluable patients enrolled in the rifampin and rifapentine arms, respectively. Seven and 13 of the random events in the rifampin and rifapentine arms, respectively, were due to MTB. At this time it is unknown if these patients relapsed at a

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later date as there are little or no follow-up data available. Also, it is of interest to note that the incidence of random positive MTB cultures found in the rifapentine arm was approximately twice that found in the rifampin arm. These results approximate the relative risk value of 2.3 for relapse found in the rifapentine arm.

Other random positive events were due to either MOTT organisms or organisms that were not identified. There were 21 MOTT events in the rifampin arm and 16 in the rifapentine arm, as well as 12 and 8 "no identification" events, respectively. The cause for this unusually high incidence of potential contamination is unknown. With the data submitted in the original NDA it is impossible to determine whether these isolates were a mycobacterial species other than tuberculosis or *M. tuberculosis* isolates that were incorrectly identified. Additional information has been requested from the sponsor to help address this issue.

Finally, there is a concern regarding the interpretation of the in vitro susceptibility test results obtained from the clinical trial. Prior to establishing susceptible and resistance breakpoints for a new agent validation studies must be performed. Studies should be conducted to assess how test conditions affect the susceptibility patterns of pertinent organisms against the new agent.

Contained in the NDA submission were preliminary results from initial validation susceptibility studies. In these studies various MTB isolates were tested against rifapentine using both the radiometric broth method and the agar proportion method. However, the studies did not evaluate the full spectrum of test conditions and their affect on rifapentine MIC values using both susceptibility methodologies. In addition, it was noted that when the proposed NCCLS radiometric broth method was employed resistance could not be detected until approximately 10% of the bacterial population was resistant. This level of resistance detection is not acceptable. Historical data show that a resistance level at or below 1% using either the agar proportion or the radiometric broth susceptibility testing methods correlates with a positive therapeutic response in the treatment of tuberculosis.

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The preliminary validation data demonstrating a lack of sensitivity in detecting low levels of resistance (i.e. <10%) using the radiometric broth method raises a question regarding the relevance of the rifapentine susceptibility results obtained during the clinical trial (using the radiometric broth method) and therapeutic outcome. Unfortunately, rifapentine MICs were not determined using the agar proportion method for the MTB isolates recovered during the clinical trial. As a result, the Division has asked the company to commit to phase IV studies to include additional in vitro susceptibility studies to establish and validate rifapentine breakpoints. A general outline of the studies to be conducted can be found in the "Recommendations" section of this review. Additional in vitro susceptibility data collected from the ongoing CDC *M. tuberculosis*/rifapentine clinical trial, USPHS 22, may also be useful in this regard.

Pre-clinical:

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Published articles submitted in this NDA application containing preclinical microbiology information will be discussed in an addendum to this review. Attached is a copy of the microbiology review that summarizes the preclinical data from published articles submitted

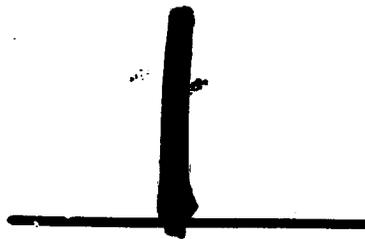
Articles describing the mechanism of action of rifapentine show that the drug inhibits DNA-dependent RNA polymerase in susceptible strains of *M. tuberculosis* but not in mammalian cells. Rifampin or rifapentine resistance development in *M. tuberculosis* strains is mainly due to one of several single point mutations that occurs in the *rpoB* region of the RNA polymerase subunit B. As a consequence, *M. tuberculosis* strains demonstrate a high level of cross-resistance to rifampin and rifapentine. 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. In vitro study results show that the 25-desacetyl metabolite also has activity against MTB strains. In addition, both rifapentine and the 25-desacetyl metabolite have been shown to concentrate in human monocyte-derived macrophages in a intracellular/ extracellular ratio of 24:1 and 7:1, respectively.

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In conclusion, with respect to microbiology this NDA is approved under the accelerated approval regulations pending the sponsor's final commitment to conduct the proposed microbiology phase IV studies.

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Linda L. Gosey
Microbiologist (HFD 590)

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- CC:
- HFD-590/ Orig.NDA#21-024
 - HFD-590/ Division File
 - HFD-590/ Asst Dir Med Affairs
 - HFD-590/MO:Korvick
 - HFD-590/CSO:AtkinsB
 - HFD-590/MicroTL:Lard
 - HFD-590/Chem:Smith
 - HFD-590/Pharm:McMaster
 - HFD-590/Review Micro:Gosey

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21024

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 21,024

Submission Date: 12/22/97, 2/9/98, 2/16/98,
3/18/98

Generic Name, Strength and Formulation:

Rifapentine, 150 mg Tablets

Brand Name: Priftin^(R)

Date Assigned: 12/30/97

Applicant: Hoechst Marion Roussel, Inc

Final Review: 6/17/98

Submission Code: 1P

Reviewer: Kofi A. Kumi, Ph.D.

BACKGROUND

This review contains a summary of the studies that were reviewed from the studies submitted to Section 6 (Human Pharmacokinetics and Bioavailability) in support of NDA 21,024. Individual data and appendices are on file in the Division of Pharmaceutical Evaluation III.

The applicant is seeking approval of rifapentine 150 mg tablet for the treatment of pulmonary tuberculosis in conjunction with at least one other antituberculosis drug to which the isolate is susceptible. The applicant is recommending a Priftin dose of 600 mg twice a week during the initial phase and weekly during the maintenance phase in the treatment of tuberculosis.

