SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

MYCOBUTIN® 150 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 150 mg rifabutin.

MYCOBUTIN capsules are sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule

Red-brown, self-locking, hard gelatin capsule, size 0, containing a violet powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of pulmonary tuberculosis caused by *M. tuberculosis*, proven to be sensitive by laboratory tests to rifabutin and resistant to rifampicin, in combination with other medicines not belonging to the rifamycin group.
- MYCOBUTIN is also effective for infections caused by *M. avium intracellulare complex* (MAC) or *M. xenopi* for the treatment of both disseminated and localised disease and also in immunocompromised HIV-infected patients.
- MYCOBUTIN is also indicated for the prophylactic treatment of infections caused by *M. avium intracellulare complex* (MAC) in patients with advanced HIV infection.

4.2 Posology and method of administration

Posology

MYCOBUTIN can be administered as a single daily dose, independent of meals. In all cases MYCOBUTIN is to be administered in combination regimens.

Newly diagnosed pulmonary tuberculosis with resistance to only rifampicin

1 capsule (150 mg) daily for 6 months.

Chronic, multidrug-resistant pulmonary tuberculosis

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

Atypical mycobacterial infections (MAC and M. xenopi)

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

Prophylaxis of MAC in patients with advanced HIV infections

2 capsules (300 mg) daily.

The above doses are indicated in adults with a body mass of greater than 35 kg. No specific dosage alterations are proposed in the elderly.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to rifabutin, other rifamycins (e.g. rifampicin) or any of the excipients of MYCOBUTIN listed in section 6.1.
- HIV-infected patients taking clarithromycin.
- For concomitant medicines not recommended with MYCOBUTIN, see section 4.5.

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 (saliva,

sputum and tears).

Soft contact lenses

These may be permanently stained by MYCOBUTIN administration.

MYCOBUTIN should always be given in combination with other anti-mycobacterial medicines not belonging to the family of rifamycins.

It is recommended that liver enzymes, white blood cell and platelet counts be monitored during therapy with MYCOBUTIN.

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 sections 4.2 and 4.5). 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 sections 4.8 and 4.5).

Protease inhibitors act as substrates or inhibitors of cytochrome (CYP)450 3A4 mediated metabolism. Therefore, due to significant interactions between protease inhibitors and MYCOBUTIN, their concomitant use should be based on the overall assessment of the patient and patient-specific medicine profile (see section 4.5).

MYCOBUTIN is a CYP450 3A inducer. Therefore, co-administration with antiretroviral products including but not limited to bictegravir, rilpivirine, or doravirine is not recommended due to the expected decrease in plasma concentrations of the antiretrovirals which may lead to loss of virologic response and possible development of resistance (see Section 4.5).

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 MYCOBUTIN, and may range in severity from mild diarrhoea to fatal colitis. Treatment with MYCOBUTIN 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 MYCOBUTIN use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial medicines such as MYCOBUTIN.

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 medicines (see section 4.8). If patients develop a skin rash they should be monitored closely and suspect medicine(s) discontinued if lesions progress. Identifying the specific medicine is difficult, as multiple anti-tuberculosis medicines 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 medicines is essential because of the syndrome's mortality and visceral involvement (e.g., liver, bone marrow or kidney).

Co-administration of ritonavir is not recommended because it substantially increases the plasma concentration of MYCOBUTIN (see section 4.5). High plasma concentrations of MYCOBUTIN may

increase the risk of side effects.

If a patient on MYCOBUTIN develops active tuberculosis, other anti-tuberculosis medicine should be added.

Special populations

Severe hepatic impairment

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)

A dosage reduction of 50 % is required. Mild to moderate renal impairment does not require any dosage adjustment.

Paediatric population

Safety and efficacy in children and adolescents have not been established.

Excipients

MYCOBUTIN contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially ‘sodium-free’.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Multiple dosing of MYCOBUTIN has been associated with induction of hepatic metabolic enzymes of the CYP450 3A subfamily. MYCOBUTIN’s predominant metabolite (25-O-desacetyl rifabutin; LM 565), may also contribute to this effect. Metabolic induction due to MYCOBUTIN is likely to produce a decrease in circulating levels of concomitantly administered medicines (especially those metabolised by the CYP450 3A pathway).

Kinetic data suggest that enzymatic induction by MYCOBUTIN is complete within 5 days and is dose-independent over the 300 to 600 mg dose-range. Similarly, concomitant medicines that competitively inhibit the CYP450 3A activity may increase circulating levels of MYCOBUTIN.

Table 1 summarises the results and magnitude of the pertinent medicine interactions assessed with MYCOBUTIN. 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 medicine profile, and the likely impact on the risk/benefit ratio.

