RIMTIB TABLETS
PM02508303

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

RIMTIB TABLETS film-coated tablets

COMPOSITION

Each film-coated tablet contains:
Rifampicin 150 mg
Isoniazid 75 mg
Pyrazinamide 400 mg
Ethambutol hydrochloride 275 mg
Sugar free
Excipients: shellac, purified talc, povidone, disodium edetate, colloidal anhydrous silica, maize starch, croscarmellose sodium, crospovidone, calcium stearate, hypromellose, polyvinyl alcohol, lecithin (soya), xanthan gum, colourants (titanium dioxide, colour lake of sunset yellow).

PHARMACOLOGICAL CLASSIFICATION

A 20.2.3 Tuberculostatic

PHARMACOLOGICAL ACTION

RIMTIB TABLETS is a combination of four medicines used in the treatment of tuberculosis. Rifampicin and pyrazinamide are bactericidal anti-tuberculosis medicines. Ethambutol is bacteriostatic and effective only against bacteria that are actively dividing. Isoniazid is bactericidal for rapidly dividing micro-organisms and bacteriostatic for resting bacilli.

Pharmacokinetics

Rifampicin
Absorption
Rifampicin is readily absorbed from the gastrointestinal tract with an oral bioavailability of 68 %, C_{max} of 8 - 20 μg/ml and t_{max} of 1,5 – 2,0 hours. Absorption of rifampicin is reduced by about 30 % when ingested with food.
Distribution
Rifampicin is widely distributed throughout the body and has good penetration into many tissues, but levels in CNS reach only approximately 5 % of those in plasma. Rifampicin is about 85 % protein bound.
Metabolism
Rifampicin is metabolised by microsomal β-esterases and cholinesterases that remove the acetyl group at position 25, resulting in 25-O-deacetyl rifampicin. Rifampicin is also metabolised by hydrolysis to 3-formyl rifampicin. A major pathway for rifampicin elimination is CYP3A. Due to autoinduction, rifampicin reduces its own area under concentration-time curve (AUC) with repeated administration.
Elimination
The half-life of rifampicin ranges from 2 – 5 hours. Rifampicin and its metabolites are excreted by bile and eliminated via faeces, with urine elimination accounting for one-third and less of metabolites.

Isoniazid
Absorption
Isoniazid is well absorbed from the gastrointestinal tract with an oral bioavailability of 100 % for a 300 mg dose; C_{max} of 3,4 – 7,4 μg/ml for rapid acetylators and C_{max} of 5,2 – 8 μg/ml for slow acetylators; t_{max} of 1,1 ± 0,5 hours for rapid acetylators and 1,1 ± 0,6 hours for slow acetylators. Absorption of isoniazid is decreased by food and antacids.
Distribution
The ratio of isoniazid in the epithelial lining fluid to that in plasma is 1 – 2 and for CSF is 0,9. Approximately 10 % of isoniazid is protein bound.
Metabolism
Isoniazid is metabolised by hepatic arylamine *N*-acetyltransferase type 2 (NAT2). Isoniazid is N-acetylated to N-acetylisoniazid in reactions that uses acetyl-coA. Acetylisoniazid is excreted by the kidney; acetylisoniazid can also be converted to acetylhydrazine and then to hepatoxic metabolites by CYP2E1. Alternatively, acetylhydrazine may be further acetylated by NAT2 to diacetylhydrazine, which is non-toxic.
Isoniazid clearance in patients is classified as one of two phenotypic groups: "slow" acetylators and "fast" acetylators. Rapid acetylators will remove acetylhydrazine while slower acetylators or induction of CYP2E1 will lead to more toxic metabolites.
Elimination
The half-life of isoniazid ranges from 1,1 ± 0,1 hours for rapid acetylators and 3,1 ± 1,1 for slow acetylators. From 75 – 95 % of a dose of isoniazid is excreted in the urine within 24 hours, mostly as acetylisoniazid and isonicotinic acid.

Pyrazinamide
Absorption
Pyrazinamide oral bioavailability is > 90 %; C_{max} of 35 (18 – 103) μg/ml; t_{max} of 8 hours.
Distribution
Pyrazinamide is concentrated 20-fold in the lung epithelial lining fluid. Approximately 10 % of pyrazinamide is protein bound.
Metabolism
Pyrazinamide is metabolised by microsomal deamidase to pyrazinoic acid (POA) and subsequently hydroxylated to 5-hydroxy-POA, which is then excreted by the kidneys.
Elimination
Cl (clearance) and V_d (volume of distribution) increase with patient mass (0,5 l/hour and 4,3 l for every 10 kg above 50 kg and V_d is large in males (by 45 l). The $t_{½}$ of pyrazinamide will vary based on weight and gender. Pyrazinamide clearance is reduced in renal failure, therefore, the dosing frequency is reduced to three times a week in at low glomerular filtration rates. Haemodialysis removes pyrazinamide, therefore, re-dosing is required after each session of haemodialysis.

Ethambutol
Absorption
Ethambutol oral bioavailability is approximately 80 %; C_{max} of 2 – 5 μg/ml; t_{max} of 2 - 4 hours.
Distribution
Approximately 10 - 40 % of ethambutol is protein bound.
Metabolism
Alcohol dehydrogenase oxidises ethambutol to an aldehyde, which is then oxidised by aldehyde dehydrogenase to dicarboxylic acid. However, 80 % of ethambutol is not metabolised at all and is renally excreted. Therefore, in renal failure, ethambutol should be dosed at 15 – 25 mg/kg, three times a week instead of daily, even in patients receiving haemodialysis.
Elimination
The decline in ethambutol is biexponential, with a $t_{½}$ of 3 hours in the first 12 hours and $t_{½}$ of 9 hours between 12 and 24 hours, due to redistribution.

INDICATIONS

RIMTIB TABLETS is used in the initial phase treatment of pulmonary and extrapulmonary tuberculosis in new adult patients and re-treatment of adult cases.

CONTRA-INDICATIONS

RIMTIB TABLETS is contra-indicated in:
- Patients with hypersensitivity to rifampicin, isoniazid, pyrazinamide, ethambutol or other chemically related medications or to any of the excipients of **RIMTIB TABLETS**.
- The presence of jaundice or active hepatic disease.
- Patients with optic neuritis.
- Patients with renal and hepatic function impairment.
- Children under 13 years of age.
- Concomitant use with nevirapine (see INTERACTIONS).

WARNINGS AND SPECIAL PRECAUTIONS

Liver function should be checked before and during treatment and special care should be exercised in alcoholic patients, the elderly or those with pre-existing liver disease.
Caution should be observed with the use of **RIMTIB TABLETS** in the following patients:
- Renal impairment: dosage adjustment may be required according to the serum concentration of ethambutol. Increased risk of toxicity of isoniazid in renal failure.
- Visual defects: should visual disturbances occur during treatment, these must be reported immediately and **RIMTIB TABLETS** discontinued pending visual evaluation. Optic neuritis has occurred after only a few days of treatment. Most cases are reversible after several weeks or months. Visual changes may be unilateral or bilateral, therefore each eye must be tested separately and both eyes together. Retinal haemorrhage had occurred less frequently.
- Patients at risk of neuropathy or pyridoxine deficiency, including those who are diabetic, alcoholic, malnourished, uraemic or pregnant; pyridoxine supplementation (in a 10 mg to 50 mg daily dose) is usually required in these instances.
- Patients with a history of gout.
- Patients with porphyria.
- Patients with epilepsy, as convulsions may be precipitated.
- Patients with a history of psychosis.
- Patients with diabetes: pyrazinamide may cause interference with urine ketone determinations.
- Rifampicin may decrease the effect of oral contraceptives and patients are advised to change to non-hormonal methods of birth control, whilst taking **RIMTIB TABLETS**.
- Treatment with **RIMTIB TABLETS** may produce reddish discolouration of the urine, tears and saliva. Contact lenses may be irreversibly stained.

In the following cases, treatment with **RIMTIB TABLETS** should be stopped immediately and the patient evaluated:
- Rash and fever (associated with isoniazid and rifampicin).
- Bleeding tendency (thrombocytopenia, purpura), shock.
- Renal failure (associated with rifampicin).
- Visual impairment (associated with ethambutol). Periodic eye examinations during treatment are suggested.
- Jaundice (associated with isoniazid, rifampicin and pyrazinamide).
- Elevated liver enzymes associated with the clinical signs of hepatitis such as nausea and vomiting or fatigue.

Hepatic function determinations are based on ALT and AST concentrations i.e. serum alanine and aspartate aminotransferase concentrations.

These tests may be required monthly during treatment, especially in the elderly, pregnant women and those with pre-existing liver damage. Severe and sometimes fatal hepatitis has been reported.

Effects on ability to drive and use machines
RIMTIB TABLETS may cause dizziness, impaired concentration, and/or drowsiness. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

INTERACTIONS

Rifampicin:
Rifampicin induces microsomal enzymes and may therefore accelerate clearance of medicines metabolised in the liver
Examples of medicines metabolised by cytochrome P-450 enzymes are
- Antidysrhythmics (e.g. disopyramide, mexiletine, quinidine, propafenone, tocainide, verapamil),
- Antiepileptics (e.g. phenytoin),
- Hormone antagonist (antioestrogens e.g. tamoxifen, toremifen, gestrinone),
- Antipsychotics (e.g. haloperidol, aripiprazole),
- Anticoagulants (e.g. warfarin),
- Antifungals (e.g. fluconazole, itraconazole, ketoconazole, voriconazole),
- Antivirals (e.g. saquinavir, indinavir, efavirenz, amprenavir, nelfinavir, atazanavir, lopinavir, nevirapine),
- Atovaquone,
- Barbiturates (e.g. hexobarbitone),
- Beta-blockers (e.g. bisoprolol, propanolol),
- Anxiolytics and hypnotics (e.g. diazepam, benzodiazepines, zopiclone, zolpidem),
- Calcium channel blockers (e.g. diltiazem, nifedipine, verapamil),
- Antibacterials (e.g. chloramphenicol, clarithromycin, dapsone, doxycycline, fluoroquinolones, telithromycin),
- Cimetidine,
- Corticosteroids,
- Cardiac glycosides (digoxin),
- Clofibrate,
- Systemic hormonal contraceptives,
- Oestrogen,
- Antidiabetic (e.g. chlorpropamide, tolbutamide, sulfonylureas, rosiglitazone),
- Immunosuppressive agents (e.g. azathioprine, ciclosporin, sirolimus, tacrolimus),
- Irinotecan,
- Thyroid hormone (e.g. levothyroxine),
- Losartan,
- Analgesics (e.g. methadone, narcotic analgesics),
- Praziquantel,
- Progestogens,
- Quinine,
- Riluzole,
- Selective 5-HT3 receptor antagonists (e.g. ondansetron),
- Statins metabolised by CYP 3A4 (e.g. simvastatin),
- Sulphasalazine,
- Theophylline,
- Tricyclic antidepressants (e.g. amitriptyline, nortriptyline).