Rifapentine is a cyclopentyl structural derivative of the rifamycin class of antibiotics to which belongs rifampin and rifabutin. The rifamycins exert their antibacterial activity by forming a stable complex with the DNA-dependent RNA polymerase of susceptible bacteria, thereby blocking messenger RNA synthesis. Rifapentine and its major metabolite, 25-desacetyl rifapentine contribute 62% and 38%, respectively to the clinical activity against Mycobacterium Tuberculosis and 86% and 14%, respectively, to Mycobacterium Avium Complex (MAC). Rifapentine is more lipophilic than rifampin and has serum half-life about five times longer than rifampin.

SYNOPSIS

Bioavailability/Bioequivalence/Food Effect: The relative bioavailability (with hydroalcoholic solution as a reference) of rifapentine tablets (prototype phase III 150 mg tablet) under fasting conditions was determined to be 70%. The absolute bioavailability of rifapentine film coated tablets has not been determined.

The proposed commercial 150 mg film coated rifapentine tablet was determined to be bioequivalent to the tablet used in the pivotal clinical and pharmacokinetic studies. The mean AUC(0-∞) and C_{max} from the 150 mg commercial tablet were 94.7% and 88.0%, respectively, of that from the 150 mg phase III tablet.

hence, met the regulatory
requirement for determination of bioequivalence.

Following administration of a single 600 mg (4 x 150 mg commercial tablets) dose with a standard high fat breakfast (approximately 33g protein, 55g of fat, 58g of carbohydrate; total 850 calories), mean AUC(0-∞) and C_{max} increased by 43% and 44%, respectively when compared to administration of a similar dose of rifapentine under fasting conditions. The increase in AUC and C_{max} were statistically significant. The percent coefficient of variation (%CV) for AUC when rifapentine was given with and without food were 35% and 44%, respectively and for C_{max} the %CV with and without food were 26% and 33%, respectively.

Distribution/Protein Binding: Rifapentine and 25-desacetyl rifapentine are 97.7% and 93.2% bound to plasma protein, respectively. Rifapentine is mainly bound to albumin. Rifapentine distributes into plasma more extensively than the blood.

Metabolism/Mass Balance: Four male subjects received a single 600 mg oral dose of [¹⁴C]rifapentine hydroalcoholic solution in an open-label study. Mass balance studies show that 87% of radioactivity is recovered after oral administration, with greater than 80% of the dose excreted from the body within 7 days. Fecal excretion is the primary route of elimination with 70% of the dose being recovered in the feces. Urinary excretion of orally administered [¹⁴C]rifapentine comprised 17% of the dose. Rifapentine is hydrolyzed by an esterase enzyme to form 25-desacetyl rifapentine. Rifapentine and 25-desacetyl rifapentine account for 99% of the plasma radioactivity. In feces, formyl derivatives of rifapentine (formed via nonenzymatic degradation) and 25-desacetyl rifapentine were observed. The majority of radioactivity in the feces comprised of rifapentine, 25-desacetyl rifapentine, and formyl derivatives.

Rifapentine is an inducer of cytochrome P4503A (CYP3A), P4502C8/9 (CYP2C8/9). The induction potential relative to rifampin and rifabutin was evaluated in vitro using human hepatocyte cultures. The rank order of induction for both CYP3A and CYP2C8/9 were rifampin > rifapentine > rifabutin. The extent of CYP3A4 induction was evaluated in vivo in healthy volunteers after multiple dosing with rifapentine, using the ratio of urinary 6-β-hydroxycortisol/cortisol ratios. Generally, rifapentine induction of CYP3A4 as measured by 6-β-hydroxycortisol/cortisol excretion was less than that reported for rifampin and greater than that previously reported for rifabutin. Rifapentine, unlike other rifamycins, does not induce its own metabolism. The in vitro studies were reviewed by Dr. Houda Mahayni.

Pharmacokinetics

Single Dose/Dose Proportionality: A disproportionate, dose-dependent increase in exposure is observed as single oral doses of rifapentine increase from 150 to 600 mg. Over the entire dose range studies, 4-fold increase in dose from 150 to 600 mg resulted in about 5.5-fold increase in mean AUC(0-∞). Two-fold increases in dose from 150 to 300 mg and from 300 to 600 mg resulted in 2.4 and 1.8 fold increases in mean C_{max}, respectively. Over the entire dose range studies, 4-fold increase in dose from 150 to 600 mg resulted in a 4.4-fold increase in C_{max}. At steady-state, a 4-fold increase in dose from 150 to 600 mg results in 5-fold increase in both AUC_{ss} (0-24) and C_{max,ss}. After a single dose administration of rifapentine, 4-fold increase in dose from 150 to 600 mg resulted in about 6 fold increases in 25-desacetyl rifapentine mean AUC(0-∞). A 4-fold increase in dose from 150 to 600 mg resulted in about 6 fold increases in 25-desacetyl rifapentine C_{max}. The sponsor is recommending a 600 mg dose.

