PRODUCT MONOGRAPH

MYCOBUTIN*

(rifabutin capsules USP)

150 mg Capsules

Antibacterial Agent

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(rifabutin capsules USP)

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THERAPEUTIC CLASSIFICATION

Antibacterial Agent

ACTION AND CLINICAL PHARMACOLOGY

MYCOBUTIN® (rifabutin) is a derivative of rifamycin S, belonging to the class of ansamycins. The rifamycins owe their antimycobacterial efficacy to their ability to penetrate the cell wall and to their ability to complex with and to inhibit DNA-dependent RNA polymerase. Rifabutin has been found to interact with and to penetrate the outer layers of the mycobacterial envelope. 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 constitutes *M. avium* complex (MAC). Rifabutin inhibited incorporation of thymidine into DNA of rifampin-resistant *M. tuberculosis* suggesting that rifabutin may also inhibit DNA synthesis which may explain its activity against rifampin-resistant organisms.

Following oral administration, at least 53% of MYCOBUTIN dose is rapidly absorbed with rifabutin peak plasma concentrations attained in 2 to 4 hours. High-fat meals slow the rate without influencing the extent of absorption of rifabutin from the capsule dosage form.

The mean (± SD) absolute bioavailability assessed in HIV positive patients in a multiple dose study was 20% (±16%, n=5) on day 1 and 12% (± 5%, n=7) on day 28.

In healthy adult volunteers administered a single oral dose of 300 mg of rifabutin, the mean (± SD) peak plasma concentration (C_{max}) was 375 (± 267) ng/mL (range: 141 to 1033 ng/mL). 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 normal volunteers. Pharmacokinetic doseproportionality over the 300 to 900 mg single dose range has been demonstrated in early symptomatic HIV positive patients and in healthy normal volunteers over the 300 to 600 mg single dose range.

Rifabutin appears to be widely distributed throughout the body and has been detected in all tissues and body fluids examined. Several times higher concentrations than those achieved in plasma have been observed in lung parenchyma, gall bladder and the small intestinal wall. The apparent volume of distribution at steady-state (V_{ss}) estimated in early symptomatic HIV positive male patients following intravenous dosing was large (8 to 9 liters/kg), suggesting extensive distribution of rifabutin into the tissues. About 85% of the drug is bound to plasma proteins over a concentration range of 50 to 1000 ng/mL. Binding is predominantly to human serum albumin, is concentration independent and does not appear to be influenced by renal or hepatic dysfunction.

Rifabutin undergoes extensive oxidative metabolism. Of the five metabolites that have been identified, 25-O-deacetyl and 31-hydroxy are the most predominant and show a plasma metabolite:parent area under the curve ratio of 0.10 for 25-O-deacetyl and 0.07 for 31-hydroxy metabolite. The 25-O-deacetyl metabolite has antimycobacterial activity equal to the parent drug and contributes up to 10% to the total antimicrobial activity. The 31-hydroxy metabolite has some antimicrobial activity (1/16 that of parent drug), but, considering its concentration in plasma, it is probably not contributing significantly to the therapeutic activity of rifabutin. Rifabutin can induce its own metabolism on multiple dosing. The area under the plasma concentration-time curve (AUC) following multiple dosing decreased by 38%, but its terminal half-life remained unchanged.

The plasma elimination profile of rifabutin is biphasic with an initial half-life of approximately 4 hours followed by a mean terminal half-life of 45 (± 17) hours (range: 16 to 69 hours). Mean systemic clearance 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). Rifabutin is mainly excreted in the urine, primarily as metabolites and to a lesser extent in the faeces. Fifty-three percent (53%) of the oral dose of ^{14}C-labelled drug was recovered in the urine by five days post-dose and 30% was recovered in the faeces over the same period. Renal and biliary excretion of unchanged drug each contribute approximately 5% to the systemic clearance.

The pharmacokinetic profile of rifabutin is not significantly modified by age or by hepatic dysfunction, although the inter-individual variability in elderly subjects (71-80 years) was slightly higher. Renal insufficiency was correlated to a decrease in urinary excretion with AUC and Cmax increases most apparent in severe disease. Caution and dose reductions may be required when treating patients with severe renal or severe hepatic impairment.

Rifabutin steady-state pharmacokinetics in early symptomatic HIV positive patients are similar to those in healthy normal volunteers but the variability between individuals is higher in the HIV positive patients. No rifabutin disposition information is currently available in children or adolescents under 18 years of age.

INDICATIONS AND CLINICAL USAGE

MYCOBUTIN® (rifabutin) is indicated for the prevention of disseminated *Mycobacterium avium* complex (MAC) disease in patients with advanced HIV infection (CD4+ cell count $\leq 200/mm^3$ with an AIDS defining diagnosis, or CD4+ cell count $\leq 100/mm^3$ without an AIDS defining diagnosis).

CONTRAINDICATIONS

MYCOBUTIN® (rifabutin) is contraindicated in patients who have had clinically significant hypersensitivity to this drug, or to any other rifamycins.

WARNINGS

General:

MYCOBUTIN® (rifabutin) prophylaxis must not be administered to patients with <u>active</u> tuberculosis. Among HIV positive patients, tuberculosis is common and may present with atypical or extrapulmonary findings. Patients are likely to have a nonreactive purified protein derivative (PPD) test 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 signs and symptoms consistent with active tuberculosis while on MYCOBUTIN prophylaxis 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 which is resistant both to MYCOBUTIN and to rifampin.

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

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including MYCOBUTIN (rifabutin). CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile*. *C. difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases.

Due to increased plasma concentrations and other pharmacokinetic considerations, a decrease in dosage may be considered in patients with severe renal impairment or severe liver insufficiency or because of potential cyp450 IIIA-related interactions in patients co-administered certain other drugs (see **PRECAUTIONS, DOSAGE AND ADMINISTRATION**).

Significant drug-drug interactions between rifabutin and protease inhibitors, among many other drugs, requires careful consideration based upon the overall assessment of the patient and patient's specific drug profile since drug safety and efficacy can be impacted. Patients should be carefully monitored to avoid uveitis. If uveitis is suspected, the patient should be referred to an ophthalmologist and, if considered necessary, treatment with MYCOBUTIN should be suspended (see **PRECAUTIONS,** Drug Interactions, **ADVERSE REACTIONS**).

PRECAUTIONS

General

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

Use in the Elderly

MYCOBUTIN administered as a single dose has been evaluated in 24 healthy, elderly (71-80 years) volunteers. The pharmacokinetic profile of MYCOBUTIN is not significantly modified by age, although the inter-individual variability in this age group was slightly higher when compared to younger (25-37 years) volunteers.

Use in Children

The safety and effectiveness of MYCOBUTIN for prophylaxis of MAC disease in children and adolescents under 18 years of age have not been established. However, limited safety data are available from 22 HIV positive children who received MYCOBUTIN as treatment for disseminated MAC disease, in combination with at least two other antimycobacterials for periods ranging from 1 to 183 weeks.