Patients using oral contraceptives should be advised to change to non-hormonal methods of birth control during **RIMTIB TABLETS** therapy (see WARNINGS AND SPECIAL PRECAUTIONS).
Concurrent use of alcohol, paracetamol, isoniazid and other hepatotoxic medication may increase the incidence of rifampicin-induced hepatotoxicity.
The effectiveness of oestrogen-containing oral preparations is reduced.
Therapeutic levels of rifampicin have been shown to inhibit standard microbiological assays for serum folate and Vitamin B12. Thus alternative assay methods should be considered.
Transient elevation of serum bilirubin has been reported. Rifampicin may impair biliary excretion of contrast media used for visualisation of the gallbladder, due to competition for biliary excretion. Therefore, these tests should be performed before the morning dose of rifampicin and therefore **RIMTIB TABLETS**.
Concomitant antacid administration may reduce the absorption of rifampicin. Daily doses of **RIMTIB TABLETS** should be given at least 1 hour before the ingestion of antacids.
If p-aminosalicylic acid and **RIMTIB TABLETS** are both included in the treatment regimen, they should be given not less than eight hours apart to ensure satisfactory blood levels.
The potential for hepatotoxicity is increased with an anaesthetic.
When **RIMTIB TABLETS** is given concomitantly with either halothane or isoniazid, the potential for hepatotoxicity is increased. The concomitant use of **RIMTIB TABLETS** and halothane should be avoided. Patients receiving both rifampicin and isoniazid such as contained in **RIMTIB TABLETS** should be monitored closely for hepatotoxicity.
Anti-retroviral Agents
Rifampicin as contained in RIMTIB TABLETS can induce the metabolism of zidovudine, the NNRTIs delavirdine, efavirenz and nevirapine and the HIV-protease inhibitors, resulting in subtherapeutic plasma concentrations. Furthermore, HIV-protease inhibitors inhibit the metabolism of rifampicin resulting in elevated plasma-rifampicin concentrations and an increased incidence of adverse effects.
The concomitant use of **RIMTIB TABLETS** and nevirapine is contra-indicated (see CONTRA-INDICATIONS).
Rifampicin as contained in **RIMTIB TABLETS** decreases the concentration of efavirenz and it is recommended that the dose of efavirenz be increased in patients weighing more than 60 kg.

Isoniazid:
Chronic use of isoniazid may decrease the plasma clearance and prolong the duration of action of alfentanil, coumarin anticoagulants (warfarin), anti-epileptics (e.g. phenytoin, primidone, carbamazepine, ethosuximide), benzodiazepines (e.g. diazepam), chlorzoxazone and theophylline.
Appropriate adjustment of the anticonvulsant dose may be required. Concurrent use of paracetamol, alcohol, rifampicin and other hepatotoxic medicine, may increase the potential for isoniazid-induced hepatotoxicity.
Aluminium-containing antacids may delay the absorption and decrease the serum concentrations of isoniazid. Ingestion of certain types of cheese e.g. Swiss or Cheshire, or fish e.g. tuna, may result in itching of the skin, rapid or pounding heart, chills or headache. Glucocorticoid corticosteroids may increase hepatic metabolism and/or excretion of isoniazid. Concurrent use of cycloserine, disulfiram and other neurotoxic medicines may increase the potential of CNS toxicity.
Isoniazid may also increase the metabolism of enflurane, resulting in the formation of potentially nephrotoxic inorganic fluoride metabolites. Interactions with ketoconazole and miconazole have been reported. False positive reactions with copper sulphate urine glucose tests may occur.
Anti-retroviral agents
The clearance of isoniazid is approximately doubled when given concomitantly with zalcitabine.
RIMTIB TABLETS should be used with caution with stavudine and zalcitabine as stavudine, zalcitabine and isoniazid have been associated with causing peripheral neuropathy. The use of **RIMTIB TABLETS** with stavudine has been reported to increase the incidence of peripheral neuropathy.

Pyrazinamide:
Pyrazinamide may decrease the efficacy of gout therapy (e.g. allopurinol, colchicine, probenecid or sulphinpyrazone) and dosage adjustments of these medicines may be necessary. Pyrazinamide may decrease serum concentrations of ciclosporin, possibly leading to inadequate immunosuppression. Use with pyrazinamide and therefore **RIMTIB TABLETS** and other diuretics: the additive potential for elevating serum urate levels should be considered.

Ethambutol:
Concurrent administration of neurotoxic medicines with ethambutol may potentiate neurotoxic effects such as optic and peripheral neuritis.

PREGNANCY AND LACTATION

Safety in pregnancy has not been established. All substances of **RIMTIB TABLETS** are excreted in breast milk. Safety during lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE

Take **RIMTIB TABLETS** with a full glass of water one hour before or 2 hours after a meal. However, if gastrointestinal irritation occurs, the tablets may be taken with food. If aluminium – containing antacids are taken, administer one hour after the tablet dose.

The recommended treatment dosages, based on the patient's body weight, given daily for the 2 month initial-phase treatment in adults and children over 13 years of age are as follows:

Pre-treatment body-weight	Once daily dose
30 - 37 kg	2 tablets
38 - 54 kg	3 tablets
55 - 70 kg	4 tablets
71 kg and over	5 tablets

SIDE-EFFECTS

Side-effects associated with rifampicin
Blood and lymphatic system disorders:
Less frequent: Blood dyscrasias, unusual bleeding or bruising, thrombocytopenia, purpura, haemolysis, eosinophilia, leucopenia, haemolytic anaemia, agranulocytosis.

Immune system disorders:
Frequency not known: Lupus-like syndrome. A 12 hour "flu" syndrome, usually occurring after 3 – 6 months of treatment and usually with doses of 20 mg/kg or more, may present as fever, chills, bone pain and malaise, shortness of breath and wheezing; decrease in blood pressure and shock; acute haemolytic anaemia, acute renal failure usually due to acute tubular necrosis or to acute interstitial nephritis; anaphylaxis.

Nervous system disorders:
Frequency not known: Headache, drowsiness, dizziness, ataxia, numbness, confusion and generalised numbness.

Eye disorders:
Less frequent: Blurred vision, visual disturbance, eye irritation.

Gastrointestinal disorders:
Frequent: Nausea, vomiting, anorexia, abdominal discomfort, diarrhoea and epigastric distress.
Less frequent: Pseudomembranous colitis.

Hepato-biliary disorders:
Less frequent: Hepatitis (which may be fatal), hepatitis prodromal symptoms which include loss of appetite, nausea or vomiting, unusual tiredness or weakness.

Skin and subcutaneous tissue disorders:
Frequent: Cutaneous reactions, which typically consist of flushing and itching, with or without a rash.
Less frequent: More serious hypersensitivity cutaneous reactions, toxic epidermal necrolysis, exfoliative dermatitis, pemphigoid reactions, erythema multiforme including Stevens-Johnson syndrome and vasculitis.

Musculoskeletal and connective tissue disorders:
Frequent: Muscle weakness and myopathy.

Renal and urinary disorders:
Less frequent: Interstitial nephritis, alteration in kidney function, renal failure, adrenal insufficiency in patients with compromised adrenal function.

Reproductive system and breast disorders:
Less frequent: Disturbances of the menstrual cycle, reduction of effectiveness of oral contraceptives.

General disorders and administrative site conditions:
Frequent: Reddish-orange to reddish-brown discolouration of the urine, faeces, saliva, sputum, sweat and tears. Soft contact lenses may be permanently stained.
Less frequent: Fungal overgrowth i.e. sore mouth or tongue.
Frequency not known: Oedema.

Side-effects associated with isoniazid
Blood and lymphatic system disorders:
Less frequent: Various haematological disturbances including anaemia, eosinophilia, sideroblastic anaemia, agranulocytosis, haemolytic anaemia, thrombocytopenia, neutropenia, aplastic anaemia.

Immune system disorders:
Less frequent: Hypersensitivity reactions including various skin eruptions, fever, lymphadenopathy, vasculitis and anaphylaxis, lupus-like reactions.

Metabolism and nutrition disorders:
Less frequent: Hyperglycaemia, metabolic acidosis, pellagra.

Psychiatric disorders:
Less frequent: Psychotic reactions (characterised by delusions, hallucinations and confusion).

Nervous system disorders:
Frequent: Peripheral neuropathy.
Less frequent: Polyneuritis associated with paraesthesia, muscle weakness, loss of tendon reflexes, convulsions, increase in frequency of fits in epileptic patients, memory impairment, toxic encephalopathy.

Eye disorders:
Less frequent: Optic neuritis (blurred vision or loss of vision, with or without eye pain).

Ear and labyrinth disorders:
Less frequent: Vertigo.

Gastrointestinal disorders:
Frequent: Diarrhoea, nausea and vomiting, stomach pain, constipation, dry mouth, pancreatitis epigastric distress.

Hepato-biliary disorders:
Frequent: Hepatitis (severe and sometimes fatal), elevated liver enzymes with clinical signs of hepatitis (loss of appetite, nausea or vomiting, unusual tiredness or weakness); the incidence of liver damage is highest in patients over 35 years of age, those who are slow acetylators and those who consume alcohol on a daily basis.

Skin and subcutaneous tissue disorders:
Frequency not known: Cutaneous reactions including rash, acne. Stevens-Johnson syndrome, exfoliative dermatitis, pemphigus, lupus-like erythematosus-like reactions.

Musculoskeletal and connective tissue disorders:
Frequency unknown: A rheumatic syndrome, hyperreflexia.

Renal and urinary disorders:
Less frequent: Urinary retention.

Reproductive system and breast disorders:
Less frequent: Gynaecomastia.

Side-effects associated with pyrazinamide
Blood and lymphatic disorders:
Less frequent: Sideroblastic anaemia, thrombocytopenia.

Immune system disorders:
Less frequent: Angioedema.

Metabolism and nutrition disorders:
Less frequent: Pellagra.

Gastrointestinal disorders:
Less frequent: Anorexia, nausea, vomiting, aggravation of peptic ulcer.

Hepato-biliary disorders:
Frequent: Hepatotoxicity (frequency appears to be dose related).

Skin and subcutaneous tissue disorders:
Less frequent: Photosensitivity, skin rash, pruritus.

Musculoskeletal, connective tissue and bone disorders:
Frequent: Arthralgia which is related to hyperuricaemia.
Less frequent: Gouty arthritis.

Renal and urinary disorders:
Less frequent: Dysuria.

General disorders and administrative site conditions:
Less frequent: Malaise, fever.

Side-effects associated with Ethambutol
Blood and lymphatic disorders:
Less frequent: Leucopenia, eosinophilia, thrombocytopenia.

Immune system disorders:
Less frequent: Hypersensitivity reactions including skin rashes, pruritus, fever, leucopenia and joint pain.

Psychiatric disorders:
Less frequent: Confusion, disorientation, hallucination.

