

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mycobutin 150mg Hard Capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 150.0mg Rifabutin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule (Capsule).

Opaque, red-brown, hard gelatin capsules marked “MYCOBUTIN” on the cap and “Pharmacia&Upjohn” on the body. Size No. 0

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Mycobutin is indicated:

As a second line treatment of patients with sensitive mycobacterium tuberculosis. Treatment should be supervised by a specialist physician.

4.2 Posology and method of administration

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

Posology

Adults

The normal dose recommended for pulmonary tuberculosis is 150-450 mg (1-3 capsules) in combination regimens for at least 6 months

When Mycobutin is given in association with clarithromycin (or other macrolides) or fluconazole (and related compounds) or certain antivirals, dosage should be reduced to 300 mg/day after the first month of treatment (see Section 4.4 Special warnings and precautions for use, and Section 4.5, Interaction with other medicinal products and other forms of interaction).

Paediatric population 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) or to any of the excipients listed in section 6.1. Patients who suffer from porphyria.

4.4 Special warnings and precautions for use

Mycobutin may impart a red-orange colour to the urine, saliva and to other 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 30ml/min) requires a dosage reduction of 50%. Mild to moderate renal impairment does not require any dosage adjustment.

It is recommended that full blood (including white, red cell and platelets) counts and liver enzymes be monitored periodically during treatment.

When Mycobutin is used concomitantly with clarithromycin, a decreased dose of Mycobutin is recommended due to the increase in plasma concentrations of Mycobutin (*see Section 4.2 Posology and Method of Administration, and Section 4.5 Interaction with other medicinal products and other forms of interaction*).

Because of the possibility of occurrence of uveitis, patients should be carefully monitored when rifabutin is given in combination with agents which increase its plasma levels e.g. clarithromycin (or other macrolides) and/or fluconazole (and related compounds) and some antivirals (*See section 4.5, Interaction with other medicinal products and other forms of interactions*). If such an event occurs, the patients should be referred to an ophthalmologist and, if considered necessary, Mycobutin treatment should be suspended.

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 Section 4.5 Interactions with other medicinal products and other forms of interaction*). For further recommendations regarding protease inhibitors, please refer to current, official product monographs or contact the specific manufacturer.

Clostridium difficile associated diarrhea (CDAC) has been reported with use of nearly all antibacterial agents, including rifabutin, 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 antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

4.5 Interaction with other medicinal products and other forms of interaction

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; LM565), 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 metabolised 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. For this reason, during Mycobutin therapy oral contraception may not be adequate and patients should be advised to use other forms of contraception. Similarly, Mycobutin might reduce the activity of analgesics, anticoagulants, corticosteroids, cyclosporin, digitalis (although not digoxin), dapsone, oral hypoglycaemics, narcotics, phenytoin and quinidine. Although pharmacokinetic data have shown that Mycobutin when given in combination with zidovudine reduces 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) or isoniazid (*See section 4.8, Undesirable effects*).

On the basis of the above metabolic considerations no significant reaction may be expected with ethambutol, theophylline, sulphonamides, pyrazinamide and zalcitabine (DDC).

An interaction, leading to an increase in rifabutin plasma levels, occurs when Mycobutin is administered together with clarithromycin and/or fluconazole. This may apply to drugs of the same classes (*See section 4.8, Undesirable effects and section 4.4, Special warnings and precautions for use*).

However Mycobutin does not affect the pharmacokinetics of fluconazole. As p-aminosalicylic acid has been shown to impede GI absorption of rifamycins it is recommended that when it and Mycobutin are both to be administered they be given with an interval of 8 – 12 hours.

Table 1 summarises 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, patients’s drug profile, and the likely impact of the risk/benefit ratio.

Although rifabutin and rifampicin 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 rifampicin. Data suggest that rifabutin is a 2 to 3-fold weaker inducer than rifampicin. 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 rifampicin.

Malabsorption. Gastric pH alterations 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
ANTIVIRALS			
Amprenavir	2.9-fold ↑ AUC, 2.2-fold ↑ Cmax	No significant change in kinetics.	A 50% reduction in the rifabutin dose is recommended when combined with amprenavir. Increased monitoring for adverse reactions is warranted.