The mean daily doses (mg/kg) for these children were: infants one year of age, 18.5 (range 15.0 to 25.0); children 2 to 10 years, 8.6 (range 4.4 to 18.8); adolescents 14 to 16 years, 4.0 (range 2.8 to 5.4). MYCOBUTIN was generally safe in this treatment group. Adverse experiences were similar to those observed in the adult population, and included leukopenia, neutropenia and skin rash. Doses of MYCOBUTIN may be administered mixed with foods such as applesauce.

Usage in Pregnancy
There are no adequate and well-controlled studies of MYCOBUTIN use in pregnant women. No teratogenic effects were observed in reproduction studies carried out in rats and rabbits. Because animal reproduction studies are not always predictive of human response, MYCOBUTIN 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 MYCOBUTIN is excreted in human milk. Because many drugs are excreted in human milk and given 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 nursing mother.

Use In Renal Impairment
Caution is recommended when treating patients with severe 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 50% reduction in the dosage of rifabutin is recommended for patients with $Cr_{cl} < 30$ mL/min. No dosage adjustment is recommended in mild to moderate renal impairment (see **DOSAGE AND ADMINISTRATION**).

Use In Hepatic Impairment
The pharmacokinetics of rifabutin were studied in 40 patients with mild (n=30), moderate (n=6) and severe (n=4) hepatic impairment. Significant variability was noted. Caution should be exercised in treating patients with severe hepatic disease. For patients with severe liver insufficiency a dose reduction should be considered. Mild and moderate hepatic impairment does not require a dose modification.

Drug Interactions

Multiple dosing of rifabutin has been associated with induction of hepatic metabolic enzymes of the cyp450 IIIA subfamily. Rifabutin's predominant metabolite (25-desacetyl rifabutin; LM 565), may also contribute to this effect. Metabolic induction due to rifabutin is likely to produce a decrease in circulating levels of concomitantly administered drugs (especially those metabolized by the cyp450 IIIA pathway). Kinetic data suggest that enzymatic induction by rifabutin is complete within 5 days and is dose-independent over the 300 to 600 mg dose-range. Similarly, concomitant medications that competitively inhibit the cyp450 IIIA activity may increase circulating levels of rifabutin.

Malabsorption
Gastric pH alteration due to progressing HIV disease has been linked with malabsorption of some drugs used in HIV-positive patients (e.g., rifampin, isoniazid). Drug serum concentration data from AIDS patients with varying disease severity (based on CD4+ counts) suggest that rifabutin absorption is not influenced by progressing HIV disease. However, when stomach pH is

increased with drug co-administration, rifabutin absorption may be impaired.

Effects on Other Drugs
Rifabutin induces cyp450 IIIA 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 (see below).

Effects on Rifabutin
Some drugs that inhibit cyp450 IIIA may significantly increase the plasma concentration of rifabutin. Because high plasma levels of rifabutin may increase the risk of adverse reactions, patients coadministered such drugs should be carefully monitored and in some cases the doses of MYCOBUTIN may need to be reduced (see below).

The following table summarizes the results and magnitude of the pertinent drug interactions assessed with rifabutin as reported in selected not all-inclusive publications from the scientific literature. The clinical relevance of these interactions and subsequent dose modifications, which are largely based upon pharmacokinetic data extrapolations, should be judged in light of the population studied, severity of the disease, patient drug profile, and the likely impact on the risk/benefit ratio.

Rifabutin Interaction Studies

Coadministered Drugs	Effect on Rifabutin	Effect on Coadministered Drug	Comments
ANTIVIRALS			
Amprenavir	2.9-fold ↑ AUC, 2.2-fold ↑ Cmax	No significant change in kinetics.	A 50% reduction in the rifabutin dose is recommended when combined with amprenavir. Increased monitoring for adverse reactions is warranted.
Delavirdine	ND	Oral clearance ↑ 5-fold resulting in significantly lower mean trough plasma concentrations (18±15 to 1.0±0.7 μM)	Study conducted in HIV-1 infected patients Rifabutin is not recommended for patients dosed with delavirdine mesylate 400 mg q8h.
Didanosine	No significant change in kinetics.	No significant change in kinetics at steady state.	Didanosine administration with pH increasing buffers may decrease rifabutin absorption
Fosamprenavir/ ritonavir *	64% ↑ AUC **	35% ↑ AUC and 36% ↑ Cmax, no effect Ctrough (amprenavir)	Dosage reduction of rifabutin by at least 75% (to 150 mg every other day or three times per week) is recommended when combined with fosamprenavir
Indinavir	204% ↑ in AUC	32%↓ in AUC	
Lopinavir/ritonavir*	5.7-fold ↑ AUC, 3.4 fold ↑ Cmax**	No significant change in lopinavir kinetics.	Dosage reduction of rifabutin by at least 75% of the usual dose of 300 mg/day is recommended (i.e., a maximum dose of 150 mg every other day or three times per week). Increased monitoring for adverse reactions is warranted. Further dosage reduction of rifabutin may be necessary.
Saquinavir	ND	40% ↓ in AUC	

Coadministered Drugs	Effect on Rifabutin	Effect on Coadministered Drug	Comments
Ritonavir *	4 fold increase in AUC, 2.5 fold increase in Cmax	ND	In the presence of ritonavir the subsequent risk of side effects, including uveitis may be increased. If a protease inhibitor is required in a patient treated with rifabutin, agents other than ritonavir should be considered.
Tipranavir/ritonavir *	2.9-fold ↑ AUC, 1.7-fold ↑ Cmax	No significant change in tipranavir kinetics.	Therapeutic drug monitoring of rifabutin is recommended.
Zidovudine	No significant change in kinetics.	Approximately 32%↓ in Cmax and AUC	A large controlled clinical study has shown that these changes are of no clinical relevance.
ANTIFUNGALS			
Fluconazole	82% ↑ in AUC	No significant change in steady-state plasma concentrations	
Itraconazole	ND	70% to 75% ↓ in Cmax and AUC	One case report suggests a kinetic interaction resulting in an increase in serum rifabutin levels and a risk for developing uveitis in the presence of itraconazole.
Posaconazole	31%↑ Cmax, 72%↑ AUC	43%↓ Cmax, 49%↓ AUC	If the drugs are coadministered, patients should be monitored for adverse events associated with rifabutin administration.
Voriconazole	195%↑ Cmax, 331%↑ AUC ***	Rifabutin (300 mg once daily) decreased the Cmax and AUC of voriconazole at 200 mg twice daily by 69% and 78%, respectively. During coadministration with rifabutin, the Cmax and AUC of voriconazole at 350 mg twice daily were 96% and 68% of the levels when administered alone at 200 mg twice daily. At a voriconazole dose of 400 mg twice daily Cmax and AUC were 104% and 87% higher, respectively, compared with voriconazole alone at 200 mg twice daily.	Concurrent administration of voriconazole and rifabutin is not recommended.
ANTI-PCP (Pneumocystis jirovecii pneumonia †)			
Dapsone	ND	Approximately 27% to 40% ↓ in AUC	Study conducted in HIV infected patients (rapid and slow acetylators).
Sulfamethoxazole-Trimethoprim	No significant change in Cmax and AUC	Approximately 15% to 20% ↓ in AUC	In another study, only trimethoprim (not sulfamethoxazole) had 14% ↓ in AUC and 6%↓ in Cmax but were not considered clinically significant.
ANTI-MAC (Mycobacterium avium intracellulare complex)			
Azithromycin	No PK interaction	No PK interaction	

