RIFABUTIN- rifabutin capsule
Lupin Pharmaceuticals, Inc.

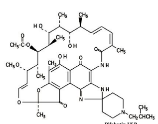
Rifabutin Capsules USP, 150 mg

Rx only

DESCRIPTION

Rifabutin Capsules USP for oral administration contain 150 mg of the rifamycin antimycobacterial agent rifabutin, USP, per capsule, along with the inactive ingredients crospovidone, gelatin, iron oxide red, magnesium stearate, microcrystalline cellulose, potassium hydroxide, shellac, silicon dioxide, sodium lauryl sulphate, and titanium dioxide.

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 $C_{46}H_{62}N_4O_{11}$, a molecular weight of 847.02 and the following structure:



Rifabutin USP

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 mg 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 mg 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 ($C_{p, min}^{ss}$; 24-hour post-dose) ranged from 50 to 65 ng/mL in HIV-positive patients and in healthy adult volunteers. About 85% of the drug is bound in a concentration-independent manner to plasma proteins over a concentration range of 0.05 to 1 mcg/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 ^{14}C-labeled rifabutin showed that 53% of the oral dose was excreted in the urine, primarily as metabolites. About 30% of the dose is excreted in the feces. Mean systemic clearance (CL_s/F) in healthy adult volunteers following a single oral dose was 0.69 (± 0.32) L/hr/kg (range: 0.46 to 1.34 L/hr/kg). Renal and biliary clearance of unchanged drug each contribute approximately 5% to CL_s/F.

Pharmacokinetics in Special Populations

Geriatric

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

Pediatric

The pharmacokinetics of rifabutin have not been studied in subjects under 18 years of age.

Renal Impairment

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 impairment (creatinine clearance below 30 mL/min) compared to patients with creatinine clearance (Cr_{cl}) between 61 to 74 mL/min. In patients with mild to moderate renal impairment (Cr_{cl} between 30 to 61 mL/min), the AUC increased by about 41%. In patients with severe renal impairment, carefully monitor for rifabutin associated adverse events. A reduction in the dosage of rifabutin is recommended for patients with Cr_{cl} <30 mL/min if toxicity is suspected *(see DOSAGE AND ADMINISTRATION)*.

Hepatic Impairment

Mild hepatic impairment does not require a dose modification. The pharmacokinetics of rifabutin in patients with moderate and severe hepatic impairment is not known.

Malabsorption in HIV-Infected Patients

Alterations in gastric pH due to progressing HIV disease has been linked with malabsorption of some drugs used in HIV-positive patients (e.g., rifampin, isoniazid). Drug serum concentrations data from AIDS patients with varying disease severity (basedon CD4+ counts) suggests that rifabutin absorption is not influenced by progressing HIV disease.

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

Multiple dosing of rifabutin has been associated with induction of hepatic metabolic enzymes of the CYP3A subfamily. Rifabutin's predominant metabolite (25-desacetyl rifabutin: LM565), may also contribute to this effect. Metabolic induction due to rifabutin is likely to produce a decrease in plasma concentrations of concomitantly administered drugs that are primarily metabolized by the CYP3A enzymes. Similarly concomitant medications that competitively inhibit the CYP3A activity may increase plasma concentrations of rifabutin.

CLINICAL STUDIES

Two randomized, double-blind clinical trials (Study 023 and Study 027) compared rifabutin (300 mg/day) to placebo in patients with CDC-defined AIDS and CD4 counts ≤200 cells/μL. 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/μL (mean 61). Study 027 enrolled 556 patients with a median CD4 cell count at study entry of 40 cells/μL (mean 58).

