Mycobutin®

1. NAME OF THE MEDICINAL PRODUCT
Mycobutin.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 150.0 mg of rifabutin.

3. PHARMACEUTICAL FORM
Opaque, red-brown, hard gelatin capsules Size N°. 0 containing 150 mg rifabutin in transparent PVC/Al blisters.
The capsules are for oral administration.

4. CLINICAL PARTICULARS
4.1 Therapeutic Indications
Mycobutin is indicated for:
- The prophylaxis of *M. avium-intracellulare complex* (MAC) infections in patients with HIV disease with CD4 counts lower than 75 cells/mcl.
- The treatment of non-tuberculous mycobacterial disease (such as that caused by MAC and *M. xenopi*).
- Pulmonary tuberculosis.

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*:**
- Prophylaxis of *M. avium intracellulare complex (MAC)* infections in patients with HIV disease with CD4 counts lower than 75 cells/mcl:
  300 mg (2 capsules) as a single agent.
- Treatment of non-tuberculous mycobacterial disease:
  450-600 mg (3 to 4 capsules) in combination regimens for up to 6 months after negative cultures are obtained.
  When Mycobutin is given in association with clarithromycin (or other macrolides) and/or fluconazole (or related compounds) the Mycobutin dosage may need to be reduced to 300 mg (see Section 4.5).
- Treatment of pulmonary tuberculosis: 150 – 450 mg (1-3 capsules) in combination regimens for at least 6 months.

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.

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

Hypersensitivity or history of hypersensitivity to the active substance, other rifamycins (e.g. rifampicin) or to any of the excipients.
Due to insufficient clinical experience in pregnant and breast-feeding women and in children, Mycobutin should not be used in these patients.

4.4 Special Warnings and Precautions for Use

Before starting Mycobutin prophylaxis, patients should be assessed to ensure that they do not have active disease caused by pulmonary tuberculosis or other mycobacteria. Prophylaxis against MAC infection may need to be continued throughout the patient's lifetime.

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

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

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

Because of the possibility of occurrence of uveitis, patients should be carefully monitored when rifabutin is given in combination with clarithromycin (or other macrolides) and/or fluconazole (and related compounds). If such an event occurs, the patient should be referred to an ophthalmologist and, if considered necessary, Mycobutin treatment should be suspended.

Uveitis associated with Mycobutin must be distinguished from other ocular complications of HIV.

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 generalized exanthematous pustulosis (AGEP) with anti-tuberculosis drugs (see Section 4.8). 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).

Excipients:
Mycobutin contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other Medicaments and other forms of Interaction

Rifabutin has been shown to induce the enzymes of the cytochrome P450 3A subfamily and therefore, may affect the pharmacokinetic behaviour of drugs metabolised by the enzymes belonging to this subfamily. Upward adjustment of the dosage of such drugs may be required when administered with Mycobutin.

Similarly, Mycobutin might reduce the activity of analgesics, anticoagulants, corticosteroids, cyclosporine, digitalis (although not digoxin), oral hypoglycaemics, narcotics, phenytoin and quinidine.

Clinical studies have shown that Mycobutin does not affect the pharmacokinetics of didanosine (DDI), and isoniazid (however, for the latter refer also to undesirable effects). On the basis of the above metabolic considerations no significant interaction may be expected with ethambutol, theophylline, sulphonamides, pyrazinamide and zalcitabine (DDC).

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 are given with an interval of 8-12 hours.

The following table provides details of the possible effects of co-administration, on rifabutin and the co-administered drug, and risk-benefit statement.

Co-administered drugs	**Effect on rifabutin**	**Effect on co-administered drug**	**Comments**
ANTIVIRALS			
Amprenavir	2.9-fold ↑ AUC, 2.2-fold ↑ C_{max}	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.

Fosamprenavir/ritonavir	64% ↑ AUC **	35% ↑ AUC and 36% ↑ C_{max}, no effect C_{trough} (amprenavir)	Dosage reduction of rifabutin by at least 75% (to 150 mg every other day or 3 times per week) is recommended when combined with fosamprenavir
Indinavir	173% ↑ in AUC, 134% ↑ C_{max}	34%↓ in AUC, 25%↓ in C_{max}	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 co-administered.
Lopinavir/ritonavir	5.7-fold ↑ AUC, 3.4-fold ↑ C_{max}**	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 3 times per week). Increased monitoring for adverse reactions is warranted. Further dosage reduction of rifabutin may be necessary.
Saquinavir	No data.	40% decrease in AUC.	
Ritonavir	4-fold increase in AUC, 2.5-fold increase in C_{max}	No data	Due to this multifold increase in rifabutin concentrations and the subsequent risk of side effects, patients requiring both rifabutin and a protease inhibitor, other protease inhibitors should be considered.
Tipranavir/ritonavir	2.9-fold ↑ AUC, 1.7-fold ↑ C_{max}	No significant change in tipranavir kinetics	Therapeutic drug monitoring of rifabutin is recommended. Co-administration of tipranavir with rifabutin may increase concentrations of rifabutin and its metabolite. Reduce rifabutin dose 75% (e.g., 150 mg every other day) and increase monitoring.
Zidovudine	No significant	Approx. 32%	A large clinical study