Coadministered Drugs	Effect on Rifabutin	Effect on Coadministered Drug	Comments
Clarithromycin	Approximately 77% ↑ in AUC	Approximately 50%↓ in AUC	Study conducted in HIV infected patients. Dose of rifabutin should be adjusted in the presence of clarithromycin
ANTI-TB (Tuberculosis)			
Ethambutol	ND	No significant change in AUC or Cmax	
Isoniazid	ND	Pharmacokinetics not affected	
Pyrazinamide	ND	ND	Study data being evaluated.
OTHER			
Methadone	ND	No significant effect	No apparent effect of rifabutin on either peak levels of methadone or systemic exposure based upon AUC. Rifabutin kinetics not evaluated.
Ethinylestradiol	ND	35%↓ AUC 20%↓ Cmax	Patients should be advised to use other methods of contraception.
Norethindrone	ND	46%↓ AUC	Patients should be advised to use other methods of contraception.
Tacrolimus	ND	ND	Authors report that rifabutin decreases tacrolimus trough blood levels.
Theophylline	ND	No significant change in AUC or Cmax compared with baseline.	

ND: Not done; AUC: Area under the Concentration vs. Time Curve; Cmax: Maximum serum concentration
* A lower dose of ritonavir was used when combined with fosamprenavir, lopinavir or tipranavir than when used alone; the PK effects upon ritonavir used alone or in combination with these antivirals were not studied.
** - Drug plus active metabolite
*** - Voriconazole dosed at 400 mg twice daily
† Formerly known as Pneumocystis carinii pneumonia

Other drugs

MYCOBUTIN has liver enzyme-inducing properties. The related drug rifampin is known to reduce the activity of a number of 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, theopylline, 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 the effects of rifabutin on hepatic microsomal enzyme activity were compared to those of 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. <u>Dosage adjustment of drugs listed above may be necessary if they are given concurrently with MYCOBUTIN</u>.

Patients using oral contraceptives should consider changing to nonhormonal methods of birth control.

Information for Patients

MYCOBUTIN is used for the prevention of serious disease caused by *Mycobacterium avium* complex (MAC) organisms in patients with advanced HIV infection. MYCOBUTIN should not be given to patients with active tuberculosis. Patients should ask their physicians to advise them of the signs and symptoms of both MAC disease and tuberculosis. Patients should consult their physicians if they develop new complaints suggestive of either MAC disease or tuberculosis.

MYCOBUTIN should be taken as a single dose (two 150 mg capsules) once daily with or without food. For those patients who experience nausea, vomiting or other stomach upsets, it may be useful to split the MYCOBUTIN dose in half (one 150 mg capsule) twice a day with food.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes, after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

The most common side-effect of MYCOBUTIN is that urine may be coloured brown-orange. Similar discoloration may affect stools, saliva, sputum, perspiration, tears or the skin. Contact lenses may be permanently stained.

Other side-effects associated with MYCOBUTIN include: a reduction in the number of white blood cells which fight infections, skin rashes, and gastrointestinal complaints such as indigestion, belching, flatulence, nausea, vomiting and abdominal pain. Very rarely, MYCOBUTIN may cause muscle aches, inflammation of the inside of the eye (uveitis), and generalized joint pains.

ADVERSE REACTIONS

MYCOBUTIN® (rifabutin) was generally well tolerated in the controlled clinical trials involving 566 patients treated with MYCOBUTIN and 580 patients treated with placebo. The most serious adverse reaction to MYCOBUTIN was neutropenia.

The most common adverse events, reported more frequently in the MYCOBUTIN treated patients than in the placebo group were: urine discoloration, neutropenia, skin rash, nausea and/or vomiting, and abdominal pain (see tables). The incidence of urine discoloration and neutropenia in patients treated with MYCOBUTIN were significantly greater than in patients treated with placebo (Fisher's Test, $p< 0.01$ and $p=0.03$ respectively).

Sixteen percent (16%) of MYCOBUTIN treated patients discontinued therapy due to an adverse event as compared to 8% of placebo-treated patients. The primary reasons for discontinuation of MYCOBUTIN were: skin rash (4%), 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 and those treated with placebo in the Phase III clinical trials.

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
Headache	3	5
Fever	2	1
Asthenia	1	1
Chest Pain	1	1
Pain	1	2
DIGESTIVE SYSTEM		
Nausea	6	5
Nausea and vomiting	3	2
Vomiting	1	1
Diarrhea	3	3
Dyspepsia	3	1
Eructation	3	1
Anorexia	2	2
Flatulence	2	1
MUSCULOSKELETAL SYSTEM		
Myalgia	2	1
NERVOUS SYSTEM		
Insomnia	1	1
SKIN AND APPENDAGES		
Rash	11	8
Pruritus	1	1
SPECIAL SENSES		
Taste Perversion	3	1
UROGENITAL SYSTEM		
Discoloured urine	30	6

Considering data from the Phase III clinical 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 the treated patients: arthralgia, chest pressure or pain with dyspnea, hemolysis, hepatitis, myositis, and skin discoloration.

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

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.

Laboratory Test Abnormalities
The following table enumerates the changes in laboratory values that were considered as laboratory test abnormalities in the Phase III clinical trials.

PERCENTAGE OF PATIENTS WITH LABORATORY ABNORMALITIES		
Laboratory Abnormality	MYCOBUTIN (n=566)%	PLACEBO (n=580)%
Chemistry:		
Increased ALT (> 150 U/L)	9	11
Increased AST (> 150 U/L)	7	12
Increased Alkaline Phosphatase (> 450 U/L)	<1	3
Hematology:		
Neutropenia (ANC < 750/mm^3)	25	20
Leukopenia (WBC < 1500/mm^3)	17	16
Anemia (Hemoglobin < 8.0 g/dL)	6	7
Thrombocytopenia (Platelet count < 50,000/mm^3)	5	4
Eosinophilia	1	1

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 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.

Post-Marketing Adverse Reactions

Adverse reactions identified through clinical trials or post-marketing surveillance by system organ class (SOC) are listed below:

Blood and lymphatic system disorders: Pancytopenia, white blood cell disorders (including agranulocytosis, leukopenia, lymphopenia, granulocytopenia, neutropenia, white blood cell count decreased, neutrophil count decreased), thrombocytopenia, platelet count decreased, anaemia.

Immune system disorders: Shock, hypersensitivity, bronchospasm, rash, eosinophilia.

Eye disorders: Uveitis, corneal deposits.

Gastrointestinal disorders: *Clostridium difficile* colitis, nausea, vomiting.

Hepato-biliary disorders: Jaundice, hepatic enzyme increased.

Skin and subcutaneous tissue disorders: Skin discolouration.

Musculoskeletal and connective tissue disorders: Arthralgia, myalgia.