Endpoints included the following:

(1) MAC bacteremia, defined as at least one blood culture positive for *Mycobacterium avium* complex (MAC) 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 rifabutin 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 rifabutin and 22% for patients randomized to placebo. In Study 027, these rates were 13% and 28% for patients receiving rifabutin 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/μL. The median and mean CD4 counts at onset of MAC bacteremia were 13 cells/μL and 24 cells/μL, 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 rifabutin 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 rifabutin and 77% for the placebo group. In Study 027, the one-year survival rates were 77% for the group receiving rifabutin 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 MIC_{99} values of ≤0.25 mcg/mL and ≤1.0 mcg/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 mcg/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 MIC_{99} values against 523 isolates of *M. avium* complex were determined utilizing the agar dilution method (Heifets, Leonid B. and Iseman, Michael D. Determination of *in vitro* susceptibility of Mycobacteria to Ansamycin. Am. Rev. Respir. Dis. 1985; 132(3):710-711).

Table 1: Susceptibility of *M. Avium* Complex Strains to Rifampin and Rifabutin

		% of Strains Susceptible/Resistant to Different Concentrations of Rifabutin (mcg/mL)			
Susceptibility to Rifampin (mcg/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* MIC_{99} values of ≤0.5 mcg/mL, 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

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

CONTRAINDICATIONS

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

WARNINGS

Tuberculosis

Rifabutin capsules must not be administered for MAC prophylaxis to patients with active tuberculosis. Patients who develop complaints consistent with active tuberculosis while on prophylaxis with rifabutin should be evaluated immediately, so that those with active disease may be given an effective combination regimen of anti-tuberculosis medications. Administration of rifabutin as a single agent to patients with active tuberculosis is likely to lead to the development of tuberculosis that is resistant both to rifabutin and to rifampin.

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

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.

MAC Treatment With Clarithromycin

When rifabutin is used concomitantly with clarithromycin for MAC treatment, a decreased dose of rifabutin is recommended due to the increase in plasma concentrations of rifabutin *(see PRECAUTIONS-Drug Interactions, Table 2)*.

Hypersensitivity and Related Reactions

Hypersensitivity reactions may occur in patients receiving rifamycins. Signs and symptoms of these reactions may include hypotension, urticaria, angioedema, acute bronchospasm, conjunctivitis, thrombocytopenia, neutropenia or flu-like syndrome (weakness, fatigue, muscle pain, nausea, vomiting, headache, fever, chills, aches, rash, itching, sweats, dizziness, shortness of breath, chest pain, cough, syncope, palpitations). There have been reports of anaphylaxis with the use of rifamycins.

Monitor patients receiving rifabutin therapy for signs and/or symptoms of hypersensitivity reactions. If these symptoms occur, administer supportive measures and discontinue rifabutin.

Uveitis

Due to the possible occurrence of uveitis, patients should also be carefully monitored when rifabutin is given in combination with clarithromycin (or other macrolides) and/or fluconazole and related compounds *(see PRECAUTIONS-Drug Interactions, Table 2)*. If uveitis is suspected, the patient should be referred to an ophthalmologist and, if considered necessary, treatment with rifabutin should be suspended *(see also ADVERSE REACTIONS)*.

Clostridium difficile Associated Diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including rifabutin capsules, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Protease Inhibitor Drug Interaction

Protease inhibitors act as substrates or inhibitors of CYP3A4 mediated metabolism. Therefore, due to significant drug-drug interactions between protease inhibitors and rifabutin, their concomitant use should be based on the overall assessment of the patient and a patient-specific drug profile. The concomitant use of protease inhibitors may require at least a 50% reduction in rifabutin dose, and

depending on the protease inhibitor, an adjustment of the antiviral drug dose. Increased monitoring for adverse events is recommended when using these drug combinations *(see PRECAUTIONS-Drug Interactions)*. For further recommendations, please refer to current, official product monographs of the protease inhibitor or contact the specific manufacturer.

PRECAUTIONS

General

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

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 rifabutin 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 rifabutin should be made aware of these possibilities.

Diarrhea is a common problem caused by antibacterials which usually ends when the antibacterial is discontinued. Sometimes after starting treatment with antibacterials, 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 antibacterial. If this occurs, patients should contact their physician as soon as possible.

