

# MYCOBUTIN™

Rifabutin 150 mg capsules

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## Pharmaceutical Form

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Each capsule for oral administration contains 150 mg Rifabutin. Capsules are opaque, red-brown, hard gelatin Size No. 0 capsules.

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## Indications

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Mycobutin is indicated for infections caused by mycobacteria, such as *M. tuberculosis*, *M. avium intracellulare complex* (MAC) and other atypical mycobacteria.

In infections caused by MAC and other atypical mycobacteria such as *M. xenopi*, Mycobutin has been shown to be effective for the treatment of both disseminated and localised disease, also in immunocompromised HIV positive patients.

Mycobutin is also indicated for the prophylaxis of *M. avium intracellulare complex* (MAC) infections in immunodepressed patients with CD4 counts lower than or equal to 100/ml.

In the treatment of tubercular disease, Mycobutin has been shown to be effective for the treatment of patients with chronic pulmonary tuberculosis, even if caused by multidrug-resistant *M. tuberculosis* strains. In accordance with the commonly accepted criteria for the treatment of mycobacterial infections, Mycobutin therapy should always be given in combination with other antimycobacterial drugs not belonging to the family of rifamycins.

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## Dosage and Administration

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Mycobutin can be administered as a single daily dose at any time independent of meals.

### Adults:

Mycobutin as a single agent:

- Prophylaxis of MAC infection in immunodepressed patients:

300 mg (2 capsules) per day.

Mycobutin in combination regimens:

- in non-tuberculosis mycobacterial disease:

450-600 mg (3 to 4 capsules) for up to 6 months after negative cultures are obtained.

- in chronic, multidrug-resistant pulmonary tuberculosis:

300-450 mg (2 to 3 capsules) for up to 6 months after negative sputum cultures are obtained.

### **Elderly:**

No specific recommendations for dosage alterations in the elderly are proposed.

### **Children:**

There are inadequate data to support the use of Mycobutin in children at the present time.

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## **Contraindications**

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Mycobutin is contraindicated in patients with a history of hypersensitivity to rifabutin or other rifamycins (eg rifampicin).

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## **Precautions**

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Mycobutin may impart a red-orange color to the urine and possibly to skin and body secretions. Contact lenses, especially soft, may be permanently stained.

In accordance with the commonly accepted criteria for the treatment of mycobacterial infections, Mycobutin should always be given in combination with other anti-mycobacterial drugs not belonging to the family of rifamycins.

For patients with severe liver insufficiency a dose reduction should be considered. Mild hepatic impairment does not require a dose modification.

Severe renal impairment (creatinine clearance below 30 ml/min) requires a dosage reduction of 50%. Mild to moderate renal impairment does not require any dosage adjustment.

It is recommended that white blood cell and platelet counts and liver enzymes be monitored periodically during treatment.

When Mycobutin is used concomitantly with clarithromycin for MAC treatment, a decreased dose of Mycobutin is recommended due to the increase in plasma concentrations of Mycobutin (See Dosage and Administration, and Interactions with other Medications & Other Forms of

Interactions). Due to the possible occurrence of uveitis, patients should also be carefully monitored when Mycobutin is given in combination with clarithromycin (or other macrolides) and/or fluconazole (and related compounds). If uveitis is suspected, the patient should be referred to an ophthalmologist and, if considered necessary, treatment with Mycobutin should be suspended (see also Undesirable Effects and Interactions).

Protease inhibitors act as substrates or inhibitors of cyp450 IIIA4 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 patient specific drug profile (see Interactions with other Medications & Other Forms of Interactions). For further recommendations regarding protease inhibitors, please refer to current, official product monographs or contact the specific manufacturer.

*Clostridium difficile* associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including rifabutin, and may range in severity from mild diarrhoea 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 diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

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## Interactions

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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.

Table 1 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.

Although rifabutin and rifampin share structural similarities, their physicochemical properties (eg, ionization and partition coefficients) suggest significant differences between them in biodistribution and cyp450 enzyme inducing potential. The enzyme-inducing properties of

rifabutin are less pronounced than those of rifampin. Data suggest that rifabutin is a 2 to 3-fold weaker inducer than rifampin. Therefore, if changes in circulating drug levels affect patient response, the clinical impact of potential drug interactions is likely to be smaller with concomitant rifabutin than with rifampin.

*Malabsorption.* Gastric pH alteration due to progressing HIV disease has been linked with malabsorption of some drugs used in HIV-positive patients (eg, 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.

