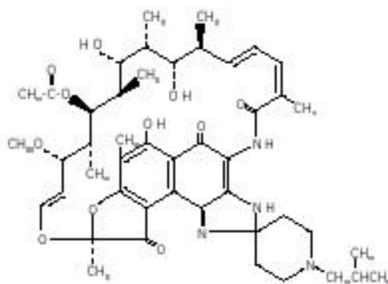


Mycobutin®
rifabutin capsules, USP

DESCRIPTION

MYCOBUTIN Capsules contain the antimycobacterial agent rifabutin, which is a semisynthetic ansamycin antibiotic derived from rifamycin S. MYCOBUTIN Capsules for oral administration contain 150 mg of rifabutin, USP, per capsule, along with the inactive ingredients microcrystalline cellulose, magnesium stearate, red iron oxide, silica gel, sodium lauryl sulfate, titanium dioxide, and edible white ink.

The chemical name for rifabutin is 1',4-didehydro-1-deoxy-1,4-dihydro-5'-(2-methylpropyl)-1-oxorifamycin XIV (Chemical Abstracts Service, 9th Collective Index) or (9*S*, 12*E*, 14*S*, 15*R*, 16*S*, 17*R*, 18*R*, 19*R*, 20*S*, 21*S*, 22*E*, 24*Z*)-6,16,18,20-tetrahydroxy-1'-isobutyl-14-methoxy-7,9,15,17,19,21,25-heptamethyl-spiro [9,4-(epoxypentadeca[1,11,13]trienimino)-2*H*-furo[2',3':7,8]naphth[1,2-*d*]imidazole-2,4'-piperidine]-5,10,26-(3*H*,9*H*)-trione-16-acetate. Rifabutin has a molecular formula of C₄₆H₆₂N₄O₁₁, a molecular weight of 847.02 and the following structure:



Rifabutin is a red-violet powder soluble in chloroform and methanol, sparingly soluble in ethanol, and very slightly soluble in water (0.19 mg/mL). Its log P value (the base 10 logarithm of the partition coefficient between n-octanol and water) is 3.2 (n-octanol/water).

CLINICAL PHARMACOLOGY

Pharmacokinetics

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 dose-proportionality was 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: Due to its high lipophilicity, rifabutin demonstrates a high propensity for distribution and intracellular tissue uptake. 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 approximately 6.5 in four surgical patients who received an oral dose. Mean rifabutin steady-state trough levels ($C_{p, \text{minss}}$; 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 mcgm/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: A mass-balance study in three healthy adult volunteers with ¹⁴C-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 .

Pharmacokinetics in Special Populations

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).

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 did 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 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 trimethoprim was given 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: 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 48% and 32%, respectively. However, zidovudine levels remained within the therapeutic range during coadministration of rifabutin. Zidovudine 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.

CLINICAL STUDIES

Two randomized, double-blind clinical trials (study 023 and study 027) compared MYCOBUTIN (300 mg/day) to placebo in patients with CDC-defined AIDS and CD4 counts ≤ 200 cells/ μ L. These studies accrued patients from 2/90 through 2/92. Study 023 enrolled 590 patients, with a median CD4 cell count at study entry of 42 cells/ μ L (mean 61). Study 027 enrolled 556 patients with a median CD4 cell count at study entry of 40 cells/ μ L (mean 58).

Endpoints included the following:

- (1) MAC bacteremia, defined as at least one blood culture positive for *M. avium* complex bacteria.
- (2) Clinically significant disseminated MAC disease, defined as MAC bacteremia accompanied by signs or symptoms of serious MAC infection, including one or more of the following: fever, night sweats, rigors, weight loss, worsening anemia, and/or elevations in alkaline phosphatase.
- (3) Survival

MAC bacteremia

Participants who received MYCOBUTIN were one-third to one-half as likely to develop MAC bacteremia as were participants who received placebo. These results were statistically significant (study 023: $p < 0.001$; study 027: $p = 0.002$).

In study 023, the one-year cumulative incidence of MAC bacteremia, on an intent to treat basis, was 9% for patients randomized to MYCOBUTIN and 22% for patients randomized to placebo. In study 027, these rates were 13% and 28% for patients receiving MYCOBUTIN and placebo, respectively.