Drug Interactions

Effect of Rifabutin on the Pharmacokinetics of 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.

Effect of Other Drugs on Rifabutin Pharmacokinetics

Some drugs that inhibit CYP3A may significantly increase the plasma concentration of rifabutin. Therefore, carefully monitor for rifabutin associated adverse events in those patients also receiving CYP3A inhibitors, which include fluconazole and clarithromycin. In some cases, the dosage of rifabutin may need to be reduced when it is coadministered with CYP3A inhibitors.

Table 2 summarizes the results and magnitude of the pertinent drug interactions assessed with rifabutin. The clinical relevance of these interactions and subsequent dose modifications should be judged in light of the population studied, severity of the disease, patient's drug profile, and the likely impact on the risk/benefit ratio.

Table 2: Rifabutin Interaction Studies

Coadministered drug	Dosing regimen of coadministered drug	Dosing regimen of rifabutin	Study population (n)	Effect on rifabutin	Effect on coadministered drug	Recommendation
ANTIVIRALS						
Amprenavir	1200 mg BID x 10 days	300 mg QD x 10 days	Healthy male subjects (6)	↑ AUC by 193%, ↑ C_{max} by 119%	↔	Reduce rifabutin dose by at least 50%. Monitor closely for adverse reactions.
Delavirdine	400 mg TID	300 mg QD	HIV-infected patients (7)	↑ AUC by 230%, ↑ C_{max} by 128%	↓ AUC by 80%, ↓ Cmax by 75%, ↓ C_{min} by 17%	**CONTRAINDICATED**
Didanosine	167 or 250 mg BID x 12 days	300 or 600 mg QD x 1	HIV-infected patients (11)	↔	↔	
Fosamprenavir/ ritonavir	700 mg BID plus ritonavir 100 mg BID x 2 weeks	150 mg every other day x 2 weeks	Healthy subjects (15)	↔ AUC[a] ↓ C_{max} by 15%	↑ AUC by 35%[b], ↑ C_{max} by 36%, ↑ C_{min} by 36%	Reduce rifabutin dose by at least 75% (to a maximum 150 mg every other day or three times per week) when given with fosamprenavir/ritonavir combination.
Indinavir	800 mg TID x 10 days	300 mg QD x 10 days	Healthy subjects (10)	↑ AUC by 173%, ↑ Cmax by 134%	↓ AUC by 34%, ↓ C_{max} by 25%, ↓ C_{min} by 39%	Reduce rifabutin dose by 50%, and increase indinavir dose from 800 mg to 1000 mg TID.
Lopinavir/ ritonavir	400/100 mg BID x 20 days	150 mg QD x 10 days	Healthy subjects (14)	↑ AUC by 203%[c] ↓ C_{max} by 112%	↔	Reduce rifabutin dose by at least 75% (to a maximum 150 mg every other day or three times per week) when given with lopinavir/ritonavir combination. Monitor closely for adverse reactions. Reduce rifabutin dosage further, as needed.
Saquinavir/ ritonavir	1000/100 mg BID x 14 or 22 days	150 mg every 3 days X 21 to 22 days	Healthy subjects	↑ AUC by 53% [d] ↑ C_{max} by 88% (n=11)	↓ AUC by 13%, ↓ C_{max} by 15%, (n=19)	Reduce rifabutin dose by at least 75% (to a maximum 150 mg every other day or three times per week) when given with saquinavir/ritonavir combination. Monitor closely for adverse reactions.
Ritonavir	500 mg BID x 10 days	150 mg QD x 16 days	Healthy subjects (5)	↑ AUC by 300%, ↑ C_{max} by 150%	ND	Reduce rifabutin dose by at least 75% (to a maximum 150 mg every other day or three times per week) when given with lopinavir/ritonavir combination. Monitor closely for adverse reactions. Reduce rifabutin dosage further, as needed.