Delavirdine	ND	Oral clearance 5-fold resulting in significantly lower mean trough plasma concentrations (18 ± 15 to $1.0 \pm 0.7 \mu\text{M}$)	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.	
Fosamprenavir/ritonavir	64% \uparrow AUC **	35% \uparrow AUC and 36% \uparrow Cmax, no effect Ctrough (amprenavir)	Dosage reduction of rifabutin by at least 75% (to 150 mg every other day or three times per week) is recommended when combined with fosamprenavir
Indinavir	173% in AUC, 134% \uparrow Cmax	34% \downarrow in AUC, 25% \downarrow in Cmax	Dose reduction of rifabutin to half the standard dose and an increase of indinavir dose are recommended when rifabutin and indinavir are coadministered.
Lopinavir/ritonavir	5.7-fold \uparrow AUC, 3.4 fold \uparrow Cmax**	No significant change in lopinavir kinetics.	Dosage reduction of rifabutin by at least 75% of the usual dose of 300 mg/day is recommended (i.e., a maximum dose of 150 mg every other day or three times per week). Increased monitoring for adverse reactions is warranted. Further dosage reduction of rifabutin may be necessary.
Saquinavir	ND	40% \downarrow 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 Section 4.4, Special Warnings & Special Precautions for Use)
Tipranavir/ritonavir	2.9-fold \uparrow AUC, 1.7-fold \uparrow Cmax	No significant change in tipranavir kinetics.	Therapeutic drug monitoring of rifabutin is recommended.
Zidovudine	No significant change in kinetics.	Approximately 32% \downarrow in Cmax and AUC	A large controlled clinical study has shown that these changes are of no clinical relevance.
ANTIFUNGALS			
Fluconazole	82% in AUC	No significant change in steady-state plasma concentrations	
Itraconazole	ND	70% to 75% \downarrow in Cmax and AUC	One case report suggests a kinetic interaction resulting in

			an increase in serum rifabutin levels and a risk for developing uveitis in the presence of itraconazole.
Posaconazole	31%↑ Cmax, 72%↑ AUC	43%↓ Cmax, 49%↓ AUC	If the drugs are co-administered, patients should be monitored for adverse events associated with rifabutin administration.
Voriconazole	195%↑ Cmax, 331%↑ AUC ***	Rifabutin (300 mg once daily) decreased the Cmax and AUC of voriconazole at 200 mg twice daily by 69% and 78%, respectively. During 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	In another study, only trimethoprim (not sulfamethoxazole) had 14% ↓ in AUC and 6%↓ in Cmax but were not considered clinically significant.
ANTI-MAC (Mycobacterium avium intracellulare complex)			
Azithromycin	No PK interaction	No PK interaction	.
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 Section 4.2, Posology and Method of Administration and also, Section 4.4, Special Warnings & Special Precautions for Use)
ANTI-TB (Tuberculosis)			
Ethambutol	ND	No significant change in AUC or Cmax	
Isoniazid	ND	Pharmacokinetics not affected	
Pyrazinamide	ND	ND	Study data being evaluated.

OTHER			
Methadone	ND	No significant effect	No apparent effect of rifabutin on either peak levels of methadone or systemic exposure based upon AUC. Rifabutin kinetics not evaluated.
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
** - Drug plus active metabolite
*** - voriconazole dosed at 400 mg twice daily

4.6 Fertility, pregnancy and 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 200mg/kg (40 times the recommended human daily dose). No teratogenicity was observed in either species. In rats, given 200mg/kg/day, there was decrease in fetal viability. In rats, at 40mg/kg/day (8 times the recommended human daily dose), rifabutin caused an increase in fetal skeletal variants. In rabbits, at 80mg/kg/day (16 times the recommended human daily dose), rifabutin caused maternotoxocity and increased fetal skeletal anomalies.