Most cases of MAC bacteremia (approximately 90% in these studies) occurred among participants whose CD4 count at study entry was ≤ 100 cells/ μ L. The median and mean CD4 counts at onset of MAC bacteremia were 13 cells/ μ L and 24 cells/ μ L, respectively. These studies did not investigate the optimal time to begin MAC prophylaxis.

Clinically significant disseminated MAC disease

In association with the decreased incidence of bacteremia, patients on MYCOBUTIN showed reductions in the signs and symptoms of disseminated MAC disease, including fever, night sweats, weight loss, fatigue, abdominal pain, anemia, and hepatic dysfunction.

Survival

The one year survival rates in study 023 were 77% for the group receiving MYCOBUTIN and 77% for the placebo group. In study 027, the one year survival rates were 77% for the group receiving MYCOBUTIN and 70% for the placebo group. These differences were not statistically significant.

MICROBIOLOGY

Mechanism of Action

Rifabutin inhibits DNA-dependent RNA polymerase in susceptible strains of *Escherichia coli* and *Bacillus subtilis* but not in mammalian cells. In resistant strains of *E. coli*, rifabutin, like rifampin, did not inhibit this enzyme. It is not known whether rifabutin inhibits DNA-dependent RNA polymerase in *Mycobacterium avium* or in *M. intracellulare* which comprise *M. avium* complex (MAC).

Susceptibility Testing

In vitro susceptibility testing methods and diagnostic products used for determining minimum inhibitory concentration (MIC) values against *M. avium* complex (MAC) organisms have not been standardized. Breakpoints to determine whether clinical isolates of MAC and other mycobacterial species are susceptible or resistant to rifabutin have not been established.

In Vitro Studies

Rifabutin has demonstrated in vitro activity against *M. avium* complex (MAC) organisms isolated from both HIV-positive and HIV-negative people. While gene probe techniques may be used to identify these two organisms, many reported studies did not distinguish between these two species. The vast majority of isolates from MAC-infected, HIV-positive people are *M. avium*, whereas in HIV-negative people, about 40% of the MAC isolates are *M. intracellulare*.

Various in vitro methodologies employing broth or solid media, with and without polysorbate 80 (Tween 80), have been used to determine rifabutin MIC values for mycobacterial species. In general, MIC values determined in broth are several fold lower than that observed with methods employing solid media. Utilization of Tween 80 in these assays has been shown to further lower MIC values.

However, MIC values were substantially higher for egg based compared to agar based solid media.

Rifabutin activity against 211 MAC isolates from HIV-positive people was evaluated in vitro utilizing a radiometric broth and an agar dilution method. Results showed that 78% and 82% of these isolates had MIC₉₉ values of ≤ 0.25 $\mu\text{g/mL}$ and ≤ 1.0 $\mu\text{g/mL}$, respectively, when evaluated by these two methods. Rifabutin was also shown to be active against phagocytized, *M. avium* complex in a mouse macrophage cell culture model.

Rifabutin has in vitro activity against many strains of *Mycobacterium tuberculosis*. In one study, utilizing the radiometric broth method, each of 17 and 20 rifampin-naive clinical isolates tested from the United States and Taiwan, respectively, were shown to be susceptible to rifabutin concentrations of ≤ 0.125 $\mu\text{g/mL}$.

Cross-resistance between rifampin and rifabutin is commonly observed with *M. tuberculosis* and *M. avium* complex isolates. Isolates of *M. tuberculosis* resistant to rifampin are likely to be resistant to rifabutin. Rifampicin and rifabutin MIC₉₉ values against 523 isolates of *M. avium* complex were determined utilizing the agar dilution method (Ref. Heifets, Leonid B. and Iseman, Michael D. 1985. Determination of in vitro susceptibility of Mycobacteria to Ansamycin. Am. Rev. Respir. Dis. 132 (3):710-711).