Tipranavir/ ritonavir	500/200 BID X 15 doses	150 mg single dose	Healthy subjects (20)	↑ AUC by 190%, ↑ C_{max} by 70%	↔	Reduce rifabutin dose by at least 75% (to a maximum 150 mg every other day or three times per week) when given with tipranavir/ritonavir combination. Monitor closely for adverse reactions. Reduce rifabutin dosage further, as needed.
Nelfinavir	1250 mg BID x 7 to 8 days	150 mg QD x 8 days	HIV-infected patients (11)	↑ AUC by 83%,[e] ↑ C_{max} by 19%	↔	Reduce rifabutin dose by 50% (to 150 mg QD) and increase the nelfinavir dose to 1250 mg BID
Zidovudine	100 or 200 mg q4h	300 or 450 mg QD	HIV-infected patients (16)	↔	↓ AUC by 32%, ↓ C_{max} by 48%	Because zidovudine levels remained within the therapeutic range during coadministration of rifabutin, dosage adjustments are not necessary.
ANTIFUNGALS						
Fluconazole	200 mg QD x 2 weeks	300 mg QD x 2 weeks	HIV-infected patients (12)	↑ AUC by 82%, ↑ C_{max} by 88%	↔	Monitor for rifabutin associated adverse events. Reduce rifabutin dose or suspend rifabutin use if toxicity is suspected.
Posaconazole	200 mg QD x 10 days	300 mg QD x 17 days	Healthy subjects (8)	↑ AUC by 72%, ↑ C_{max} by 31%	↓ AUC by 49%, ↓ C_{max} by 43%	If co-administration of these two drugs cannot be avoided, patients should be monitored for adverse events associated with rifabutin administration, and lack of posaconazole efficacy.
Itraconazole	200 mg QD	300 mg QD	HIV-Infected patients (6)	↑[f]	↓ AUC by 70%, ↓ C_{max} by 75%	If co-administration of these two drugs cannot be avoided, patients should be monitored for adverse events associated with rifabutin administration, and lack of itraconazole efficacy. In a separate study, one case of uveitis was associated with increased serum rifabutin levels following coadministration of rifabutin (300 mg QD) with itraconazole (600 to 900 mg QD).
Voriconazole	400 mg BID x 7 days (maintenance dose)	300 mg QD x 7 days	Healthy male subjects (12)	↑ AUC by 331%, ↑ C_{max} by 195%	↑ AUC by ~100%, ↑ C_{max} by ~100%[g]	**CONTRAINDICATED**
ANTI-PCP (Pneumocystis carinii pneumonia)						
Dapsone	50 mg QD	300 mg QD	HIV-infected patients (16)	ND	↓ AUC by 27 to 40%	
Sulfamethoxazole-Trimethoprim	800/160 mg	300 mg QD	HIV-infected patients (12)	↔	↓ AUC by 15 to 20%	
ANTI-MAC (Mycobacterium avium intracellulare complex)						
Azithromycin	500 mg QD x 1 day, then 250 mg QD x 9 days	300 mg QD	Healthy subjects (6)	↔	↔	
Clarithromycin	500 mg BID	300 mg QD	HIV-infected patients (12)	↑ AUC by 75%	↓ AUC by 50%	Monitor for rifabutin associated adverse events. Reduce dose or suspend use of rifabutin if toxicity is suspected. Alternative treatment for clarithromycin should be considered when treating patients receiving rifabutin
ANTI-TB (Tuberculosis)						
Ethambutol	1200 mg	300 mg QD X 7 days	Healthy subjects (10)	ND	↔	
Isoniazid	300 mg	300 mg QD X 7 days	Healthy subjects (6)	ND	↔	
OTHER						
Methadone	20 to 100 mg QD	300 mg QD X 13 days	HIV-infected patients (24)	ND	↔	
Ethinylestradiol (EE)/ Norethindrone (NE)	35 mg EE / 1 mg NE X 21 days	300 mg QD X 10 days	Healthy female subjects (22)	ND	EE: ↓ AUC by 35%, ↓ Cmax by 20% NE: ↓ AUC by 46%	Patients should be advised to use additional or alternative methods of contraception.
Theophylline	5 mg/kg	300 mg X 14 days	Healthy subjects (11)	ND	↔	

