**PACKAGE INSERT**

**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, disodium edetate, colloidal anhydrous silica, maize starch, croscarmellose sodium, crospovidone, calcium stearate, diethyl phthalate, castor oil, magnesium stearate, 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*-desacetyl 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 – 9 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 (19 – 103) µg/mℓ; $t_{max}$ of 6 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 NNRTI's 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), chrozoxazone 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 film 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

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**DATE OF PUBLICATION OF THE PACKAGE INSERT**

25 November 2016