PACKAGE INSERT

SCHEDULING STATUS: S4

PROPRIETARY NAMES AND DOSAGE FORMS:

RIMACTANE 150 (capsules)

RIMACTANE 300 (capsules)

RIMACTANE 450 (tablets)

RIMACTANE 600 (tablets)

RIMACTANE 300 VIAL (vials)

COMPOSITION:

Capsules: Rifampicin 150 mg and 300 mg.

Tablets: Rifampicin 450 mg and 600 mg.

Vials: Rifampicin sodium equivalent to rifampicin 300 mg, with 1,6 % *m/m* sodium sulphoxylate formaldehyde as preservative.

Inactive ingredients:

Rimactane 150 contains ammonium hydroxide 28 % E527, calcium stereate, dehydrated ethanol, gelatine, isopropyl alcohol, iron oxide black E 172, iron oxide red (EEC No. E172) (C.I. 77491), N-Butyl alcohol, propylene glycol E1520, shellac glaze 45% (20 % Esterified) in ethanol, titanium dioxide (EEC No. E171) (C.I. 77891)

Rimactane 150 contains sugar (lactose 25 mg per capsule).

Rimactane 300 contains calcium stereate, iron oxide black (C.I. 77492), iron oxide red (C.I. 77491), iron oxide yellow (C.I. 77491), gelatine, titanium dioxide (C.I. 77891 and C.I. 77499)

Rimactane 300 contains sugar (lactose 50 mg per capsule).

Rimactane 450 contains calcium stearate, hydroxypropyl methylcellulose, iron oxide red (C.I. 77491), maize starch, microcrystalline cellulose, polyethylene glycol 8000, povidone K30, purified talc, sodium lauryl sulphate, sodium carboxymethyl cellulose, titanium dioxide (C.I. 77891), vinylpyrrolidone/vinyl acetate copolymer.

Rimactane 450 contains sugar (sucrose 173,95 mg per tablet).

Rimactane 600 contains calcium stearate, dispersed yellow 15093 anstead (consisting of titanium dioxide 95 % (C.I. 77891) and iron oxide, yellow 5 % (C.I. 77492)), hydroxypropyl methylcellulose, iron oxide red (C.I. 77491), maize starch, microcrystalline cellulose, polyethylene glycol 8000, povidone K30, purified talc, sodium lauryl sulphate, sodium carboxymethyl cellulose, titanium dioxide (C.I. 77891), vinylpyrrolidone/vinyl acetate copolymer.
Rimactane 600 contains sugar (sucrose 235,67 mg per tablet).

Rimactane 300 vial contains sodium sulphoxylate formaldehyde pyrogen free
Rimactane 300 vial is sugar free.

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.3 Tuberculostatics

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

RIMACTANE contains a semi-synthetic antibiotic, rifampicin, which is highly active by mouth. It exerts a bactericidal action on mycobacteria. The spectrum of its bactericidal action also includes *M. leprae*, as well as *N.meningitidis*.

In vivo it exerts its bactericidal effect on both extracellular and intracellular microorganisms.

Rifampicin inhibits the DNA-dependent RNA polymerase of sensitive bacterial strains, however, does not affect the corresponding mammalian enzyme. Bacteria resistant to rifampicin are likely to be cross-resistant to other rifamycins.

Pharmacokinetic properties:

RIMACTANE is well absorbed by the oral route. Following a single dose of 600 mg rifampicin on an empty stomach, maximum plasma concentrations of approximately 10 μg/mℓ are attained after 2 to 3 hours. Plasma concentrations then gradually decrease over a period of 8 to 12 hours. Ingestion of rifampicin with food reduces its absorption.

An intravenous drip infusion of rifampicin over 1 to 3 hours produces plasma profiles similar to that after administration of the same dose in the form of a capsule or coated tablet. A 3 hour infusion of 600 mg yields peak plasma concentrations of approximately 10 μg/mℓ.