Nervous system disorders:
Frequent: Headache, dizziness, peripheral neuropathy.

Eye disorders:
Less frequent: Optic neuritis, retrobulbar neuritis with a reduction in visual acuity, which appears to be dose-related, occurring most frequently with daily doses of 25 mg per kg of body weight (mg/kg) and after 2 months of therapy, constriction of visual field, central or peripheral scotoma and green-red colour blindness affecting one or both eyes.

Gastrointestinal disorders:
Frequent: Abdominal pain, anorexia, nausea, vomiting and metallic tastes.

Hepato-biliary disorders:
Less frequent: Jaundice, transient liver dysfunction.

Musculoskeletal, connective tissue and bone disorders:
Less frequent: Acute gouty arthritis.

Renal and urinary disorders:
Less frequent: Reduced renal clearance of urate.

General disorders and administrative site conditions:
Less frequent: Malaise.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

For symptoms of overdosage, refer to **SIDE-EFFECTS**. Treatment of overdosage consists of gastric lavage, symptomatic and supportive therapy.

IDENTIFICATION

Light buff coloured, biconvex, capsule shaped film-coated tablets with plain surface on both sides.

PRESENTATION

HDPE Container:
Silver coloured triple laminated aluminium sachet (PET/Al/LLDPE), kept in a white plastic container (HDPE), which is sealed at the mouth with an aluminium tagger and is closed with a white HDPE screw-on lid. Pack sizes include 500 and 1000 tablets.
Blister:
Silver coloured aluminium backing foil with amber coloured (PVC/PE/PVdC) lidding foil. The blister is packed in a pre-printed carton. Pack sizes include 28 (1 blister of 28 tablets), 56 (2 blisters of 28 tablets), 84 tablets (3 blisters of 28 tablets), 112 tablets (4 blisters of 28 tablets) and 100 tablets (10 blisters of 10 tablets).
Strip Pack:
Tablets are packed in silver-metallic coloured aluminium foil (soft tempered) laminated with low density polyethylene films as the lidding and forming material. The aluminium strip is packed in a pre-printed carton. Pack sizes include 28 (1 strip of 28 tablets), 56 (2 strips of 28 tablets), 84 tablets (3 strips of 28 tablets), 112 tablets (4 strips of 28 tablets) and 100 tablets (10 strips of 10 tablets).

STORAGE INSTRUCTIONS

Store at or below 25 °C. Protect from moisture and light.
Keep the aluminium sachet in the HDPE container until required for use.
Keep the blister or strip pack in the carton until required for use.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

49/20.2.3/0381

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

Macleods Pharmaceuticals SA (Pty) Ltd.
Office Block 1,
Bassonia Estate Office Park (East),
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DATE OF PUBLICATION OF THE PACKAGE INSERT

25 November 2016

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS

S4

PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM

RIMTIB TABLETS (film coated tablet)
Rifampicin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg, ethambutol hydrochloride 275 mg

READ ALL OF THIS LEAFLET CAREFULLY BEFORE YOU START TAKING RIMTIB TABLETS

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- **RIMTIB TABLETS** has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

WHAT RIMTIB TABLETS CONTAINS

RIMTIB TABLETS
Each film-coated tablet contains:
Rifampicin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg, ethambutol hydrochloride 275 mg.
Sugar free.
Excipients: shellac, purified talc, povidone, disodium edetate, colloidal anhydrous silica, maize starch, croscarmellose sodium, crospovidone, calcium stearate, hypromellose, polyvinyl alcohol, lecithin (soya), xanthan gum, colourants (titanium dioxide, colour lake of sunset yellow).

WHAT RIMTIB TABLETS IS USED FOR

RIMTIB TABLETS is an antimicrobial agent used in the treatment of tuberculosis (TB infection) in adults.

BEFORE YOU TAKE RIMTIB TABLETS

Do not take RIMTIB TABLETS if you suffer from any of the conditions mentioned below:
- If you are hypersensitive (allergic) to rifamycins including rifampicin, isoniazid, pyrazinamide, ethambutol or to any of the ingredients contained in **RIMTIB TABLETS**.
- If you have any kind of liver disease or jaundice (yellowing of the eyes and skin).
- If you develop thrombocytopenia and purpura (bruising, nosebleeds or bleeding in the mouth and gums, rash with pinpoint red spots) while taking **RIMTIB TABLETS**.
- If you suffer from any eye disease e.g. inflammation of the nerves of the eyes (optic neuritis).
- Children under 13 years of age should not be given **RIMTIB TABLETS**.
- Concomitant use with nevirapine (medicine used for HIV treatment).

Take special care with RIMTIB TABLETS
Before you take **RIMTIB TABLETS, tell** your doctor if:
- You have any kidney or liver disease.
- You suffer from alcoholism.
- You have porphyria.
- You have epilepsy.
- You suffer from any mental illness.
- You have a history of gout.
- You are diabetic.
- If you are using oral contraceptives you should change to alternate methods of birth control.

While taking **RIMTIB TABLETS**:
- Tell your doctor immediately if you notice any problems with your eyes and eyesight.
- If you are diabetic, alcoholic, malnourished and suffer from kidney disease and if you are at risk of developing numbness or weakness of the arms and legs, your doctor will prescribe additional pyridoxine (Vitamin B6) supplementation.
- Urine, stools, saliva, sputum, sweat and tears may be discoloured.
- Soft contact lenses may be permanently stained.

Taking RIMTIB TABLETS with food and drink
RIMTIB TABLETS should be taken without food. Avoid tyramine-containing foods (e.g. cheese, red wine) and histamine-containing foods (e.g. skipjack, tuna, tropical fish). Avoid alcohol.

Pregnancy and breastfeeding

> If you are pregnant or if you are breastfeeding your baby, please consult your doctor, pharmacist or healthcare professional for advice before taking **RIMTIB TABLETS**.

Safety and efficacy of **RIMTIB TABLETS** during pregnancy and breastfeeding has not been established.

Driving and using machinery
RIMTIB TABLETS may cause dizziness, impaired concentration, and/or drowsiness. If you feel dizzy or drowsy while taking **RIMTIB TABLETS** do not drive and do not use any tools or machines.

Taking other medicines with RIMTIB TABLETS
RIMTIB TABLETS may change the effect of other medicines and other medicines may change the effect of **RIMTIB TABLETS**
When you are taking **RIMTIB TABLETS**, it is especially important to tell your doctor or healthcare professional if you are taking any of the following:
- Paracetamol, aspirin and other analgesics or pain killers.
- Antacids containing magnesium trisilicate, aluminium hydroxide or sodium bicarbonate.
- Medicines used to treat epilepsy such as ethosuximide, phenytoin and carbamazepine.
- Medicines such as itraconazole, fluconazole and ketoconazole used for treating fungal infections.
- Corticosteroids for treating inflammatory conditions.
- Theophylline used in cough mixtures and asthma medication.
- HIV medicine such as zidovudine, delavirdine, efavirenz, nevirapine, saquinavir, ritonavir, lopinavir, darunavir, atazanavir, fosamprenavir, stavudine and zalcitabine.
- Thyroid hormones.
- Oral hypoglycaemic medicines used in diabetes treatment (e.g. chlorpropamide, tolbutamide, sulfonylureas, rosiglitazone).
- Medicines used for gout (e.g. allopurinol, colchicine, probenecid or sulphinpyrazone)
- Other medicines include tamoxifen, toremifen (for breast cancer), gestrinone (for endometriosis), halothane (anaesthetic medicine), azathioprine, ciclosporin, sirolimus, tacrolimus (immune suppressants), atovaquone, chloramphenicol, cycloserine, dapsone, doxycycline (medicines used for infections), cimetidine (used to treat stomach ulcers), clofibrate, simvastatin (lowers cholesterol), warfarin (thins blood), diazepam, amitriptyline, nortriptyline (for anxiety and depression), zopiclone, zolpidem (for sleep disorders), hexobarbitone (sedative), haloperidol, aripiprazole (for mental illness), methadone (for pain), sulphasalazine (used for rheumatoid arthritis and inflammatory bowel disease), quinine (used in malaria), oral contraceptives, riluzole (for sclerosis), praziquantel (for worm infection), irinotecan (for cancer), disulfiram (for alcohol dependence) and medicines such as digoxin, disopyramide, lorcainide, mexiletine, propafenone, quinidine, tocainide, verapamil, propranolol, enalapril, losartan used in the treatment of heart disease.
- Enflurane used in general anaesthesia should not be used with **RIMTIB TABLETS**.
- Alcohol.

> Always tell your healthcare professional if you are taking any other medicine. (This includes complementary or traditional medicines)

HOW TO TAKE RIMTIB TABLETS

> Do not share medicines prescribed for you with any other person.
> Always take **RIMTIB TABLETS** exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. If you have the impression that the effect of **RIMTIB TABLETS** is too strong or too weak talk to your doctor or pharmacist.

Your doctor will prescribe the required number of tablets to be taken on a daily basis based on your body weight.
The tablets should preferably be taken on an empty stomach (one hour before or 2 hours after a meal) as a single dosage. However, if stomach irritation occurs, the tablets may be taken with food.
RIMTIB TABLETS should be taken at least 1 hour before aluminium containing antacids are taken.

The recommended number of **RIMTIB TABLETS**, based on body weight, taken daily for the 2 month initial-phase treatment in adults and children over 13 years of age are as follows:

Pre-treatment body-weight	Once daily dose
30 - 37 kg	2 tablets
38 - 54 kg	3 tablets
55 - 70 kg	4 tablets
71 kg and over	5 tablets

Do not stop taking RIMTIB TABLETS because you feel better.
If the full treatment prescribed by your doctor is not completed, some of the bacteria causing the TB infection may not be killed. These bacteria may continue to grow and multiply so the TB infection may not clear completely or it may return.

If you take more RIMTIB TABLETS than you should
Symptoms include nausea, vomiting, stomach pain, dizziness, high blood sugar levels, high levels of acid in the blood, hallucinations, difficulty in breathing and central nervous system depression with seizures and coma. Other signs of overdosage includes bright-red discolouration of the skin and mucous membranes, decreased mental alertness, swelling of the face and "puffy eyes" and generalised itching.
If any of the above symptoms occur, get medical help immediately by calling your nearest doctor or healthcare professional.

> In the event of overdosage, consult your doctor or pharmacist. If neither is available contact the nearest hospital or poison control centre.

If you forget to take RIMTIB TABLETS
If you have missed a dose of **RIMTIB TABLETS** take it as soon as you remember. However if it is almost time for the next dose, skip the missed dose and go back to your regular scheduling. Never double the dose.