↑ indicates increase; ↓ indicates decrease; ↔ indicates no significant change
QD-once daily; BID-twice daily; TID – thrice daily
ND -No Data
AUC -Area under the Concentration vs. Time Curve; C_{max} -Maximum serum concentration
[a]compared to rifabutin 300 mg QD alone
[b]compared to historical control (fosamprenavir/ritonavir 700/100 mg BID)
[c]also taking zidovudine 500 mg QD
[d]compared to rifabutin 150 mg QD alone
[e]compared to rifabutin 300 mg QD alone
[f]data from a case report
[g]compared to voriconazole 200 mg BID alone

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 a weaker enzyme inducer than rifampin, rifabutin 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 P_1* 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

Rifabutin should be used in pregnant women only if the potential benefit justifies the potential risk to the fetus. There are no adequate and well-controlled studies in pregnant or breastfeeding women.

Reproduction studies have been carried out in rats and rabbits given rifabutin using dose levels up to 200 mg/kg (about 6 to 13 times the recommended human daily dose based on body surface area comparisons). No teratogenicity was observed in either species. In rats, given 200 mg/kg/day, (about 6 times the recommended human daily dose based on body surface area comparisons), there was a decrease in fetal viability. In rats, at 40 mg/kg/day (approximately equivalent to the recommended human daily dose based on body surface area comparisons), rifabutin caused an increase in fetal skeletal variants. In rabbits, at 80 mg/kg/day (about 5 times the recommended human daily dose based on body surface area comparisons), rifabutin caused maternotoxicity and increase in fetal skeletal anomalies. 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 rifabutin 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 1 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 rifabutin 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 rifabutin may be administered mixed with foods such as applesauce.

Geriatric Use

Clinical studies of rifabutin 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

Adverse Reactions from Clinical Trials

Rifabutin 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 rifabutin, compared to 8% of patients receiving placebo in these trials. Primary reasons for discontinuation of rifabutin 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 rifabutin in studies 023 and 027.

Table 3: Clinical Adverse Experiences Reported in ≥ 1% of Patients Treated With Rifabutin

Adverse event	Rifabutin (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
Blood and lymphatic system		
Leucopenia	10	7
Anemia	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 Rifabutin

Considering data from the 023 and 027 pivotal trials, and from other clinical studies, rifabutin 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, skin discoloration, thrombocytopenia, pancytopenia and jaundice.

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

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

Mild to severe, reversible uveitis has been reported less frequently when rifabutin is used at 300 mg as monotherapy in MAC prophylaxis versus rifabutin in combination with clarithromycin for MAC treatment *(see also WARNINGS)*.

Uveitis has been infrequently reported when rifabutin is used at 300 mg/day as montherapy in MAC prophylaxis of HIV-infected persons, even with the concomitant use of fluconazole and/or macrolide antibacterials. However, if higher doses of rifabutin are administered in combination with these agents, the incidence of uveitis is higher. FDA proposes moving this paragraph from below with some revisions.

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

Corneal deposits have been reported during routine ophthalmologic surveillance of some HIV-positive pediatric patients receiving rifabutin 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.

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

Table 4: Percentage of Patients With Laboratory Abnormalities

Laboratory abnormalities	Rifabutin (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[6]	5	4

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

Adverse Reactions from Post-Marketing Experience

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

Blood and lymphatic system disorders

White blood cell disorders (including agranulocytosis, lymphopenia, granulocytopenia, neutropenia, white blood cell count decreased, neutrophil count decreased), platelet count decreased.

Immune system disorders

Hypersensitivity, bronchospasm, rash, and eosinophilia.

