AUSTRALIAN PRODUCT INFORMATION – MYCOBUTIN (RIFABUTIN)

1. NAME OF THE MEDICINE

Rifabutin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Mycobutin (rifabutin) is a wide spectrum, semi-synthetic ansamycin antibiotic particularly active on acid-fast bacilli, including atypical and multidrug-resistant mycobacteria.

Each Mycobutin capsule for oral administration contains 150 mg of rifabutin.

3. PHARMACEUTICAL FORM

The hard gelatin capsules are opaque and red-brown in colour with the words "Pharmacia & Upjohn" and "Mycobutin" imprinted on the capsule in white ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mycobutin is indicated for:

The prophylaxis of *M. avium-intracellulare* complex (MAC) infections in patients with advanced HIV infection (CD4 counts lower than 200/μL).

The treatment of infections caused by MAC and other atypical mycobacteria, including in immunocompromised patients.

The treatment of chronic multidrug-resistant pulmonary tuberculosis in the presence of rifampicin resistant, rifabutin-sensitive *M. tuberculosis* strains.

The treatment of newly diagnosed pulmonary tuberculosis in the presence of rifampicin resistant, rifabutin-sensitive *M. tuberculosis* strains.

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.

4.2 Dose and method of administration

Dosage

Mycobutin can be administered as a single, daily, oral dose at any time independently of meals.

Caution should be applied when rifabutin is coadministered with any of the other drugs listed in Section 4.5 Interactions with other medicines and other forms of interactions. Dosages of either drug may need to be adjusted on a case-by-case basis.

Adults

Mycobutin as a single agent:

– prophylaxis of MAC infection in immunodepressed patients: 300 mg (2 capsules) daily.

Mycobutin in combination regimens:

– In non-tuberculosis mycobacterial disease: 300-600 mg (2 to 4 capsules) daily for up to 6 months after negative cultures are obtained.
– In chronic, multidrug-resistant pulmonary tuberculosis: 300-450 mg (2 to 3 capsules) daily for up to 6 months after negative sputum cultures are obtained.
– In newly-diagnosed pulmonary tuberculosis: 150-300 mg (1 to 2 capsules) daily for 6 months.
– When Mycobutin is given in association with clarithromycin, the dosage of Mycobutin should be reduced to 300 mg once daily (see Sections 4.4 Special warnings and precautions for use and 4.5 Interactions with other medicines and other forms of interactions).
– When Mycobutin and indinavir are coadministered, the dosage of Mycobutin should be halved and the dosage of indinavir increased to 1,000 mg four times a day.

Children

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

Elderly

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

4.3 Contraindications

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

Due to insufficient clinical experience in children, Mycobutin should not be used in these patients.

Concomitant use of ritonavir and rifabutin is contraindicated.

Concomitant use with rilpivirine prolonged-release suspension for injection is contraindicated (see Section 4.5 Interactions with other medicines and other forms of interactions).

4.4 Special warnings and precautions for use

Mycobutin may impart a red-orange colour to the urine and possibly to skin and body secretions. Contact lenses, especially the soft variety, 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.

It is recommended that white blood cell and platelet counts and liver enzymes be monitored periodically during treatment, because Mycobutin may be associated with neutropenia and, more rarely, thrombocytopenia.

Rifamycins have been associated with drug-induced hepatic breakdown of vitamin K in pregnant women and their offspring (see Section 4.6 Fertility, pregnancy and lactation - Use in pregnancy).

HIV protease inhibitors act as substrates or inhibitors of the CYP450 3A4 enzyme and have significant drug interactions with rifabutin. As a result, before concomitant use of these drugs, an overall assessment of the patient and their medication should be made (see Section 4.5 Interactions with other medicines and other forms of interactions).

Rifabutin is a CYP450 3A inducer. Therefore, co-administration with antiretroviral products including but not limited to bictegravir, elvitegravir, oral rilpivirine, or doravirine and anti-HCV products including but not limited to sofosbuvir (alone or in combination) is not recommended due to the expected decrease in plasma concentrations of the antiretrovirals and anti-HCV products which may lead to loss of virologic response and possible development of resistance (see Section 4.5 Interactions with other medicines and other forms of interaction). For further recommendations, please refer to the most recent prescribing information of the antiretrovirals 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.

