NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Mycobutin 150 mg capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule for oral administration contains 150 mg rifabutin.

Excipient(s) with known effect

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule

Capsules are opaque, red-brown, hard gelatin Size No. 0 capsules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mycobutin is indicated for infections caused by mycobacteria, such as *M. tuberculosis, M. avium intracellulare* complex (MAC) and other atypical mycobacteria.

In infections caused by MAC and other atypical mycobacteria such as *M. xenopi*, Mycobutin has been shown to be effective for the treatment of both disseminated and localised disease, also in immunocompromised HIV positive patients.

Mycobutin is also indicated for the prophylaxis of *M. avium intracellulare* complex (MAC) infections in immunodepressed patients with CD4 counts lower than or equal to 100/mL.

In the treatment of tubercular disease, Mycobutin has been shown to be effective for the treatment of patients with chronic pulmonary tuberculosis, even if caused by multidrug-resistant *M. tuberculosis* strains. In accordance with the commonly accepted criteria for the treatment of mycobacterial infections, Mycobutin therapy should always be given in combination with other antimycobacterial drugs not belonging to the family of rifamycins.

4.2 Dose and method of administration

Dose

Mycobutin can be administered as a single daily dose at any time independent of meals.

Adults

Mycobutin as a single agent:

- Prophylaxis of MAC infection in immunodepressed patients:

300 mg (2 capsules) per day.

Mycobutin in combination regimens:

- in non-tuberculosis mycobacterial disease:

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

- in chronic, multidrug-resistant pulmonary tuberculosis:

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

Elderly Population

No specific recommendations for dosage alterations in the elderly are proposed.

Paediatric Population

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

4.3 Contraindications

Mycobutin is contraindicated in patients with a history of hypersensitivity to rifabutin or other rifamycins (e.g. rifampicin).

Concomitant use with rilpivirine containing prolonged-release suspension for injection is contraindicated (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. 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.

It is recommended that white blood cell and platelet counts and liver enzymes be monitored periodically during treatment.

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). For further recommendations regarding protease inhibitors, please refer to current, official product monographs or contact the specific manufacturer.

Rifabutin is a CYP450 3A inducer. Therefore, co-administration with antiretroviral products including but not limited to bictegravir, elvitegravir, oral rilpivirine, or doravirine and anti-HCV products 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 products 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 generalised 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).

Uveitis

When Mycobutin is used concomitantly with clarithromycin for MAC treatment, a decreased dose of Mycobutin (300 mg after the first month of treatment) is recommended due to the increase in plasma concentrations of Mycobutin (see sections 4.5 and 4.8)). 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 4.5 and 4.8).

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.

Hepatic Impairment

Mycobutin should be used with caution in cases of liver insufficiency. For patients with severe liver insufficiency a dose reduction should be considered. Mild hepatic impairment does not require a dose modification.

Renal Impairment

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%.

4.5 Interaction with other medicines 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; 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 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.

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.

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.
Atazanavir/Ritonavir	48% ↑ in AUC, 149% ↑ Cmax of rifabutin. 990% ↑ in AUC, 677% ↑ Cmax of 25-O-desacetyl-rifabutin	No significant change in kinetics.	A 75% reduction in the dose of rifabutin (to 150 mg daily) is recommended. Increased monitoring for rifabutin-related adverse reactions is warranted.
Bictegravir	ND	AUC ↓38% Cmin ↓56% Cmax ↓20%	Although not studied, co-administration of rifabutin with a combination product containing 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% ↑ Cmax of 25-O-desacetyl-rifabutin	57% ↑ in AUC, 42% ↑ Cmax of darunavir. 66% ↑ in AUC, 68% ↑ Cmax of ritonavir.	A 75% reduction in the dose of rifabutin (to 150 mg daily) is recommended. Increased monitoring for rifabutin-related 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.	
Dolutegravir	ND	No significant change in dolutegravir kinetics at steady state.	
Doravirine	ND	50% ↓ in AUC 68% ↓ in C_{24} ↔ 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% ↑ 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% ↑ in 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 rifabutin-related 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 a combination product containing 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 section 4.4).
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.
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% ↑ in AUC	No significant change in steady-state plasma concentrations	Uveitis was associated with the combination of rifabutin and fluconazole. Patients receiving rifabutin and fluconazole concomitantly should be carefully monitored (see section 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%↑ 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	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	ND	ND	Study under analysis. Preliminary data do not suggest an 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 sections 4.2 and 4.4).
ANTI-TB (Tuberculosis)			
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.
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 due to increased levels of its active metabolites. Co-administration of bedaquiline with rifabutin may decrease bedaquiline plasma concentrations – refer to the bedaquiline data sheet.
ORAL CONTRACEPTIVES			
Ethinylestradiol/ Norethindrone	ND	Ethinylestradiol: 20% ↓ in Cmax, 35% ↓ in AUC. Norethindrone: 32% ↓ in Cmax, 46% ↓ in AUC.	Contraceptive cover may not be adequate during concomitant therapy with rifabutin. Patients should be advised to use other 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.	