Multiple Dose Pharmacokinetics: Healthy Volunteers

Twenty-four healthy male volunteers between _____ received oral doses of rifapentine in a randomized 2-way incomplete block crossover design study. Each subject received 2 of the following 4 treatments: Treatment A: A single oral dose of 150 mg of rifapentine (1x150 mg tablet) given on day 1, followed by 150 mg daily dosing on days 4-10 for a total of 8 doses. Treatment B: A single oral dose of 300 mg of rifapentine (2x150 mg tablets) given on day 1, followed by 300 mg daily dosing on days 4-10 for a total of 8 doses. Treatment C: A single oral dose of 600 mg of rifapentine (4x150 mg tablets) given on day 1, followed by 600 mg daily dosing on days 4-10 for a total of 8 doses. Treatment D: A single oral dose of 600 mg of rifapentine (4x150 mg tablets) given on day 1, followed by a dose of 600 mg on days 4, 7 and 10 for a total of 4 doses. The mean steady-state plasma rifapentine and 25-deacetyl rifapentine pharmacokinetic parameters following administration of 600 mg rifapentine every 72 hour are presented in the following tables

Comparisons for Single Dose and Steady-State Rifapentine Pharmacokinetic Parameters Following Q72h Dosing						
Dose Level (Dose Schedule)	Parameter	Adjusted mean*	Pairwise Comparisons			
			Pair	Ratio (%)	90% CI on Ratio	P Value
600 mg (Q72h)	$C_{max,ss}$ (µg/mL)	15.71	$C_{max,ss}/C_{max}$	111	(83, 147)	0.405
	C_{max} (µg/mL)	14.18				
600 mg (Q72h)	$AUC_{ss}(0-72)$ (µg·h/mL)	335	$AUC_{ss}(0-72)/AUC(0-\infty)$	97	(83, 114)	0.624
	$AUC(0-\infty)$ (µg·h/mL)	346				
600 mg (Q72h)	$t_{1/2,ss}$ (h)	12.51	$t_{1/2,ss}/t_{1/2}$	87	(70, 109)	0.212
	$t_{1/2}$ (h)	14.33				

Adjusted means and statistical comparisons are based on least square means.
 CV: Coefficient of variation
 CI: Confidence interval

Comparisons for Single Dose and Steady-State 25-deacetyl Rifapentine Pharmacokinetic Parameters Following Q72h Dosing						
Dose Level (Schedule)	Parameter	Adjusted Mean*	Pairwise Comparisons			
			Pair	Ratio (%)	90% CI on Ratio	P Value
600 mg (Q72h)	C_{max} (µg/mL)	5.47	$C_{max,ss}/C_{max}$	122	(94, 158)	0.162
	$C_{max,ss}$ (µg/mL)	6.66	-	-	-	-
600 mg (Q72h)	$AUC(0-\infty)$ (µg·h/mL)	255	$AUC_{ss}(0-72)/AUC(0-\infty)$	86	(61, 120)	0.318
	$AUC_{ss}(0-72)$ (µg·h/mL)	219	-	-	-	-
600 mg (Q72h)	$t_{1/2}$ (h)	14.54	$t_{1/2,ss}/t_{1/2}$	79	(64, 96)	0.089
	$t_{1/2,ss}$ (h)	11.49	-	-	-	-

CV: Coefficient of variation
 CI: Confidence interval
 * Adjusted means and statistical comparisons are based on least square means

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Following administration of 600 mg rifapentine every 72 hours, mean C_{max} value at steady-state was about 10% higher than the corresponding C_{max} value after a single 600mg dose; but, this difference was not significant. Similarly, mean $AUC_{ss}(0-72)$ values for rifapentine were not significantly different from mean $AUC(0-\infty)$ values after single dose. No significant autoinduction was observed when 600 mg oral doses of rifapentine was administered every 72 hours.

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Following the oral administration of 600 mg rifapentine every 72 hours, 25-desacetyl rifapentine mean C_{max} values at steady-state were 22% higher than their corresponding single dose C_{max} values. Mean $AUC_{ss}(0-72)$ of 25-desacetyl rifapentine were 14% lower than $AUC(0-\infty)$; however, the difference was not significant. $T_{1/2,ss}$ estimates at steady-state were 21% shorter than the corresponding single dose $t_{1/2}$ estimates, however, this difference was not significant.

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After daily dosing of 600 mg rifapentine, mean C_{max} at steady-state were 58% higher than their corresponding single dose C_{max} values. $AUC_{ss}(0-24)$ and $AUC(0-\infty)$ estimates were similar when rifapentine was dosed every 24 hours.

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Population Pharmacokinetic Analysis: In the pivotal clinical trial, blood samples were collected periodically from 351 patients who were receiving 600 mg of rifapentine in combination with other antituberculous agents (isoniazid, pyrazinamide and ethambutol). Population pharmacokinetic analysis was conducted to evaluate the pharmacokinetics of rifapentine in patients with previously untreated pulmonary tuberculosis. The population pharmacokinetic model best describing the data is a one-compartment oral model with separate apparent oral clearance (Cl_{po}) values based upon gender and treatment period (continuation (late) phase, weeks 14+), separate apparent volume of distribution values based upon surface area and treatment period (intensive (middle) phase, weeks 7-14), and separate absorption rate constant (k_a) values based upon race (black) and treatment period (intensive (middle) phase). For rifapentine, the population estimated apparent oral clearance is 2.37 L/h and 1.61 L/h for male and female patients, respectively. The population estimated apparent volume of distribution is 44.3 L/m².

For 25-desacetyl rifapentine, the population estimated apparent oral clearance is 73% greater for male patients than for female patients and is 28% greater for patients over 35 years of age than for patients under 35 years of age. The clinical significance of the observed differences in the pharmacokinetics of rifapentine and its 25-desacetyl metabolite was not apparent in this study and needs further exploration. Dr. He Sun assisted in the review of the population pharmacokinetic data.