The apparent distribution volume is 1,6 ℓ/kg in adults and 1,1 ℓ/kg in children. 84 to 91 % of rifampicin is protein bound.

RIMACTANE also passes rapidly into the various body fluids and tissues, including bone tissue. It crosses the blood brain barrier only when the meninges are inflamed, however, concentrations in the CSF may remain above the MIC for *Mycobacterium tuberculosis* for up to 2 months with continuous therapy of 600 mg/day orally. Rifampicin crosses the human placenta and is secreted in human breast milk; however, a breastfed infant would receive no more than 1 % of the usual therapeutic dose.

Rifampicin is metabolised in the liver. Its microbiologically active principal metabolite being 25-O-deacetylrifampicin, which like rifampicin is subject to enterohepatic circulation. Rifampicin is a strong microsomal enzyme inducer and induces its own metabolism.

The plasma elimination half-life of rifampicin increases with increasing doses. After a few days of repeated 600 mg daily administration, the bioavailability of rifampicin diminishes and the half-life value falls to 1 to 2 hours. Due to rifampicin accelerating its own metabolism, its systemic clearance is approximately 6 ℓ/h after the first dose, rising to approximately 9 ℓ/h after repeated dosing. It is excreted mainly in the bile but also in the urine, in which high concentrations are likewise attained. In a dosage range of 150 to 900 mg, 4 to 18 % of a dose is excreted dose-dependently in the urine in the unchanged form.

Due to its mechanism of excretion, RIMACTANE may also be used in patients with impaired renal function. Provided that hepatic excretory function is normal, the dosage in patients with impaired renal function need not be reduced below 600 mg daily. Rifampicin is eliminated by peritoneal or haemodialysis. Dosage adjustment is not necessary during dialysis.

Plasma concentrations in the elderly are comparable to those in young patients.

In patients with impaired liver function, plasma concentrations are raised and the elimination half-life prolonged, therefore with severe hepatic dysfunction the dosage may have to be adjusted accordingly.

INDICATIONS

Tuberculosis:

All forms of tuberculosis including tuberculosis meningitis. Tuberculosis is the main indication for RIMACTANE. RIMACTANE must always be given in combination with other anti-tuberculous agents.

Leprosy:

In combination with other anti-leprosy drugs as treatment for multibacillary forms of leprosy, such as Lepromatous leprosy (LL), Borderline Lepromatous (BL) and Borderline leprosy (BB), for paucibacillary forms of leprosy, i.e. Tuberculoid leprosy (TT), and Borderline Tuberculoid (BT) leprosy, as well as in patients with other forms of leprosy in whom intolerance of, or resistance to, other anti-leprosy drugs is encountered.

Prevention of meningococcal meningitis:

Prophylactic use in persons having had close contact (e.g. at home, in a day-nursery, at school, or while living in mass accommodation) with a patient who develops meningococcal meningitis. In such persons, combating or eliminating the pathogens (*Neisseria meningitidis*) from the nasopharynx can significantly reduce the increased risk of infection. Since the pathogens may rapidly become resistant, a close watch should be kept for any initial signs of an overt infection.

RIMACTANE must not be employed to treat overt meningococcal meningitis.

CONTRAINDICATIONS:

Hypersensitivity to rifamycins.

Premature and newborn infants:

Premature and newborn infants, in whom the liver enzyme system is not yet fully developed, should be given RIMACTANE only in grave emergencies and with extreme caution.

WARNINGS AND SPECIAL PRECAUTIONS:

The danger of immunological reactions when using the intermittent dosage regimen is especially high after 12 weeks of treatment.

In patients with chronic liver disease, as well as in chronic alcoholics and undernourished patients, treatment with RIMACTANE entails a higher risk. This applies particularly to the combination of isoniazid and/ or pyrazinamide with rifampicin. In the presence of severely impaired liver function or jaundice the dosage may have to be reduced.

Daily treatment with RIMACTANE is generally better tolerated than intermittent therapy.