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

Table 1: MYCOBUTIN interaction studies:

Co-administered medicines	**Effect on MYCOBUTIN**	**Effect on co-administered medicine**	**Comments**
ANTIVIRALS			
Amprenavir	2,9-fold increase in AUC, 2,2-fold increase in C_{max}	No significant change in kinetics	A 50 % reduction in the MYCOBUTIN dose is recommended when combined with amprenavir. Increased monitoring for adverse reactions is warranted.
Bictegravir	No data	38 % decrease in AUC 56 % decrease in C_{min} 20 % decrease in C_{max}	Although not studied, co-administration of MYCOBUTIN with a medicine containing bictegravir/emtricitabine /tenofovir alafenamide is not recommended due to an expected decrease in tenofovir

			alafenamide in addition to the reported reduction in bictegravir.
Delavirdine	No data	Oral clearance increased 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. MYCOBUTIN is not recommended for patients dosed with delavirdine mesylate 400 mg every 8 hours.
Didanosine	No significant change in kinetics	No significant change in kinetics at steady-state	
Doravirine	No data	50% decrease in AUC 68% decrease in C24 No significant changes in Cmax	If concomitant use is necessary, increase the doravirine dosage as instructed in doravirine-containing product prescribing information.
Fosam-prenavir/ ritonavir	64 % increase in AUC*	35 % increase in AUC and 36 % increase in C_{max}, no effect C_{trough} (amprenavir)	Dosage reduction of MYCOBUTIN by at least 75 % (to 150 mg every other day or three times per week) is recommended when combined with fosamprenavir.

Indinavir	173 % increase in AUC, 134 % increase in C_{max}	34 % decrease in AUC, 25 % decrease in C_{max}	Dose reduction of MYCOBUTIN to half the standard dose and increase of indinavir from 800 mg to 1 000 mg every 8 hours are recommended when MYCOBUTIN and indinavir are co-administered.
Lopinavir/ ritonavir	5,7-fold increase in AUC, 3,4 fold increase in C_{max}*	No significant change in lopinavir kinetics	Dosage reduction of MYCOBUTIN by 50 % of the dose of 300 mg/day is recommended (i.e. a maximum dose of 150 mg once daily). Increased monitoring for adverse reactions e.g. nausea, leukopenia, uveitis, is warranted. Further dosage reduction of MYCOBUTIN may be necessary.
Saquinavir	No data	40 % decrease in AUC	
Rilpivirine	No data	42 % decrease in AUC	Although not studied, co-administration of

		48 % decrease in C_{min} 31 % decrease in C_{max}	MYCOBUTIN with a medicine containing rilpivirine/tenofovir alafenamide/ emtricitabine is not recommended due to an expected decrease in tenofovir alafenamide in addition to the reported reduction in rilpivirine.
Ritonavir	4-fold increase in AUC, 2,5-fold increase in C_{max}	No data	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, medicines other than ritonavir should be considered (see section 4.4).
Tipranavir/ ritonavir	2,9-fold increase in AUC, 1,7-fold increase in C_{max}	No significant change in tipranavir kinetics	Therapeutic medicine monitoring of MYCOBUTIN is recommended.
Zidovudine	No significant change in kinetics	Approximately 32 % decrease in C_{max} and AUC	A clinical study 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	One case report suggests a kinetic interaction resulting in an increase in serum MYCOBUTIN levels and a risk for developing uveitis in the presence of itraconazole.
Keto-conazole	No data	No data	Co-administration is not recommended. If concomitant use is clinically warranted, carefully monitor patients for increased MYCOBUTIN levels or adverse reactions and for reduced ketoconazole efficacy
Posa-conazole	31 % increase in C_{max}, 72 % increase in AUC	43 % decrease in C_{max}, 49 % decrease in AUC	If the medicines are co-administered, patients should be monitored for adverse events associated with

			MYCOBUTIN administration.
Voriconazole	195 % increase in C_{max}, 331 % increase in AUC **	MYCOBUTIN (300 mg once daily) decreased the C_{max} and AUC of voriconazole administered orally at 200 mg twice daily by 69 % and 78 %, respectively. During co-administration with MYCOBUTIN, the C_{max} 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, C_{max} and AUC were 104 % and 87 % higher,	If the benefit outweighs the risk, MYCOBUTIN 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 than 40 kg). Careful monitoring of full blood counts and adverse events to MYCOBUTIN (e.g. uveitis) is recommended when MYCOBUTIN is co-administered with voriconazole.

		respectively, compared with voriconazole alone at 200 mg twice daily.	
ANTI-PCP (Pneumocystis jiroveci pneumonia)			
Dapsone	No data	Approximately 27 – 40 % decrease in AUC	Study conducted in HIV-infected patients (rapid and slow acetylators).
Sulfa-methoxazole - trimethoprim	No significant change in C_{max} and AUC	Approximately 15 – 20 % decrease in AUC	In another study, only trimethoprim (not sulfamethoxazole) had 14 % decrease in AUC and 6 % decrease in C_{max} but were not considered clinically significant.
ANTI-MAC (Mycobacterium avium intracellulare complex)			
Azithromycin	No phar-macokinetic interaction	No pharmacokinetic interaction	The combination of MYCOBUTIN and azithromycin resulted in a high frequency of adverse effects.
ANTI-TB (tuberculosis)			
Ethambutol	No data	No significant change in AUC or C_{max}	
Isoniazid	No data	Pharmacokinetics not affected	