POSSIBLE SIDE-EFFECTS

Tell your doctor immediately or go to the nearest hospital, you may need urgent medical attention if you notice any of the following:
- Red and/or itchy skin, blisters or pimples.
- Swelling of the face, lips, tongue or throat which may cause difficulty in breathing or swallowing.
- Shortness of breath and wheezing.
- Confused, sleepy, cold clammy skin, shallow or difficult breathing, a racing heartbeat or your skin is paler than normal. These could be signs of shock.
- Blistering, peeling, bleeding, scaling or fluid filled patches on any part of your skin.
- Sudden changes in vision, blurred or distorted eye sight.
- Blood in the urine or any other urination disturbances, swelling especially of the legs, ankles or feet.
- Fever, chills, headache or dizziness.
- Bone pain.
- Bruising, nosebleeds or bleeding in the mouth and gums, rash with pinpoint red spots.
- Fatigue, weakness, malaise (feeling unwell), anorexia (loss of appetite), nausea or vomiting.
- Inability to see the colours red and green.

Tell your doctor immediately if you notice any of the following side-effects, particularly if they occur several weeks after stopping treatment with RIMTIB TABLETS:
- Severe stomach cramps.
- Watery and severe diarrhoea, which may also be bloody.
- Fever, in combination with one or both of the above.

You may have a serious condition affecting your bowel, which may need urgent medical attention. Do not take any diarrhoea medicines without first checking with your doctor.

Tell your doctor if you notice any of the following and they worry you:
- Yellow discolouration of skin or eyes.
- Heartburn, anorexia, nausea, vomiting, wind, cramps or diarrhoea, constipation, dry mouth, aggravation of peptic ulcer, metallic taste.
- Headache, drowsiness, fatigue, inability to concentrate or confusion.
- Numbness and tingling in the hands or feet.
- Your fits get worse or you start to have fits.
- Poor coordination, muscle weakness, muscle pain, pain in the fingers or toes, hot skin over affected joints, or numbness, unusually increased reflexes or twitching.
- Oral thrush - white, furry, sore tongue and mouth.
- Blurred vision or loss of vision with or without eye pain, eye irritation.
- Menstrual cycle disturbances.
- Temporary hearing loss.
- Vertigo (feeling dizzy with a spinning sensation).
- Enlarged breasts.
- Skin rash, flushing and itching of the skin, acne.
- Mental illness with strange or disturbing thoughts or moods, short term memory loss, being less alert or responsive.
- Water retention (oedema) which may cause swollen face, stomach, arms or legs.
- Increased thirst, going to the toilet more often and feeling tired; your blood sugar levels may be high.

Not all the side-effects reported for **RIMTIB TABLETS** are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking **RIMTIB TABLETS**, please consult your doctor, pharmacist or health care professional for advice.
If you notice any side-effects not mentioned in this leaflet, please inform your doctor or pharmacist.

STORAGE AND DISPOSAL INFORMATION FOR RIMTIB TABLETS

Store at or below 25 °C.
Keep aluminium sachet in the HDPE container until required for use. Keep the blister or strip pack in the carton until required for use.
Store this medicine away from light and moisture.
Any expired or outdated medicines and unused medicines can be returned to your nearest pharmacy.
STORE ALL MEDICINES OUT OF REACH OF CHILDREN.

PRESENTATION

RIMTIB TABLETS
HDPE Container:
Silver coloured triple laminated aluminium sachet (PET/Al/LLDPE), kept in a white plastic container (HDPE), which is sealed at the mouth with an aluminium tagger and is closed with a white HDPE screw-on lid. Pack sizes include 500 and 1000 tablets.
Blister:
Silver coloured aluminium backing foil with amber coloured (PVC/PE/PVdC) lidding foil. The blister is packed in a pre-printed carton. Pack sizes include 28 tablets (1 blister of 28 tablets), 56 tablets (2 blisters of 28 tablets), 84 tablets (3 blisters of 28 tablets), 112 tablets (4 blisters of 28 tablets) and 100 tablets (10 blisters of 10 tablets)
Strip Pack:
Tablets are packed in silver-metallic coloured aluminium foil (soft tempered) laminated with low density polyethylene films as the lidding and forming material. The aluminium strip is packed in a pre-printed carton. Pack sizes include 28 (1 strip of 28 tablets), 56 (2 strips of 28 tablets), 84 tablets (3 strips of 28 tablets), 112 tablets (4 strips of 28 tablets) and 100 tablets (10 strips of 10 tablets).

IDENTIFICATION

Light buff coloured, biconvex, capsule shaped film-coated tablets with plain surface on both sides.

REGISTRATION NUMBER

49/20.2.3/0381

NAME AND BUSINESS ADDRESS OF HOLDER OF THE CERTIFICATE OF REGISTRATION

Macleods Pharmaceuticals SA (Pty) Ltd.
Office Block 1,
Bassonia Estate Office Park (East),
1 Cussonia Drive,
Bassonia Rock, Ext. 12,
Alberton.

DATE OF PUBLICATION OF THE PATIENT INFORMATION LEAFLET

25 November 2016

SKEDULERINGSTATUS

S4

EIENDOMSNAAM EN DOSEERVORM
RIMTIB TABLETS filmbedekte tablette.

SAMESTELLING
Elke filmbedekte tablet bevat:
Rifampisien 150 mg
Isoniasied 75 mg
Pirasinamied 400 mg
Etambutolhidrochloried 275 mg
Suikervry
Eksipiënte: skellak, gesuiwerde talk, povidon, dinatriumedetaat, anhidriese kolloïdale silika, mieliestysel, kroskarmellose natrium, krospovidoon, kalsiumstearaat, hipromellose, polivinielalkohol, lesitien (soja), Xanthan kougom, kleurstowwe (titaandioksied, sonskyngeel).

FARMAKOLOGIESE KLASSIFIKASIE
A 20.2.3 Tuberkulostatiese middels

FARMAKOLOGIESE WERKING
RIMTIB TABLETS is 'n kombinasie van vier medisyne wat in die behandeling van tuberkulose gebruik word. Rifampisien en pirasinamied is bakteriedodende anti-tuberkulose medisyne. Etambutol is bakteriostaties en slegs effektief teen bakterieë wat aktief verdeel. Isoniasied is bakteriedodend vir sneldelende mikroörganismes en bakteriostaties vir rustende basille.

Farmakokinetika
Rifampisien
Absorpsie
Rifampisien word geredelik vanuit die maagdermkanaal geabsorbeer, met 'n orale biobeskikbaarheid 68 %, K_{max} van 8 – 20 μg/ml en t_{max} van 1,5 tot 2 ure. Die absorpsie van rifampisien neem met ongeveer 30 % af wanneer dit saam met voedsel geneem word.
Verspreiding
Rifampisien word wyd deur die liggaam versprei en besit goeie penetrasie in meeste weefsels. Die vlakke in die SSS bereik egter slegs ongeveer 5 % van dié in plasma. Rifampisien is ongeveer 85 % proteïengebonde.
Metabolisme
Rifampisien word deur mikrosomale β-esterases en cholienesterases gemetaboliseer, wat die asetielgroep by posisie 25 verwyder, wat tot 25-O-desasetielrifampisien lei. Rifampisien word ook deur hidrolise na 3-formielrifampisien gemetaboliseer. 'n Belangrike baan vir die eliminasie van rifampisien is CYP3A4. Weens die outo-induksie verminder rifampisien met herhaalde toediening sy eie area onder die konsentrasietydkurwe (AOK).
Eliminasie:
Die halfleeftyd van rifampisien wissel van 2 - 5 ure. Rifampisien en sy metaboliete word deur die gal uitgeskei en via die fases geëlimineer, met eliminasie deur die uriene minder as een derde en minder vir die metaboliete.

Isoniasied
Absorpsie
Isoniasied word goed vanuit die maagdermkanaal geabsorbeer met 'n orale biobeskikbaarheid van 100 % vir 'n 300 mg dosis; K_{max} van 3,4 - 7,4 μg/ml vir vinnige asetileerders en K_{max} van 5,2 - 9 μg/ml vir stadige asetileerders; t_{max} van 1,1 ± 0,5 ure vir vinnige asetileerders en 1,1 ± 0,6 ure vir stadige asetileerders. Die absorpsie van isoniasied word deur voedsel en teensuurmiddels verminder.
Verspreiding
Die verhouding van isoniasied in die epiteel voeringsvloeistof tot dié in plasma is 1 - 2 en vir SSV 0,9. Ongeveer 10 % van die isoniasied is proteïengebonde.
Metabolisme
Isoniasied word deur hepatiese arielamien N-asetieltransferase tipe 2 (NAT-2) gemetaboliseer. Isoniasied word na ge-N-asetileerde na N-asetielisoniasied in reaksies wat asetiel-koA gebruik. Asetielisoniasied word deur die niere uitgeskei; asetielisoniasied kan ook deur CYP2E1 na asetielhidrasien omgeskakel word en dan na hepatotoksiese metaboliete. Alternatiewelik kan asetielhidrasien verder deur NAT-2 na di-asetielhidrasien wat nie toksies is nie, ge-asetileer word. Die opruiming van isoniasied in pasiënte word geklassifiseer as een van twee fenotipiese groepe: "stadige" en "vinnige" asetileerders. Vinnige asetileerders sal asetielhidrasien verwyder, terwyl stadige asetileerders of induksie van CYP2E1 tot meer toksiese metaboliete sal lei.
Eliminasie
Die halfleeftyd van isoniasied wissel van 1,1 ± 0,1 ure vir vinnige asetileerders en 3,1 ±1,1 ure vir stadige asetileerders. Tot soveel as 75 - 95 % van 'n dosis isoniasied word binne 24 uur in die uriene uitgeskei, hoofsaaklik as asetielisoniasied en isonikotiensuur.

Pirasinamied
Absorpse
Die orale biobeskikbaarheid van pirasinamied is > 90 %; K_{max} 35 μg/ml (19 - 103 μg/ml); t_{max} 8 ure.
Verspreiding
Pirasinamied word 20-voudig in die voeringsvloeistof van die longepiteel gekonsentreer. Ongeveer 10 % van pirasinamied word deur mikrosomale deamidase na pirasinoësuur (POA) gemetaboliseer en daarna na 5-hidroksi-POA gehidroksileer, wat dan deur die niere uitgeskei word.
Eliminasie
Cl (opruiming) en V_d (volume van verspreiding) neem toe namate die massa van die pasiënt toeneem (0,5 l/uur en 4,3 l vir elke 10 kg bó 50 kg en V_d is groot in mans (met 45 l). Die $t_{1/2}$ van pirasinamied sal op grond van massa en geslag wissel. Die suiwering van pirasinamied word in nierversaking verminder, daarom word die frekwensie van dosering verminder na drie keer per week in pasiënte met lae glomerulêre filtrasietempos. Pirasinamied word deur dialise verwyder. Daarom word herdosering na elke dialisesessie vereis.

