Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mycobutin 150mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 150.0mg Rifabutin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule (Capsule).
Opaque, red-brown, hard gelatin capsules marked "MYCOBUTIN" on the cap and "Pharmacia&Upjohn" on the body.
Size No. 0

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Mycobutin is indicated:
As a second line treatment of patients with sensitive mycobacterium tuberculosis. Treatment should be supervised by a specialist physician.

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
The normal dose recommended for pulmonary tuberculosis is 150-450 mg (1-3 capsules) in combination regimens for at least 6 months.

When Mycobutin is given in association with clarithromycin (or other macrolides) or fluconazole (and related compounds) or certain antivirals, dosage should be reduced to 300 mg/day 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).

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

Mycobutin is contraindicated in patients with a history of hypersensitivity to rifabutin or 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).
Patients who suffer from porphyria.

4.4 Special warnings and precautions for use

Mycobutin may impart a red-orange colour to the urine, saliva and to other 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 30ml/min) requires a dosage reduction of 50%. Mild to moderate renal impairment does not require any dosage adjustment.

It is recommended that full blood (including white, red cell and platelets) counts and liver enzymes be monitored periodically during treatment.

When Mycobutin is used concomitantly with clarithromycin, a decreased dose of Mycobutin is recommended due to the increase in plasma concentrations of Mycobutin (see Section 4.2 Posology and Method of Administration and Section 4.5 Interaction with other medicinal products and other forms of interaction). Because of the possibility of occurrence of uveitis, patients should also be carefully monitored when Mycobutin is given in combination with agents which increase its plasma levels e.g. clarithromycin (or other macrolides) and/or fluconazole (and related compounds) and some anti-virals (see section 4.5, Interaction with other medicinal products and other forms of interactions). If such an event occurs, the patients should be referred to an ophthalmologist and, if considered necessary, Mycobutin treatment should be suspended.

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, Interaction with other medicinal products & other forms of interaction).

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-hepatitis C virus (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 Interaction with other medicinal products & other forms of interaction).

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, including rifabutin (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:

This medicinal product 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

Multiple dosing of rifabutin has been associated with induction of hepatic metabolic enzymes of the CYP450 3A subfamily. Rifabutin's predominant metabolite (25-desacetyl rifabutin; LM565), 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 metabolised by the CYP450 3A 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. Similarly, concomitant medications that competitively inhibit the CYP450 3A activity may increase circulating levels of rifabutin.
For this reason, during Mycobutin therapy oral contraception may not be adequate and patients should be advised to use other forms of contraception.
Similarly, Mycobutin might reduce the activity of analgesics, anticoagulants, corticosteroids, cyclosporin, digitalis (although not digoxin), dapsone, oral hypoglycaemics, narcotics, phenytoin and quinidine.
Although pharmacokinetic data have shown that Mycobutin when given in combination with zidovudine reduces plasma levels of the latter, a large controlled clinical study has shown that these changes are of no clinical relevance. Clinical studies have shown that Mycobutin does not affect the pharmacokinetics of didanosine (DDI) or isoniazid *(See section* 4.8, *Undesirable effects)*.

On the basis of the above metabolic considerations no significant reaction may be expected with ethambutol, theophylline, sulphonamides, pyrazinamide and zalcitabine (DDC).

An interaction, leading to an increase in rifabutin plasma levels, occurs when Mycobutin is administered together with clarithromycin and/or fluconazole. This may apply to drugs of the same classes *(See section* 4.8, *Undesirable effects and section* 4.4, *Special warnings and precautions for use)*.

However, Mycobutin does not affect the pharmacokinetics of fluconazole.
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.

Table 1 summarises 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, patients's drug profile, and the likely impact of the risk/benefit ratio.

Although rifabutin and rifampicin 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 rifampicin. Data suggest that rifabutin is a 2 to 3-fold weaker inducer than rifampicin. 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 rifampicin.
Malabsorption. Gastric pH alterations 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**
ANTIRETROVIRALS			
Amprenavir	2.9-fold ↑ in AUC, 2.2-fold ↑ in 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.
Atazanavir/Ritonavir	48% ↑ in AUC, 149% ↑ in Cmax of rifabutin. 990% ↑ in AUC, 677% ↑ in Cmax of 25-O-desacet	No significant change in kinetics.	Rifabutin dose reduction to 150 mg daily is recommended. Patients should be closely monitored for rifabutin adverse reactions.

	yl-rifabutin		
Bictegravir	ND	38% ↓ in AUC 56% ↓ in Cmin 20% ↓ in Cmax	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.
Darunavir/Ritonavir	No significant change in rifabutin kinetics.[#] 881% ↑ in AUC, 377% ↑ in Cmax of 25-O-desacetyl-rifabutin.	57% ↑ in AUC, 42% ↑ in Cmax of darunavir. 66% ↑ in AUC, 68% ↑ in Cmax of ritonavir.	Rifabutin dose reduction to 150 mg daily is recommended. Patients should be closely monitored for rifabutin adverse reactions.
Delavirdine	ND	Oral clearance 5-fold resulting in significantly lower mean trough plasma concentrations (18±15 to 1.0±0.7 mM)	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.	
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.[##] 525% ↑ in AUC, 384% ↑ in Cmax of 25-O-desacetyl-rifabutin.	No change in elvitegravir except 67% ↓ in Cmin of elvitegravir. No change in cobicistat exposure except 66% ↓ in Cmin of cobicistat.	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 a protease inhibitor (PI) booster (e.g. ritonavir). No interaction study has been performed with etravirine given with a PI booster.
Fosamprenavir/ritonavir	64% ↑ in AUC **	35% ↑ in AUC and 36% ↑ in 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,	34%¯ in AUC,	Dose reduction of rifabutin to half the standard dose and an

