SCHEDULING STATUS: **S4**

PROPRIETARY NAME AND DOSAGE FORM:

Rimactazid 150/75 (tablets)

COMPOSITION:

Per tablet:

Rifampicin	150 mg
Isoniazid	75 mg

Inactive ingredients:

Copovidon, crospovidone, hypromellose, maize starch, magnesium stearate, Opadry Clear (consists of hypromellose, macrogol), Opadry Pink (hypromellose, iron oxide red, macrogol, titanium dioxide), pregelatinised maize starch, sodium lauril sulphate, talc, titanium dioxide E171.

Sugar free.

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.3 Tuberculostatics

PHARMACOLOGICAL ACTION:

Antimicrobial agent.

INDICATIONS:

Pulmonary tuberculosis for adults in the continuous phase of treatment.

CONTRAINDICATIONS:

This medicine is contra-indicated in patients with a history of hypersensitivity to rifamycins or isoniazid. It is contra-indicated in the presence of jaundice, and in patients with liver damage.

Safety during pregnancy and lactation has not been established.

Caution is advised in patients with impaired renal or liver function, diabetes mellitus and chronic alcoholism, a history of gout, patients suffering from convulsive disorders and acute porphyria.

WARNINGS AND SPECIAL PRECAUTIONS:

Rifampicin:

Liver function should be checked before and during treatment with rifampicin and special care should be taken in alcoholic patients or those with pre-existing liver disease. Patients with impaired liver function should only be given this medicine in case of necessity, and then with caution, under strict medical supervision. In these patients, careful monitoring of liver function, especially serum glutamic pyruvic transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT) should be carried out prior to therapy and repeated every 2 to 4 weeks during therapy.

Dosage adjustment is necessary where there is other evidence of hepatic function impairment and treatment may need to be changed where there is more serious liver toxicity. If signs of hepatocellular damage occur, this medicine should be withdrawn. Blood counts should be monitored during prolonged treatment and in patients with hepatic disorders. Should thrombocytopenia or purpura occur, rifampicin should be withdrawn permanently.

A report showing a moderate rise in bilirubin and/or transaminase level is not in itself an indication for interrupting treatment; rather, the decision should be made after repeating the test, noting trends in the levels and considering them in conjunction with the patient's clinical condition.

Isoniazid:

Liver function should be checked before and during treatment with isoniazid and special care should be taken in alcoholic patients or those with pre-existing liver disease. Use of isoniazid should be carefully monitored in patients with current chronic liver disease or renal dysfunction. Severe and sometimes fatal hepatitis associated with isoniazid therapy may occur and may develop even after many months of treatment. The risk of developing hepatitis is age related. Patients should be monitored for prodromal symptoms of hepatitis; such as fatigue, weakness, malaise, anorexia, nausea or vomiting. If these

symptoms appear or if signs suggestive of hepatic damage are detected, treatment should be discontinued promptly. Continued use of this medicine in these cases may cause a more severe form of liver damage.

May exacerbate convulsive disorders.

Periodic eye examinations during isoniazid treatment have been suggested.

INTERACTIONS:

Rifampicin:

Halothane, when given concomitantly with rifampicin has been reported to increase the hepatotoxicity of both agents. Ketoconazole has been reported to diminish the serum concentrations of both agents when given concomitantly.

Rifampicin has liver enzyme-inducing properties and may reduce the activity of azathioprine, chloramphenicol, cimetidine, clofibrate, corticosteroids, coumarin anticoagulants, cyclosporin, dapsone, diazepam, doxycycline, fluconazole, haloperidol, hexobarbitone, itraconazole, ketoconazole, methadone, oral hypoglycaemic agents, phenytoin, quinine, sulphasalazine, thyroid hormones, theophylline, zidovudine and several cardiovascular drugs including beta-adrenoceptor blocking agents, digitoxin, digoxin and antiarrhythmic agents such as disopyramide, lorcainide, mexiletine, propafenone, quinidine, tocainide, and verapamil and other calcium-channel blocking agents, oral contraceptives, narcotics, analgesics and barbiturates.

It may be necessary to adjust the dosage of these medicines if they are given concurrently with this medicine. Patients using oral contraceptives should be advised to change to non-hormonal methods of birth control during therapy with this medicine.