General disorders and administration site conditions: Pyrexia.

Pyrexia, rash and rarely other hypersensitivity reactions such as eosinophilia, bronchospasm and shock might occur as has been seen with other antibiotics. A limited number of skin discoloration has been reported. Mild to severe, reversible uveitis has been reported less frequently when MYCOBUTIN is used at 300 mg as monotherapy in MAC prophylaxis versus MYCOBUTIN in combination with clarithromycin for MAC treatment (see **WARNINGS, PRECAUTIONS**). Corneal deposits have been reported during routine ophthalmologic surveillance of some HIV-positive pediatric patients receiving MYCOBUTIN as part of a multiple drug regimen for MAC prophylaxis. The deposits are tiny, almost transparent, asymptomatic peripheral and central corneal deposits, and do not impair vision.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms:
No information is available on accidental overdosage in humans.

Treatment:
While there is no experience in the treatment of overdose with MYCOBUTIN® (rifabutin), 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.

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

For management of suspected overdosage, please contact your regional Poison Control Centre.

DOSAGE AND ADMINISTRATION

It is recommended that MYCOBUTIN (rifabutin) 300 mg be administered once daily with or without food. For those patients who experience nausea, vomiting or other gastrointestinal upsets, it may be useful to split the MYCOBUTIN dose in half (one 150 mg capsule) twice a day with food.

Limited pharmacokinetic data suggests that dose reductions may be required in patients with severe renal or hepatic impairment and in patients receiving concomitant treatment with certain drugs (see **PRECAUTIONS**).

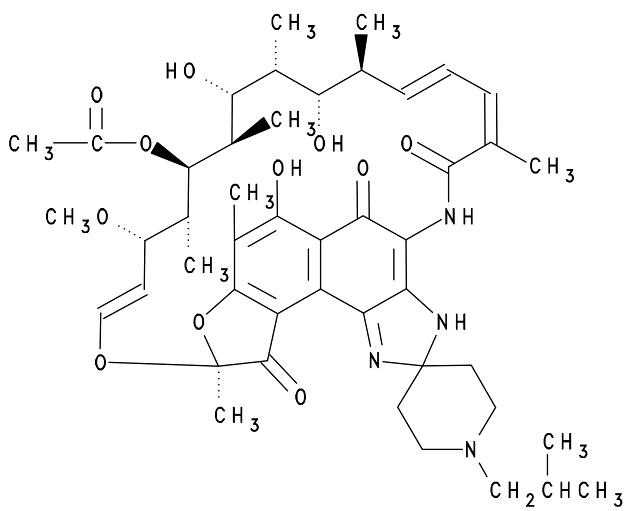
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Rifabutin capsules USP

Chemical Name: (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-methyoxy-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.

Structural Formula:



Molecular Formula: $C_{46}H_{62}N_4O_{11}$

Molecular Weight: 847.02

Description:
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).

Melting Point	=	148ºC - 156ºC (with decomposition)
pKa Value	=	6.9 in methanol/water (l/l, v/v)
Partition Coefficient	=	The partition coefficient of rifabutin between n-octanol and pH 6.8 buffer was determined to be > 100.

COMPOSITION

MYCOBUTIN® (rifabutin) is supplied as hard gelatin capsules having an opaque red-brown cap and body, imprinted with PHARMACIA & UPJOHN/ MYCOBUTIN, in white ink, each containing 150 mg rifabutin. The capsules also contain, as inactive ingredients, microcrystalline cellulose, magnesium stearate, red iron oxide, silica gel, sodium lauryl sulfate, titanium dioxide, and edible white ink.

STABILITY AND STORAGE RECOMMENDATIONS

Store at controlled room temperature, 15º-30ºC. Keep container tightly closed.

AVAILABILITY OF DOSAGE FORMS

MYCOBUTIN® (rifabutin) 150 mg
Bottles of 100 capsules

MICROBIOLOGY

Action

MYCOBUTIN® (rifabutin) inhibits DNA-dependant 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-dependant RNA polymerase in *Mycobacterium avium* or in *M. intracellulare* which constitutes *M. avium* complex (MAC). Rifabutin inhibited incorporation of thymidine into DNA of rifampin-resistant *M. tuberculosis* suggesting that rifabutin may also inhibit DNA synthesis which may explain its activity against rifampin-resistant organisms.

In vitro Susceptibility Studies

There are no standardized methods for identification or susceptibility testing for *M. avium* complex. Various *in vitro* methodologies employ radiometric broth (7H12) or solid media. In general the radiometric broth (7H12) procedure has been used for isolation of mycobacteria with specific identification by DNA probes. Susceptibility testing is often performed using a radiometric broth method. However, neither method has been optimized for *M. avium* complex.

The MIC of rifabutin against *M. avium* in broth media were 2 to 4 times lower when polysorbate 80 (Tween 80) was present. This effect was attributed to an increase in the permeability of the cell envelope caused by Tween 80. It is recommended that susceptibility testing of rifabutin against *M. avium* be carried out in the absence of Tween 80 or other detergents.

Mycobacterium avium Complex (MAC)

Rifabutin has demonstrated *in vitro* activity against *M. avium* Complex (MAC) organisms isolated from both HIV positive and HIV negative people. These studies predated the widespread use of gene probe techniques to distinguish between the two organisms, although it is now known that the vast majority of isolates from MAC-infected, HIV positive people are *M. avium*, whereas in HIV negative people, about 40% of the isolates are *M. intracellulare*.

In one reported study on 100 MAC isolates from AIDS patients summarized in the table below, 83% had MIC_{99} values of ≤0.25 µg/mL, and 96% had MIC_{99} values of ≤0.5 µg/mL when evaluated by a radiometric method 7H12 broth. In comparison, higher MICs were observed when the same isolates were tested in 7H11 by the agar proportion method. Twenty-three percent (23%) and 46%, of isolates had MIC_{99} values of ≤0.25 and ≤0.5, respectively.

***In Vitro* Minimum Inhibitory Concentrations of Rifabutin Against *Mycobacterium avium-intracellulare* Isolated from AIDS Patients**

No. Isolates Tested (Method)	Number of Isolates (cumulative %)			
	MIC (µg/mL)			
	≤0.25	0.5	1.0	2.0
100(agar)	23(23)	23(46)	25(71)	29(100)
100(broth)	83(83)	13(96)	2(98)	2(100)

Other studies to determine the susceptibilities of MAC isolates from AIDS patients have yielded similar results.

The susceptibility to rifabutin of the initial positive MAC isolates from AIDS patients who developed MAC bacteremia during two large, rifabutin, multicenter placebo-controlled trials for prevention of MAC is as follows:

Susceptibility to Rifabutin of the First Blood Isolates of MAC Recovered from Patients Receiving Prophylaxis with Rifabutin or Placebo

Prophylaxis	No. of Isolates Tested	Number of Isolates (cumulative %)					
		MIC (µg/mL)					
		≤0.12	0.25	0.5	1.0	2.0	>2.0
Placebo	59	4 (6.8)	8 (20.3)	20 (54.2)	15 (79.7)	11 (98.3)	1 (100)
Rifabutin	29	3 (10.3)	3 (20.7)	16 (75.9)	4 (89.7)	3 (100)	0 (100)

For people who received placebo and rifabutin prophylaxis, 20.3% and 20.7% of the MAC isolates had MIC_{99} values of ≤0.25 µg/mL, 54.2% and 75.9% had MIC_{99} values of ≤0.5 µg/mL, and 79.7% and 89.7% had MIC_{99} values of ≤1.0 µg/mL, respectively, when evaluated by the radiometric 7H12 broth method. The distribution of MICs in the two groups did not differ significantly (Kruskal-Wallis p-value = 0.143).