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Pharmacokinetics in Special Populations

Pediatrics: The pharmacokinetics of rifapentine and 25 desacetyl rifapentine were studied in adolescents (12-15 years old) following a single oral administration of 600 mg of rifapentine. Ten of the 12 children studied weight was ≥ 45 kg. The mean $AUC(0-\infty)$ and C_{max} values for rifapentine were 388.1 $\mu\text{g}\cdot\text{h}/\text{mL}$ and 12.9 $\mu\text{g}/\text{mL}$, respectively for the children who weighed ≥ 45 kg. The pharmacokinetics of rifapentine in adolescents who weigh ≥ 45 kg were similar to that reported for adults. For the two children who weighed < 45 kg, the average AUC and C_{max} were 439.19 $\mu\text{g}\cdot\text{h}/\text{mL}$ and 10.39 $\mu\text{g}/\text{mL}$, respectively. The pharmacokinetics of 25-desacetyl rifapentine in adolescents were similar to that reported for adults. The study did not evaluate the pharmacokinetics in children less than 12 years; hence, the pharmacokinetics of rifapentine and 25-desacetyl rifapentine in children under 12 years old is not known.

The sponsor is requesting additional 6-month exclusivity based on the pharmacokinetic evaluation in adolescents from this study. The subject population in the pediatric study submitted in the NDA were ≥ 12 years old, therefore the use of rifapentine in children under 12 years old should not be allowed. The reviewing medical officer has been informed that pharmacokinetic studies in children under 12 were not submitted.

Gender Analysis: In an across studies comparison of the pharmacokinetics of rifapentine and 25-desacetyl rifapentine after a single dose administration of 600 mg rifapentine in healthy young (18-45 years) female and male volunteers, the mean C_{max} and $AUC(0-\infty)$ of rifapentine and 25-desacetyl rifapentine were similar. The mean apparent oral clearance (Cl_{po}) were also similar between young healthy male and female volunteers.

In a population pharmacokinetic analysis of sparse blood samples obtained from 351 tuberculosis patients who received 600 mg rifapentine in combination with other antituberculous agents (isoniazid, pyrazinamide and ethambutol), the apparent oral clearance of rifapentine for males and females was 2.51 ± 0.14 L/h and 1.69 ± 0.41 L/h, respectively.

Elderly Male Subjects: The pharmacokinetics of rifapentine and its 25-desacetyl rifapentine metabolite were determined in healthy, elderly male volunteers (at least 65 years) and compared to healthy young male volunteers following single oral administration of 600 mg rifapentine. Mean C_{max} and $AUC(0-\infty)$ values for rifapentine were 28% and 41% higher in healthy, elderly male volunteers as compared to healthy, young male volunteers, respectively. Mean Cl_{po} of rifapentine was 24% lower in healthy, elderly male volunteers as compared to healthy, young male volunteers. The mean 25-desacetyl rifapentine C_{max} and $AUC(0-\infty)$ were also 30% and 58% higher in healthy, elderly male volunteers as compared to healthy, young male volunteers. Despite the increase in exposure, rifapentine was reported to be well tolerated in the elderly.

The pharmacokinetics of rifapentine and 25-desacetyl rifapentine were not evaluated in healthy elderly females; however, the pharmacokinetics is expected to be similar to healthy elderly males since no gender differences were found in healthy young male and female subjects.

Hepatic Impaired Patients: The pharmacokinetics of rifapentine and 25-desacetyl rifapentine were evaluated in subjects with mild to moderate and moderate to severe hepatic impairment. Following single oral administration of 600 mg rifapentine to subjects with various degrees of liver failure, similar plasma exposure of rifapentine and 25-desacetyl rifapentine were observed in subjects with various degrees of liver impairment in this study. No serious adverse event was reported for the patients in the hepatic impairment study. There is no information on rifapentine pharmacokinetics after multiple dose in hepatic impaired patients.

Renally Impaired Patients: The pharmacokinetics of rifapentine and 25-desacetyl rifapentine were not evaluated in renally impaired patients. However, urine excretion of rifapentine and 25-desacetyl rifapentine account for only about 17% of an administered dose. The clinical significance of impaired renal function is not known.

Asymptomatic HIV-infected Subjects: The pharmacokinetics of rifapentine and 25-desacetyl rifapentine were determined in asymptomatic HIV+ patients following a single oral administration of 600 mg rifapentine. The mean C_{max} and $AUC(0-\infty)$ values of rifapentine were in asymptomatic HIV+ patients as compared the values obtained for healthy volunteers in other studies. Mean Cl_{po} value of rifapentine was in asymptomatic HIV+ patients as compared to healthy, young male volunteers. C_{max} and $AUC(0-\infty)$ values for 25-desacetyl rifapentine were generally similar to that

observed in other studies in healthy subjects. The applicant is encouraged to evaluate the pharmacokinetics in symptomatic HIV+ patients. Food increases the AUC and Cmax of rifapentine observed under fasting conditions by about 50%.

DRUG INTERACTIONS

The applicant conducted one drug interaction study (rifapentine with indinavir) and predicted the likely of an interaction based on a literature search of drugs metabolized by CYP 3A4, CYP2C8/9, or UDPGT and displacement potential based on protein binding capabilities. The result of the literature evaluation are contained in the appendix.

Coadministration with indinavir had no effect on rifapentine plasma concentrations. The statistical comparisons did not indicate any significant difference in the pharmacokinetic parameters of rifapentine when it was administered alone compared to when it was administered with indinavir. Statistical comparisons indicated that administration of rifapentine with indinavir did not influence the pharmacokinetics of the 25-desacetyl rifapentine.