	134% ↑ in Cmax	25%¯ in Cmax	increase of indinavir dose are recommended when rifabutin and indinavir are coadministered.
Lopinavir/ritonavir	5.7-fold ↑ in AUC, 3.4 fold ↑ in 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	
Rilpivirine	ND	42% ¯ in AUC 48% ¯ in Cmin 31% ¯ in Cmax	Although not studied, co-administration of rifabutin with 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 rilpivirine prolonged-release injectable suspension is contraindicated (see section 4.3).
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 ↑ in AUC, 1.7-fold ↑ in 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.
ANTI-HEPATITIS C VIRUS (HCV) DRUGS			
Sofosbuvir	ND	36% ↓ in Cmax and 24% ↓ in AUC	Co-administration of rifabutin with sofosbuvir (alone or in combination) is not recommended (see section 4.4).
ANTIFUNGALS			
Fluconazole	82% in AUC	No significant change in steady-state plasma concentrations	Patients receiving rifabutin and fluconazole concomitantly should be carefully monitored (see sections 4.2 and 4.4).
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% ↑ in Cmax, 72% ↑ in AUC	43% ↓ in Cmax, 49% ↓ in AUC	If the drugs are co-administered, patients should be monitored for adverse events associated with rifabutin administration.
Voriconazole	195% ↑ in Cmax, 331% ↑ in 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%	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

		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.	
ANTI-PCP (Pneumocystis carinii pneumonia)			
Dapsone	ND	Approximately 27% to 40% ¯ in AUC	Study conducted in HIV infected patients (rapid and slow acetylators).
Sulfamethoxazole-Trimethoprim	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 & Special Precautions for Use)
ANTI-TB (Tuberculosis)			
Bedaquiline	ND	No change in bedaquiline kinetics. 40% ↑ in overall exposure ($AUC_{0-\infty}$) of M2 and approximately 200% ↑ in peak concentrations of M3 metabolites of bedaquiline.	If the drugs are co-administered, patients should be monitored for adverse events associated with bedaquiline administration.
Ethambutol	ND	No significant change in AUC or Cmax	
Isoniazid	ND	Pharmacokinetics not affected	
Pyrazinamide	No significant change in AUC or Cmax	No significant change in AUC or Cmax.	No dose adjustment needed.
ORAL CONTRACEPTIVES			

Ethinylestradiol/ Norethisterone	ND	Ethinylestradiol: 20% ↓ in Cmax, 35% ↓ in AUC. Norethisterone: 32% ↓ in Cmax, 46% ↓ in AUC.	Patients should be advised to use other additional non-hormonal methods of contraception.
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.
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
# rifabutin was dosed at 300 mg once daily when administered alone and 150 mg every other day when co-administered with darunavir/ritonavir
rifabutin was dosed at 300 mg once daily when administered alone and 150 mg every other day when co-administered with elvitegravir/cobicistat

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 200mg/kg (40 times the recommended human daily dose). No teratogenicity was observed in either species. In rats, given 200mg/kg/day, there was decrease in fetal viability. In rats, at 40mg/kg/day (8 times the recommended human daily dose), rifabutin caused an increase in fetal skeletal variants. In rabbits, at 80mg/kg/day (16 times the recommended human daily dose), rifabutin caused maternotoxocity and increased fetal skeletal anomalies.

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, Interaction with other medicinal products and other forms of interactions*).

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 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
	Not known	Acute generalised exanthematous pustulosis (AGEP), Dermatitis bullous, Drug reaction with eosinophilia and systemic symptoms (DRESS), Erythema multiforme, Exfoliative rash, Toxic skin eruption, Stevens-Johnson syndrome (SJS)
Musculoskeletal and connective tissue disorders	***Common***	Myalgia
	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.

In addition, mild to severe, reversible uveitis has been reported less frequently when Mycobutin is used at 300 mg as monotherapy in *M.avium-intracellulare* (MAC) prophylaxis versus Mycobutin in combination with clarithromycin (or other macrolides) for MAC treatment (see Section 4.4).
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 changes are tiny, almost transparent, asymptomatic peripheral and central corneal deposits, and do not impair vision.

Anti-tuberculosis drug SCARs.
Anti-tuberculosis drug use may lead to the occurrence of SCARs such as DRESS, SJS, TEN, and AGEP (see Section 4.4 Special warnings and precautions for use).

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 via HPRA Pharmacovigilance. Website: www.hpra.ie.

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

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) mycobacterial 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

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 micrograms/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 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.
Rifabutin and its metabolites are eliminated mainly by the urinary route. The $t_{½}$b 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 in mice, rats and monkey are liver, stomach, gonads 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 laurilsulfate
Magnesium stearate
Silica gel

Gelatin
Red iron oxide
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland Unlimited Company
The Watermarque Building
Ringsend Road
Dublin 4
D04 K7N3
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0822/109/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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