There have been reports of severe cutaneous adverse reactions (SCARs), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) with anti-tuberculosis drugs (see Section 4.8 Adverse effects (undesirable effects)). If patients develop a skin rash they should be monitored closely and suspect drug(s) discontinued if lesions progress. Identifying the specific drug is difficult, as multiple anti-tuberculosis drugs are prescribed in association concurrently. Specifically, for DRESS, a multi-system potential life-threatening SCAR, time to onset of the first symptoms may be prolonged. DRESS is a clinical diagnosis, and its clinical presentation remains the basis for decision making. An early withdrawal of the suspect drug is essential because of the syndrome's mortality and visceral involvement (e.g., liver, bone marrow or kidney).

Uveitis

When Mycobutin is given in association with clarithromycin, the dosage of Mycobutin should be reduced to 300 mg (see Sections 4.2 Dose and method of administration, 4.5 Interactions with other medicines and other forms of interactions and 4.8 Adverse effects (undesirable effects) - Uveitis/Corneal deposits).

Because of the possibility of occurrence of uveitis, patients should be carefully monitored when Mycobutin is given in combination with clarithromycin (or other macrolides) and/or fluconazole (and related compounds).

If uveitis occurs, the patient should be referred to an ophthalmologist. If considered necessary Mycobutin treatment should be discontinued and appropriate treatment given (see Sections 4.5 Interactions with other medicines and other forms of interactions and Section 4.8 Adverse effects (undesirable effects)).

Malabsorption

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

Use in hepatic impairment

Mycobutin should be used with caution in cases of liver insufficiency. For patients with severe liver insufficiency a dose reduction should be considered. Mild hepatic impairment does not require a dose modification.

Use in renal impairment

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

Use in the elderly

No data available.

Paediatric use

Due to insufficient clinical experience in children, Mycobutin should not be used in these patients.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

Although structurally similar to rifampicin, rifabutin appears to induce enzymes of the P450 system to a lesser extent.

Therefore, as rifabutin has been shown to induce the enzymes of the cytochrome P450 3A subfamily, treatment may affect the pharmacokinetic behaviour of drugs metabolised by the enzymes belonging to that subfamily (as is seen with rifampicin).

Rifabutin accelerates the metabolism of:

Fluconazole	Oral contraceptives
Methadone	Phenytoin

Rifabutin decreases the concentration of:

Atovaquone	Sulfamethoxazole
Benzodiazepines	Tacrolimus
Opiate analgesics	Trimethoprim

Rifabutin accelerates the metabolism and may decrease plasma concentrations of:

Astemizole	Lovastatin
Calcium channel blockers	Midazolam
Cisapride	Nevirapine
Clarithromycin	Oestrogens
Corticosteroids	Quinidine
Cyclosporin	Ritonavir
	Saquinavir
Erythromycin	Terfenadine
Indinavir	Theophylline
Itraconazole	Triazolam
Ketoconazole	Warfarin
Lidocaine	Zidovudine

Upward adjustment of the dosage of some of the drugs listed above may be required when administered with Mycobutin keeping in mind that some of the interactions show wide interindividual variability. The drugs normally subject to this include: dapsone, narcotic analgesics (including methadone), anticoagulants, corticosteroids, cardiac glycoside preparations (although not digitalis), quinidine, oral hypoglycaemic agents and oral contraceptives. It is important to note that during Mycobutin therapy oral contraception may not be adequate and patients should be advised to use other forms of contraception.

There are insufficient data to assess whether dose adjustments are necessary when nevirapine and rifabutin are coadministered. Concomitant use of these drugs should be carefully monitored and the combination only used if clearly indicated.

When rifabutin is used concomitantly with clarithromycin, a decreased dose of rifabutin is recommended due to the increase in plasma concentrations of rifabutin (see Sections 4.2 Dose and method of administration and 4.4 Special warnings and precautions for use).

Other macrolide antibiotics may also inhibit metabolism of rifabutin.

When administered with indinavir, the dosage of rifabutin should be reduced by half.

Protease inhibitors act as substrates or inhibitors of CYP450 3A4 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.

Other drugs such as ketoconazole, barbiturates, benzodiazepines, verapamil, β-blocking drugs, disopyramide, mexiletine, chloramphenicol and anticonvulsants may also require consideration

for potential dose adjustment, during concomitant therapy based on the known effects of rifampicin.

In contrast, no significant interactions may be expected with ethambutol, pyrazinamide, theophylline, sulfonamides and zalcitabine (DDC).