Concurrent administration of rifapentine and indinavir resulted in a decrease of the adjusted mean indinavir steady state Cmax by 55% while AUC was reduced by 70%. Clearance of indinavir increased about 3-fold in the presence of rifapentine while half-life did not change. The individual concentration profiles showed that each subject displayed a decrease of varying degrees in indinavir AUCss(0-8) when co-administered with rifapentine. There was a greater than 4-fold decrease in the mean plasma trough concentrations of indinavir during concurrent administration with rifapentine. The mean trough concentrations of indinavir during treatment alone ranged [redacted] but when coadministered with rifapentine, mean trough levels [redacted]. It is recommended that indinavir is used with extreme caution, if at all, in patients on rifapentine.

The magnitude of the effect of rifapentine on other protease inhibitors, such as saquinavir and ritonavir, and other CYP 3A substrates is not known.

DISSOLUTION

RECOMMENDATION

The studies submitted to the Human Pharmacokinetics and Bioavailability Section of NDA 21,024 to fulfil sections 320 and 201.5 of 21 CFR are acceptable and support a recommendation for approval.

APPROVED BY
[Signature]

[Signature]

/S/

6/17/98

Kofi A. Kumi, Ph.D.
Pharmacokinetics Reviewer,
HFD 590 Section
Division of Pharmaceutical Evaluation III
OCPB

/S/

6/17/98

Concurrence:

Funmi Ajayi, Ph.D.
Team Leader (Ag)
HFD-590 Section
Division of Pharmaceutical Evaluation III
OCPB

CC:

NDA 21,024 (Original)
HFD-590

HFD-344
HFD-880

CDR

Division Files
/MO/JKorvick
/PM/BAtkins
/Viswanathan
/TLDPEIII/FAjayi
/DPEIII/KKumi
/DPEIII Drug Files
/BMurphy

file: Wpfiles\data/kumiwp/rifapent/overall

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21024

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

Alkins
540

JUN 5 1998

NDA 50-752

Hoechst Marion Roussel, Inc.
Attention: Dr. Dhiren Shah
10236 Marion Park Drive
P.O. Box 9627
Kansas City, MO 64134-0627

Dear Dr. Shah:

Please refer to your pending December 22, 1997 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic act for Priftin (rifapentine) Tablets, 150 mg.

We also refer to your submission dated May 22, 1998.

We are reviewing the Chemistry section of your submission and have identified the following comments and information requests:

1. Please clarify the response concerning the reference to _____ as a _____
It is our view that _____ is _____ Rather,
an _____ The _____ of this
_____ as described in _____ in NDA 50-752 by reference.
Future changes in the _____
may also need to be documented in NDA 50-752 as appropriate for the _____
from _____ to manufacture marketed
product until a supplement for the use of material from that source is approved. Please
acknowledge that you are in full agreement with this assessment of
2. The use of the term _____ used _____ the drug substance
because _____ are used to make them falls short of preventing
the use of other additives that may be considered undesirable. Please establish
_____ comply with 21 CFR regulations governing the use of
If a _____ is used, please explain how it
compares with the FDA requirements.

3. Please commit to testing and releasing
4. Please make a Phase 4 commitment

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

APPEARS THIS WAY
ON ORIGINAL

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the use fee reauthorization agreements, these comments have been reviewed only to the level of the discipline team leader. They do not reflect division director input or concurrence and should not be construed to do so. These comments are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you respond in the current review cycle, we may or may not consider your response prior to taking an action on your application. In the meantime, we are continuing our review of your application.

APPEARS THIS WAY
ON ORIGINAL

If you have any questions, contact Brenda Atkins, Project Manager, at (301) 827-2423.

Sincerely yours,

/S/

Norman R. Schmuff, Ph.D.
Chemistry Team Leader, DNDCIII
Division of Special Pathogens and
Immunologic Drugs/HFD-590
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: NDA 50-752
Div File
HFD-590/MO/JKorvick
HFD-590/ChemTL/NSchmuff
HFD-590/Chem/JSmith
HFD-590/ProjMgr/BAtkins
HFD-830/DivDir/CChen

INFORMATION REQUEST



MEMORANDUM TO THE RECORD

Date: June 17, 1998

To: NDA 21-024

Through: Ellen Frank, R.Ph, Acting Supervisory, CSO
Marc Cavaillé-Coll, M.D., Ph.D., Medical Team Leader

From: Brenda J. Atkins, B.S., Project Manager

Subject: New NDA number for PRIFTIN® (rifapentine) 150 mg Tablets

For administrative purposes this memorandum explains why the PRIFTIN® (rifapentine) NDA numbered 50-752, has been renumbered with a 20,000 series number. Under section 125 of the Title I of the Food and Drug Administration Modernization Act of 1997 (FDAMA), section 507 of the Federal Food, Drug, and Cosmetic Act (FFDCA) was repealed. FDAMA was signed into law by President Clinton on November 21, 1997. The NDA submission for PRIFTIN® (rifapentine) was submitted on December 22, 1997, after enactment of FDAMA.

FDAMA makes clear that antibiotic applications received before November 21, 1997, are not subject to certain provisions of the FFDCA that pertain to those submitted after November 21, 1997. CDER issued a "Guidance to Industry and Reviewers" (revised, May 1998)¹ describing its policies for implementing this change, including the NDA numbering conventions it intends to follow which will differentiate "old" antibiotics (those received before November 21, 1997) from "new" antibiotics.

In accordance with the guidance, the application for PRIFTIN (rifapentine) should have been assigned a number in the 20,000 series to differentiate it as an antibiotic first received after the repeal of section 507.