Since influenza-like symptoms, which may occur during intermittent therapy, may be a prelude to more serious complications such as thrombocytopenia, purpura, haemolytic anaemia, dyspnoea and asthma-like attacks, shock and renal failure, their onset calls for a decision to be made whether to risk complications developing or to switch to daily treatment. In patients developing a pronounced "flu syndrome" it is always preferable to change to daily medication.

In the event of thrombocytopenia, purpura, haemolytic anaemia, anaphylaxis or renal failure, treatment with RIMACTANE should be stopped at once and not re-instituted at a later date.

When changing from intermittent to daily medication, RIMACTANE should be administered in small, gradually increasing doses, i.e. in adults, commence with a dose of 75 to 150 mg daily, raising this subsequently by 150 mg per day until the desired therapeutic dose is reached within 3 to 4 days. During this period, renal function should be monitored. Corticosteroids may be a useful adjunct in attenuating possible immunopathological reactions.

Resumption of treatment with RIMACTANE after termination of a course of long-term therapy with the drug involves risks such as shock and renal failure and should, therefore, be avoided if possible. Where this proves unavoidable, these risks can possibly be minimized by incremental dosing under close surveillance.

Resistance:

To prevent the emergence of rifampicin-resistant mycobacteria, rifampicin should always be prescribed with other antimycobacterial agents.

Tests to be performed:

In patients receiving long-term treatment with RIMACTANE, it is advisable to perform blood counts and liver function tests from time to time, and at baseline if possible.

A slight and transient rise in the serum bilirubin, transaminase, or alkaline phosphatase levels does not necessitate withdrawal of the medication.

Porphyria:

Due to its enzyme-inducing effect, rifampicin must be employed with extreme caution in patients with porphyria, because activation of delta-aminolaevulinic acid synthetase may lead to an acute manifestation of porphyria.

Contraception:

To preclude all possibility of pregnancy during treatment with RIMACTANE, non-hormonal means of contraception must be employed.

Prevention of meningococcal meningitis:

Owing to the possibility of bacterial resistance developing, contacts undergoing prophylactic treatment should be kept under careful surveillance; special attention should be paid to any signs of an overt infection. RIMACTANE must not be employed to treat an overt meningococcal infection.

Intravenous administration:

Since nursing staff preparing and administering infusions may develop hypersensitivity reactions affecting the face and hands, due care should be exercised.

Lactose intolerance:

RIMACTANE capsules and tablets contains lactose, therefore, it should not be used by patients with rare hereditary problems of lactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

INTERACTIONS

In patients with pre-existing liver damage, combined use of RIMACTANE and isoniazid may lead to more frequent and more marked disorders of hepatic function than treatment with RIMACTANE alone. In such cases, appropriate tests should be performed periodically.

Isoniazid and rifampicin exhibit synergism with regard to toxicity, even when no pre-existing liver damage is present.

Antacids, opiates, anticholinergic drugs and ketoconazole reduce the bioavailability of rifampicin when it is given concomitantly by mouth.

Where RIMACTANE is prescribed in combination with PAS preparations containing bentonite (aluminium hydrosilicate), the possibility exists of the one interfering with the absorption of the other. RIMACTANE should be taken at least 4 hours before these preparations.

Rifampicin may induce certain liver enzymes, accelerate the metabolism of many concomitantly administered drugs and thus impair the activity of various preparations such as oral anticoagulants; oral anti-diabetic agents; dapsone; digitoxin preparations; antiarrhythmic agents (disopyramide, pirmenol, quinidine, mexiletine, tocainide, lorcainide, propafenone); methadone (withdrawal signs may set in); hydantoins (phenytoin, ethotoin, mephenytoin); hexobarbitone; nortriptyline; benzodiazepines; corticosteroids (Addison's patients may develop a crisis; exacerbation of pemphigus may occur; treatment for corticoid-dependent asthma may become more difficult or impossible); sex hormones (menstrual disorders may appear); oral contraceptives (their effect cannot be relied upon); theophylline; chloramphenicol; azole antifungals (ketoconazole, itraconazole); cyclosporin A; azathioprine (transplants may be rejected), beta-blockers; calcium-channel blockers (nifedipine, verapamil); enalapril and cimetidine.