Although pharmacokinetic data have shown that Mycobutin, when given in combination with zidovudine, reduces the plasma levels of the latter, a large, controlled clinical study has shown that these changes are of no clinical relevance.

Clinical studies have shown that Mycobutin does not affect the pharmacokinetics of didanosine (DDI), isoniazid (for the latter refer also to Section 4.8 Adverse effects (undesirable effects) - Blood and lymphatic system) and fluconazole. Fluconazole however increases rifabutin plasma levels. Zidovudine and DDI were shown not to affect the pharmacokinetics of rifabutin.

In addition, some drugs increase the concentration of rifabutin and these include the following:

Ciprofloxacin
Clarithromycin
Enoxacin
Erythromycin
Fluconazole
Indinavir
Itraconazole
Ketoconazole
Ritonavir
Saquinavir

Major interactions in this category leading to a significant increase in side effects, occur with clarithromycin, fluconazole, indinavir, ritonavir and, in particular, saquinavir.

Table 1 summarises the results and magnitude of the various drug interactions 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 1: Rifabutin Interaction Studies

Coadministered Drugs	Effect on Rifabutin	Effect on Coadministered Drug	Comments
ANTIRETROVIRALS			
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.

Coadministered Drugs	Effect on Rifabutin	Effect on Coadministered Drug	Comments
Atazanavir/Ritonavir	48% ↑ in AUC, 149% ↑ Cmax of rifabutin [a] 990% ↑ in AUC, 677% ↑ Cmax of 25-O-desacetyl-rifabutin [a]	No significant change in kinetics.	A 75% reduction in the dose of rifabutin (to 150 mg daily) is recommended. Increased monitoring for adverse reactions is warranted in patients receiving the combination. Further dose reduction of rifabutin may be necessary. Concomitant use of ritonavir and rifabutin is contraindicated.
Bictegravir	ND	AUC ↓38% Cmin ↓56% Cmax ↓20%	Although not studied, co-administration of rifabutin with a combination product containing bictegravir/ emtricitabine/ tenofovir alafenamide is not recommended due to an expected decrease in tenofovir alafenamide in addition to the reported reduction in bictegravir.
Darunavir/Ritonavir	No significant change in rifabutin kinetics. 881% ↑ in AUC, 377% ↑ Cmax of 25-O-desacetyl-rifabutin [b]	57% ↑ in AUC, 42% ↑ Cmax of darunavir [b] 66% ↑ in AUC, 68% ↑ Cmax of ritonavir [b]	A 75% reduction in the dose of rifabutin (to 150 mg daily) is recommended. Increased monitoring for adverse reactions is warranted. Concomitant use of ritonavir and rifabutin is contraindicated.
Didanosine	No significant change in kinetics.	No significant change in kinetics at steady state.	
Dolutegravir	ND	No significant change in dolutegravir kinetics at steady state.	
Doravirine	ND	50% ↓ in AUC 68% ↓ in C_{24} ↔ in Cmax	If concomitant use is necessary, increase the doravirine dosage as instructed in doravirine-containing product prescribing information.
Elvitegravir/ Cobicistat	No significant change in rifabutin kinetics.	No change in elvitegravir except 67% ↓ Ctrough of elvitegravir.	Co-administration of rifabutin with elvitegravir/cobicistat is not recommended due to an expected decrease in

Coadministered Drugs	Effect on Rifabutin	Effect on Coadministered Drug	Comments
	6.3-fold ↑ in AUC, 4.8-fold ↑ Cmax of 25-O-desacetyl-rifabutin	No change in cobicistat exposure.	elvitegravir exposure (see Section 4.4).
Etravirine	No significant change in rifabutin kinetics.	37% ↓ in AUC, 37% ↓ in Cmax and 35% ↓ in Cmin.	No dose adjustment of rifabutin is required when etravirine is not coadministered with ritonavir (Concomitant use of ritonavir and rifabutin is contraindicated).
Fosamprenavir/ Ritonavir	64% ↑ AUC [c]	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. Concomitant use of ritonavir and rifabutin is contraindicated.
Indinavir	173%↑ in AUC, 134% ↑ in Cmax [d]	34% ↓ in AUC, 25% ↓ in Cmax [d]	Dose reduction of rifabutin to half the standard dose and increase of indinavir to 1000 mg every 8 hours are recommended when rifabutin and indinavir are coadministered.
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. Concomitant use of ritonavir and rifabutin is contraindicated.
Saquinavir	ND	43% ↓ in AUC	