/S/

Brenda J. Atkins, Project Manager

¹"Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act"

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of Orphan Products Development (HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

June 9, 1995

Marion Merrell Dow, Inc.
Attention: Jack J. Dunn, Ph.D.
Technical Leader, U.S. Regulatory Affairs
P.O. Box 9627 (Park A)
Kansas City, MO 64137

RECEIVED JUN 15 1995

Dear Dr. Dunn:

Reference is made to your orphan drug application of March 30, 1995 submitted pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act for the designation of rifapentine as an orphan drug.

We have completed the review of this application and have determined that rifapentine qualifies for orphan designation for the treatment of pulmonary tuberculosis. Please note that it is rifapentine and not its formulation that has received orphan designation.

Prior to marketing approval, sponsors of designated orphan products are requested to submit written notification to this Office of their intention to exercise orphan drug exclusivity if they are the first sponsor to obtain such approval for the drug. This notification will assist FDA in assuring that approval for the marketing of the same drug is not granted to another firm for the statutory period of exclusivity. Also please be advised that if rifapentine were approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA. Therefore, prior to final marketing approval, sponsors of designated orphan products are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

In addition, please inform this office annually as to the status of the development program, and at such time as a marketing application is submitted to the FDA for the use of rifapentine as designated. If you need further assistance in the development of your product for marketing, please feel free to contact Dr. C. Carnot Evans at (301) 443-4718.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan drug designation.

Sincerely yours,

/S/

Marlene E. Haffner, M.D./M.P.H.
Director

APPROVED BY
DATE

APPROVED BY
DATE

Hoechst Marion Roussel

June 22, 1998

Marlene E. Haffner, MD, MPH
Office of Orphan Products Development
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Hoechst Marion Roussel, Inc.

10236 Marion Park Drive
Mail: P.O. Box 9627
Kansas City, MO 64134-0627
Telephone (816) 966-5000

BY FAX: 301-443-4915

Subject: **NDA 21-024**
PRIFTIN®
(rifapentine)

Intent to Exercise Orphan Exclusivity

BEST POSSIBLE COPY

Dear Dr. Haffner:

The purpose of this letter is to inform you of Hoechst Marion Roussel's intent to exercise the exclusivity provided to rifapentine for the indication of treatment of pulmonary tuberculosis under orphan drug designation granted June 9, 1995.

Rifapentine has been reviewed in the Division of Special Pathogens and Immunologic Drug Products since submission of the NDA on December 22, 1997, and was the subject of an Antiviral Drugs Advisory Panel meeting on May 5, 1998.

Please note that earlier correspondence on PRIFTIN was under NDA number 50-752. Passage of FDAMA in late November required assigning a new number.

Please contact me at 816-966-7185 or pager 888-497-7848 should you need further information.

Sincerely,

Libby Hayes
Libby Hayes, Manager
U.S. Drug Regulatory Affairs

cc: ODE IV, 301-827-2520

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ON ORIGINAL

Hoechst Marion Roussel
A member of the Hoechst Group

Hoechst 

Hoechst Marion Roussel

June 22, 1998

M. Dianne Murphy, MD
Office of Drug Evaluation IV
Center for Drug Evaluation and Research Food and Drug Administration
9201 Corporate Blvd., 4th Floor
Rockville, MD 20857

Hoechst Marion Roussel, Inc.

316 Marion Park Drive
Mail: P.O. Box 9627
Kansas City, MO 64134-0627
Telephone (816) 966-5000

BY FAX: 301-827-2520

BEST POSSIBLE COPY

Subject: **NDA 50-752**
PRIFTIN®
(rifapentine)

**Label revision incorporating labeling
statement related to Accelerated Approval**

APPROVED FOR
ON 6/22/98

Dear Dr. Murphy:

Hoechst Marion Roussel has reviewed and evaluated the labeling statement related to Accelerated Approval provided to us midday, June 22, 1998. Our decision is to accept your proposed language and to further accept option 2, the addition of the labeling statements provided to the "Indications and Usage" section and the "Clinical Trials" section of the labeling.

A copy of the PRIFTIN label designated "clean008", is attached to this letter. The requested changes are on pages 6 and 9

APPEARS THIS WAY
ON ORIGINAL

Please contact me if you have any questions regarding this submission.

Sincerely,

Libby Hayes
Libby Hayes, Manager
U.S. Drug Regulatory Affairs

APPROVED FOR
ON 6/22/98

BEST POSSIBLE COPY

Hoechst Marion Roussel
A member of the Hoechst Group



rifapentine 150 mg tablet

13/14. Patent Information/Certification

13/14. Patent Information/Certification

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

As an Orphan Drug under section 526 of the Federal Food, Drug and Cosmetic Act, rifapentine is entitled to seven years of exclusivity from the date of NDA approval.

EXCLUSIVITY SUMMARY for NDA # 21-024 SUPPL # _____

Trade Name PRIFTIN® Generic Name rifapentine

Applicant Name Hoechst Marion Roussel, Inc. HFD-590

Approval Date June 22, 1998

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA?
YES / / NO / /

b) Is it an effectiveness supplement?

YES / / NO / /

If yes, what type? (SE1, SE2, etc.) _____

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:

d) Did the applicant request exclusivity?