The dosages of these preparations should therefore be reassessed when commencing or discontinuing treatment with RIMACTANE.

Although concurrent use of isoniazid, pyrazinamide and rifampicin is common and therapeutically valuable, hepatic toxicity may be increased.

Rifampicin can delay the biliary excretion of contrast media employed to X-ray the gall bladder.

RIMACTANE causes temporary competitive inhibition of bromsulphthalein excretion. To guard against false positive results, the bromsulphthalein test should be performed in the morning before administration of RIMACTANE.

Microbiological techniques for assaying folic acid and vitamin B_{12} in the serum are not suitable for use during treatment with RIMACTANE.

PREGNANCY AND LACTATION

In women of childbearing age, the possibility of pregnancy should be excluded prior to treatment with RIMACTANE and pregnancy should be avoided during treatment.

During the first trimester of pregnancy, RIMACTANE must only be used in life-threatening conditions and where no suitable alternative drug is available.

In the remaining 6 months, the possible risk to the foetus must be weighed against the benefits of the treatment for the mother.

When administered during the last few weeks of pregnancy, RIMACTANE can cause post-natal haemorrhages in the mother and infant, for which treatment with vitamin K may be indicated.

Although rifampicin passes into the breast milk, no adverse effects on breast-fed infants have been observed.

DOSAGE AND DIRECTIONS FOR USE

Oral forms:

To ensure optimum absorption, it is recommended that RIMACTANE be taken on an empty stomach, i.e. preferably at least half an hour before a meal.

Intravenous infusion:

RIMACTANE for intravenous infusion is particularly advisable when the patient's clinical picture (e.g. surgery, altered gastro-enteric absorption) or gastric tolerability does not permit or indicate the administration of the antibiotic by the oral route.

Preparation of the ready-to-use solution:

RIMACTANE 300: Add 5 mℓ water for injection to the vial.

After adding the solvent to the dry substance, shake the vial vigorously for 30 to 60 seconds until the dry substance is completely dissolved. Dilute the resultant solution with a suitable infusion solution (5 % glucose) - use 250 mℓ for the 300 mg vials.

Freshly prepared solutions must be used within 6 hours. It is recommended that the infusion rate be adjusted as to ensure that the infusion is completed after about 3 hours.
Only freshly prepared solutions of RIMACTANE and antibiotic should be administered.

Tuberculosis:

Dosage for adults:

Mass less than 50 kg: 450 mg daily

Mass 50 kg or more: 600 mg daily

RIMACTANE should preferably be taken in the morning.
The daily dose of rifampicin should not exceed 600 mg.
To prevent the possible emergence of rifampicin-resistant strains of mycobacteria, additional anti-tuberculous agents should be prescribed concomitantly with RIMACTANE in their usual dosage.

Dosage in infants and children:

10 to 20 mg/kg daily

The chemotherapeutic agents usually employed today as combined therapy for tuberculosis are rifampicin (RMP), isoniazid (INH), pyrazinamide (PZA), ethambutol (EMB) and streptomycin (STM).

Leprosy:

For the treatment of leprosy the WHO recommends the following regimens:

Multibacillary forms (LL, BL, BB):

Adults: Rifampicin (RIMACTANE) 600 mg once a month under direct supervision, plus dapsone 100 mg once a day, plus clofazimine (LAMPRENE) 300 mg once a month under supervision, plus 50 mg once a day.

Children: Rifampicin (RIMACTANE) 10 mg/kg once a month under direct supervision, plus dapsone 1 to 2 mg/kg daily, plus clofazimine (LAMPRENE) 200 mg once a month under supervision, plus 50 mg on alternate days.

Duration of treatment: at least 2 years, preferably until negative skin smears are obtained.