SUSCEPTIBILITY OF M. AVIUM COMPLEX STRAINS TO RIFAMPIN AND RIFABUTIN					
		% of Strains Susceptible/Resistant to Different Concentrations of Rifabutin ($\mu\text{g/mL}$)			
Susceptibility to Rifampin ($\mu\text{g/mL}$)	Number of Strains	Susceptible to 0.5	Resistant to 0.5 only	Resistant to 1.0	Resistant to 2.0
Susceptible to 1.0	30	100.0	0.0	0.0	0.0
Resistant to 1.0 only	163	88.3	11.7	0.0	0.0
Resistant to 5.0	105	38.0	57.1	2.9	2.0
Resistant to 10.0	225	20.0	50.2	19.6	10.2
TOTAL	523	49.5	36.7	9.0	4.8

Rifabutin in vitro MIC₉₉ values of ≤ 0.5 μmL , determined by the agar dilution method, for *M. kansasii*, *M. gordonae* and *M. marinum* have been reported; however, the clinical significance of these results is unknown.

INDICATIONS AND USAGE

MYCOBUTIN Capsules are indicated for the prevention of disseminated *Mycobacterium avium* complex (MAC) disease in patients with advanced HIV infection.

CONTRAINDICATIONS

MYCOBUTIN Capsules are contraindicated in patients who have had clinically significant hypersensitivity to rifabutin or to any other rifamycins.

WARNINGS

MYCOBUTIN Capsules must not be administered for MAC prophylaxis to patients with active tuberculosis. Tuberculosis in HIV-positive patients is common and may present with atypical or extrapulmonary findings. Patients are likely to have a nonreactive purified protein derivative (PPD) despite active disease. In addition to chest X-ray and sputum culture, the following studies may be useful in the diagnosis of tuberculosis in the HIV-positive patient: blood culture, urine culture, or biopsy of a suspicious lymph node.

Patients who develop complaints consistent with active tuberculosis while on prophylaxis with MYCOBUTIN should be evaluated immediately, so that those with active disease may be given an effective combination regimen of anti-tuberculosis medications. Administration of MYCOBUTIN as a single agent to patients with active tuberculosis is likely to lead to the development of tuberculosis that is resistant both to MYCOBUTIN and to rifampin.

There is no evidence that MYCOBUTIN is effective prophylaxis against *M. tuberculosis*. Patients requiring prophylaxis against both *M. tuberculosis* and *Mycobacterium avium* complex may be given isoniazid and MYCOBUTIN concurrently.

PRECAUTIONS

General

Because treatment with MYCOBUTIN Capsules may be associated with neutropenia, and more rarely thrombocytopenia, physicians should consider obtaining hematologic studies periodically in patients receiving prophylaxis with MYCOBUTIN.

Information for Patients

Patients should be advised of the signs and symptoms of both MAC and tuberculosis, and should be instructed to consult their physicians if they develop new complaints consistent with either of these diseases. In addition, since MYCOBUTIN may rarely be associated with myositis and uveitis, patients should be advised to notify their physicians if they develop signs or symptoms suggesting either of these disorders.

Urine, feces, saliva, sputum, perspiration, tears, and skin may be colored brown-orange with rifabutin and some of its metabolites. Soft contact lenses may be permanently stained. Patients to be treated with MYCOBUTIN should be made aware of these possibilities.

Drug Interactions

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term carcinogenicity studies were conducted with rifabutin in mice and in rats. Rifabutin was not carcinogenic in mice at doses up to 180 mg/kg/day, or approximately 36 times the recommended human daily dose. Rifabutin was not carcinogenic in the rat at doses up to 60 mg/kg/day, about 12 times the recommended human dose.

Rifabutin was not mutagenic in the bacterial mutation assay (Ames Test) using both rifabutin-susceptible and resistant strains. Rifabutin was not mutagenic in *Schizosaccharomyces pombe P₁* and was not genotoxic in V-79 Chinese hamster cells, human lymphocytes in vitro, or mouse bone marrow cells in vivo.

Fertility was impaired in male rats given 160 mg/kg (32 times the recommended human daily dose).