Coadministered Drugs	Effect on Rifabutin	Effect on Coadministered Drug	Comments
Rilpivirine	ND	42% ↓ in AUC 48% ↓ in Cmin 31% ↓ in Cmax	Although not studied, co-administration of rifabutin with a combination product containing rilpivirine/ tenofovir alafenamide/ emtricitabine is not recommended due to an expected decrease in tenofovir alafenamide in addition to the reported reduction in rilpivirine (see Section 4.4). Co-administration of rifabutin with rilpivirine prolonged-release injectable suspension is contraindicated (see Section 4.3).
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. Concomitant use of ritonavir and rifabutin is contraindicated.
Tipranavir/Ritonavir	2.9-fold ↑ AUC, 1.7-fold ↑ Cmax	No significant change in tipranavir kinetics.	Therapeutic drug monitoring of rifabutin is recommended. Concomitant use of ritonavir and rifabutin is contraindicated.
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.
ANTI-HCV DRUGS			
Sofosbuvir	ND	36% ↓ in Cmax and 24% ↓ AUC	Co-administration of rifabutin with sofosbuvir (alone or in combination) is not recommended (see Section 4.4).
ANTIFUNGALS			
Fluconazole	82% ↑ in AUC	No significant change in steady-state plasma concentrations	Uveitis was associated with the combination of rifabutin and fluconazole. Patients receiving rifabutin and fluconazole concomitantly should be carefully monitored (see Section 4.4).

Coadministered Drugs	Effect on Rifabutin	Effect on Coadministered Drug	Comments
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	Co-administration of posaconazole with rifabutin increases rifabutin plasma concentrations and decreases posaconazole plasma concentrations. Concomitant use of rifabutin and posaconazole should be avoided unless the benefit to the patient outweighs the risk. However, if concomitant administration is required, close monitoring of breakthrough fungal infections as well as frequent monitoring for adverse reactions due to increased rifabutin plasma concentrations (e.g., uveitis, leukopenia) are recommended.

Coadministered Drugs	Effect on Rifabutin	Effect on Coadministered Drug	Comments
Voriconazole	195%↑ Cmax, 331%↑ AUC [e]	Rifabutin (300 mg once daily) decreased the Cmax and AUC of voriconazole at 200 mg twice daily by 69% and 78%, respectively. During co-administration 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.	If the benefit outweighs the risk, rifabutin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased to 5 mg/kg intravenously every 12 hours or from 200 mg to 350 mg orally, every 12 hours (100 mg to 200 mg orally, every 12 hours in patients less than 40 kg). Careful monitoring of full blood counts and adverse events to rifabutin (e.g., uveitis) is recommended when rifabutin is coadministered with voriconazole.
ANTI-PCP (Pneumocystis carinii 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	There was a 19%↓ in the AUC for trimethoprim and a 14%↓ in the AUC for sulfamethoxazole when cotrimoxazole was given with rifabutin compared to when cotrimoxazole was given alone.
ANTI-MAC (Mycobacterium avium intracellulare complex)			
Azithromycin	No PK interaction	No PK interaction	
Clarithromycin	Approximately 77% ↑ in AUC	Approximately 50%↓ in AUC	Study conducted in HIV infected patients. Dose of rifabutin should be reduced in the presence of clarithromycin. (See Sections 4.2 and 4.4)

Coadministered Drugs	Effect on Rifabutin	Effect on Coadministered Drug	Comments
ANTI-TB (Tuberculosis)			
Ethambutol	ND	No significant change in AUC or Cmax	
Isoniazid	ND	Pharmacokinetics not affected	
Bedaquiline	ND	No change in bedaquiline kinetics. 1.4-fold ↑ in M2 and approximately 3.0-fold ↑ in M3 metabolites of bedaquiline.	If the drugs are coadministered, patients should be monitored for adverse events associated with bedaquiline administration.
ORAL CONTRACEPTIVES			
Ethinylestradiol/ Norethisterone	ND	Ethinylestradiol: 20% ↓ in Cmax, 35% ↓ in AUC. Norethisterone: 32% ↓ in Cmax, 46% ↓ in AUC.	Contraceptive cover may not be adequate during concomitant therapy with rifabutin. Patients should be advised to use other methods of contraception.
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.
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

Cmin - Minimum serum concentration

a – AUC and Cmax based on interaction with 150 mg rifabutin twice weekly

b – AUC and Cmax based on interaction between darunavir/ritonavir 600/100 mg twice daily plus rifabutin 150 mg every other day

c – AUC data based on the effect on drug plus active metabolite

d – AUC and Cmax based on interaction with 300 mg rifabutin daily

e – AUC and Cmax based on voriconazole dosed at 400 mg twice daily

4.6 Fertility, pregnancy and lactation

Effects on fertility

Studies in rats at oral doses of rifabutin at 160 mg/kg/day have shown impairment of spermatogenesis and effects on the gonads without any significant effect on the numbers of live offspring.

