SCHEDULING STATUS: **S4**

PROPRIETARY NAME (AND DOSAGE FORM):

MYCOBUTIN® (Capsules)

COMPOSITION:

Each capsule contains 150 mg rifabutin.

The other ingredients are microcrystalline cellulose, sodium lauryl sulphate, magnesium stearate, gelatin, silica gel, red iron oxide and titanium dioxide.

PHARMACOLOGICAL CLASSIFICATION:

A 20.1.1 Broad and medium spectrum antibiotics

PHARMACOLOGICAL ACTION:

Rifabutin is a wide spectrum, semi-synthetic ansamycin antibiotic particularly active on acid-fast bacilli, including atypical and rifampicin-resistant mycobacteria.

Rifabutin was seen to be active *in vitro* against laboratory strains and clinical isolates of *M. tuberculosis* (MIC: 0,03 - 0,06 μg/ml). Many strains of *M. tuberculosis* resistant to rifampicin were partially susceptible to rifabutin (MIC: 0,03 - 16 μg/ml), indicating that cross resistance between the two antibiotics is incomplete.

Activity has also been demonstrated against non-tuberculous mycobacteria that are usually resistant to other rifamycins, in particular *M. avium intracellulare complex* (MAC) and *M. xenopi* (MIC: 0,25 - 2 μg/ml).

M. marinum, *M. kansasii*, *M. plei*, *M. smegmatis*, *M. bovis*, *M. fortuitum* and *M. ulcerans* are sensitive *in vitro* to rifabutin. *In vitro* sensitivity does not necessarily imply *in vivo* efficacy.

In man, rifabutin is rapidly absorbed after oral administration with peak plasma levels being reached within 2 to 4 hours. Plasma concentrations are maintained above the MIC values for *M. tuberculosis* up to 30 hours after administration.

Rifabutin is extensively distributed both in animals and man, and high tissue concentrations are observed.

Rifabutin is mainly metabolised by the liver and 50 % is excreted through the urine, primarily as metabolites.

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*, where it has been shown to be effective for the treatment of both disseminated and localised disease and also in immuno-compromised HIV positive patients.

MYCOBUTIN is also effective for the prophylactic treatment of infections caused by *M. avium intracellulare complex* (MAC) in patients with advanced HIV infection.

CONTRA-INDICATIONS:

Hypersensitivity to rifabutin or other rifamycins.

WARNINGS:

Severe renal impairment (creatinine clearance below 30 ml/min):

A dosage reduction of 50 % is recommended.

Severe hepatic impairment:

MYCOBUTIN should be used with caution in cases of severe liver insufficiency.

Soft contact lenses:

These may be permanently stained by MYCOBUTIN administration.

When MYCOBUTIN is given in association with clarithromycin, the dosage of MYCOBUTIN should be reduced to 300 mg. 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, MYCOBUTIN treatment should be discontinued and the patient referred to an ophthalmologist for treatment.

Co-administration of ritonavir is not recommended because it substantially increases the plasma concentration of MYCOBUTIN (see INTERACTIONS). High plasma concentrations of MYCOBUTIN may increase the risk of side effects.

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

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

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 agents such as MYCOBUTIN.

NTERACTIONS:

MYCOBUTIN induces enzymes of the CYP450 IIIA subfamily and therefore may reduce the plasma concentrations of medicines metabolised by those enzymes. This effect may reduce the efficacy of standard doses of such medicines, which include itraconazole, clarithromycin and saquinavir. Upward adjustment of the dosage of such medicines may be required.

Similarly, some medicines that competitively inhibit the CYP450 IIIA activity may significantly increase the plasma concentration of MYCOBUTIN. Because high plasma levels of MYCOBUTIN may increase the risk of adverse reactions, patients receiving co-administration of such medicines, which include fluconazole and clarithromycin should be carefully monitored. In some cases, the dosage of MYCOBUTIN may need to be reduced when it is co-administered with such a medicine.