Due to lack of data in pregnant women, as a precautionary measure, Mycobutin should not be administered to pregnant women or those breast-feeding children even though in experimental animal studies the drug was not teratogenic. Mycobutin may interact with oral contraceptives (*See section 4.5, Interaction with other medicinal products and other forms of interactions*).

4.7 Effects on ability to drive and use machines

There have been no report of adverse effects on ability to drive and use machines.

4.8 Undesirable effects

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

Bearing in mind that Mycobutin was often given in these studies as part of a multidrug regimen it is not possible to define with certainty a drug-event relationship. Treatment discontinuation was necessary only in a very few cases.

Adverse reactions identified through clinical trials or post-marketing surveillance by system organ class (SOC) are listed below in the following frequencies,

very common $\geq 1/10$; common $\geq 1/100$ to $< 1/10$; uncommon $\geq 1/1,000$ to $< 1/100$, rare $\geq 1/10,000$ to $< 1/1,000$, very rare $< 1/10,000$ and ‘not known’

MedDRA System Organ Class	Frequency	Undesirable Effects
<i>Blood and lymphatic system disorders</i>	Very common	Leukopenia
	Common	Anaemia
	Uncommon	Pancytopenia Agranulocytosis Lymphopenia Granulocytopenia Neutropenia White blood cell count decreased Neutrophil count decreased Thrombocytopenia Platelet count decreased
<i>Immune system disorders</i>	Common	Rash
	Uncommon	Hypersensitivity Bronchospasm Eosinophilia
<i>Eye disorders</i>	Uncommon	Uveitis Corneal deposits
<i>Gastrointestinal disorders</i>	Common	Nausea
	Uncommon	Vomiting
<i>Hepatobiliary disorders</i>	Uncommon	Jaundice Hepatic enzyme increased
<i>Skin and subcutaneous tissue disorders</i>	Uncommon	Skin discolouration
<i>Musculoskeletal and connective tissue disorders</i>	Common	Myalgia
	Uncommon	Arthralgia
<i>General disorders and administration site conditions</i>	Common	Pyrexia

Clostridium difficile colitis is a mandated adverse reaction for the pharmacological class; this event was neither observed in the clinical trials nor in the spontaneous reporting for rifabutin.

Anaphylactic shock has occurred with other antibiotics of the same class.

In addition, mild to severe, reversible uveitis has been reported less frequently when Mycobutin is used at 300 mg as monotherapy in *M.avium-intracellulare* (MAC) prophylaxis versus Mycobutin in combination with clarithromycin (or other macrolides) for MAC treatment (see Section 4.4).
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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Gastric lavage and diuretic treatment should be carried out. Supportive care and symptomatic treatment should be

administered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibiotics, ATC code: J04AB04

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) mycobacterial including *M. avium-intracellulare* (MAC), *in vitro* as well as in experimental infections caused by these pathogens in mice with induced immunodeficiency.

5.2 Pharmacokinetic properties

In man rifabutin is rapidly absorbed and maximum plasma concentrations are reached around 2-4 hours after oral administration. The pharmacokinetics of rifabutin is linear after single administration of 300, 450, and 600 mg to healthy volunteers. With these doses, C_{max} is in the range of 0.4-0.7 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 intracellular/extracellular concentration ratios which ranged from 9 in neutrophils to 15 in monocytes, both obtained from human sources.

The high intracellular concentration 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. The t_{1/2} of rifabutin in man is approximately 35-40 hours.

5.3 Preclinical safety data

Preclinical safety studies of rifabutin indicate a good safety margin in rodents and in monkeys.

In repeated dose studies, target organs were identified at doses producing blood levels higher than those achieved with recommended doses for human therapy. The main target organs in mice, rats and monkey are liver, stomach, gonads and, to a lesser degree, erythrocytes.

Rifabutin did not show any teratogenic, mutagenic or carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Sodium laurilsulfate
Magnesium stearate
Silica gel
Gelatin
Red iron oxide
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Transparent PVC/Al blisters in cardboard cartons containing 30 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Centre
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0822/109/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 12 January 2011

10 DATE OF REVISION OF THE TEXT

February 2015