



NDA 50-689/S-011, S-013

Pharmacia and Upjohn
Attention: Gregory A. Brier
Regulatory Manager
Unit 0633-298-113
7000 Portage Rd.
Kalamazoo, MI 49001-0199

09 NOV 2001

Dear Mr. Brier:

Please refer to your supplemental new drug applications dated February 23, 1998 and February 10, 2000, received February 24, 1998 and February 11, 2000, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mycobutin[®] (rifabutin) Capsules, 150 mg.

We acknowledge receipt of your submissions dated April 1, 1999, August 21, 2001 and September 28, 2001.

These supplemental new drug applications provide for the following changes to the Mycobutin[®] package insert. The deleted text is noted by ~~strike through~~ and the added text is noted by double underline as follows:

1. CLINICAL PHARMACOLOGY

• In the **Pharmacokinetics** subsection new subheadings were added and the text was re-ordered and revised for clarity as follows:

Absorption: Following a single oral dose of 300 mg to nine healthy adult volunteers, rifabutin was readily absorbed from the gastrointestinal tract with mean (+/-SD) peak plasma levels (C_{max}) of 375 (+/-267) ng/mL (range: 141 to 1033 ng/mL) attained in 3.3 (+/-0.9) hours (T_{max} range: 2 to 4 hours). Absolute bioavailability assessed in five HIV-positive patients, who received both oral and intravenous doses, averaged 20%. Total recovery of radioactivity in the urine indicates that at least 53% of the orally administered rifabutin dose is absorbed from the gastrointestinal tract. The bioavailability of rifabutin from the capsule dosage form, relative to an oral solution, was 85% in 12 healthy adult volunteers. High-fat meals slow the rate without influencing the extent of absorption from the capsule dosage form. Plasma concentrations post- C_{max} declined in an apparent biphasic manner. Pharmacokinetic kinetic dose-proportionality has been established over the 300 to 600 mg dose range in nine healthy adult volunteers (crossover design) and in 16 early symptomatic human immunodeficiency virus (HIV)-positive patients over a 300 to 900 mg dose range.

Distribution: Rifabutin, Due to its high lipophilicity, rifabutin demonstrates a high propensity for distribution and intracellular tissue uptake. ~~Estimates of apparent steady-state distribution volume (9.3 ± 1.5 L/kg) in five HIV-positive patients, following I.V. dosing, exceed total body water by approximately 15-fold. Substantially higher intracellular tissue levels than those seen in plasma have been observed in both rat and man.~~ Following intravenous dosing, estimates of apparent steady-state distribution volume (9.3 ± 1.5 L/kg) in five HIV-positive patients exceeded total body water by approximately 15-fold. Substantially higher intracellular tissue levels than those seen in plasma have been observed in both rat and man. The lung to plasma concentration ratio, obtained at 12 hours, was found to be approximately 6.5 in four surgical patients administered an oral dose. Mean rifabutin steady-state trough levels ($C_{p,\min}^{SS}$; 24-hour post-dose) ranged from 50 to 65 ng/mL in HIV-positive patients and in healthy adult volunteers. About 85% of the drug is bound in a concentration-independent manner to plasma proteins over a concentration range of 0.05 to 1 μ g/mL. Binding does not appear to be influenced by renal or hepatic dysfunction. Rifabutin was slowly eliminated from plasma in seven healthy adult volunteers, presumably because of distribution-limited elimination, with a mean terminal half-life of 45 (+/- 17) hours (range: 16 to 69 hours). Although the systemic levels of rifabutin following multiple dosing decreased by 38%, its terminal half-life remained unchanged.

Metabolism: Of the five metabolites that have been identified, 25-O-desacetyl and 31-hydroxy are the most predominant, and show a plasma metabolite:parent area under the curve ratio of 0.10 and 0.07, respectively. The former has an activity equal to the parent drug and contributes up to 10% to the total antimicrobial activity.