Use in pregnancy – Pregnancy Category C

Reproduction studies have been carried out in rats and rabbits given rifabutin at oral dose levels up to 200 and 80 mg/kg/day, respectively. Teratogenicity was not observed in either species. In rats, at an oral dose of 40 mg/kg/day, rifabutin caused an increase in skeletal variants. In rabbits, at an oral dose of 80 mg/kg/day, rifabutin caused maternotoxicity and an increase in fetal skeletal anomalies. There are no adequate and well-controlled studies in pregnant women.

Because animal reproduction studies are not always predictive of human response, rifabutin should be used in pregnant women only if the potential benefit justifies the potential risk to the fetus.

During the late stages of pregnancy, rifampicin has been associated with serious vitamin K deficiency in mother and neonate, resulting in haemorrhagic disturbances. Mycobutin has not been studied in pregnancy. This should be borne in mind if, in exceptional cases, the physician considers the benefit of treatment outweighs the risk and wishes to treat a pregnant woman with Mycobutin.

Use in lactation

It is not known whether rifabutin is excreted in human breast milk. Because many drugs are excreted in human milk and 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.

4.7 Effects on ability to drive and use machines

There have been no reports of adverse effects of Mycobutin on the ability to drive and use machines.

4.8 Adverse effects (undesirable effects)

The tolerability of Mycobutin in multiple drug regimens was 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 in approximately 13% of patients with HIV infection and 5% of patients with tuberculosis in clinical trials, related to gastrointestinal symptoms, liver function test abnormalities and blood or lymphatic system disorders.

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

*Adverse Reactions not observed in a clinical trial.

**Adverse Reactions neither observed in the clinical trials nor in the spontaneous reporting for rifabutin and are mandated for the pharmacological class.

Blood and lymphatic system: Pancytopenia, white blood cells disorder (including agranulocytosis*, leukopenia, lymphopenia*, granulocytopenia*, neutropenia*, white blood cell count decreased*, neutrophils count decreased*), thrombocytopenia, platelet count decreased* and anaemia (approximately 4-9%). The frequency and severity of haematological reactions may be increased by combined administration of isoniazid.

Immune system disorders: Anaphylactic shock**, hypersensitivity*, bronchospasm*, rash, eosinophilia.

Eye disorders: Uveitis*, corneal deposits*.

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

Hepatobiliary disorders: Jaundice (approximately 8-12%), hepatic enzyme increased*.

Skin and subcutaneous tissue disorders: Skin discolouration.

Musculoskeletal and connective tissue disorders: Arthralgia, myalgia (approximately 3%).

General disorders and administration site condition: Pyrexia (approximately 2-4%), rash (approximately 3-4%) and, rarely (<1%), other hypersensitivity reactions such as eosinophilia, bronchospasm and shock might occur, as has been seen with other antibiotics.

Uveitis/Corneal deposits

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 Section 4.4 Special warnings and precautions for use). Corneal deposits have been reported during routine ophthalmologic surveillance of some HIV-positive paediatric 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.

Anti-tuberculosis drug SCARs

Anti-tuberculosis drug use may lead to the occurrence of drug reaction with eosinophilia and systemic symptoms (DRESS) as well as other SCARs such as SJS, TEN, and AGEP (see Section 4.4 Special warnings and precautions for use).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

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 rifabutin 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 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Rifabutin has activity *in vitro* against laboratory strains and clinical isolates of *M. tuberculosis*. To date, *in vitro* studies 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* is about 3 to 10 times greater than that of rifampicin in agreement with the *in vitro* findings.

Rifabutin has been shown to be active against non-tuberculous (atypical) mycobacteria including *M. avium-intracellulare* complex (MAC), *in vitro* as well as *in vivo* on experimental infections caused by these pathogens in mice with induced immunodeficiency.