Paucibacillary forms (TT, BT):

Adults: Rifampicin (RIMACTANE) 600 mg once a month under direct supervision, plus dapsone 100 mg (1 to 2 mg/kg) once a day.

Children: Rifampicin (RIMACTANE) 10 mg/kg once a month under direct supervision plus dapsone 1 to 2 mg/kg daily.

Duration of treatment at least 6 months.

Do not exceed the corresponding daily dose for adults.

RIMACTANE should always be prescribed in combination with other suitable anti-leprotic agents.

A daily dose of 8 mg per kg body mass should not be exceeded in patients with impaired liver function.

Prevention of meningococcal meningitis:

Adults:

600 mg twice daily (i.e. every 12 hours) for 2 days.

Children (1 month of age and over):

10 mg/kg twice daily (i.e. every 12 hours) for 2 days.

Infants (up to 1 month of age):

5 mg/kg twice daily (i.e. every 12 hours) for 2 days.

This prophylactic treatment should be started as soon as possible.

SIDE EFFECTS

RIMACTANE has a bright, brownish-red colour and may cause reddish discolouration of the body fluids, and other body secretions e.g. urine, sputum, lacrimal fluid, faeces, saliva and sweat. It may also permanently discolour soft contact-lenses.

Side effects which may occur during continuous daily or intermittent therapy include.

Cutaneous reactions:

Frequently: flushing, itching, with or without skin rash and reddening of the eyes, urticaria.

Less frequently: severe signs and symptoms such as exudative conjunctivitis or generalised hypersensitivity reactions involving the skin (exfoliative dermatitis, Lyell's syndrome) and pemphigoid reactions.

Gastro-intestinal reactions:

Frequently: anorexia, nausea, abdominal pains, gaseous distension.

Less frequently: vomiting or diarrhoea, erosive gastritis and occurrences of pseudomembranous colitis.

Hepatic reactions:

Frequently: an asymptomatic increase in liver enzymes.

Less frequently: induction of porphyria. Hepatitis which may be severe and potentially fatal. Account should be taken of the liver toxicity of chemotherapeutic agents, e.g. isoniazid or pyrazinamide, employed in combination with rifampicin.

Reactions involving the central and peripheral nervous system:

Frequently: tiredness, drowsiness, headache, lightheadedness, dizziness.

***Less frequently*:** ataxia, mental confusion, muscular weakness and visual disturbances.

Haematological reactions:

Less frequently: transient leucopenia, eosinophilia, thrombocytopenia and thrombocytopenic purpura may occur more frequently under intermittent therapy than with continuous daily treatment.

Endocrine reactions:

***Less frequently*:** disturbances in the menstrual cycle, induction of a crisis in Addison's patients.

Unwanted effects chiefly occurring during intermittent therapy or on resumption of treatment after its interruption include:

Influenza-like symptoms ("flu syndrome") characterised by fever, shivering, and possibly headache, dizziness, and musculo-skeletal pains; this is probably an immunopathological reaction. It occurs more often when RIMACTANE is given only once a week in high doses (25 mg/kg or more).

When RIMACTANE is administered in lower doses (600 mg) 2 to 3 times a week, the syndrome occurs less frequently, its incidence then being comparable to that observed during daily medication.

Less frequently the "flu syndrome" may be followed by thrombocytopenia, purpura, dyspnoea, asthma-like attacks, haemolytic anaemia, anaphylactic shock and acute renal failure. These serious complications may however, also set in suddenly with no preceding "flu syndrome", chiefly when treatment is resumed after its interruption.

Unwanted effects during intravenous administration:

During prolonged (more than 30 days) intravenous administration, local thrombophlebitis occurs less frequently; nursing staff preparing and administering infusions may develop hypersensitivity reactions affecting the face and hands.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Treatment:

Symptomatic and supportive.