Excretion:

Changed from:

~~"Mean systemic clearance (CL_s/F) in healthy adult volunteers following a single oral dose was 0.69 (± 0.32) L/hr/kg (range: 0.46 to 1.34 L/hr/kg). Renal and biliary clearance of unchanged drug each contribute approximately 5% to CL_s/F . About 30% of the dose is excreted in the feces. A mass-balance study in three healthy adult volunteers with ^{14}C -labeled drug has shown that 53% of the oral dose was excreted in the urine, primarily as metabolites.~~

to:

"A mass-balance study in three healthy adult volunteers with ^{14}C -labeled rifabutin showed that 53% of the oral dose was excreted in the urine, primarily as metabolites. About 30% of the dose is excreted in the feces. Mean systemic clearance (CL_s/F) in healthy adult volunteers following a single oral dose was 0.69 (+/- 0.32) L/hr/kg (range: 0.46 to 1.34 L/hr/kg). Renal and biliary clearance of unchanged drug each contribute approximately 5% to CL_s/F ."

The following sentence was deleted:

~~"No rifabutin disposition information is currently available in children or adolescents under 18 years of age."~~

- A new **Pharmacokinetics in Special Populations** subsection was added as follows:

Geriatric:

Compared to healthy volunteers, steady-state kinetics of MYCOBUTIN are more variable in elderly patients (>70 years).

Pediatric: The pharmacokinetics of MYCOBUTIN have not been studied in subjects under 18 years of age.

Renal Insufficiency: The disposition of rifabutin (300 mg) was studied in 18 patients with varying degrees of renal function. Area under plasma concentration time curve (AUC) increased by about 71% in patients with severe renal insufficiency (creatinine clearance below 30 mL/min) compared to patients with creatinine clearance (Cr_{cl}) between 61-74 mL/min. In patients with mild to moderate renal insufficiency (Cr_{cl} between 30-61 mL/min), the AUC increased by about 41%. A reduction in the dosage of rifabutin is recommended for patients with $Cr_{cl} < 30$ mL/min (see **DOSAGE AND ADMINISTRATION**).

- A **Drug-Drug Interactions** subsection was added as follows:

Drug-Drug Interactions (see also PRECAUTIONS-Drug Interactions)

Rifabutin induces the enzymes of the cytochrome P450 3A subfamily (CYP3A) and therefore may reduce the plasma concentrations of drugs that are principally metabolized by those enzymes. Rifabutin is also metabolized by CYP3A. Thus, some drugs that inhibit CYP3A may significantly increase plasma concentrations of rifabutin.

Antifungals:

Fluconazole: Fluconazole (200 mg/day for 2 weeks) increased the AUC of rifabutin (300 mg/day for 2 weeks) by 82% and C_{max} by 88% in 12 HIV-infected patients who were on zidovudine (500 mg/day) maintenance therapy (see **PRECAUTIONS-Drug Interactions**). Rifabutin does not affect the pharmacokinetics of fluconazole.

Itraconazole: Coadministration of itraconazole (200 mg/day) with rifabutin (300 mg/day) in six HIV-infected patients reduced both the AUC and C_{max} of itraconazole by 70% to 75% (see **PRECAUTIONS-Drug Interactions**).

Antipneumocystis Agents:

Dapsone: Rifabutin (300 mg/day) decreased the AUC of dapsone (50 mg/day) in HIV-infected patients (n=16) by about 27% to 40%.

Sulfamethoxazole-trimethoprim: Coadministration with of rifabutin (300 mg/day) and sulfamethoxazole-trimethoprim (double strength) in 12 HIV-infected patients decreased the AUC of sulfamethoxazole-trimethoprim by about 15% to 20%. When rifabutin trimethoprim was given

with trimethoprim alone, the AUC of trimethoprim was decreased by 14% and the C_{max} by 6%. Sulfamethoxazole-trimethoprim did not alter the pharmacokinetics of rifabutin.

Antiretroviral Agents:

Delavirdine: In 7 HIV-infected patients, rifabutin (300 mg/day) decreased delavirdine (400 mg q 8h) AUC by about 80%, C_{max} by about 75%, and mean trough plasma concentrations by about 95%. Based on comparisons with historical data, delavirdine appeared to increase the AUC of rifabutin by at least 100% (see **PRECAUTIONS-Drug Interactions**).

Didanosine: In 12 HIV-infected patients, coadministration of rifabutin (300 or 600 mg/day) and didanosine (167-375 mg BID) did not alter the pharmacokinetics of either drug.

Indinavir: In healthy volunteers, coadministration of indinavir (800 mg q 8h) and rifabutin (300 mg/day) decreased the AUC of indinavir by about 30% and increased the AUC of rifabutin by about 200% (see **PRECAUTIONS-Drug Interactions**).

