SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Mycobutin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 150.0 mg rifabutin.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Hard capsule.

Opaque, red-brown, Size N°. 0 hard gelatin capsules.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Mycobutin is indicated for:

- the treatment of chronic tuberculosis where there is evidence of acid fast bacteria resistant to rifampicin or to two other alternative drugs.
- the treatment of infections caused by MAC or other atypical mycobacteria where there is evidence of resistant bacteria as above.
- treatment of infections caused by MAC or other atypical mycobacteria in AIDS patients in all cases not subject to the above restrictions.
- prevention of MAC infections in AIDS patients whose CD4 counts lower or eqval to 200/mm^3

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 Special Precautions For Use, and Section 4.5, Interactions with Other Medications & Other Forms of Interactions)

- 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.

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 listed in section 6.1.

Concomitant use with rilpivirine containing prolonged-release suspension for injection is contraindicated (see section 4.5).

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.

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 Interactions with other Medications & Other Forms of Interactions).
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.

HIV protease inhibitors act as substrates or inhibitors of CYP450 3A4 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).

Rifabutin is a CYP450 3A inducer. Therefore, co-administration with antiretroviral medicines including but not limited to bictegravir, elvitegravir, oral rilpivirine, or doravirine and anti-HCV medicines including but not limited to sofosbuvir (alone or in combination) is not recommended due to the expected decrease in plasma concentrations of the antiretrovirals and anti-HCV medicines 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 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 medicinal products and other forms of interaction

Rifabutin has been shown to induce the enzymes of the cytochrome P450 3A (CYP450 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, cyclosporin, 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, sulfonamides, 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 be 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.

Table 1: Rifabutin Interaction Studies

Coadministered Drugs	Effect on Rifabutin	Effect on Coadministered Drug	Comments
ANTIRETROVIRALS			
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.
Bictegravir	ND	AUC ↓38% Cmin ↓56% Cmax ↓20%	Although not studied, co-administration of rifabutin with Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) is not recommended due to an expected decrease in tenofovir alafenamide in addition to the reported reduction in bictegravir.
Dolutegravir	ND	No significant change in dolutegravir kinetics at steady state.	
Doravirine	ND	50% ↓ in AUC 68% ↓ in C24 ↔ in Cmax	If concomitant use is necessary, increase the doravirine dosage as instructed in doravirine-containing product prescribing information.
Elvitegravir/ Cobicistat	No significant change in rifabutin kinetics. 6.3-fold ↑ in AUC, 4.8-fold ↑ Cmax of 25-O-desacetyl-rifabutin	No change in elvitegravir except 67% ↓ Ctrough of elvitegravir. No change in cobicistat exposure.	Co-administration of rifabutin with elvitegravir/cobicistat is not recommended due to an expected decrease in elvitegravir exposure (see section 4.4).

Etravirine	No significant change in rifabutin kinetics.	37% ↓ in AUC, 37% ↓ in Cmax and 35% ↓ in Cmin.	No dose adjustment of rifabutin is required when etravirine is not co-administered with ritonavir.
Fosamprenavir/ritonavir	64% ↑ AUC.**	35% ↑ AUC and 36% ↑ C_{max}, 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% ↑ $C_{max.}$	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 coadministered.
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 three 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.	
Rilpivirine	ND	42% ↓ in AUC 48% ↓ in Cmin 31% ↓ in Cmax	Although not studied, co-administration of rifabutin rilpivirine/tenofovir alafenamide/emtricitabine is not recommended due to an expected decrease in tenofovir alafenamide in addition to the reported reduction in rilpivirine (see section 4.4). Co-administration of rifabutin with cabotegravir/rilpivirine prolonged-release injectable suspension is contraindicated (see section 4.3).
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. Coadministration 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 change in kinetics.	Approx. 32% decrease in C_{max} and AUC.	A large clinical study has shown that these changes are of no clinical relevance.
Delavirdine	No data.	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.	
ANTI-HCV DRUGS			
Sofosbuvir	ND.	36% ↓ in Cmax and 24% ↓ AUC	Co-administration of rifabutin with sofosbuvir (alone or in combination) is not recommended (see section 4.4).
ANTIFUNGALS			
Fluconazole	82% increase in AUC.	No significant change in steady-state plasma concentrations.	Patients receiving rifabutin and fluconazole concomitantly should be carefully monitored (see section 4.4).
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 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.	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.
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.

Coadministered Drugs	Effect on Rifabutin	Effect on Coadministered Drug	Comments
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 patientsDose 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	No data.	No significant change in AUC or Cmax	
Isoniazid	No data.	Pharmacokinetics not affected	
Bedaquiline	ND	No change in bedaquiline kinetics. 1.4-fold ↑ in M2 and approximately 3.0-fold ↑ in M3 metabolites of bedaquiline.	If the drugs are co-administered, patients should be monitored for adverse events associated with bedaquiline administration.
Pyrazinamide	No significant change in AUC or Cmax	No significant change in AUC or Cmax	No dose adjustment needed.
ORAL CONTRACEPTIVES			
Ethinylestradiol/ Norethindrone	ND	Ethinylestradiol: 20% ↓ in Cmax, 35% ↓ in AUC. Norethindrone: 32% ↓ in Cmax, 46% ↓ in AUC.	Patients should be advised to use other additional non-hormonal methods of contraception.
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.
Tacrolimus	No data.	No data.	Rifabutin decreases tacrolimus trough blood levels.
Theophylline	No data.	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
Ctrough - Concentration immediately prior to administration of the next dose
** - Drug plus active metabolite
*** - voriconazole dosed at 400 mg twice daily

4.6. Fertility, 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

Mycobutin has no or negligible influence on the 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 'not known'.

MedDRA System Organ Class	**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
	Common	Myalgia

Musculoskeletal and connective tissue disorders	***Uncommon***	Arthralgia
General disorders and administration site conditions	***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.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

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

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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Microcrystalline cellulose
Sodium lauryl sulphate
Magnesium stearate
Silica gel
Gelatin Ph.Eur.
Red iron Oxide
Titanium dioxide

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4. Special precautions for storage

Store below 25°C

6.5. Nature and contents of container

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

6.6. Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer PFE Pharmaceuticals Israel Ltd. 9 Shenkar St., Herzliya Pituach 46725

8. **LICENSE NUMBER**

068-76-28228

Revised in 12/2023 according to MOH guidelines.