YES / / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

7

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES / / NO / /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

ADMITTED TO MARKET
ON

ADMITTED TO MARKET
ON

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. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S 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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (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 / /

APPEARS THIS WAY
ON ORIGINAL

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: _____

APPEARS THIS WAY
ON ORIGINAL

- (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: _____

APPEARS THIS WAY
ON ORIGINAL

- (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:

Investigation #1, Study # 00473PR0008

Investigation #2, Study # _____

Investigation #3, Study # _____

APPEARS THIS WAY
ON ORIGINAL

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 / <input checked="" type="checkbox"/> /
Investigation #2	YES /__/	NO /__/
Investigation #3	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:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

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 / <input checked="" type="checkbox"/> /
Investigation #2	YES /__/	NO /__/
Investigation #3	YES /__/	NO /__/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

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BY THE NATIONAL ARCHIVES

- 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"):

Investigation #_, Study # 00473PR0008

Investigation #_, Study # _____

Investigation #_, Study # _____

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 _____ 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 / _____ / Explain _____ NO / _____ / Explain _____

NOT TO BE REPRODUCED
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

J/BLA # 21-024 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-590 Trade and generic names/dosage form: Priftin® (rifapentine) Action: (AP) AE NA

Applicant Hoechst Marion Roussel, Inc. Therapeutic Class Anti-tuberculosis

Indication(s) previously approved None

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ✓

Indication proposed in this application Treatment of pulmonary tuberculosis

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___ Yes (Continue with questions) ___ No (Sign and return the form)

IN WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

___ Neonates (Birth-1month) ✓ Infants (6months-2yrs) ✓ Children (2-12yrs) ✓ Adolescents(12-16yrs)

1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

c. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing,

___ (2) Protocols were submitted and approved.

___ (3) Protocols were submitted and are under review.

✓ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply, attach an explanation, as necessary.**

ARE THERE ANY PEDIATRIC PHASE 4 COMMITMENTS IN THE ACTION LETTER? ✓ Yes ___ No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Marc Cavaille-Coll, Medical Team Leader (e.g., medical review, medical officer, team leader)

JSI Project Manager
Signature of Preparer and Title

June 19, 1998
Date

Orig NDA/BLA # 21-024
HFD-590/Div File
NDA/BLA Action Package
HFD-006/ KRoberts

APPROVED
ORIGINAL

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM, CONTACT KHYATI ROBERTS, HFD-6 (ROBERTSK)

Debarment Certification

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



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



Date

733

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Antiviral Drug Products		HFD-530
Attention: Dan Boring		Phone: 827-2391
Date: 01-16-97		
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product		
Proposed Trademark: PRIFTIN		NDA/ANDA#
Established name, including dosage form: Rifapentine		
Other trademarks by the same firm for companion products: RIFADIN • Rifampin capsules 150mg, 30mg capsules RIFADIN • I.V. Rifampin for injection 600mg vials RIFAMATE • Rifampin and Isoniazid capsules RIFATER • Rifampin, Isoniazid, and Pyrazinamid tablets		
Indications for Use (may be a summary if proposed statement is lengthy): Treatment of Pulmonary Tuberculosis		
Initial Comments from the submitter (concerns, observations, etc.):		

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev. December 95

Consult #733 (HFD-530)

PRIFTIN

rifapentine tablets

The Committee noted the following look-alike/sound-alike conflict: CEFTIN. The Committee feels this conflict has a low potential for confusion. There were no misleading aspects found in the proposed proprietary name.

The Committee has no reason to find the proposed name unacceptable.

/S/ 3/4/97, Chair
CDER Labeling and Nomenclature Committee

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
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ON ORIGINAL



Public Health Service
Food and Drug Administration
Rockville MD 20857

Memorandum of Industry Telephone Conference

Date: 21 October 1997

Type of Meeting: Chemistry, Manufacturing, Controls

NDA: 50,752

Drug: PRIFTIN (rifapentine)

Sponsor: Hoechst Marion Roussel, Inc.

Chair: Chi Wan Chen, Ph.D.

Facilitator/Recorder: Lisa M. Hubbard, R.Ph. */S/*

Sponsor Chair: Libby Hayes, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

FDA Participants:

Chi Wan Chen, Ph.D., Director, Office of New Drug Chemistry (ONDC)
Norman Schmuff, Ph.D., Chemistry Team Leader, ONDC
Dorota Matecka, Ph.D., Chemist, ONDC
Marianne Mann, M.D., Medical Officer, Division of Special Pathogens (DSPIDP)
Lisa Hubbard, R.Ph., Regulatory Management Officer, DSPIDP

APPEARS THIS WAY
ON ORIGINAL

External Participants:

Libby Hayes, B.S., Senior Regulatory Analyst, USDRA, HMR
Dhiren N. Shah, Ph.D., Director/Technical Leader, CMC
John Claudius, Ph.D., Associate Scientist, Preclinical Development
Jeff Ottarson, B.S., Senior Packaging Engineer, Package Engineering
Gregory Beck, M.S., Scientist, Preclinical Development Analytics
Mary Brownback, M.S., Associate Scientist CMC Specialist, Preclinical Development
Charles W. Gorodetzky, M.D., Ph.D., Medical Advisor, North American Development

Meeting Objectives:

To provide comment on submission serial number 096 . The submission contains an explanation of a packaging integrity issue for the commercial packaging of rifapentine tablets. A marketing application for this new molecular entity is scheduled to be submitted December 1997.

Public Health Service
Food and Drug Administration
Rockville MD 20857

Discussion Points:

The following question was provided in the sponsors background package submitted October 16, 1997:

Would FDA concur with the sponsor's proposal to compare three-month accelerated stability data from the proposed foil pouched package to the data from the primary stability studies and on that basis, request 18 month expiration dating? Further, would FDA accept an amendment no later than 1 May 1998 with this additional stability data and review it on the six month clock associated with the NDA review?