Etambutol
Absorpse
Die orale biobeskikbaarheid van etambutol is ongeveer 80 %; K_{max} van 2 - 5 μg/ml; t_{max} van 2 - 4 ure.
Verspreiding
Ongeveer 10 - 40 % is proteïengebonde.
Metabolisme
Alkoholdehidrogenase oksideer etambutol na 'n aldehied, wat dan deur aldehieddehidrogenase na dikarboksielsuur geoksideer word. 80 % van etambutol word egter gladnie gemetaboliseer nie en word deur die niere uitgeskei. Daarom behoort etambutol teen 15 - 25 mg/kg, drie keer per week in plaas van daagliks, in pasiënte met nierversaking toegedien te word, selfs in pasiënte wat hemodialise ondergaan.
Eliminasie
Weens herverspreiding is die afname in etambutol bi-eksponensieel, met 'n $t_{1/2}$ van 3 ure in die eerste 12 ure en $t_{1/2}$ van 9 ure tussen 12 en 24 ure.

INDIKASIES
RIMTIB TABLETS word gebruik in die aanvanklike fase van behandeling van pulmonêre en ekstra-pulmonêre tuberkulose in nuwe volwasse pasiënte en die herbehandeling van alle pasiënte.

KONTRA-INDIKASIES
RIMTIB TABLETS word teenaangedui in:
- Pasiënte met 'n hipersensitiwiteit teen rifampisien, isoniasied, pirasinamied, etambutol of ander chemies verwante medikasies of teen enige van die eksipiënte van **RIMTIB TABLETS**.
- Die teenwoordigheid van geelsug of aktiewe lewersiekte.
- Pasiënte met optiese neuritis.
- Pasiënte met ingekorte nier- of lewerfunksie.
- Kinders jonger as 13 jaar oud.
- Gelyktydige gebruik van nevirapien (sien INTERAKSIES).

WAARSKUWINGS EN SPESIALE VOORSORGSMAATREËLS
Lewerfunksie behoort nagegaan te word vóór en gedurende behandeling en spesiale sorg behoort aan die dag gelê te word in pasiënte met alkoholisme, bejaardes en diegene met reeds bestaande lewersiekte.
Sorg behoort aan die dag gelê te word met die gebruik van **RIMTIB TABLETS** in die volgende pasiënte:
- Ingekorte nierfunksie: Dosisaanpassing mag nodig wees volgens die serumkonsentrasies van etambutol. Toename in die risiko van isoniasiedtoksisiteit in nierversaking.
- Gesigsdefekte: Indien visuele afwykings gedurende behandeling sou voorkom, moet hulle onmiddellik aangemeld en **RIMTIB TABLETS** gestaak word, afhangende van visuele evaluering. Optiese neuritis het na slegs 'n paar dae van behandeling voorgekom. Die meeste gevalle is na 'n paar weke of maande omkeerbaar. Visuele veranderinge kan unilateraal of bilateraal wees. Daarom behoort elke oog afsonderlik, asook beide oë saam getoets te word. Retinale bloeding het minder dikwels voorgekom.
- Pasiënte met 'n risiko van neuropatie of piridoksientekort, insluitende diegene met diabetes, alkoholisme, ondervoed, uremies of swanger; piridoksienaanvulling (in 'n daaglikse dosis van 10 tot 50 mg) word gewoonlik in hierdie gevalle vereis.
- Pasiënte met 'n geskiedenis van jig.
- Pasiënte met porfirie.
- Pasiënte met epilepsie aangesien dit stuipaanvalle kan presipiteer.
- Pasiënte met 'n geskiedenis van psigose.
- Pasiënte met diabetes: pirasinamied kan met urienketoonbepalings inmeng.
- Rifampisien kan die effek van orale voorbehoedmiddels verminder en pasiënte behoort aangeraai te word om na nie-hormoon metodes van geboortebeperking oor te skakel terwyl hulle **RIMTIB TABLETS** neem.
- Behandeling met **RIMTIB TABLETS** kan 'n rooi verkleuring van die uriene, trane en speeksel veroorsaak. Kontaklense kan onherstelbaar verkleur word.

In die volgende gevalle behoort die behandeling met **RIMTIB TABLETS** onmiddellik gestaak en die pasiënt geëvalueer te word:
- Uitslag en koors (geassosieer met isoniasied en rifampisien).
- Neiging tot bloeding (trombositopenie, purpura), skok.
- Nierversaking (geassosieer met rifampisien).
- Ingekorte gesig (geassosieer met etambutol). Periodieke oogondersoeke gedurende behandeling word voorgestel.
- Geelsug (geassosieer met isoniasied, rifampisien en pirasinamied).
- Verhoogde lewerensieme geassosieer met die kliniese tekens van hepatitis soos naarheid en braking of moegheid.

Lewerfunksiebepalings word op ALT en AST konsentrasies (d.i. serumalanien en aspartaat aminotransferase konsentrasies) gebaseer.

Hierdie toetse mag maandeliks gedurende behandeling nodig wees, veral in bejaardes, swanger vroue en diegene met reeds bestaande lewerbeskadiging. Erge en soms fatale hepatitis is aangemeld.

Effekte op die vermoë om te bestuur en met masjinerie te werk
RIMTIB TABLETS kan duiseligheid, ingekorte konsentrasie en/of lomerigheid veroorsaak. Pasiënte behoort aangesê te word dat as hulle hierdie simptome ondervind, hulle potensieel gevaarlike take soos motor bestuur en met masjinerie werk, moet vermy.

INTERAKSIES
Rifampisien:
Rifampisien induseer mikrosomale ensieme en kan daarom die opruiming van medisyne wat deur die lewer gemetaboliseer word, versnel.
Voorbeelde van medisyne wat deur sitochroom P 450 ensieme gemetaboliseer word is:
- Anti-disritmiese middels (bv. disopiramied, meksiletien, kinidien, propafenoon, tokainied, verapamiel),
- Anti-epileptika (bv. fenitoïen),
- Hormoonantagoniste (anti-estrogene bv. tamoksifen, toremifen, gestrinoon),
- Anti-psigotika (bv. haloperidol, aripiprasool),
- Anti-koagulante (bv. warfarien),
- Swamwerende middels (bv. flukonasool, itrakonasool, ketokonasool, vorikonasool),
- Anti-virusmiddels (bv. sakinavir, indinavir, efavirens, amprenavir, nelfinavir, atasanavir, lopinavir, nevirapien),
- Atovakuoon,
- Barbiturate (bv. heksabarbitoon),
- Beta-blokkeerders (bv. bisoprolol, propanolol),
- Ansiolitika en hipnotika (bv. diasepaam, bensodiasepien, soplikloon, solpidem),
- Kalsiumkanaal blokkeerders (bv. diltiaseem, nifedipien, verapamiel),
- Anti-bakteriese middels (bv. chlooramfenikol, klaritromisien, dapsoon, doksisiklien, fluorokinolone, telitromisien),
- Simetidien,
- Kortikosteroïede,
- Hartglikosiede (digoksien),
- Klofibraat,
- Sistemiese hormonale voorbehoedmiddels,
- Estrogeen,
- Anti-diabetiese middels (bv. chloorpropamied, tolbutamied, sulfonilureas, rosiglitasoon),
- Immuunonderdrukkende middels (bv. siklosporien, sirolimus, takrolimus),
- Irinotekan,
- Tiroïedhormoon (bv. levotiroksien),
- Losartaan,
- Pynstillers (bv. metadoon, narkotiese pynstillers),
- Prasikwantel,
- Progestogene,
- Kinien,
- Riluzool,
- Selektiewe 5-HT3 reseptorantagoniste (bv. ondansetron),
- Statiene wat deur CYP 3A4 gemetaboliseer word (bv. simvastatien).
- Sulfasalasien,
- Teofillien,
- Trisikliese antidepressante (bv. amitriptilien, nortriptilien).

Pasiënte wat orale kontrasepsie gebruik behoort aangesê te word om na nie-hormonale metodes van geboortebeperking gedurende terapie met **RIMTIB TABLETS** oor te skakel. (sien WAARSKUWINGS EN SPESIALE VOORSORGSMAATREËLS).

Die gelyktydige gebruik van alkohol, parasetamol, isoniasied en ander hepatotoksiese medikasie kan die voorkoms van rifampisiengeïnduseerde hepatotoksisiteit verhoog.

Die effektiwiteit van estrogeenbevattende orale preparate word verminder.

Daar is aangetoon dat terapeutiese vlakke van rifampisien die standaard mikrobiologiese bepalings vir serumfolaat en vit. B12 inhibeer. Alternatiewe bepalingsmetodes behoort oorweeg te word.

Verbygaande verhogings van bilirubien is aangemeld. Weens kompetisie vir biliêre uitskeiding kan rifampisien die biliêre uitskeiding van kontrasmedia wat vir die visualisering van die galblaas gebruik word, inkort. Daarom behoort hierdie toetse vóór die oggenddosis van rifampisien en derhalwe **RIMTIB TABLETS** uitgevoer te word.

Die gelyktydige toediening van teensuurmiddels kan die absorpsie van rifampisien verminder. Die daaglikse dosisse van **RIMTIB TABLETS** behoort ten minste een uur voor die inname van 'n teensuurmiddel toegedien te word.

As pirasinamied-aminosalisielsuur en **RIMTIB TABLETS** saam in 'n behandelingsregimen ingesluit word, behoort hulle nie minder as agt ure uit mekaar toegedien nie word om bevredigende bloedvlakke te verseker.

Die potensiaal vir lewertoksisiteit word met narkose verhoog.

Wanneer **RIMTIB TABLETS** saam met halotaan of isoniasied toegedien word, neem die potensiaal vir hepatotoksisiteit toe. Die gelyktydige gebruik van **RIMTIB TABLETS** en halotaan behoort vermy te word. Pasiënte wat beide rifampisien en isoniasied, soos bevat in **RIMTIB TABLETS** neem, behoort noukeurig vir hepatotoksisiteit gemonitor te word.

Antiretrovirusmiddels:
Rifampisien, soos bevat in **RIMTIB TABLETS**, kan die metabolisme van sidovudien, die NNTTIs delavirdien, efavirens, en nevirapien en die MIV-proteaseïnhibeerders induseer, wat tot sub-terapeutiese plasmakonsentrasies lei. Verder inhibeer MIV-proteaseïnhibeerders die metabolisme van rifampisien, wat tot verhoogde plasmakonsentrasies van rifampisien en 'n toename in die voorkoms van newe-effekte lei.

Die gelyktydige gebruik van **RIMTIB TABLETS** en nevirapien word teenaangedui (sien **KONTRA-INDIKASIES**).

Rifampisien, soos bevat in **RIMTIB TABLETS**, verminder die konsentrasie van efavirens en daar word aanbeveel dat die efavirens dosis in pasiënte wat meer as 60 kg weeg, verhoog word.

Isoniasied:
Die chroniese gebruik van isoniasied kan die plasma-opruiming en die duurte van werking van alfentaniel, kumaren anti-stolmiddels (warfarien), anti-epileptika (bv. fenitoïen, primidoon, karbamasepien, etosuksimied), bensodiasepiene (bv diasepam), chloorsoksasoon en teofillien verleng. 'n Toepaslike aanpassing van die anti-stuipmiddel kan nodig wees. Die gelyktydige gebruik van parasetamol, alkohol, rifampisien en ander hepatotoksiese medisyne kan die potensiaal vir isoniasiedgeïnduseerde hepatotoksisiteit verhoog.