Pregnancy

Pregnancy Category B: Reproduction studies have been carried out in rats and rabbits given rifabutin using dose levels up to 200 mg/kg (40 times the recommended human daily dose). No teratogenicity

was observed in either species. In rats, given 200 mg/kg/day, there was a decrease in fetal viability. In rats, at 40 mg/kg/day (8 times the recommended human daily dose), rifabutin caused an increase in fetal skeletal variants. In rabbits, at 80 mg/kg/day (16 times the recommended human daily dose), rifabutin caused maternotoxicity and increase in fetal skeletal anomalies. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, rifabutin should be used in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether rifabutin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of rifabutin for prophylaxis of MAC in children have not been established. Limited safety data are available from treatment use in 22 HIV-positive children with MAC who received MYCOBUTIN in combination with at least two other antimycobacterials for periods from 1 to 183 weeks. Mean doses (mg/kg) for these children were: 18.5 (range 15.0 to 25.0) for infants one year of age; 8.6 (range 4.4 to 18.8) for children 2 to 10 years of age; and 4.0 (range 2.8 to 5.4) for adolescents 14 to 16 years of age. There is no evidence that doses greater than 5 mg/kg daily are useful. Adverse experiences were similar to those observed in the adult population, and included leukopenia, neutropenia and rash. 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. Doses of MYCOBUTIN may be administered mixed with foods such as applesauce.

Geriatric Use

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).

ADVERSE REACTIONS

MYCOBUTIN Capsules were generally well tolerated in the controlled clinical trials. Discontinuation of therapy due to an adverse event was required in 16% of patients receiving MYCOBUTIN compared to 8% of patients receiving placebo in these trials. Primary reasons for discontinuation of MYCOBUTIN were rash (4% of treated patients), gastrointestinal intolerance (3%), and neutropenia (2%).

The following table enumerates adverse experiences that occurred at a frequency of 1% or greater, among the patients treated with MYCOBUTIN in studies 023 and 027.

CLINICAL ADVERSE EXPERIENCES REPORTED IN ≥1% OF PATIENTS TREATED WITH MYCOBUTIN		
ADVERSE EVENT	MYCOBUTIN (n = 566) %	PLACEBO (n = 580) %
BODY AS A WHOLE		
Abdominal Pain	4	3
Asthenia	1	1
Chest Pain	1	1
Fever	2	1
Headache	3	5
Pain	1	2
DIGESTIVE SYSTEM		
Anorexia	2	2
Diarrhea	3	3
Dyspepsia	3	1
Eructation	3	1
Flatulence	2	1
Nausea	6	5
Nausea and Vomiting	3	2
Vomiting	1	1
MUSCULOSKELETAL SYSTEM		
Myalgia	2	1
NERVOUS SYSTEM		
Insomnia	1	1
SKIN AND APPENDAGES		
Rash	11	8
SPECIAL SENSES		
Taste Perversion	3	1
UROGENITAL SYSTEM		
Discolored Urine	30	6

CLINICAL ADVERSE EVENTS REPORTED IN <1% OF PATIENTS WHO RECEIVED MYCOBUTIN

Considering data from the 023 and 027 pivotal trials, and from other clinical studies, MYCOBUTIN appears to be a likely cause of the following adverse events which occurred in less than 1% of treated patients: flu-like syndrome, hepatitis, hemolysis, arthralgia, myositis, chest pressure or pain with dyspnea, and skin discoloration.

The following adverse events have occurred in more than one patient receiving MYCOBUTIN, but an etiologic role has not been established: seizure, paresthesia, aphasia, confusion, and non-specific T wave changes on electrocardiogram.

When MYCOBUTIN was administered at doses from 1050 mg/day to 2400 mg/day, generalized arthralgia and uveitis were reported. These adverse experiences abated when MYCOBUTIN was discontinued.

The following table enumerates the changes in laboratory values that were considered as laboratory abnormalities in studies 023 and 027.