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

Co-administered medicines	**Effect on MYCOBUTIN**	**Effect on co-administered medicine**	**Comments**
ANTIVIRALS			
Didanosine	No significant change in kinetics	No significant change in kinetics at steady state	
Indinavir	204 % increase in AUC	32 % decrease in AUC	

Saquinavir	No data	40 % decrease in AUC	
Ritonavir	4-fold increase in AUC, 2,5-fold increase in Cmax	No data	Due to this multifold increase in rifabutin concentrations and the subsequent risk of side effects, patients requiring both MYCOBUTIN and a protease inhibitor, agents other than ritonavir should be considered (See WARNINGS).
Zidovudine	No significant change in kinetics	Approximately 32 % decrease in Cmax and AUC	A large 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 Cmax and AUC	A case report indicates an increase in MYCOBUTIN serum levels in the presence of itraconazole.
ANTI-PCP (Pneumocystis carinii (jiroveci) 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 Cmax and AUC	Approximately 15 - 20 % decrease in AUC	In another study, only trimethoprim (not sulfamethoxazole) had a 14 % decrease in AUC and 6 % in Cmax but were not considered clinically significant.
ANTI-MAC (Mycobacterium avium intracellulare complex)			
Azithromycin	No data	No data	Study under analysis. Preliminary data do not suggest an interaction.
Clarithromycin	Approximately 77 % increase in AUC	Approximately 50 % decrease in AUC	Study conducted in HIV infected patients. Dose of MYCOBUTIN should be adjusted in the presence of clarithromycin.
ANTI-TB (Tuberculosis)			
Ethambutol	No data	No significant change in AUC or Cmax	
Isoniazid	No data	Pharmacokinetics not affected	
Pyrazinamide	No data	No data	Study data being evaluated.
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 contraceptives	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 Cmax compared with baseline.	

AUC - Area under the Concentration vs. Time Curve

Cmax - Maximum serum concentration

Cross resistance between rifampicin and rifabutin is commonly observed with *M.tuberculosis* and *M.avium intracellulare complex* isolates. Isolates of *M.tuberculosis* resistant to rifampicin are likely to be resistant to rifabutin.

Protease inhibitors act as substrates or inhibitors of CYP450 IIIA4 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.

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE:

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 rifampicin-resistant pulmonary tuberculosis:

1 capsule (150 mg) daily for 6 months.

Chronic, rifampicin-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.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

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

The table below contains side effects categorized as follows utilising the incidence rates: Very Common ≥ 1/10 (≥ 10 %); Common ≥ 1/100 and < 1/10 (≥ 1 % and < 10 %); Uncommon ≥ 1/1000 and < 1/100 (≥ 0,1 % and < 1 %); Rare ≥ 1/10 000 and < 1/1000 (≥ 0,01 % and < 0,1 %); Very Rare < 1/10 000 (< 0,01 %).

MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
Blood and lymphatic system disorders	***Very common***	Leucopenia
	Common	Anaemia
	Uncommon	Thrombocytopenia
Immune system disorders	***Common***	Rash
	Uncommon	Hypersensitivity Bronchospasm Eosinophilia Shock
Eye disorders	***Uncommon***	Uveitis Corneal deposits
Gastrointestinal disorders	***Common***	Nausea
	Uncommon	Vomiting
Hepatobiliary disorders	***Uncommon***	Jaundice Increased hepatic enzyme
Skin and subcutaneous tissue disorders	***Uncommon***	Skin pigmentation/discolouration
Musculoskeletal and connective tissue disorders	***Common***	Myalgia
	Uncommon	Arthralgia
General disorders and administration site conditions	***Common***	Pyrexia

MYCOBUTIN may impart a red-orange colour to the urine and possibly to skin and body secretions (saliva, sputum and tears).

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

isoniazid.

Mild to severe, reversible uveitis has been reported. The risk is 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 or fluconazole.

Laboratory abnormalities seen:

Chemistry: Increased alkaline phosphatase/ALT/AST.

Haematology: Anaemia, leucopenia, neutropenia and thrombocytopenia.

Post marketing:

The table below contains side effects from post marketing data.

MedDRA **System Organ Class**	**Side effects**
Blood and lymphatic system disorders	Eosinophilia
Respiratory, thoracic and mediastinal disorders	Bronchospasm
Gastrointestinal disorders	Tongue discoloration, tooth discolouration
Hepato-biliary disorders	Hepatic function abnormal
Skin and subcutaneous tissue disorders	Rash/erythema/dermatitis
Investigations	Liver function tests abnormal, transaminases increased

Special Precautions:

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

Driving and using machinery

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms as under SIDE EFFECTS. Gastric lavage should be carried out and diuretic treatment initiated. Supportive care and symptomatic treatment are indicated.

IDENTIFICATION:

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

PRESENTATION:

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

STORAGE INSTRUCTIONS:

Store below 25 °C and protect from light and moisture.

Keep out of reach of children.

REGISTRATION NUMBER:

Z/20.1.1/395

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

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2196

South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

26 October 2012

BOTSWANA: S2

Reg. No.: BOT1302406A (30 Caps)

Reg. No.: BOT1302406B (100 Caps)

NAMIBIA: S4

Reg. No.: 06/20.1.1/0255