In these studies there was no significant difference between the results of the broth and agar methods; the geometric means of MIC_{99} values for all isolates were 0.64 and 0.78 μg/mL, respectively.

Mycobacterium tuberculosis

Rifabutin has *in vitro* activity against many strains of *M. tuberculosis* including some which are rifampin-resistant. In one study, utilizing the 7H12 broth dilution method, each of 20 rifampin-naive clinical isolates tested from Taiwan, had an MIC_{99} value of ≤0.125 μg/mL. The table below shows susceptibilities of 122 strains of *M. tuberculosis* isolates from rifampin-treated patients to rifampin and rifabutin in another study.

Susceptibility of Rifampin-Resistant Strains of *M. tuberculosis* to Rifabutin+

No. Strains	RIFAMPIN MIC (μg/mL)			RIFABUTIN MIC (μg/mL)		
	1.0	5.0	10.0	0.5	1.0	2.0
122	0	12.3	24.6	27.0	41.8	63.9

\+ Values are cumulative percentages

Other Mycobacterial Species

Rifabutin has shown activity against other mycobacterial species. Most strains of the following organisms were susceptible to concentrations of rifabutin of 0.5 μg/mL using the agar dilution method:

Isolates Tested	No. of Isolates (Cumulative %) MIC_{99} (μg/mL)		
	0.5	1.0	2.0
Mycobacterium gordonae	100	100	100
Mycobacterium kansasii	100	100	100
Mycobacterium marinum	100	100	100
Mycobacterium terrae	71.4	100	100
Mycobacterium xenopi	100	100	100

Rifabutin was active against *Mycobacterium leprae* with MIC_{99} values of 3.1 to 12.5 ng/mL when tested by the broth dilution method (BACTEC 460). It has an MIC_{99} value of 0.016 to 2 μg/mL against *Mycobacterium phlei* when tested by the agar dilution method.

Rifabutin is rapidly taken up by macrophages and monocytes and has been shown to be active against phagocytized *M. avium intracellulare* and *M. tuberculosis*.

Resistance

Mycobacterium avium Complex:

The cross-resistance relationship between rifampin and rifabutin appears to be partial. Rifampin and rifabutin MIC_{99} values against 523 isolates of *M. avium* complex were determined utilizing the agar dilution method.

SUSCEPTIBILITY OF *M. AVIUM* COMPLEX STRAINS TO RIFAMPIN AND RIFABUTIN					
		% of Strains Susceptible/Resistant to Different Concentrations of Rifabutin (µg/mL)			
Susceptibility to Rifampin (µg/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

The majority of the strains (94%) were "naturally" resistant to rifampin (1.0 µg/mL or higher). Approximately 13% of those resistant strains were resistant to rifabutin in a concentration of ≥ 1.0 µg/mL.

Mycobacterium tuberculosis

The cross-resistance between rifampin and rifabutin is frequently observed with *M. tuberculosis* isolates but it is not complete. Analysis of cross-resistance between rifampin and rifabutin among 302 *M. tuberculosis* strains indicate that all strains that were susceptible to 1.0 µg/mL of rifampin were also susceptible to 0.5 µg/mL of rifabutin. 46.7% of the strains that were resistant to 5.0 µg/mL of rifampin and 12.0% of the strains that were resistant to 10.0 µg/mL of rifampin were susceptible to rifabutin at concentrations of 0.5 µg/mL.

SUSCEPTIBILITY OF *M. TUBERCULOSIS* STRAINS TO RIFAMPIN AND RIFABUTIN					
		% of Strains Susceptible/Resistant to Different Concentrations of Rifabutin (µg/mL)			
Susceptibility to Rifampin (µg/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	180	100.0	0.0	0.0	0.0
Resistant to 1.0 only	15	100.0	0.0	0.0	0.0
Resistant to 5.0	15	46.7	33.3	13.3	6.7

Resistant to 10.0	92	12.0	14.1	27.2	45.7
TOTAL	302	70.5	6.0	8.9	14.6

In Vivo Studies

Mycobacterium avium Complex

Rifabutin and rifampin, each at doses of 6.25, 12.5 and 25 mg/kg orally, given six days per week for 12 weeks starting immediately after infection, were efficacious in ddY mice infected I.V. with *Mycobacterium avium-intracellulare* (MAI or MAC). Rifabutin was more effective than rifampin. In control mice, 96% developed macroscopic lung lesions. In mice treated with rifampin, 79% showed lung lesions, and in mice treated with rifabutin, 70% showed lung lesions. Advanced disease developed in 67% of control mice, 42% of rifampin-treated mice, and 31% of rifabutin-treated mice.

In another study, rifabutin and rifampin at doses of 20 and 80 mg/kg orally, given 6 days per week for 4 weeks, exhibited comparable efficacy in ddY mice infected with two different strains of MAI (N-260 and N-276).

Treatment, via the drinking water, was started 24 hours post-infection. Effectiveness was determined by counting the number of colony-forming units (CCU) in lungs and spleen homogenate plated on agar.

Rifabutin, at doses of 20 mg/kg three days per week, prevented *M. avium* infection in cyclosporine-treated rats. In a treatment study, at doses of 20 mg/kg five days per week, rifabutin reduced the number of mycobacteria in the spleen and liver by 200-fold in cyclosporine rats infected with *M. avium*.

Rifabutin was also effective in reducing the number of mycobacteria in tissues of thymectomized T-cell deficient mice infected with *M. avium*. Enhanced activity was observed in this animal model when rifabutin was combined with either ethambutol or a combination of ethambutol, clofazimine, amikacin and ciprofloxacin.

Rifabutin was also effective in T-cell deficient mice infected with various strains of *M. intracellulare* or *M. tuberculosis* but not with the severely virulent *M. avium* 724. In this study, rifabutin was given in the drinking water at a dose of 40 mg/kg for 2 months beginning 20-40 days after infection.

Rifabutin and rifampin were also compared at a dose of 40 mg/kg daily for 120 days, alone and in combination with other antibiotics with anti-mycobacterial activity (all via drinking water) in T-cell deficient mice infected with AIDS-associated strains of *M. avium*.

Rifabutin was more active than the other drugs against most of the strains, and the combinations containing rifabutin exhibited greater efficacy than those containing rifampin.

When rifabutin at a dose of 10 mg/kg was added to a combination of amikacin (50 mg/kg intramuscularly) and clofazimine (20 mg/kg orally) and administered by gavage to MAI-infected beige mice, no additional improvement to the efficacy was observed.