Aluminiumbevattende teensuurmiddels kan die absorpsie van isoniasied vertraag en die serumkonsentrasies daarvan verlaag. Die inname van sekere soorte kaas bv. switsers of cheshire, of vis bv. tuna kan tot 'n jeukerige vel, vinnigkloppende hart, kouerillings of hoofpyn lei. Glukokortikoïede kortikosteroïede kan die lewermetabolisme en/of uitskeiding van isoniasied verander. Die gelyktydige gebruik van siklosserien, disulfiram en ander neurotoksiese medisyne kan die potensiaal van SSS-toksisiteit verhoog.

Isoniasied kan ook die metabolisme van enfluraan verhoog, wat tot die vorming van potensieel nefrotoksiese anorganiese fluoriedmetaboliete kan lei. Interaksies met ketokonasool en mikonasool is aangemeld. Vals-positiewe reaksies met die kopersulfaat urienglukosetoets kan voorkom.

Antivirusmiddels:
Die opruiming van isoniasied word ongeveer verdubbel wanneer dit saam met saksitabien toegedien word. **RIMTIB TABLETS** behoort met sorg saam met stavudien en salsitabien gebruik te word aangesien stavudien, salsitabien en isoniasied geassosieer is met die ontwikkeling van perifere neuropatie. Daar is aangetoon dat die gebruik van **RIMTIB TABLETS** saam met stavudien die voorkoms van perifere neuropatie verhoog.

Pirasinamied:
Pirasinamied kan die effektiwiteit van jigterapie (bv. allopurinol, kolgisien, probenesied of sulfinpirasoon) verlaag en dosisaanpassings van hierdie medisyne mag nodig wees. Pirasinamied kan die serumkonsentrasies van siklosporien verlaag wat moontlik tot onvoldoende immuunonderdrukking kan lei. Die gebruik van pirasinamied en derhalwe **RIMTIB TABLETS** en ander diuretika: Die bykomende potensiaal vir die verhoging van serumuraatvlakke behoort oorweeg te word.

Etambutol:
Die gelyktydige toediening van neurotoksiese medisyne saam met etambutol kan neurotoksiese effekte soos optiese en perifere neuritis potensieer.

SWANGERSKAP EN LAKTASIE
Die veiligheid is nie in swangerskap vasgestel nie. Al die komponente van **RIMTIB TABLETS** word in borsmelk uitgeskei. Die veiligheid gedurende laktasie is nie vasgestel nie.

DOSIS EN GEBRUIKSAANWYSINGS
Neem **RIMTIB TABLETS** met 'n vol glas water een uur vóór of 2 ure na 'n maaltyd. As gastrointestinale irritasie egter voorkom, kan die tablette saam met voedsel geneem word. As aluminiumbevattende teensuurmiddels geneem word, moet dit een uur vir die tabletdosis geneem word.

Die aanbevole dosisse, gebaseer op die pasiënt se liggaamsmassa, toegedien vir die 2-maande aanvanklike behandeling in volwassenes en kinders ouer as 13 jaar is as volg:

Voor-behandelings liggaamsmassa	Een keer daaglikse dosering
30 - 37 kg	2 tablette
38 - 54 kg	3 tablette
55 - 70 kg	4 tablette
71 kg en meer	5 tablette

NEWE-EFFEKTE
Newe-effekte geassosieer met rifampisien
Afwykings van die bloed- en limfstelsel:
Minder dikwels: Bloeddiskrasieë, ongewone bloeding of kneusing, trombositopenie, purpura, hemolise, eosinofilie, leukopenie, hemolitiese anemie, agranulositose.

Afwykings van die immuunstelsel:
Frekwensie onbekend: Lupusagtige sindroom. 'n 12-uur Griepsindroom wat gewoonlik na 3 - 6 maande van behandeling voorkom, gewoonlik met dosisse van 20 mg/kg of meer; kan as koors, kouekoors, beenpyn en malaise, kortademigheid en hyging presenteer; afname van bloeddruk en skok; akute hemolitiese anemie, akute nierversaking, gewoonlik weens buisnekrose of akute interstisiële nefritis; anafilakse.

Afwykings van die senuweestelsel:
Frekwensie onbekend: Hoofpyn, lomerigheid, duiseligheid, ataksie, gevoelloosheid, verwardheid en algemene gevoelloosheid.

Oogafwykings:
Minder dikwels: Onduidelike gesig, gesigsafwykings, oogirritasie.

Gastrointestinale afwykings:
Dikwels: Naarheid, braking, anoreksie, buikongemak, diarree en epigastriese ongemak.
Minder dikwels: Pseudomembraneuse kolitis.

Hepatobiliêre afwykings:
Minder dikwels: Hepatitis (wat fataal mag wees), prodromale hepatitissimptome wat die verlies aan eetlus, naarheid of braking en ongewone moegheid of swakheid kan insluit.

Afwykings van die vel en subkutane weefsels:
Dikwels: Kutane reaksies wat tipies uit hittegloede en jeuk, met of sonder uitslag bestaan.
Minder dikwels: Meer ernstige kutane hipersensitiwiteitsreaksies, toksiese epidermale nekrolise, afskilferende dermatitis, pemfigoïede reaksies, erythema multiforme insluitende Stevens-Johnson se sindroom en vaskulitis.

Muskuloskeletale en bindweefselafwykings:
Dikwels: Spierswakheid en miopatie.

Nier- en urienafwykings:
Minder dikwels: Interstisiële nefritis, verandering van nierfunksie, nierversaking, ontoereikende bynierfunksie in pasiënte met beklemde bynierfunksie.

Afwykings van die reproduksiestelsel en bors:
Minder dikwels: Afwykings van die menstruele siklus, afname in die effektiwiteit van orale voorbehoedmiddels.

Algemene afwykings en kondisies by die plek van toediening:
Dikwels: Rooi-oranje verkleuring van die uriene, feses, speeksel, sputum, sweet en trane. Kontaklense kan permanent verkleur word.
Minder dikwels: Swam oorgroeiing bv. seer mond en tong.
Frekwensie onbekend: Edeem.

Newe-effekte geassosieer met isoniasied:
Afwykings van die bloed- en limfstelsel:
Minder dikwels: Verskeie hematologiese afwykings, insluitende anemie, eosinofilie, sideroblastiese anemie, agranulositose, hemolitiese anemie, trombositopenie, neutropenie, aplastiese anemie.

Afwykings van die immuunstelsel:
Minder dikwels: Hipersensitiwiteitsreaksies insluitende verskeie velerupsies, koors, limfadenopatie, vaskulitis en anafilakse, lupusagtige reaksies.

Metabolisme en voedingsafwykings:
Minder dikwels: Hiperglukemie, metaboliese asidose, pellagra.

Psigiatriese afwykings:
Minder dikwels: Psigotiese reaksies (gekenmerk deur delusies, hallusinasies en verwardheid).

Afwykings van die senuweestelsel:
Dikwels: Perifere neuropatie.
Minder dikwels: Polineuritis geassosieer met parestesie, spierswakheid, verlies aan tendonrefleksie, stuipaanvalle, toename in die frekwensie van stuipaanvalle in pasiënte met epilepsie, ingekorte geheue, toksiese enkefalopatie.

Oogafwykings:
Minder dikwels: Optiese neuritis (onduidelike gesig of gesigsverlies, met of sonder oogpyn).

Afwykings van die oor en labirint:
Minder dikwels: Vertigo.

Gastrointestinale afwykings:
Dikwels: Diarree, naarheid en braking, maagpyn, hardlywigheid, droë mond, pankreatitis, epigastriese ongemak.

Hepatobiliêre afwykings:
Dikwels: Hepatitis (erg en soms fataal), verhoogde lewerensieme met kliniese tekens van hepatitis (verlies aan eetlus, naarheid of braking, ongewone moegheid of swakheid); die voorkoms van lewerbeskadiging is die hoogste in pasiënte ouer as 35 jaar, diegene wat stadige asetileerders is, asook dié wat alkohol op 'n daaglikse basis gebruik.

Afwykings van die vel en subkutane weefsel:
Frekwensie onbekend: Kutane reaksies insluitende uitslag, akne, Stevens-Johnson se sindroom, afskilferende dermatitis, pemfigus, lupusagtige, erteemagtige reaksies.

Muskuloskeletale en bindweefselafwykings:
Frekwensie onbekend: 'n Rumatieksindroom, hiperrefleksie.

Nier- en urienafwykings:
Minder dikwels: Urienretensie.

Afwykings van die reproduksiestelsel en bors:
Minder dikwels: Ginekomastie.

Newe-effekte wat met pirasinamied geassosieer word.
Afwykings van die bloed- en limfstelsel:
Minder dikwels: Sideroblastiese anemie, trombositopenie.

Afwykings van die immuunstelsel:
Minder dikwels: Angioëdeem.

Metabolisme en voedingsafwykings:
Minder dikwels: Pellagra.

Gastrointestinale afwykings:
Minder dikwels: Anoreksie, naarheid, braking, agteruitgang van maagulkus.

Hepatobiliêre afwykings:
Dikwels: Hepatotoksisiteit (dit wil voorkom asof die frekwensie dosisafhanklik is).

Afwykings van die vel en subkutane weefsels:
Minder dikwels: Fotosensitiwiteit, veluitslag, pruritus.

Muskuloskeletale, bindweefsel- en beenafwykings:
Dikwels: Artralgie wat met hiperurisemie verband hou.
Minder dikwels: Jigagtige artritis.

Nier- en urienafwykings:
Minder dikwels: Disurie.

Algemene afwykings en kondisies by die plek van toediening:
Minder dikwels: Malaise, koors.

Newe-effekte geassosieer met etambutol:
Afwykings van die bloed- en limfstelsel:
Minder dikwels: Leukopenie, eosinofilie, trombositopenie.

Afwykings van die immuunstelsel:
Minder dikwels: Hipersensitiwiteitsreaksies insluitende veluitslag, pruritus, koors, leukopenie en gewrigspyn.

Psigiatriese afwykings:
Minder dikwels: Verwardheid, disoriëntering, hallusinering.

Afwykings van die senuweestelsel:
Dikwels: Hoofpyn, duiseligheid, perifere neuropatie.

Oogafwykings:
Minder dikwels: Optiese neuritis, retrobulbêre neuritis met 'n afname in visuele skerpheid wat lyk asof dit dosisverwant is en wat mees dikwels met daaglikse dosisse van 25 mg/kg liggaamsmassa en na 2 maande van terapie voorkom; vernouing van die gesigsveld; sentrale of perifere skotoom en groen/rooi kleurblindheid wat een of beide oë aantas.

Gastrointestinale afwykings:
Dikwels: Buikpyn, anoreksie, naarheid, braking, en metaalsmake.