Pyra-zinamide	No data	No data	
OTHER			
Methadone	No data	No significant effect	No apparent effect of MYCOBUTIN on either peak levels of methadone or systemic exposure based upon AUC. MYCOBUTIN kinetics not evaluated.
Oral contra-ceptives	No data	No data	Contraceptive cover may not be adequate during concomitant therapy with MYCOBUTIN; therefore, patients should be advised to use other methods of contraception.
Tacrolimus	No data	No data	MYCOBUTIN decreases tacrolimus trough blood levels.
Theophylline	No data	No significant change in AUC or C_{max} compared with baseline	

AUC – Area under the concentration vs. time curve

C_{max} – Maximum serum concentration

* Medicine plus active metabolite

** Voriconazole dosed at 400 mg twice daily

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

4.7 Effects on ability to drive and use machines

MYCOBUTIN is not expected to have any adverse effects on the ability to drive and use machines.

4.8 Undesirable effects

The tolerability of MYCOBUTIN in multiple medicine 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 the studies in tuberculosis as part of a multi-medicine regimen, and it was not always possible to define with certainty a medicine-event relationship.

Tabulated summary of adverse reactions

Side effects identified through clinical trials or post-marketing surveillance by system organ class are listed below.

The table below contains side effects categorised as follows utilising the incidence rates: 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).

MedDRA system organ class	**Frequency**	**Undesirable effects**
Blood and	Very common	Leukopenia

lymphatic system disorders	Common	Anaemia
	Uncommon	Pancytopenia, thrombocytopenia, eosinophilia
Immune system disorders	Uncommon	Hypersensitivity
Eye disorders	Uncommon	Corneal deposits
Gastrointestinal disorders	Common	Nausea, vomiting
Hepato-biliary disorders	Common	Increased hepatic enzymes
	Uncommon	Jaundice
Skin and subcutaneous tissue disorders	Common	Rash
	Uncommon	Skin pigmentation/ discolouration
Musculoskeletal and connective tissue disorders	Common	Myalgia
	Uncommon	Arthralgia
General disorders and administration site conditions	Common	Pyrexia

The frequency and severity of haematologic reactions could be increased by combined administration of isoniazid.

Anti-tuberculosis medicine SCARs

Anti-tuberculosis medicine use may lead to the occurrence of medicine reaction with eosinophilia and systemic symptoms (DRESS) as well as other SCARs such as SJS, TEN, and AGEP (see section 4.4).

Post-marketing experience

Skin discolouration has been reported. Mild to severe, reversible uveitis has been reported when MYCOBUTIN was used at 300 mg as monotherapy in MAC prophylaxis. MYCOBUTIN in combination with clarithromycin

for MAC treatment was more frequently associated with uveitis (see section 4.4). Corneal deposits have been reported during routine ophthalmologic surveillance of HIV-positive paediatric patients receiving MYCOBUTIN as part of a multiple medicine regimen for MAC prophylaxis. The deposits are tiny, almost transparent, asymptomatic peripheral and central corneal deposits, and do not impair vision.

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

The table below contains side effects from post-marketing data.

MedDRA system organ class	**Side effects**
Blood and lymphatic system disorders	Agranulocytosis, lymphopenia, granulocytopenia, neutropenia, decreased white blood cell count, decreased neutrophil count, decreased platelet count
Immune system disorders	Bronchospasm
Eye disorders	Uveitis
Gastrointestinal disorders	*Clostridium difficile* colitis, tongue discolouration, tooth discolouration
Hepato-biliary disorders	Abnormal hepatic function
Skin and subcutaneous tissue disorders	Erythema/ dermatitis
Investigations	Increased alkaline phosphatase/ALT/AST

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms as under section 4.8. Supportive care and symptomatic treatment are indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.1.1 Broad and medium spectrum antibiotics

Rifabutin is a semi-synthetic ansamycin antibiotic. It inhibits incorporation of thymidine into DNA of *M. tuberculosis*.

In vitro activity of rifabutin against laboratory strains and clinical isolates of *M. tuberculosis* has been shown to be very high.

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.

5.2 Pharmacokinetic properties

In man, rifabutin peak plasma levels are reached around 2 to 4 hours after oral administration. The pharmacokinetics of rifabutin is linear after single dose administration of 300, 450 and 600 mg to healthy volunteers. With these doses, C_{max} 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. In animals, rifabutin is widely distributed in various organs with the exception of the brain.

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 medicine. The elimination half-life of rifabutin in man is approximately 35 – 40 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatine

Magnesium stearate

Microcrystalline cellulose

Red iron oxide

Silica gel

Sodium lauryl sulphate

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light and moisture.

6.5 Nature and contents of container

Transparent PVC/aluminium blisters in packs containing 30 and 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

Tel: +27(0)11 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBER

Z/20.1.1/395

9. DATE OF FIRST AUTHORISATION

28 January 1994

10. DATE OF REVISION OF THE TEXT

24 April 2024

Manufacturer:

Pfizer Italia S.r.l., Ascoli Piceno, Italy

BOTSWANA: S2 Reg. No.: BOT1302406A (30 Caps) Reg. No.: BOT1302406B (100 Caps)
NAMIBIA: S4 Reg. No.: 06/20.1.1/0255