The activity of rifabutin alone or in combination with clofazimine or ethambutol or both against acute and chronic experimental MAI infections were studied. Groups of male beige mice were infected intravenously with *M. intracellulare*, Strain 571-8 (serotype 8) isolated from a hospital patient. Drug treatment was rifabutin, given at 5, 10, or 20 mg/kg day alone, or at 10 mg/kg/day in combination with clofazimine (20 mg/kg/day) and/or ethambutol (125 mg/kg/day), via oral gavage. Administration of drugs was begun three weeks before infection, immediately after infection, or three weeks after infection, and continued seven days a week for 4-8 weeks following infection.

Given immediately after infection, rifabutin at 5 mg/kg/day alone showed no antibacterial effect. At 10 mg/kg/day, lung tissue, 6 weeks after infection, showed a significant ($p<0.05$) reduction in CCU. At 20 mg/kg/day, both lung and spleen showed significant reductions in CCU. Given three weeks after infection, 5 mg/kg/day of rifabutin showed no significant protection. At 10 mg/kg/day, significant reductions in CCU of the spleen and complete elimination of CCU in the lungs were observed.

When treatment at 10 mg/kg/day was started three weeks before infection, CCU counts were eliminated in the lungs at 4 weeks and in the spleen at 8 weeks after infection. The lungs of untreated animals were cleared spontaneously 8 weeks after infection. Thus, the effectiveness of rifabutin was especially pronounced when the drug was given prophylactically, three weeks before infection.

When combined therapy with rifabutin and clofazimine was initiated immediately after infection, complete sterilization of the tissues was achieved within 6 to 8 hours. Addition of ethambutol did not improve the efficacy. The same combinations given 3 weeks after infection was less effective.

The combination of rifabutin (10 mg/kg p.o.) with either clofazimine (20 mg/kg p.o.) or kanamycin (20 mg/kg s.c.) or both was more effective than any of these drugs given alone to *M. intracellulare*-infected mice (C57BL/6) strain for six days/week for 12 weeks starting 24 hours post-infection. The combination of rifabutin and clofazimine plus kanamycin was the most effective of the treatments tested giving complete protection against pulmonary lesions and significant reductions in bacterial counts in the lungs, liver and spleen.

Rifabutin in combination with clarithromycin was significantly more efficacious than clarithromycin alone in Beige mice infected with *M. avium* complex.

Mycobacterium tuberculosis
The efficacy of rifabutin (up to 10 mg/kg/day x three days) and rifampin (up to 25 mg/kg/day x ten days) was evaluated in CD1 (COBS) mice infected I.V. with *M. tuberculosis* H37 Rv. Drug treatment was started at either three days or ten days post-infection. Rifabutin was more effective than rifampin, although plasma levels of drug were much higher in rifampin-treated mice. In COBS rats, plasma levels of rifampin were higher than those of rifabutin but, except for liver, tissue levels of rifabutin were much higher than those observed with rifampin. This was

especially true in the lung.

Mycobacterium fortuitous
In CD1 mice infected intravenously with *M. fortuitous*, rifampin was marginally active at 30 mg/kg/day, 5 days a week for 6 weeks, starting from 24 hours post-infection. Rifabutin exhibited significant activity at doses of 4 and 10 mg/kg/day.

Mycobacterium leprae
In a study in which rifabutin (0.00003 - 0.001%) or rifampin (0.01%) were administered in the diet to BALL/C mice infected with a rifampin-resistant of *M. leprae*, for approximately 6 months, rifabutin was found to be highly effective even at the lowest dose, while rifampin had no effect.

Antibacterial
Several non-Mycobacterial organisms were tested for *in vivo* susceptibility to rifabutin. In CD1 (COBS) mice infected with *Staphylococcus aureus*, single oral doses of rifabutin, administered 1-4 hours after infection, showed good antibiotic activity. The ED_{50} value (on the basis of mortality) for rifabutin given to mice two hours after infection with *S. aureus* strain PV-1 was 0.4 mg/kg. Gram-negative bacterial infections were more susceptible to rifampin than to rifabutin, while *Streptococci* and *Diplococci* infections were more susceptible to rifabutin.

In the majority of the above *in vivo* studies, where doses equivalent to human doses were given, rifabutin was bacteriostatic, not bactericidal. Bactericidal activity was achieved when additional drugs were given.

PHARMACOLOGY

Clinical Pharmacology

Pharmacodynamics:
Over a dose range of 300 to 900 mg/day, administration of multiple, daily rifabutin doses did not elicit any serious/unexpected adverse events in 34 HIV positive patients. Doses higher than 900 mg/day produced chest discomfort, flu-like syndromes, lower back pain, skin discoloration, and gastrointestinal symptoms. However, a steep dose-related increase in the incidence of arthralgia, from 0% at 900 mg/day to 100% at 1200 mg/day, and the occurrence of uveitis at doses higher than 1800 mg/day was seen. No apparent effects on hematological or hepatic parameters were seen for doses up to 1200 mg/day, except mild leukopenia. Rifabutin in HIV positive patients was well tolerated up to 900 mg/day. The minimum effective dose and the optimal dose of rifabutin for prophylaxis, are not known.

Pharmacokinetics:
Rifabutin pharmacokinetics have been studied using daily doses ranging from 150 mg to 1200 mg (600 mg bid) in the pivotal pharmacokinetics and dose-tolerance studies involving both healthy normal volunteers and HIV positive patients, for periods of up to 28 days.

Absorption: In normal volunteers, a nominal therapeutic dose of 300 mg produces a mean C_{max} of 375 ng/mL which is attained at approximately 3 hours post dose. At least 53% of the oral dose is absorbed.

Absolute Bioavailability: The mean (± SD) absolute bioavailability (F) of rifabutin from the capsule formulation in 15 early symptomatic HIV positive patients was found to be 20% (± 16%, n=5) following a single dose (first day), and was 12% (± 5%, n=7), after daily dosing for 4 weeks. This change was not statistically significant. The possible decrease in absolute bioavailability on day 28 may be due to autoinduction of rifabutin metabolism.

Effect of Food on Oral Absorption: A single study simultaneously examined the absorption of rifabutin from the capsule dosage form relative to a solution and also assessed the effect of food. A single 150 mg dose was administered to 12 male volunteers in a crossover manner. The administration of rifabutin with a high fat content meal decreased mean C_{max} by 17% (156.2 vs. 187.9 ng/mL), increased mean T_{max} from 3.0 to 5.4 hours and increased mean percent of dose excreted unchanged in urine by 26% (11.4% vs 9.1%). Only the changes in mean T_{max} and the percent of dose excreted unchanged in urine were statistically significant. The data indicate that a high-fat content meal decreased the rate of absorption and increased urinary excretion of rifabutin with no change in extent of absorption. The relative bioavailability of the capsule with respect to the solution was estimated to be 85%.