Hepatobiliêre afwykings:
Minder dikwels: Geelsug, verbygaande lewerdisfunksie.

Muskuloskeletale, bindweefsel- en beenafwykings:
Minder dikwels: Akute jigagtige artritis.

Nier- en urienafwykings:
Minder dikwels: Afname in die nieropruiming van uraat.

Algemene afwykings en kondisies by die plek van toediening:
Minder dikwels: Malaise.

BEKENDE SIMPTOME VAN OODOSERING EN BESONDERHEDE VAN DIE BEHANDELING DAARVAN
Vir simptome van oordosering, verwys na **NEWE-EFFEKTE**. Die behandeling van oordosering bestaan uit maagspoeling, simptomatiese en ondersteunende terapie.

IDENTIFIKASIE
Ligte dofgeel, bikonvekse, kapsulevormige, filmbedekte tablet met ongedrukte oppervlakkies aan beide kante.

AANBIEDING
HDPE houer:
Silwergekleurde, driedubbel gelamineerde aluminium sakkie (PET/Al/LLDPE) in 'n wit plastiese (HDPE) houer wat by die mond met aluminium geseël word en met 'n wit HDPE skroefdeksel afgesluit is. Pakgroottes sluit 500 en 1000 tablette in.
Stolpverpakking:
Silwergekleurde aluminiumbasis foelie met 'n ambergekleurde (PVC/PE/PVdC) dekfoelie. Die stolpstrokie word in 'n voorafgedrukte karton verpak. Pakgroottes sluit 28 (1 stolpstrokie van 28 tablette), 56 (2 stolpstrokies van 28 tablette), 84 tablette (3 stolpstrokies van 28 tablette), 112 tablette (4 stolpstrokies van 28 tablette) en 100 (10 stolpstrokies van 10 tablette) in.
Strookverpakking:
Tablette word in silwergekleurde aluminiumfoelie (sag getemper), gelamineer met lae digtheid poliëtileen film as die dek-en vormingsmateriaal. Die aluminium strook word in 'n voorafgedrukte karton verpak. Pakgroottes sluit 28 (1 strokie van 28 tablette), 56 (2 strokies van 28 tablette), 84 tablette (3 strokies van 28 tablette), 112 tablette (4 strokies van 28 tablette) en 100 (10 strokies van 10 tablette) in.

BERGINGSINSTRUKSIES
Berg by of onder 25 °C. Beskerm teen vog en lig.
Hou die aluminiumsakkie in die HDPE tot wanneer vir gebruik benodig word.
Hou die stolpstrokie of strookverpakking in die karton tot wanneer vir gebruik benodig word.
HOU BUITE BEREIK VAN KINDERS

REGISTRASIENOMMER
49/20.2.3/0381

NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE SERTIFIKAAT VAN REGISTRASIE
Macleods Pharmaceuticals SA(Edms.) Bpk.
Kantoorblok 1,
Bassonia Estate Office Park (Oos),
Cussonialaan 1,
Bassonia Rock, Uitb. 12,
Alberton.

DATUM VAN PUBLIKASIE VAN HIERDIE VOUBILJET
25 November 2016

INLIGTINGSBLAADJIE VIR PASIËNTE

SKEDULERINGSTATUS
S4

EIENDOMSNAAM, STERKTE EN FARMASEUTIESE VORM
RIMTIB TABLETS (Filmbedekte tablet).
Rifampisien 150 mg, isoniasied 75 mg, pirasinamied 400 mg, Etambutolhidrochloried 275 mg

LEES DIE HELE BROSJURE SORGVULDIG VOORDAT U BEGIN OM RIMTIB TABLETS TE NEEM
- Hou hierdie blaadjie. U mag dit moontlik weer wil lees.
- Indien u enige verdere vrae het, moet u asseblief u dokter of apteker raadpleeg.
- **RIMTIB TABLETS** is vir u persoonlik voorgeskryf en u behoort nie u medisyne met ander mense te deel nie. Dit mag hulle skade aandoen, ookal het hulle dieselfde simptome as u.

WAT RIMTIB TABLETS BEVAT
Elke filmbedekte tablet bevat:
Rifampisien 150 mg, isoniasied 75 mg, pirasinamied 400 mg, Etambutolhidrochloried 275 mg.
Suikervry.
Eksipiënte: skellak, gesuiwerde talk, povidon, dinatriumedetaat, anhidriese kolloïdale silika, mieliestysel, kroskarmellose natrium, krospovidoon, kalsiumstearaat, hipromellose, polivinielalkohol, lesitien (soja), Xanthan kougom, kleurstowwe (titaandioksied, sonskyngeel).

WAARVOOR RIMTIB TABLETS GEBRUIK WORD
RIMTIB TABLETS is 'n antimikrobiese middel wat in die behandeling van tuberkulose (TB-infeksie) in volwassenes gebruik word.

VOORDAT U RIMTIB TABLETS NEEM
Moenie RIMTIB TABLETS neem as u aan enige van die kondisies hieronder ly nie:
- As u hipersensitief (allergies) teen rifamisiene is, insluitende rifampisien, isoniasied, pirasinamied, etambutol of enige van die ander bestanddele van **RIMTIB TABLETS**.
- As u aan enige soort lewersiekte of geelsug (geel verkleuring van die vel en oë) ly.
- As u trombositopenie en purpura (kneusing, neusbloei of bloeding in die mond en tandvleis, veluitslag met speldepunt rooi kolletjies) ontwikkel terwyl u **RIMTIB TABLETS** neem.
- As u aan enige oogsiekte bv. inflammasie van die oogsenuwees (optiese neuritis) ly.
- **RIMTIB TABLETS** behoort nie aan kinders jonger as 13 jaar oud gegee word nie.
- Die gelyktydige gebruik saam met nevirapien (medisyne wat vir die behandeling van MIV gebruik word).

Neem spesiale sorg met RIMTIB TABLETS
- Voordat u **RIMTIB TABLETS** neem, moet u u dokter in kennis stel:
- As u aan 'n nier- of lewersiekte ly.
- As u aan alkoholisme ly.
- As u aan porfirie ly.
- As u aan epilepsie ly.
- As u 'n geskiedenis van jig het.
- As u 'n diabeet is.
- As u orale voorbehoedmiddels gebruik, behoort u na alternatiewe metodes van geboortebeperking te verander.

Terwyl u **RIMTIB TABLETS** neem:
- Moet u onmiddellik u dokter in kennis stel as u enige oogprobleme of probleme met u sig waarneem.
- As u 'n diabeet of alkoholis is, of ondervoed is en u ly aan 'n niersiekte, en u het 'n risiko om gevoelloosheid of swakheid van u arms en bene te ontwikkel, sal u dokter bykomende piridoksienaanvulling (vitamien B6) voorskryf.
- Kan u uriene, stoelgang, speeksel, sweet en trane verkleur wees.
- Kan u kontaklense permanent verkleur.

Die neem van RIMTIB TABLETS saam met voedsel en vloeistof
RIMTIB TABLETS behoort sonder voedsel geneem te word. Vermy tiramienbevattende voedsel (bv. kaas, rooiwyn) en histamienbevattende kosse (bv. katonkel, tuna en tropiese vis). Vermy alkohol.

Swangerskap en borsvoeding

> As u swanger is of u baba borsvoed, moet u asseblief u dokter, apteker of ander professionele gesondheidswerker vir advies nader voordat u **RIMTIB TABLETS** neem.

Die veiligheid van **RIMTIB TABLETS** gedurende swangerskap en borsvoeding is nie vasgestel nie.

Bestuur en die gebruik van masjinerie
RIMTIB TABLETS kan duiseligheid, ingekorte konsentrasie en/of lomerigheid veroorsaak. As u duiselig of lomerig voel terwyl u **RIMTIB TABLETS** neem, moet u nie bestuur of met enige gereedskap of masjinerie werk nie.

Die neem van ander medisyne saam met RIMTIB TABLETS:
RIMTIB TABLETS kan die effek van ander medisyne en ander medisyne kan die effek van **RIMTIB TABLETS** beïnvloed.
Terwyl u **RIMTIB TABLETS** neem, is dit veral belangrik om u dokter of professionele gesondheidswerker daarvan in kennis te stel as u enige van die volgende neem:
- Parasetamol, aspirien, en ander pynstillers.
- Teensuurmiddels wat magnesiumtrisilikaat, aluminiumhidroksied of natriumbikarbonaat bevat.
- Medisyne wat gebruik word om epilepsie te behandel soos etosuksimied, fenitoïen en karbamasepien.
- Medisyne soos itrakonasool, flukonasool en ketokonasool wat gebruik word om swaminfeksies te behandel.
- Kortikosteroïede wat vir inflammatoriese kondisies gebruik word.
- Teofillien wat in hoesmiddels en asmamedikasie gebruik word.
- MIV-medisyne soos sidovudien, delavirdien, efavirens, nevirapien, sakinavir, ritonavir, lopinavir, durunavir, atasanavir, fosamprenavir, stavudien en salsitabien.
- Tiroïedhormone.
- Orale hipoglukemiese medisyne, soos gebruik in behandeling van diabetes (bv. chloorpropamied, tolbutamied, sulfonilureas, rosiglitasoon)
- Medisyne gebruik vir jig (bv. allopurinol, kolgisien, probenesied of sulfinpirasoon).
- Ander medisyne, insluitende tamoksifen, toremifen (vir borskanker), gestrinoon (vir endometriose), halotaan verdowingsmedisyne), asatioprien, siklosporien, sirolimus, takrolimus (immuunonderdrukkers), atovakoon, chlooramfenikol, siklosserien, dapsoon, doksisiklien, (medisyne gebruik vir infeksies), simetidien (gebruik vir maagulkusse), klofibraat, simvastatien (verlaag cholesterol), warfarien (verdun die bloed), diasepam, amitriptilien, nortriptilien (vir angs en depressie), sopikloon, solpidem (vir slaapafwykings), heksobarbitoon (sedeermiddel), haloperidol, mariprasool (vir geestesiektes), metadoon (vir pyn), sulfasalasien (gebruik vir rumatiese artritis en inflammatoriese dermsiekte), kinien (gebruik in malaria), irinotikan (vir kanker), disulfiram (vir alkoholafhanklikheid) en medisyne soos digoksien, disopiramied, lorkaïnied, meksilitien, propafenoon, kinidien, tokainied, verapamiel, propranolol, enalapriel, losartan, gebruik in die behandeling van hartsiektes.
- Enfluraan, gebruik in algemene narkose behoort nie saam met **RIMTIB TABLETS** gebruik te word nie.
- Alkohol.

> Stel altyd u professionele gesondheidswerker in kennis as u enige ander medisyne gebruik. Dit sluit komplementêre en tradisionele medisyne in.