**Table 1. Rifabutin Interaction Studies\***

Coadministered Drugs	Effect on Rifabutin	Effect on Coadministered Drug	Comments
<b>ANTIVIRALS</b>			
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.	
Indinavir	204% ↑ in AUC	32% ↓ in AUC	
Saquinavir	ND	40% ↓ in AUC	
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.(See also Special Warnings & Special Precautions for Use)
Zidovudine	No significant	Approximately 32% ↓ in Cmax	A large controlled clinical study has shown that these changes are of no

	change in kinetics.	and AUC	clinical relevance.
<b>ANTIFUNGALS</b>			
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.
<b>ANTI-PCP (Pneumocystis carinii pneumonia)</b>			
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.
<b>ANTI-MAC (Mycobacterium avium intracellulare complex)</b>			
Azithromycin	ND	ND	Study under analysis. Preliminary data do not suggest an interaction.
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. (See Dosage and Administration and also Special Warnings & Special Precautions for Use)
<b>ANTI-TB (Tuberculosis)</b>			
Ethambutol	ND	No significant change in AUC or Cmax	

Isoniazid	ND	Pharmacokinetics not affected	
Pyrazinamide	ND	ND	Study data being evaluated.
<b>OTHER</b>			
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.
Oral Contraceptives	ND	ND	Study data being evaluated. 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 - No data

AUC - Area under the Concentration vs. Time Curve

Cmax - Maximum serum concentration

## Pregnancy & Lactation

There are no adequate and well-controlled studies in pregnant or breastfeeding women.

Reproduction studies have been conducted in rats and rabbits given rifabutin using dose levels up to 200 mg/kg (40 times the recommended human daily dose). No teratogenicity was observed in either species. In rats, given 200 mg/kg/day, there was decrease in foetal viability. In rats, at 40 mg/kg/day (8 times the recommended human daily dose), rifabutin caused an increase in foetal skeletal variants. In rabbits, at 80 mg/kg/day (16 times the recommended human daily dose), rifabutin caused maternotoxicity and increased foetal 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 foetus.

## Effects on Ability to Drive & Use Machines

There is no reason to believe that Mycobutin has any adverse effect on the ability to drive and use machines.

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## Adverse Effects

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The tolerability of Mycobutin in multiple drug regimens, has been assessed in long-term studies with daily dosages up to 600 mg in both immunocompetent and immunocompromised patients, suffering from tuberculosis and non-tuberculous mycobacteriosis.

Mycobutin was often given in these studies as part of a multidrug regimen, and it is not possible to define with certainty a drug-event relationship. Treatment discontinuation was necessary only in a very few cases. The most commonly reported adverse events, were primarily related to:

- the gastrointestinal system, such as nausea, vomiting, increase of liver enzymes, jaundice;
- the blood and lymphatic system, such as leucopenia, thrombocytopenia and anemia;
- the musculoskeletal system, such as arthralgia and myalgia.

Fever, 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. In addition, mild to severe, reversible uveitis has been reported. The risk is very low when Mycobutin is used at 300 mg as monotherapy in MAC prophylaxis but increases when Mycobutin is administered at higher doses in combination with clarithromycin for MAC treatment (see Special Warnings & Special Precautions for Use). The possible role of fluconazole (and related compounds) in increasing the risk of uveitis has not yet been established. Uveitis has not been reported in patients treated with Mycobutin (150 to 600 mg daily) in combination with other drugs for pulmonary tuberculosis. 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 changes are tiny, almost transparent, asymptomatic peripheral and central corneal deposits, and do not impair vision.

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## Overdosage

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A specific toxic dose of rifabutin has not been established, although a syndrome of arthralgia/arthritis has been reported following daily monotherapy of 1 gram or more. Other signs and symptoms of overdosage are likely to be similar to adverse effects from normal therapeutic doses.

There is no specific antidote. Treatment is symptomatic and supportive, including respiratory and cardiovascular function. Plasma rifubutin levels may confirm overdosage but are not clinically useful. Monitor complete blood count, liver enzyme levels and fluid-electrolyte status as indicated, and perform an ophthalmologic examination if the patient exhibits ocular symptoms.

An aqueous slurry of activated charcoal may be administered after a potentially toxic ingestion, but it is most effective within one hour of ingestion. In patients who are not fully conscious or

have impaired or gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected.

Rifabutin is approximately 85% protein-bound, is extensively distributed into various tissues and is not primarily excreted via the urinary route, therefore neither haemodialysis nor forced diuresis are expected to be of any benefit.