Distribution: In a radio-tracer intravenous study for unchanged rifabutin, a triexponential concentration versus time disposition profile was observed. The fastest distributive phase ($\lambda 1$) has a half-life of 9-15 minutes. The half-lives associated with the slow distributive phase ($\lambda 2$) and terminal elimination (λz) seem comparable to those following oral dosing, after which absorption, distribution and elimination phases are clearly observed. The half-life of the slow distributive phase ($t1/2,\lambda 2$) was estimated to be 3.5 to 4.5 hours in healthy males, and 1.7-3.3

hours in early symptomatic HIV patients, thus suggesting a lack of disease effects on the slow distributive phase. The volume of distribution at steady-state (V_{ss}) was determined to be 8-9 L/kg in early symptomatic HIV patients. This estimate is approximately 13 to 15-fold larger than the total body water (TBW: 0.6 L/kg).

Tissue Distribution: A study in 4 surgical patients provided limited but useful information regarding tissue uptake. Rifabutin (measured as total antimicrobial activity) was found in all tissues studied, e.g. lung, gall bladder, ileum, jejunum, and muscle. Tissue concentrations were several times higher than those found in plasma. The lung to plasma ratio ranged from 1.4 to 8.6 at about 6 hours and 5.6 to 6.8 at 12 hours post-oral dosing. Even when plasma levels were undetectable, measurable levels of rifabutin persisted in lung up to 48 hours. The partitioning of rifabutin into ileum, jejunum, and bile appeared higher than the lung, and supports biliary excretion as a significant route of elimination. Distribution of rifabutin was lowest in the muscle, with a muscle:plasma ratio of < 1.

Plasma Protein Binding: The extent of *in vitro* protein binding of ^{14}C-rifabutin in fresh human plasma was assessed by equilibrium dialysis. Approximately 90% of rifabutin was bound to plasma proteins over a concentration range of 0.1-10.0 μg/mL. The binding decreased to approximately 85% at higher concentrations of 20-100 μg/mL. At a concentration of 100 ng/mL, rifabutin was 68.3 ± 1.9% bound to human serum albumin (HSA) and 19.6 ± 3.1% bound to α-acid glycoprotein (AAG). These results suggest that rifabutin is predominantly bound to HSA. The free fraction (f_u) in plasma is approximately 0.15 (95% CI: 0.138-0.158) and is independent of drug concentration within the concentration range observed following the standard 300 mg dose. Protein binding was assessed at 20 μg/mL by equilibrium dialysis in healthy subjects, the elderly, patients with alcoholic liver disease and renal insufficiency. Mean % bound averaged 95% in healthy subjects, 91% in the elderly, 90% in patients with alcoholic liver disease, and 92-94% in patients with renal insufficiency. Protein binding was therefore > 90% for all cases.

Metabolism: Investigations elucidating the metabolic profile of rifabutin suggest extensive biotransformation. Urinary metabolism studies, using mass spectrometry, ^{1}H-NMR spectrometry, and HPLC, have shown that rifabutin is metabolized to more than 20 different metabolites. Five among them have been identified: 25-O-deacetyl rifabutin (M1), 31-OH-rifabutin (M2), 32-OH rifabutin, 32-OH-25-O-deacetyl rifabutin, and 25-O-deacetyl rifabutin-N-oxide. The M1 derivative was determined to be as equally active as rifabutin microbiologically. The M2 derivative seems to possess approximately 1/16 of the activity of rifabutin.
The evidence of rifabutin autoinduction comes from estimates of CL_T in early symptomatic HIV positive patients administered tracer intravenous ^{14}C-rifabutin doses. The mean CL_T was estimated to be 10.2 L/h on day 1 and 18.5 L/h on day 28, following 4 weeks of daily dosing, an increase of 80%. This estimate of CL_T was not confounded by absolute bioavailability (F).

Excretion: Urinary and faecal excretion are the two major routes of elimination for rifabutin. The excretion characteristics of rifabutin and its metabolites have been assessed in a radiolabelled study. Following an oral dose (270 mg) as ^{14}C-rifabutin solution (100 μCi) to 3 healthy volunteers, 53% of the dose was recovered in the urine over a 120 hour period and 30% in the faeces. Approximately 8% of the administered radioactive dose was recovered in urine as unchanged parent drug. After administration of rifabutin in the capsule dosage form, 5.17% was eliminated through bile, and 5.8% was eliminated in urine as unchanged drug.

Animal Safety Pharmacology

Neuropharmacology
Oral doses of 200 mg/kg rifabutin in the mouse and 100 mg/kg in the rat caused CNS depression lasting up to six hours post dose. Rifabutin (50 mg/kg) did not antagonize amphetamine, pentylenetetrazol or reserpine in the mouse. Rifabutin did not affect neuromuscular coordination (rotorod) or conditioned avoidance response in the rat at 50 mg/kg. There were no consistent effects on body temperature in mice, rats or dogs treated with rifabutin.

Cardiovascular
In the rat, single intravenous doses of up to 36 mg/kg or oral doses of up to 200 mg/kg daily for four days did not affect blood pressure or heart rate or the responses of these parameters to several autocoids. There was an increase of about 50% in respiratory rate beginning about 100 minutes following an intraduodenal dose of 50 mg/kg in the anaesthetized dog. There were, however, no other significant changes in cardiovascular or respiratory system parameters.

Gastrointestinal
Oral doses of up to 20 mg/kg rifabutin did not affect gastric emptying rate in the rat.

Genitourinary
Rifabutin, at oral doses of up to 100 mg/kg, did not affect urinary volume, pH or electrolytes in the rat.

Immunopharmacology
The effects of rifabutin and rifampin on humoral and cell-mediated immunity were determined in mice and guinea pigs. Neither rifabutin nor rifampin affected humoral antibody response to SRBC in the mouse at intraperitoneal doses of up to 300 mg/kg and 150 mg/kg, respectively. Although there was no effect on delayed hypersensitivity (DH) when give oral doses of 50 mg/kg in the mouse, both drugs did reduce DH when given intraperitoneal dose of 150 mg/kg. Also, both drugs reduced DH to tuberculin in the mouse but in guinea pigs, rifampin decreased DH to tuberculin whereas rifabutin had no effect. These studies, however, were not extensive and it is difficult to assess their significance.

A study was also conducted to determine the effect of rifabutin on the phagocytic and bactericidal activities of splenic macrophages in the mouse. The mice were given 300 mg/kg rifabutin daily for 30 days and macrophage function was determined for up to 30 days following cessation of treatment.

The results indicated that rifabutin and/or its active metabolites persist in the lungs, liver, and spleen at measurable concentrations for up to 15 days post-treatment and that the phagocytic and bactericidal activities of splenic macrophages as measured using *L. monocytogenes* as a target were not affected despite the lipidotic effect which rifabutin has on macrophages.

Rifabutin and rifampin were found to inhibit random migration but not chemotaxis of human PMNL. In a study comparing the effects of rifabutin and rifampin on rabbit PMNL, it was found that rifabutin reduced cellular respiration at concentrations of 50 and 100 µg/mL but had no effect on their phagocytic or bactericidal functions. Rifampin inhibited phagocytic function at

100 µg/mL. Since the concentrations of rifabutin used in this study were much higher than those found in plasma of patients treated with rifabutin, it is unlikely that rifabutin will affect PMNL function clinically.