HOE OM RIMTIB TABLETS TE NEEM

> Moenie medisyne wat vir u voorgeskryf is met enigiemand anders deel nie.
> Neem **RIMTIB TABLETS** altyd presies soos deur u dokter voorgeskryf. Bevestig met u dokter of apteker as u onseker is. As u van mening is dat die effek van **RIMTIB TABLETS** te sterk of te swak is, moet u u dokter of apteker raadpleeg.

U dokter sal die aantal tablette wat u daagliks benodig op grond van u liggaamsmassa voorskryf.
Die tablette behoort verkieslik op 'n leë maag (een uur vóór of twee ure na 'n maaltyd) as 'n enkeldosis geneem te word. As maagirritasie egter voorkom, kan die tablette saam met voedsel geneem word.
RIMTIB TABLETS behoort ten minste een uur voor die inname van aluminiumbevattende teensuurmiddels geneem te word.

Die aanbevole aantal **RIMTIB TABLETS**, gebaseer op die pasiënt se liggaamsmassa, toegedien vir die 2-maande aanvanklike behandeling in volwassenes en kinders ouer as 13 jaar is as volg:

Voor-behandelings liggaamsmassa	Een keer daaglikse dosering
30 - 37 kg	2 tablette
38 - 54 kg	3 tablette
55 - 70 kg	4 tablette
71 kg en meer	5 tablette

Moenie die gebruik van RIMTIB TABLETS staak omdat u beter voel nie.
As die volle behandeling soos deur u dokter voorgeskryf, nie voltooi word nie, mag sommige van die bakterieë wat vir die TB-infeksie verantwoordelik is, nie gedood word nie. Hierdie bakterieë kan aanhou om te groei en vermenigvuldig sodat die infeksie nie heeltemal opklaar nie, of dit kan terugkeer.

As u te veel RIMTIB TABLETS geneem het
Simptome sluit naarheid, braking maagpyn, duiseligheid, hoë bloedsuikervlakke, hoë suurvlakke in die bloed, hallusinasies, moeilike met asemhaling en onderdrukking van die sentrale senuweestelsel met stuipaanvalle en koma. Ander tekens van oordosering sluit helder rooi verkleuring van die vel en slymvliese, afname in geestelike skerpheid, swelling van die gesig en oë en algemene jeuk.
As enige van hierdie simptome voorkom, moet u onmiddellik mediese hulp kry deur u dokter of professionele gesondheidswerker te raadpleeg.

> In die geval van oordosering, raadpleeg u dokter of apteker. As hulle nie beskikbaar is nie, kontak u naaste hospitaal of gifbeheersentrum.

As u vergeet het om RIMTIB TABLETS te neem
As u vergeet het om 'n dosis **RIMTIB TABLETS** te neem, moet u dit neem sodra u daarvan onthou. As dit egter byna tyd vir die volgende dosis is, slaan die oorgeslaande dosis oor en gaan met die gereelde doseringskedule voort. Moet nooit die dosis verdubbel nie.

MOONTLIKE NEWE-EFFEKTE
Stel u dokter onmiddellik in kennis of gaan na die naaste hospitaal, u het moontlik dringende mediese aandag nodig as u een van die volgende waarneem:
- Rooi en/of jeukerige vel, blasies of puisies.
- Swelling van die gesig, lippe, tong of keel wat moeite met asemhaling of sluk veroorsaak.
- Kortademigheid en hyging.
- Verwardheid, slaperigheid, koue, klam vel, vlak of moeilike asemhaling, vinnige hartklop of u vel is bleker as normaal. Hierdie kan tekens van skok wees.
- Blaasvorming, velafskilfering, bloeding, korsvorming of vloeistofgevulde kolle op enige gedeelte van die vel.
- Skielike veranderinge in sig, onduidelike of verwronge sig.
- Bloed in die uriene of enige afwykings in urinering, swelling veral van die bene, enkels of voete.
- Koors, kouekoors, hoofpyn of duiseligheid.
- Kneusing, neusbloeding of bloeding van die mond en tandvleis, uitslag met speldepunt rooi kolletjies.
- Moegheid, swakheid, malaise (algemene gevoel van ongesteldheid), anoreksie (verlies aan eetlus), naarheid of braking.
- Onvermoë om rooi en groen te sien.

Stel u dokter onmiddellik in kennis as u enige van die volgende newe-effekte waarneem, veral as hulle 'n paar weke nadat u met die behandeling met RIMTIB TABLETS gestaak het, voorkom:
- Erge maagkrampe.
- Waterige en erge diarree, wat ook bloederig kan wees.
- Koors in kombinasie met een of beide van bogenoemde.

U mag aan 'n ernstige kondisie van die dermkanaal ly wat dringende mediese aandag vereis.
Moenie enige medisyne vir diarree neem voordat u nie u dokter geraadpleeg het nie.

Stel u dokter in kennis wanneer u een van die volgende waarneem en dit u bekommer:
- Geel verkleuring van die vel of oë.
- Sooibrand, anoreksie, naarheid, braking, winderigheid, krampe of diarree, hardlywigheid, droë mond, agteruitgang van maagulkus, metaalsmaak.
- Hoofpyn, lomerigheid, moegheid, onvermoë om te konsentreer of verwardheid.
- Gevoelloosheid en prikkeling in die hande of voete.
- U stuipaanvalle raak erger of u begin om stuipaanvalle te kry.
- Swak koördinasie, spierswakheid, spierpyn, pyn in die vingers of tone, warm vel oor die aangetaste gewrigte, gevoelloosheid, ongewone toename in refleksie en trekkings.
- Mondsproei - wit kolletjies, seer tong en mond.
- Onduidelike sig, of verlies aan sig met of sonder oogpyn, oogirritasie.
- Menstruele afwykings.
- Tydelike gehoorverlies.
- Vertigo (duiseligheid met 'n draaigevoel).
- Vergroting van die borste.
- Veluitslag, gloede en jeukerige vel, aknee.
- Geestesiekte met vreemde of kommerwekkende gedagtes of buie, korttermyn geheueverlies, tekort aan skerpheid en reaktiwiteit.
- Waterretensie (edeem) wat swelling van die gesig, maag, arms of bene kan veroorsaak.
- Toename in dors, meer gereelde toiletbesoeke en moegheid: u suiker bloedvlakke mag hoog wees.

Nie al die newe-effekte wat vir **RIMTIB TABLETS** aangemeld is, word in hierdie brosjure ingesluit nie. As u algemene gesondheid agteruitgaan of as u enige ongewone effekte ondervind terwyl u **RIMTIB TABLETS** neem, moet u asseblief u dokter, apteker of ander professionele gesondheidswerker om advies raadpleeg.
As u enige newe-effekte ondervind wat nie in hierdie brosjure genoem word nie, moet u asseblief u dokter of apteker raadpleeg.

OPBERGING EN WEGDOEN VAN RIMTIB TABLETS
Berg by of onder 25 °C.
Hou die aluminiumsakkie in die HDPE tot wanneer vir gebruik benodig word. Hou die stolpstrokie of strookverpakking in die karton tot wanneer vir gebruik benodig word.
Bewaar hierdie medisyne weg van lig en vog.
Enige medisyne wat verval het en enige ongebruikte medisyne kan na u apteker teruggeneem word.
BERG ALLE MEDISYNE BUITE DIE BEREIK VAN KINDERS.

AANBIEDING
RIMTIB TABLETS
HDPE houer:
Silwergekleurde, driedubbel gelamineerde aluminium sakkie (PET/Al/LLDPE) in 'n wit plastiese (HDPE) houer wat by die mond met aluminium geseël word en met 'n wit HDPE skroefdeksel afgesluit is. Pakgroottes sluit 500 en 1000 tablette in.
Stolpverpakking:
Silwergekleurde aluminiumbasis foelie met 'n ambergekleurde (PVC/PE/PVdC) dekfoelie. Die stolpstrokie word in 'n voorafgedrukte karton verpak. Pakgroottes sluit 28 (1 stolpstrokie van 28 tablette), 56 (2 stolpstrokies van 28 tablette), 84 tablette (3 stolpstrokies van 28 tablette), 112 tablette (4 stolpstrokies van 28 tablette) en 100 (10 stolpstrokies van 10 tablette) in.
Strookverpakking:
Tablette word in silwergekleurde aluminiumfoelie (sag getemper), gelamineer met lae digtheid poliëtileen film as die dek-en vormingsmateriaal. Die aluminium strook word in 'n voorafgedrukte karton verpak. Pakgroottes sluit 28 (1 strokie van 28 tablette), 56 (2 strokies van 28 tablette), 84 tablette (3 strokies van 28 tablette), 112 tablette (4 strokies van 28 tablette) en 100 (10 strokies van 10 tablette) in.

IDENTIFIKASIE
Ligte dofgeel, bikonvekse, kapsulevormige, filmbedekte tablet met ongedrukte oppervlakkies aan beide kante.

REGISTRASIENOMMER
49/20.2.3/0381

NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE SERTIFIKAAT VAN REGISTRASIE
Macleods Pharmaceuticals SA(Edms.) Bpk.
Kantoorblok 1,
Bassonia Estate Office Park (Oos),
Cussonialaan 1,
Bassonia Rock, Uitb. 12,
Alberton.

DATUM VAN PUBLIKASIE VAN HIERDIE INLIGTINGSBROSJURE
25 November 2016

MACLEODS

PACKAGING RESEARCH & DEVELOPMENT

Restricted Circulation

(Front Page)

ARTWORK / PRINTPROOF APPROVAL FORM

Note : Change in composition of coating materials.

1. Product: RIMTIB TABLETS	
2. Country: South Africa	3. Packaging component: Package Insert & Patient Information Leaflet
4. No. of Colours: 1 Colour	5. Pantone Shade No.: Black
6. Specification: 40 gsm bible paper	
7. Machine Layout No.: NA	8. Dimensions: 435 x 490 mm
9. Design / Style: NA	10. Item code No.: PM02508303
11. Artwork has been made: Actual Size	12. Pharma code No.: 27677 mini
13. Barcode/NDC no: NA	14. Supersedes Item code No: PM02508302
15. Revision no: 02	16. File Name E:\ANDA Regulatory\South Africa\RIMTIB\MS\RIMTIB TABLETS PI & PIL PM02508303.cdr
Approved By:	17. Location: Daman

PRD	M.A. HOLDER	RAD	QC	PRODN.	QA
08/09/24	Vanita Rajoo	08/09/24	09/09/24	09/09/24	09/09/24

Note: 1. To follow overleaf checklist for approval of Artwork / Print proof.

Instructions to Vendor :

1. Before processing, please ensure First pull out / Commercial supply should match with approved Artwork with respect to Design, Size, Fonts & Text.
2. Print proof to represent full printing area with Station Numbers.

FRM/CQA/021/04-01

Reason for revision :	Item code	Artwork Release Date	Artwork Implementation Date
1) New Artwork for South Africa	PM02508301	31-10-17	08/02/2018
2) Address change	PM02508302	12-6-18	27/06/2018
3) Change in composition of coating materials.	PM02508303		