Gastrointestinal disorders

Clostridium difficile colitis/ *Clostridium difficile* associated diarrhea.

Pyrexia, rash and other hypersensitivity reactions such as eosinophilia and bronchospasm might occur, as has been seen with other antibacterials.

A limited number of skin discoloration have been reported.

Rifamycin hypersensitivity reactions

Hypersensitivity to rifamycins have been reported including flu-like symptoms, bronchospasm, hypotension, urticaria, angioedema, conjunctivitis, thrombocytopenia or neutropenia.

To report SUSPECTED ADVERSE REACTIONS, contact Lupin Pharmaceuticals, Inc. at 1-800-399-2561 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

ANIMAL TOXICOLOGY

Liver abnormalities (increased bilirubin and liver weight) occurred in mice, rats and monkeys at doses (respectively) 0.5, 1 and 3-times the recommended human daily dose based on body surface area comparisons. Testicular atrophy occurred in baboons at doses 2 times the recommended human dose based on body surface area comparisons and in rats at doses 6 times the recommended human daily dose based on body surface area comparisons.

OVERDOSAGE

No information is available on accidental overdosage in humans.

Treatment

While there is no experience in the treatment of overdose with rifabutin capsules, clinical experience with rifampicin suggests 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 (Vss/F is 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 rifabutin.

DOSAGE AND ADMINISTRATION

It is recommended that rifabutin capsules USP be administered at a dose of 300 mg once daily. For those patients with propensity to nausea, vomiting, or other gastrointestinal upset, administration of rifabutin at doses of 150 mg twice daily taken with food may be useful.

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

Mild hepatic impairment does not require a dose modification. The pharmacokinetics of rifabutin in patients with moderate and severe hepatic impairment is not known.

HOW SUPPLIED

Rifabutin Capsules USP are supplied as size '0' capsules having opaque red-brown cap imprinted with 'LU' in white ink and opaque red-brown body imprinted with '0010' in white ink, containing red-violet granular powder equivalent to 150 mg of rifabutin USP.

Rifabutin Capsules USP are available as follows:

Bottles of 60 capsules - NDC 68180-285-07

Bottles of 100 capsules - NDC 68180-285-01

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

Keep tightly closed and dispense in a tight container as defined in the USP. Protect from light and from excessive heat.

Manufactured for:

Lupin Pharmaceuticals, Inc.

Baltimore, Maryland 21202

United States

Manufactured by:

Lupin Limited

Aurangabad 431 210

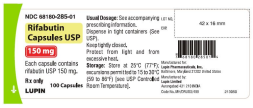
INDIA

Revised: October 2015 ID#: 242333

Rifabutin Capsules USP, 150 mg

NDC 68180-285-01

A Bottle Label containing 100 capsules



RIFABUTIN

rifabutin capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68180-285
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
RIFABUTIN (UNII: 1N5W1T6A4Q) (RIFABUTIN - UNII:1N5W1T6A4Q)	RIFABUTIN	150 mg

Inactive Ingredients

Ingredient Name	Strength
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
CROSPOVIDONE (UNII: 68401960MK)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
GELATIN (UNII: 2G86QN327L)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POTASSIUM SORBATE (UNII: 1VPU26JZZ4)	
SHELLAC (UNII: 46N107B71O)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	BROWN (Opaque red-brown cap) , BROWN (Opaque red-brown body)	**Score**	no score
Shape	CAPSULE	**Size**	23mm
Flavor		**Imprint Code**	LU;0010
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68180-285-01	100 in 1 BOTTLE; Type 0: Not a Combination Product		
2	NDC:68180-285-07	60 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA090010	01/28/2004	

Labeler - Lupin Pharmaceuticals, Inc. (089303873)

Registrant - LUPIN LIMITED (677812016)

Establishment

Name	Address	ID/FEI	Business Operations
LUPIN LIMITED		918233750	manufacture(68180-285)