	change in kinetics	decrease in C_{max} and AUC.	has shown that these changes are of no clinical relevance.
ANTIFUNGALS			
Fluconazole	82% increase in AUC.	No significant change in steady-state plasma concentrations	
Itraconazole	No data.	70%-75% decrease in C_{max} and AUC.	A case report indicates an increase in rifabutin serum levels in the presence of itraconazole.
Posaconazole	31%↑ C_{max}, 72%↑ AUC	43%↓ C_{max}, 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.
Voriconazole	195%↑ C_{max}, 331%↑ AUC ***	Rifabutin (300 mg once daily) decreased the C_{max} and AUC of voriconazole at 200 mg twice daily by 69% and 78%, respectively. During co-administration with rifabutin, the C_{max} and AUC of voriconazole at	If the benefit outweighs the risk, rifabutin may be co-administered 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

		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 C_{max} and AUC were 104% and 87% higher, respectively, compared with voriconazole alone at 200 mg twice daily.	than 40 kg). Careful monitoring of full blood counts and adverse events to rifabutin (e.g. uveitis) is recommended when rifabutin is co-administered with voriconazole
Ketoconazole/miconazole	No data.	No data.	Co-administered medications, such as ketoconazole, that competitively inhibit the Cyt P450IIIA activity may increase circulating drug levels of rifabutin.
ANTI-PCP (Pneumocystis carinii pneumonia)			
Dapsone	No data.	Approximately 27% - 40% decrease in AUC.	Study conducted in HIV infected patients (rapid and slow acetylators)
Sulfamethoxazole - Trimethoprim	No significant change in C_{max} and AUC.	Approx. 15%-20% decrease in AUC.	In another study, only trimethoprim (not sulfamethoxazole) had 14% decrease in AUC and 6% in C_{max} but were not considered clinically significant.
ANTI-MAC (Mycobacterium avium intracellulare complex)			
Azithromycin	No PK interaction	No PK interaction	
Clarithromycin	Approx. 77% increase in AUC.	Approx. 50% decrease in AUC.	Study conducted in HIV infected patients
OTHER			

Methadone	No data.	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	No data.	No data.	Contraceptive cover may not be adequate during concomitant therapy with rifabutin, therefore, patients should be advised to use other methods of contraception.
Tacrolimus	No data.	No data.	Rifabutin decreases tacrolimus trough blood levels.

** - Drug plus active metabolite.
*** - voriconazole dosed at 400 mg twice daily.

4.6. Pregnancy and Lactation

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).

4.7. Effects on Ability to Drive and Use Machines

There have been no reports 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 always 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 ≥1/10; Common ≥1/100 to <1/10; Uncommon ≥1/1,000 to <1/100, Rare ≥1/10,000 to <1/1,000, Very rare <1/10,000 and 'Frequency not known'.

	Frequency	**Undesirable Effects**
Blood and lymphatic system disorders	**Very common**	Leukopenia

	Common	Anaemia
	Uncommon	Pancytopenia Agranulocytosis Lymphopenia Granulocytopenia Neutropenia White blood cell count decreased Neutrophil count decreased Thrombocytopenia Platelet count decreased
Immune system disorders	**Common**	Rash
	Uncommon	Hypersensitivity Bronchospasm Eosinophilia
Eye disorders	**Uncommon**	Uveitis Corneal deposits
Gastrointestinal disorders	**Common**	Nausea
	Uncommon	Vomiting
Hepatobiliary disorders	**Uncommon**	Jaundice Hepatic enzyme increased
Skin and subcutaneous tissue disorders	**Uncommon**	Skin discolouration
Musculoskeletal and connective tissue disorders	**Common**	Myalgia
	Uncommon	Arthralgia
General disorders and administration site conditions	**Common**	Pyrexia

Shock and *Clostridium difficile* colitis are mandated adverse reactions for the pharmacological class; both events were neither observed in the clinical trials nor in the spontaneous reporting for rifabutin.
Mild to severe, reversible uveitis has been reported less frequently when Mycobutin is used at 300 mg as monotherapy in MAC prophylaxis, versus Mycobutin in combination with clarithromycin (or other macrolides) for MAC treatment (see Section 4.4).
Flu-like syndrome, chest pressure or pain with dyspnoea and rarely hepatitis and haemolysis has been reported.

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).

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.

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
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 mice with induced immuno-deficiency.

5.2. Pharmacokinetic Properties
Absorption
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.

Distribution
Rifabutin 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 were about 5-10 times higher than the plasma levels.
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.

Elimination
Rifabutin and its metabolites are eliminated mainly by the urinary route. The $t_{½}$ 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 are liver and, to a lesser degree, erythrocytes.
Rifabutin did not show any teratogenic, mutagenic or carcinogenic potential.

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