Nelfinavir: Coadministration of nelfinavir (750 mg q 8h for 8 days) and rifabutin (300 mg/day for 7-8 days) decreased the AUC and C_{max} of nelfinavir by about 32% and 25%, respectively, and increased the AUC and C_{max} of rifabutin by about 207% and 146%, respectively (see **PRECAUTIONS-Drug Interactions**).

Ritonavir: In 24 healthy volunteers, Coadministration of ritonavir (500 mg q 12h) and rifabutin (150 mg/day) increased the AUC and C_{max} of rifabutin by more than 400% and 250%, respectively (see **PRECAUTIONS-Drug Interactions**).

Saquinavir: In 12 HIV-infected patients, rifabutin (300 mg/day) decreased the AUC of saquinavir (600 mg TID) by about 40% (see **PRECAUTIONS-Drug Interactions**).

Zidovudine: In 16 HIV-infected patients, on zidovudine (100 or 200 mg q 4h), rifabutin (300 or 450 mg/day) lowered the C_{max} and AUC of zidovudine by about 30% 48% and 32%, respectively. However, zidovudine levels remained within the therapeutic range during coadministration of rifabutin. Zidovudine does did not affect the pharmacokinetics of rifabutin.

Antituberculosis Agents:

In studies conducted in healthy volunteers, rifabutin (300 mg) did not alter the pharmacokinetics of ethambutol (n=10) or isoniazid (n=10).

Macrolides:

Clarithromycin: In studies conducted in HIV-infected patients, coadministration of rifabutin (300 mg/day) and clarithromycin (500 mg q 12h) decreased the AUC of clarithromycin by about 50% (n=12) and increased the AUC of rifabutin by about 75% (n=14) (see **PRECAUTIONS-Drug Interactions**).

Other Drugs:

Methadone: Rifabutin did not alter the pharmacokinetics of methadone in 24 HIV-infected, methadone-maintained, former intravenous drug users.

Oral contraceptives: In 22 healthy female volunteers receiving an oral contraceptive (35 mcg ethinylestradiol (EE) and 1 mg norethindrone (NE) daily for 21 days, rifabutin decreased EE (AUC) and C_{max} by 35% and 20%, respectively, and NE AUC by 46% (see **PRECAUTIONS-Drug Interactions**).

Theophylline: Rifabutin did not alter the pharmacokinetics of theophylline when coadministered in 11 healthy volunteers.

Other drugs: The structurally similar drug, rifampin, is known to reduce the plasma concentrations of a number of other drugs (see prescribing information for rifampin). Although rifabutin is a weaker enzyme inducer than rifampin, rifabutin may be expected to have some effect on those drugs as well.

- The **CLINICAL STUDIES** subsection was moved from **INDICATIONS AND USAGE** and now appears as a separate subsection in **CLINICAL PHARMACOLOGY**.
- The **MICROBIOLOGY** subsection was moved and now appears following **CLINICAL STUDIES**.

2. PRECAUTIONS

- The **Drug Interactions** subsection was revised as follows:

Changed from:

~~In 10 healthy adult volunteers and 8 HIV-positive patients, steady-state plasma levels of zidovudine (ZDV), an antiretroviral agent which is metabolized mainly through glucuronidation, were decreased after repeated dosing with MYCOBUTIN; the mean decrease in C_{max} and AUC was decreased by 48% and 32%, respectively. In vitro studies have demonstrated that rifabutin does not affect the inhibition of HIV by ZDV.~~

~~Steady-state kinetics in 12 HIV-positive patients show that both the rate and extent of systemic availability of didanosine (ddl), was not altered after repeated dosing of MYCOBUTIN. Rifabutin has liver enzyme inducing properties. The related drug rifampin is known to reduce the activity of a number of other drugs, including dapsone, narcotics (including methadone), anticoagulants, corticosteroids, cyclosporine, cardiac glycoside preparations, quinidine, oral contraceptives, oral hypoglycemic agents (sulfonylureas), and analgesics. Rifampin has also been reported to decrease the effects of concurrently administered ketoconazole, barbiturates, diazepam, verapamil, beta-adrenergic blockers, clofibrate, progestins, disopyramide, mexiletine, theophylline, chloramphenicol, and anticonvulsants. Because of the structural similarity of rifabutin and rifampin, MYCOBUTIN may be expected to have some effect on these drugs as well. However, unlike rifampin, MYCOBUTIN appears not to affect the acetylation of isoniazid. When rifabutin was compared with rifampin in a study with 8 healthy normal volunteers, rifabutin appeared to be a less potent enzyme inducer than rifampin. The significance of this finding for clinical drug interactions is not known. Dosage adjustment of drugs listed above may be necessary if they are given concurrently with MYCOBUTIN. Patients using oral contraceptives should consider changing to nonhormonal methods of birth control.~~

to:

Effects on Other Drugs: Rifabutin induces CYP3A enzymes and therefore may reduce the plasma concentrations of drugs metabolized by those enzymes. This effect may reduce the efficacy of standard doses of such drugs, which include itraconazole, clarithromycin, and saquinavir (see **CLINICAL PHARMACOLOGY-Drug-Drug Interactions**).

Effects on Rifabutin: Some drugs that inhibit CYP3A may significantly increase the plasma concentration of rifabutin. Because high plasma levels of rifabutin may increase the risk of adverse reactions, carefully monitor patients receiving coadministration of such drugs, which include fluconazole and clarithromycin (see **CLINICAL PHARMACOLOGY-Drug-Drug Interactions**). In some cases, the dosage of MYCOBUTIN may need to be reduced when it is coadministered with such a drug (see below).

Antiretrovirals:

Delavirdine: Coadministration of rifabutin and delavirdine is not recommended because rifabutin substantially decreases the plasma concentrations of delavirdine, and delavirdine increases the plasma concentrations of rifabutin (see **CLINICAL PHARMACOLOGY-Drug-Drug Interactions**).

Indinavir: Coadministration of indinavir and rifabutin increases the plasma concentration of rifabutin. In patients receiving coadministration of indinavir, reduce the dosage of MYCOBUTIN by half (see **CLINICAL PHARMACOLOGY-Drug-Drug Interactions**).

Nelfinavir: Coadministration of nelfinavir increases the plasma concentration of rifabutin. In patients receiving nelfinavir, reduce the dosage of MYCOBUTIN by half (see **CLINICAL PHARMACOLOGY-Drug-Drug Interactions**).

Ritonavir: Coadministration of ritonavir is not recommended because it substantially increases the plasma concentration of rifabutin (see **CLINICAL PHARMACOLOGY-Drug-Drug Interactions**). High plasma concentrations of rifabutin may increase the risk of adverse reactions, including uveitis.

Other Drugs:

Oral contraceptives: Rifabutin may decrease the efficacy of oral contraceptives by inducing drug metabolism of ethinylestradiol and norethindrone. Women using oral contraceptives should be advised to change to or supplement with nonhormonal methods of birth control during treatment with MYCOBUTIN.

Other drugs: The structurally similar drug, rifampin, is known to reduce the plasma concentrations of a number of other drugs (see prescribing information for rifampin). Although rifabutin is a weaker enzyme inducer than rifampin, it may be expected to have some effect on those drugs as well.

- The following sentence was added near the end of the **Pediatric Use** statement as follows:

In addition, corneal deposits have been observed in some patients during routine ophthalmologic surveillance of HIV-positive pediatric patients receiving MYCOBUTIN as part of a multiple-drug regimen for MAC prophylaxis. These are tiny, almost transparent, asymptomatic peripheral and central corneal deposits which do not impair vision.

- A **Geriatric Use** subsection was added as follows:

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

3. DOSAGE AND ADMINISTRATION

The following sentences were added to this section:

For patients with severe renal impairment (creatinine clearance less than 30mL/min), the dose of MYCOBUTIN should be reduced by 50%. No dosage adjustment is required for patients with mild to moderate renal impairment. Reduction of the dose of MYCOBUTIN may also be needed for patients receiving concomitant treatment with certain other drugs (see PRECAUTIONS-Drug Interactions).

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted September 28, 2001).

Please submit the copies of final printed labeling (FPL) electronically to each application according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 50-689/S-011, S-013." Approval of these submissions by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

NDA 50-869/S-011, S-013

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Robin Anderson, Labeling Reviewer, at (301) 827-2127.

Sincerely,

Renata Albrecht, M.D.
Acting Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research