Decisions reached:

1. HMR will prepare an NDA for submission in December 1997. The sponsor/applicant will proceed with the proposed plan to provide extra protection to the blister pack. The batches of commercial product will be placed on stability in November. The sponsor/applicant will conduct control studies that will provide data on the new blister card in comparison to the data. One-month data will be available and submitted to FDA during late February 1998. Three-month data will be submitted to the Division by 1 May 1998. The data available at three months will be submitted with all information regarding the materials.
2. Given the agreement reached in item one above, ONDC will not consider the sponsor/applicants failure to supply stability data on a commercial package within sixty days of the submission of NDA 50-752 a refuse-to-file issue. FDA will review data submitted as late as 1 May 1998 as quickly as possible. ONDC representatives cautioned HMR that this is not a precedent setting agreement. The agreement reflects the priority designation assigned to NDA 50-752 and the potential public health benefit of the investigational product under subpart H.
3. Concerning the application summary for NDA 50-752, Dr. Mann agreed that severe adverse events and treatment related adverse events should be incorporated into the application summary. Dr. Mann further agreed that discrepancies in the clinical laboratory database for the November 8th patient visit cut-off date can be reconciled in an amendment to NDA 50-752.

Unresolved Issues

The final expiration dating can not be established prior to submission of NDA 50-752 and review of all available stability data.

Action Items

The sponsor will submit NDA 50-752 during December 1997 with the information as agreed upon above.

ORIGINAL

Hoechst Marion Roussel

March 4, 1998

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~~ORIG~~ AMENDMENT

Mark Goldberger, MD
Director, Division of Special Pathogens and
Immunologic Drug Products (DSPIDP)
Center for Drug Evaluation and Research (HFD-590)
Food and Drug Administration
9201 Corporate Blvd., 4th floor
Rockville, MD 20850

Hoechst Marion Roussel, Inc.

10236 Marion Park Drive
Mail: P.O. Box 9627
Kansas City, MO 64134-0627
Telephone (816) 966-5000

Attn: Central Document Room

Subject: **Amendment to New Drug Application**
PRIFTIN® (rifapentine)
NDA 50-752

Dear Dr. Goldberger:

NDA 50-752, submitted December 22, 1997, provides data to support the use of rifapentine in the treatment of pulmonary tuberculosis. The NDA represents a database that included patient visits through a visit cutoff date of November 8, 1996. It was agreed with the Division, initially in July, 1994, and confirmed in October, 1996 at a pre-NDA meeting, that this NDA submission would be based on interim data from 000473PR0008. Hoechst Marion Roussel hereby submits for review additional interim data from 000473PR0008, an ongoing phase III, open label, randomized, multicenter, comparative treatment trial.

This amendment updates clinical efficacy and safety data with eight months additional data and includes patient visits through a visit cutoff date of July 8, 1997. Of the patients who completed 6 months of active treatment and entered follow-up, 96% had reached the 6-month follow-up efficacy timepoint and 68% had reached the 12-month follow-up efficacy timepoint by July 8, 1997 and are thus included in the amendment database. This Efficacy/Safety Update Amendment also updates microbiological data and serves as the 120-day safety update, all by prior agreement. It has been agreed that submission of this clinical amendment in the timeframe outlined (no later than March 20, 1998) will not result in a time penalty under the six month priority review clock for PRIFTIN®. Hoechst Marion Roussel has provided the amendment within the timeframe specified.

The amendment is organized with an alphabetical outline structure in Sections A through G. The review copy of each section is supplied in the appropriate colored jacket. A copy of Section A-Introduction is provided for reviewers whose NDA section is not affected by this amendment. The table below gives details of the organization of the submission:

Section Name	Number of Volumes	Volume Numbers
A. Index and Introduction	1	1
B. Microbiology	1	2
C. Clinical Data	43	3 through 45
D. Literature Update	1	46
E. References	1	47
F. Tabulations	124	48 through 171
G. Case Report Forms	29	172 through 200

Hoechst Marion Roussel
A member of the Hoechst Group



This submission is paginated to reflect the Section number (S), followed by the Volume number (V), and by the Page number (P). Pagination begins on page 1 for each volume, providing a unique number for each page. Detailed tables of contents with submission page numbers (S-V-P) and extensive cross-referencing provide access to the specific page(s) of supporting documentation. This Efficacy/Safety Update Amendment is also being provided as an ONDA that is cross-linked to the original NDA ONDA. Installation of the electronic files for the ONDA is scheduled for March 4, 1998.

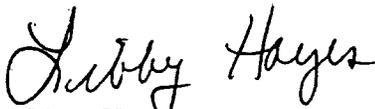
A separate submission of diskettes is planned for March 5, 1998. Diskettes submitted January 29, 1998 containing NDA adverse event and microbiologic data in EXCEL format and PC SAS programs/datasets will be updated to reflect the Efficacy/Safety Update Amendment data. In addition, other data or files on diskette as requested, will be provided. Full details and data documentation will be included in that submission.

We look forward to your continued review of our New Drug Application for rifapentine. Please be advised that the information submitted is considered confidential under 21 CFR 314.430.

Please contact the undersigned for assistance in locating any materials or in providing any additional information concerning this application:

Libby Hayes, MS H3-2516
Hoechst Marion Roussel, Inc.
P.O. Box 9627
Kansas City, MO 64134-0627
(816) 966-7185 phone, 3200 fax

Sincerely,



Libby Hayes
Manager
US Drug Regulatory Affairs