Contact the Poisons Information Centre for advice on the management of an overdose.

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## Pharmacology

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### Pharmacodynamic Properties

Rifabutin has been shown to inhibit DNA-dependent RNA polymerase in susceptible strains of prokaryotic organisms (*Escherichia coli* and *Bacillus subtilis*) but not in mammalian cells. It inhibits incorporation of thymidine into DNA of rifampicin-resistant *M. tuberculosis* suggesting that rifabutin may also inhibit DNA synthesis which may explain its activity against rifampicin-resistant organisms.

*In vitro* activity of rifabutin against laboratory strains and clinical isolates of *M. tuberculosis* has been shown to be very high. *In vitro* studies carried out so far have shown that from one-third to half of *M. tuberculosis* strains resistant to rifampicin are susceptible to rifabutin, indicating that cross-resistance between the two antibiotics is incomplete.

The *in vivo* activity of rifabutin on experimental infections caused by *M. tuberculosis* was about 10 times greater than that of rifampicin in agreement with the *in vitro* findings.

Rifabutin was seen to be active against non-tuberculous (atypical) mycobacteria including *M. avium-intracellulare* (MAC) *in vitro* as well as in experimental infections caused by these pathogens in immunodeficient mice. The spectrum of rifabutin includes Gram + and Gram - bacteria.

### Pharmacokinetic Properties

In man, rifabutin is rapidly absorbed and maximum plasma concentrations are reached around 2 to 4 hours after oral administration. The pharmacokinetics of rifabutin is linear after single administration of 300, 450 and 600 to healthy volunteers. With these doses, C<sub>max</sub> is in the range of 0.4 to 0.7 µg/ml. Plasma concentrations are maintained above the MIC values for *M. tuberculosis* up to about 30 hours from administration. Rifabutin is widely distributed in various animal organs with the exception of the brain. Human tissue concentrations were several times higher than plasma levels in lung parenchyma, gall bladder, and intestinal walls.

The intracellular penetration of rifabutin is very high as demonstrated by the intracellular to extracellular concentration ratios, which ranged from 9 in neutrophils to 15 in monocytes, both obtained from human sources.

The high intracellular concentrations is likely to play a crucial role in sustaining the efficacy of rifabutin against intracellular pathogens such as mycobacteria. Rifabutin and its metabolites are eliminated mainly by the urinary route. Of the five metabolites that have been identified, the 25 O-desacetyl derivative and the 31-hydroxyl derivative are the most predominant. The former has an antibacterial activity equal to the parent drug. The  $t_{1/2}$  of rifabutin in man is approximately 35-40 hours.

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## Preclinical Safety Data

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### Toxicology

Preclinical safety studies of rifabutin indicate a good safety margin in rodents and in monkeys. The acute oral toxicity of rifabutin in rats given single oral doses up to 5 g/kg and in beagle dogs and cynomolgus monkeys given 2 and 4 g/kg was low, with no mortality. The oral LD50 in mice was 4.8 g/kg for males and 3.3 g/kg females. In repeated dose studies, target organs were identified only at doses producing blood levels higher than those achieved with recommended doses for human therapy. The main target organs in mice, rats and monkeys are liver, stomach, gonads and, to a lesser degree, erythrocytes. Rifabutin was not genotoxic in any of the *in vitro* or *in vivo* tests.

### Carcinogenicity/Mutagenicity

No carcinogenic effect was seen in either mice or rats treated for up to two years at the maximum tolerated dose.

### Reproduction

In all reproduction studies, the no effect level was 40-50 mg/kg. At all doses no teratogenic effect was seen. The changes in fertility and foetal development noticed at high dose levels are related to lesions in reproductive organs and to the toxic effect of the compound on dams.

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## Pharmaceutical Particulars

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### List of Excipients

Microcrystalline cellulose  
Sodium lauryl sulphate

Magnesium stearate  
Silica gel

### **Incompatibilities**

None known

### **Storage Instructions**

Store below 25°C.

### **Special Precautions for Storage**

None

### **Preparation & Handling**

There are no special instructions for handling.

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### **Medicine Classification**

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Prescription Medicine

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### **Presentation**

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150mg capsules in blister packs of 30 capsules.

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### **Name and Address of Sponsor**

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Pfizer New Zealand Ltd  
PO Box 3998  
Auckland, New Zealand  
Toll Free number: 0800 736 363

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### **Date of Preparation**

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18 February 2008

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