Also, rifabutin did not affect the ability of human PMNL to phagocytize *S. aureus in vitro* and did not interfere with superoxide formation by human neutrophils *in vitro*.

TOXICOLOGY

The acute oral toxicity of rifabutin in rats, given single oral doses up to 5 g/kg, or in beagle dogs and cynomolgus monkeys, given 2 and 4 g/kg rifabutin was low with no mortality. The oral LD_{50} in mice was 4.8 g/kg for males and 3.3 g/kg for females. The pharmacotoxic effects observed were relatively minor and consisted of decreased spontaneous activity in mice and rats and gastrointestinal disturbances, i.e. emesis and/or diarrhea in dogs and monkeys. These results are consistent with the antimicrobial properties of the drug.

Subchronic 13-week studies were performed in mice (0,12.5, 25, 50 and 100 mg/kg/day; 0,50,100 and 200 mg/kg/day), rats (0,25,50,100 and 200 mg/kg/day; 0,25,50 and 100 mg/kg/day on alternate days; 0,50,100 and 200 mg/kg/day), cynomolgus monkeys (0,10,20,40 and 80 mg/kg/day) and baboons (0,10,40,and 80 mg/kg/day). No drug-related mortality occurred in all species.
In mice, only slight functional hepatic changes were seen. Body weight gain was reduced at all doses in male mice in one study, and relative spleen weights were increased in both sexes at all doses in another mouse study. Some liver inflammation was seen in high dose female mice.

In rats, multinucleated hepatocytes were observed both following daily administration of rifabutin or administration on alternate days. Ultrastructurally, the multiple nuclei and nucleoli closely resemble those in mononucleated cells.   This was not seen in any other species. Rifabutin induced slight dose-related decreases in RBC and related parameters, hyperplasia of the gastric mucosa, increased spleen and liver weights, reduced body weight gains in high-dose rats, decreased spermatogensis in male rats, and uterine hyperplasia in female rats.

In cynomolgus monkeys, the daily oral administration of rifabutin at doses up to 80 mg/kg/day for 13 weeks had minimal effects, the most important of which was an increased bilirubin and decreased LAP at the 80 mg/kg/day dose. Slight fatty infiltration of the liver was seen in cynomolgus monkeys and in baboons at all doses. Decreased testes weight, beginning at a dose of 10 mg/kg/day, was also noted in baboons.

Twelve month toxicity studies were carried out in mice (0,8,32 and 128 mg/kg/day), rats (0,10,28 and 80 mg/kg/day) and cynomolgus monkeys (0,8,24 and 72 mg/kg/day). These results were in agreement with the previous 13-week studies. No drug-related mortality was noted in all species. In mice, body weight gains were increased in high dose females. In males there was a dose-related increase in plasma cholesterol, with bilirubin and reticulocytes increased at the high dose. High dose females had increased ALT. At 128 mg/kg/day in males, testes weight decreased while liver and lung weights increased. In high-dose females, adrenal, lung, liver and spleen weights increased.

There was a dose-related increase at the 32 and 128 mg/kg/day dose in the incidence of Heinz bodies in reticulocytes.

Both male and female rats showed increased plasma bilirubin at the high dose, and high dose males had increased ALT and AST. Multinucleated hepatocytes were seen in males at all dose groups and in females at 28 and 80 mg/kg/day. Liver and spleen weights increased in mid-dose males and in both sexes at the high dose. High dose males also had decreased testes weights and atrophy of seminiferous tubules. Hyperplasia of the gastric mucosa occurred in both sexes given 80 mg/kg/day.

Male monkeys experienced occasional episodes of emesis at 24 and 72 mg/kg/day. High dose animals showed an increase in plasma bilirubin and triglycerides with lipid deposits in hepatocytes and increased liver weight.

Multinucleated hepatocytes were seen in rats only; liver hypertrophy with functional effects (increased ALT and/or AST, cholesterol, triglycerides and bilirubin values) was observed in all species. Minor changes included slight decreases in RBC and related parameters, sclerosis/hyperplasia of the glandular mucosa of the stomach, and atrophy of the testes in rats.

The significance of the multinucleated hepatocytes found in rats given repeated oral doses of rifabutin is not clear. They have been reported in association with various physiological, nutritional and disease states, and after administration of several structurally and pharmacologically diverse chemical and drug substances. In any case, the presence of multinucleated hepatocytes must be considered rat specific, as they were not found in the other species.

There was no increase of the multinucleated hepatocytes with time and there was no effect in their life span. As expected, this finding is not preneoplastic, as confirmed by the oncogenicity study in rats.

Reproductive Toxicology
Fertility studies have been performed in male and female rats given rifabutin orally at 0,10,40 and 160 mg/kg/day. Fertility was impaired in male rats given 160 mg/kg/day (32 times the recommended human daily dose). The 160 mg/kg/day dose resulted in a reduced number of implants and offspring. In the 160 mg/kg/day treated females, there was an 18% decrease in the number of fetuses per dam associated with a 5-fold increase in post implantation losses. At 40 mg/kg/day (8 times the human dose), rifabutin caused an increase in skeletal variants. Peri- and post-natal studies have been performed in rats given rifabutin orally at 0,12.5,50 and 200 mg/kg/day. At 200 mg/kg/day (40 times the human dose), there was a decrease in fetal viability.

Teratogenicity
Embryotoxicity studies have been performed in rats and rabbits given rifabutin orally at 0,20,40 and 80 mg/kg/day. At all doses and in both species no teratogenic effects were seen. In rats, at 40 and 80 mg/kg/day, and in rabbits, at 80 mg/kg/day (16 times the human dose), rifabutin caused maternotoxicity and an increase in fetal minor skeletal anomalies.

Mutagenicity

Rifabutin (0.125 - 1000 μg/mL) was not mutagenic in the bacterial point mutation assay (Ames Test) using both rifabutin-susceptible and resistant strains of *Salmonella typhimurium*. Rifabutin was not mutagenic in *Schizosaccharomyces pombe* P_1 and was not genotoxic in V-79 Chinese hamster cells, human lymphocytes *in vitro*, or mouse bone marrow cells *in vivo*.

Carcinogenicity

Long term carcinogenicity studies were conducted with rifabutin in mice (0,20,60 and 180/100 mg/kg/day) and rats (0,15,30,and 60 mg/kg/day). Rifabutin was not carcinogenic in mice at doses up to 180 mg/kg/day, or approximately 36 times the recommended human daily dose. The high dose was reduced from 180 mg/kg/day to 100 mg/kg/day on Day 561, due to excessive mortality in males.

This high-dose treatment group was terminated after 21 months of treatment. Necropsy and histopathological findings indicated that deaths were caused by myocardial vacuolation and fibrosis. Rifabutin was not carcinogenic in the rat at doses up to 60 mg/kg/day, about 12 times the recommended human daily dose. There was a significant increase in the incidence of incidental tumours in the liver of the high dose females but most of these were adenomas. In summary, rifabutin was not carcinogenic in either mice or rats when administered in the diet for up to two years at the MTD.

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