PERCENTAGE OF PATIENTS WITH LABORATORY ABNORMALITIES		
LABORATORY ABNORMALITIES	MYCOBUTIN (n = 566) %	PLACEBO (n = 580) %
Chemistry:		
Increased Alkaline Phosphatase ¹	<1	3
Increased SGOT ²	7	12
Increased SGPT ²	9	11
Hematology:		
Anemia ³	6	7
Eosinophilia	1	1
Leukopenia ⁴	17	16
Neutropenia ⁵	25	20
Thrombocytopenia	5	4

INCLUDES GRADE 3 OR 4 TOXICITIES AS SPECIFIED:

- 1 all values >450 U/L
- 2 all values >150 U/L
- 3 all hemoglobin values < 8.0 g/dL
- 4 all WBC values < 1,500/mm³
- 5 all ANC values < 750/mm³
- 6 all platelet count values < 50,000/mm³

The incidence of neutropenia in patients treated with MYCOBUTIN was significantly greater than in patients treated with placebo (p = 0.03). Although thrombocytopenia was not significantly more common among patients treated with MYCOBUTIN in these trials, MYCOBUTIN has been clearly linked to thrombocytopenia in rare cases. One patient in study 023 developed thrombotic thrombocytopenic purpura, which was attributed to MYCOBUTIN.

Uveitis is rare when MYCOBUTIN is used as a single agent at 300 mg/day for prophylaxis of MAC in HIV-infected persons, even with the concomitant use of fluconazole and/or macrolide antibiotics. However, if higher doses of MYCOBUTIN are administered in combination with these agents, the incidence of uveitis is higher.

Patients who developed uveitis had mild to severe symptoms that resolved after treatment with corticosteroids and/or mydriatic eye drops; in some severe cases, however, resolution of symptoms occurred after several weeks.

When uveitis occurs, temporary discontinuance of MYCOBUTIN and ophthalmologic evaluation are recommended. In most mild cases, MYCOBUTIN may be restarted; however, if signs or symptoms recur, use of MYCOBUTIN should be discontinued (Morbidity and Mortality Weekly Report, September 9, 1994).

ANIMAL TOXICOLOGY

Liver abnormalities (increased bilirubin and liver weight), occurred in all species tested, in rats at doses 5 times, in monkeys at doses 8 times, and in mice at doses 6 times the recommended human daily dose. Testicular atrophy occurred in baboons at doses 4 times the recommended human dose, and in rats at doses 40 times the recommended human daily dose.

OVERDOSAGE

No information is available on accidental overdosage in humans.

Treatment

While there is no experience in the treatment of overdose with MYCOBUTIN Capsules, clinical experience with rifamycins suggest that gastric lavage to evacuate gastric contents (within a few hours of overdose), followed by instillation of an activated charcoal slurry into the stomach, may help absorb any remaining drug from the gastrointestinal tract.

Rifabutin is 85% protein bound and distributed extensively into tissues (V_{ss} : 8 to 9 L/kg). It is not primarily excreted via the urinary route (less than 10% as unchanged drug), therefore, neither hemodialysis nor forced diuresis is expected to enhance the systemic elimination of unchanged rifabutin from the body in a patient with an overdose of MYCOBUTIN.

DOSAGE AND ADMINISTRATION

It is recommended that MYCOBUTIN Capsules be administered at a dose of 300 mg once daily. For those patients with propensity to nausea, vomiting, or other gastrointestinal upset, administration of MYCOBUTIN at doses of 150 mg twice daily taken with food may be useful. For patients with severe renal impairment (creatinine clearance less than ~~300~~ 30 mL/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).

HOW SUPPLIED

MYCOBUTIN Capsules (rifabutin capsules, USP) are supplied as hard gelatin capsules having an opaque red-brown cap and body, imprinted with MYCOBUTIN/PHARMACIA & UPJOHN in white ink, each containing 150 mg of rifabutin, USP.

MYCOBUTIN is available as follows:

NDC 0013-5301-17 Bottles of 100 capsules

Keep tightly closed and dispense in a tight container as defined in the USP. Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

Rx only

Manufactured for: Pharmacia & Upjohn Company
 A subsidiary of Pharmacia Corporation
 Kalamazoo, MI 49001, USA

By: Pharmacia & Upjohn S.p.A.
 Ascoli Piceno, Italy

Revised

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/s/

Renata Albrecht
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