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Rev. 1

Mycobutin®

Rifabutin

Capsules

CDS

AfME markets using the same as LPD: Nigeria

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MYCOBUTIN Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 150 mg rifabutin.

3. PHARMACEUTICAL FORM

Capsules for oral administration. Capsules are opaque, red-brown, hard gelatin Size No. 0.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Prophylaxis of *M.avium-intracellulare* complex (MAC) infections in immunodepressed patients with CD4 counts lower than or equal to 200/mcl
- Treatment of symptomatic disseminated *Mycobacterium avium* infection in AIDS patients
- Treatment of pulmonary tuberculosis
  - chronic resistant
  - newly diagnosed

4.2. Posology and method of administration

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

Adults

Mycobutin as a single agent:

- Prophylaxis of MAC infection in immunodepressed patients: 300 mg (2 capsules).

Mycobutin in combination regimens:

- Non-tuberculous mycobacterial disease: 450-600 mg (3 to 4 capsules) for up to 6 months after negative cultures are obtained.
- MAC treatment: when Mycobutin is given in association with clarithromycin, the dosage of Mycobutin should be reduced to 300 mg 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**)

- Pulmonary tuberculosis: 150 mg daily (1 capsule), for 6-9 months, or for at least 6 months after negative cultures are obtained. This dosage should be increased to 300-450 mg/day in patients previously treated with antituberculous drugs.

Children

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

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).

4.4. Special warnings and precautions for use

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 Section **4.2 Posology & method of administration**, and Section **4.5 Interaction with other medicinal products and other forms of interaction**). 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 Section **4.5 Interaction 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 (CDAD) 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.

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 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).

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; 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[28]. 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
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±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.	
Fosamprenavir/ritonavir	64% ↑ AUC **	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
Indinavir	173% ↑ in AUC, 134% ↑ Cmax	34%↓ in AUC, 25%↓ in Cmax	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.
Saquinavir	ND	40% ↓ in AUC	

Table 1. Rifabutin Interaction Studies*

Coadministered Drugs	Effect on Rifabutin	Effect on Coadministered Drug	Comments
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 ↑ AUC, 1.7-fold ↑ Cmax	No significant change in tipranavir kinetics.	Therapeutic drug monitoring of rifabutin is recommended.
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.
ANTIFUNGALS			
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.
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[57]	ND	Approximately 27% to 40% ↓ in AUC	Study conducted in HIV infected patients (rapid and slow acetylators).

Table 1. Rifabutin Interaction Studies*

Coadministered Drugs	Effect on Rifabutin	Effect on Coadministered Drug	Comments
Sulfamethoxazole-Trimethoprim[58,59]	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 and 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 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 fetal viability. In rats, at 40 mg/kg/day (8 times the recommended human daily dose), rifabutin caused an increase in fetal skeletal variants. In rabbits, at 80 mg/kg/day (16 times the recommended human daily dose), rifabutin caused maternotoxicity and increased fetal skeletal anomalies. Because animal

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

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

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 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.

Blood and lymphatic system disorders: Pancytopenia, white blood cell disorders (including agranulocytosis, leukopenia, lymphopenia, granulocytopenia, neutropenia, white blood cell count decreased, neutrophil count decreased), thrombocytopenia, platelet count decreased, anaemia.

Immune system disorders: Hypersensitivity, bronchospasm, rash, eosinophilia.

Eye disorders: Uveitis, corneal deposits.

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

Hepato-biliary disorders: Jaundice, hepatic enzyme increased.

Skin and subcutaneous tissue disorders: Skin discolouration.

Musculoskeletal and connective tissue disorders: Arthralgia, myalgia.

General disorders and administration site conditions: Pyrexia.

A limited occurrence of skin discoloration has been reported. 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 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 pediatric 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[138].

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

<u>Anti-tuberculosis drug SCARs</u>

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**).

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

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.

5.2. 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, Cmax 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 $t_{1/2}ß$ of rifabutin in man is approximately 35-40 hours.

5.3. Preclinical safety data

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 fetal development noticed at high dose levels are related to lesions in reproductive organs and to the toxic effect of the compound on dams.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Microcrystalline cellulose

Sodium lauryl sulphate

Magnesium stearate

Silica gel

6.2. Incompatibilities

None known

6.3. Shelf life

Please refer to outer carton for expiry date.

Keep out of the sight and reach of children.

Do not use MYCOBUTIN after the expiry date which is stated on the Carton/Blister after EXP:. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6.4. Special precautions for storage

Store below 25ºC

6.5. Nature and contents of container

6.6. Transparent PVC/AI blisters in cardboard containing 30 capsules.Special precautions for disposal and other handling

There are no special instructions for handling

7. FURTHER INFORMATION

MANUFACTURED BY

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8. PRESCRIPTION STATUS

Prescription only medicine

9. DATE OF REVISION OF THE TEXT

June 2021

Document Approval Record

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