Signs and symptoms:

Reddish-brown or orange discolouration of the skin, sputum, lacrimal fluid, sweat and faeces ("red man syndrome"), nausea, vomiting, abdominal pains, enlargement of the liver, jaundice, elevated liver enzyme levels, possibly acute pulmonary oedema, lethargy, clouding of consciousness and convulsions.

IDENTIFICATION:

150 mg capsule: Brownish-red, opaque body and cap. Branding in black ink “150” on the body and “NG” on the cap. Capsule size no. 2. The capsules contain an orange to reddish-brown powder.

300 mg capsule: Two coloured, opaque, reddish brown body, brown cap. Branding in black ink. “NG” on the cap and “300” on the body. Capsule size no. 1.

450 mg tablet: Pink brown, biconvex capsule-shaped, sugar-coated tablet.

600 mg tablet: Red brown, biconvex capsule-shaped, sugar-coated tablet.

300 mg vials: Vials of clear neutral glass having an available capacity of 10 ml and containing spongy, fragile tablets (lyophilisate), amorphous, red to brick-red in colour, sealed with a butyl rubber stopper and an aluminium cap.

PRESENTATIONS:

RIMACTANE is supplied as capsules of 150 mg and 300 mg and tablets of 450 mg and 600 mg in packs of 30 or 100 in blisters strips, tristar foil for multiple-unit packs. The material used for packing Rimactane 150 capsules consist of a triplex foil of 3 layers (Polyvinylchloride: 250 µm; Polyethylene: 25 µm; Polyvinylidene Copolymer 90 g/m^2) and aluminium foil. PVC/Aclar Foil consists of layers consisting of two layers of Polyvinylchloride: 0,250 mm and Polychlorotrifluorethylene: 0,019 mm and aluminium foil.
The blisters are packed into a printed cardboard box together with a package insert. The carton is printed with the batch number and expiry date.

Opaque white cylindrical securitainers made of polypropylene closed with clip-on pilfer proof seal
or amber glass bottles made of soda lime and silica gel conforming to neutral glass in packs of 30 or 100.

RIMACTANE 300 vials are supplied as 10 ml glass vials, glass type III, Ph. Eur., with rubber stoppers and aluminium caps each containing 300 mg dry active substance.

STORAGE INSTRUCTIONS:

For capsules and tablets: Store at or below 25 °C and protect from moisture.

For vials: Store at or below 25 °C and protect from light. The reconstituted IV solution is sufficiently stable to be stored up to 24 hours at room temperature.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBERS:

Rimactane 150 (capsules):	A/20.2.3/784
Rimactane 300 (capsules):	C/20.2.3/65
Rimactane 450 (tablets):	H/20.2.3/68
Rimactane 600 (tablets):	H/20.2.3/69
Rimactane 300 VIAL (vials):	Q/20.2.3/28

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATIONS:

Sandoz SA (Pty) Ltd[1]

Waterfal 5-lr

Magwa crescent west

Waterfall City

Jukskei view

2090

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

Date of registration:

Rimactane 150 (capsules):	07 August 1969
Rimactane 300 (capsules):	11 August 1970
Rimactane 450 (tablets):	12 November 1975
Rimactane 600 (tablets):	12 November 1975
Rimactane 300 VIAL (vials):	15 May 1986

Date of most recent approval of professional information: 15 May 1998

Additional country registration details:

Country	*Product name*	*Scheduling status (or Category of distribution)*	*Registration number*
Botswana	Rimactane 150	S2	B9309330
Namibia	Rimactane 150	NS2	90/20.2.3/001438

ATC Code: J04AB02 – Antibiotics (rifampicin)

Name and address of manufacturer:

Kiara Health (Pty) Ltd.
72 Steel Road, Spartan
Kempton Park, Johannesburg
1619, South Africa

or

Sandoz Private Limited
MIDC, Plot No.8 A/2 and 8B,
T.T.C Industrial Area, Kalwe Block,
Village Dighe,
Navi Mumbai 400 708
India

[1]Company Reg. No.: 1990/001979/07