In vitro susceptibility testing methods and diagnostic procedures used for determining minimum inhibitory concentration (MIC) values against MAC organisms and other mycobacterial species have not been standardised.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

In humans, rifabutin maximum plasma concentrations are reached around 2-4 hours after oral administration. The pharmacokinetics of rifabutin is linear after single dosing of 300, 450, and 600 mg to healthy volunteers. With these doses, Cmax is in the range of 0.4-0.7 µg/mL. Although systemic levels of rifabutin following multiple dosing decreased by 38%, its terminal half-life remained unchanged.

Rifabutin, due to its high lipophilicity, demonstrates a high propensity for distribution and intracellular tissue uptake. It is widely distributed in various animal organs with the exception of the brain. In particular, in human lung tissue the concentrations measured up to 24 hours after dosing are about 5-10 times higher than the plasma levels. Substantially higher intracellular tissue levels than those seen in plasma have been observed in both rat and man.

About 85% of the drug is bound to plasma proteins. Binding does not appear to be influenced by renal or hepatic dysfunction.

Renal and biliary clearance of unchanged drug each contribute approximately 5% to CL_s/F. About 30% of the dose is excreted in the faeces. Rifabutin and its metabolites are eliminated mainly by the urinary route. The $t_{1/2}\beta$ of Mycobutin in humans is approximately 35-40 hours.

The bioavailability of rifabutin from the capsule dosage form, relative to a solution, was 85% in healthy adult volunteers. High fat meals slow the rate without influencing the extent of absorption from the capsule.

5.3 Preclinical safety data

Genotoxicity

Rifabutin was not mutagenic in a standard series of assays for gene mutations and chromosomal damage.

Carcinogenicity

Long-term carcinogenicity studies were conducted with rifabutin in mice and rats. Rifabutin was not carcinogenic in mice at oral doses up to 180 mg/kg/day, giving rise to rifabutin plasma levels of 2.6 µg/mL and 1.8 µg/mL in female and male mice, respectively. Rifabutin was not carcinogenic in rats at oral doses up to 60 mg/kg/day, giving rise to rifabutin plasma levels of 9.2 µg/mL and 7.1 µg/mL in male and female rats, respectively. Serum levels in humans after dosing with 600 mg rifabutin were in the order of µg/mL.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

microcrystalline cellulose

sodium lauryl sulfate

magnesium stearate

silicon dioxide

iron oxide red

titanium dioxide

OPACODE monogramming ink S-1-7085 WHITE

TekPrint SB-0007P White Ink

gelatin

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Mycobutin is supplied as 150 mg capsules in:

- PVC/Al blister packs of 30 (3 strips of 10 capsules)

- Glass bottles of 30 – *not marketed*

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

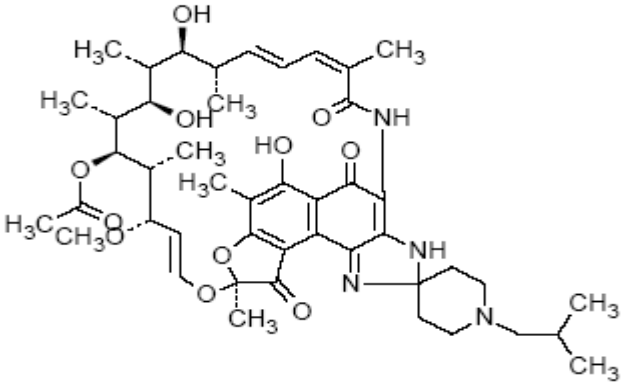
6.7 Physicochemical properties

Chemical structure

Chemical name: (12E,22E,24Z)-(9S,14S,15R,16S,17R,18R,19R,20S,21S)-3,5,9,10-Tetrahydro-6,18,20-trihydroxy-1'-isobutyl-14-methoxy-7,9,15,17,19,21,25-

heptamethyl-5,10,26-trioxospiro[9,4-(epoxypentadeca[1,11,13]trienimino)-2H-furo[2',3':7,8]naphtho [1,2-d]imidazole-2,4-piperidine]-16-yl acetate

The empirical formula is $C_{46}H_{62}N_4O_{11}$ and the structural formula is as follows:



CAS number

72559-06-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine).

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

3 August 1994

10. DATE OF REVISION

12 November 2024

Summary Table of Changes

Section changed	Summary of new information
4.5	Addition of DDI information for atazanavir/ritonavir, darunavir/ritonavir.