AUC - Area under the Concentration vs. Time Curve
Cmax - Maximum serum concentration
Cmin - Minimum serum concentration
* - ND = No data
** - Drug plus active metabolite
*** - Voriconazole dosed at 400 mg twice daily

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies in pregnant 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 foetal viability. In rats, at 40 mg/kg/day (8 times the recommended human daily dose), rifabutin caused an increase in foetal skeletal variants. In rabbits, at 80 mg/kg/day (16 times the recommended human daily dose), rifabutin caused maternotoxicity and increased foetal 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 foetus.

During the late stages of pregnancy, rifampicin has been associated with serious vitamin K deficiency in mother and neonate, resulting in haemorrhagic disturbances. Mycobutin has not been studied in pregnancy. This should be borne in mind if, in exceptional cases, the physician considers the benefit of treatment outweighs the risk and wishes to treat a pregnant woman with Mycobutin.

Breast-feeding

There are no adequate and well-controlled studies in breast feeding women.

It is not known whether rifabutin is excreted in human breast milk. Because many drugs are excreted in human milk and the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Fertility

Studies in rats at oral doses of rifabutin at 160 mg/kg/day have shown impairment of spermatogenesis and effects on the gonads without any significant effect on the numbers of live offspring.

4.7 Effects on ability to drive and use machinery

There have been no reports of adverse effects of Mycobutin 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 possible to define with certainty a drug-event relationship.

Treatment discontinuation was necessary in approximately 13% of patients with HIV infection and 5% of patients with tuberculosis in clinical trials, related to gastrointestinal symptoms, liver function test abnormalities and blood or lymphatic system disorders.

Adverse reactions identified through either clinical trials or post-marketing surveillance by system organ class (SOC) are listed below:

*Adverse Reactions not observed in a clinical trial.

**Adverse Reactions neither observed in the clinical trials nor in the spontaneous reporting for rifabutin and are mandated for the pharmacological class.

Blood and lymphatic system: Pancytopenia, white blood cells disorder (including agranulocytosis*, leukopenia, lymphopenia*, granulocytopenia*, neutropenia*, white blood cell count decreased*, neutrophils count decreased*), thrombocytopenia, platelet count decreased* and anaemia. The frequency and severity of haematological reactions may be increased by combined administration of isoniazid.

Immune system disorders: Anaphylactic shock**, hypersensitivity*, bronchospasm*, rash, eosinophilia.

Eye disorders: Uveitis*, corneal deposits*.

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

Hepatobiliary disorders: Jaundice, hepatic enzyme increased*.

Skin and subcutaneous tissue disorders: Skin discolouration.

Musculoskeletal and connective tissue disorders: Arthralgia, myalgia.

General disorders and administration site condition: Pyrexia.

Uveitis/Corneal Deposits

Mild to severe, reversible uveitis has been reported. The risk is very 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 for MAC treatment (see section 4.4). The possible role of fluconazole (and related compounds) in increasing the risk of uveitis has not yet been established. Uveitis has not been reported in patients treated with Mycobutin (150 to 600 mg daily) in combination with other drugs for pulmonary tuberculosis. Corneal deposits have been reported during routine ophthalmologic surveillance of some HIV-positive paediatric 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.

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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

A specific toxic dose of rifabutin has not been established, although a syndrome of arthralgia/arthritis has been reported following daily monotherapy of 1 gram or more. Other signs and symptoms of overdosage are likely to be similar to adverse effects from normal therapeutic doses.

There is no specific antidote. Treatment is symptomatic and supportive, including respiratory and cardiovascular function. Plasma rifabutin levels may confirm overdosage but are not clinically useful. Monitor complete blood count, liver enzyme levels and fluid-electrolyte status as indicated, and perform an ophthalmologic examination if the patient exhibits ocular symptoms.

An aqueous slurry of activated charcoal may be administered after a potentially toxic ingestion, but it is most effective within one hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected.

Rifabutin is approximately 85% protein-bound, is extensively distributed into various tissues and is not primarily excreted via the urinary route, therefore neither haemodialysis nor forced diuresis are expected to be of any benefit.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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 mg 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 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. 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 $t_{½}$ β of rifabutin in man is approximately 35-40 hours.

5.3 Preclinical safety data

Repeated dose toxicity

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.

Genotoxicity

Rifabutin was not genotoxic in any of the *in vitro* or *in vivo* tests. Rifabutin was not mutagenic in a standard series of assays for gene mutations and chromosomal damage.

Carcinogenicity

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 foetal 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 sulfate,
Magnesium stearate,
Silicon dioxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

150 mg capsules in blister packs of 30 capsules.

6.6 Special precautions for disposal and other handling

There are no special instructions for handling.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand

Toll Free Number: 0800 736 363

www.pfizermedicalinformation.co.nz

www.pfizer.co.nz

9. DATE OF FIRST APPROVAL

01 April 1993

10. DATE OF REVISION OF THE TEXT

10 October 2023

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.3	Addition of contraindication for concomitant use with rilpivirine.
4.4	Addition of DDI information for Elvitegravir, and Anti-HCV drugs containing Sofosbuvir.
4.5	Addition of DDI information for atazanavir/ritonavir, darunavir/ritonavir, dolutegravir, elvitegravir/cobicistat, etravirine, sofosbuvir, bedaquilline, ethinylestradiol/norethindrone.
4.4, 4.5, 4.8	Minor editorial changes, addition and removal of text in cross referencing to improve readability