Magnesium trisilicate, aluminium hydroxide or sodium bicarbonate reduce the bioavailability of rifampicin.

Isoniazid:

Isoniazid is an inhibitor of hepatic drug metabolism and may therefore enhance the effects of some medicines taken concomitantly.

Adverse reactions have occurred when isoniazid has been given with phenytoin, primidone, carbamazepine, ethosuximide, benzodiazepines such as diazepam or triazolam and warfarin. Appropriate adjustments of the doses of the anticonvulsants should be made.

Theophylline plasma concentrations can be increased.

Increased central nervous system adverse effects have occurred when isoniazid is given with cycloserine and disulfiram.

Isoniazid can be affected by compounds such as alcohol, aminosalicylic acid, antacids, corticosteroids, ketoconazole, propranolol and large doses of pyridoxine.

DOSAGE AND DIRECTIONS FOR USE:

RIMACTAZID 150/75 tablets are recommended in the continuation phase of the treatment of pulmonary tuberculosis. During this phase, which lasts for 4 months, this medicine should be administered on a continuous daily basis.

The total dosage requirement is as follows:

	Daily (dose range)	
Rifampicin	10 mg/kg (8 to 12)	maximum 600 mg per day
Isoniazid	5 mg/kg (4 to 6)	maximum 300 mg per day

The daily dosage is as follows:

Patient body mass (kg)	***Amount of tablets (daily)***
30 to 37*	2
38 to 54	3
55 to 70	4
71 and more*	5

* In practice, most patients taking rifampicin-containing FDC tablets will receive either 3 or 4 tablets daily. Only a small proportion of adult TB patients will fall into the categories with a body-mass from 30 to 37 kg or body-mass above 70 kg. This might necessitate the maximum dose of rifampicin of 600 mg per day to be exceeded; however the dose limit of 12 mg/kg will still be observed which does not pose an additional risk.

SIDE EFFECTS:

RIMACTAZID 150/75 is a combination of 2 medicines, each of which has been associated with liver dysfunction.

The side effects of TB medication are rare provided that it is given as prescribed. However, some patients may be hypersensitive to some of the compounds of the medication, in which case the medication should be stopped. The responsible agent should be identified and desensitising procedures initiated.

Rifampicin:

Adverse reactions associated with rifampicin are probably of immunological/allergic origin, such as fever, a febrile reaction with influenza-like symptoms, skin rashes, renal failure and haematological abnormalities (e.g. thrombocytopenia, purpura, haemolysis) have been reported, particularly in connection with intermittent, interrupted, or repeated treatment.

Eosinophilia, leucopenia and haemolytic anaemia have been reported to occur in patients treated with rifampicin.

Gastrointestinal side effects include nausea, vomiting, anorexia, diarrhoea and epigastric distress. Rifampicin produces transient abnormalities in liver function. A rise in serum transaminase levels may also occur.

Pseudomembranous colitis has been reported.

Disturbances of the menstrual cycle have been reported in women receiving long-term antitubercular therapy with regimens containing rifampicin, and the effectiveness of oral contraceptives may also be reduced.

Rifampicin may produce an orange-red discolouration of the urine, sputum, tears, saliva and other body fluids and the patient should be forewarned of this. Soft contact lenses worn by patients receiving rifampicin may become permanently stained.

Some patients may experience a cutaneous syndrome which presents 2 to 3 hours after a daily or intermittent dose as facial flushing, itching, rash or rarely eye irritation.

Other side effects include headache, drowsiness, muscular weakness, ataxia, dizziness, peripheral neuropathy, blurred vision, transient hearing loss, confusion and shock.

Isoniazid:

Hepatotoxicity: transient elevation of liver enzymes occurs in 10 % of patients. Overt hepatitis occurs in less than 1 % but may be fatal. There is an increased risk of hepatitis in patients over 50 years of age, slow acetylators and those who consume alcohol on a daily basis. Liver function tests should be performed every 3 months during treatment and isoniazid discontinued if liver enzymes are raised more than five times the normal upper limit. Patients who develop malaise, anorexia and nausea together with raised liver enzyme levels should discontinue isoniazid promptly pending investigation.

Polyneuritis associated with isoniazid presenting as paraesthesia, muscle weakness, loss of tendon reflexes, etc., may occur with the recommended daily dose of this medicine. Peripheral neuropathy may be common if vitamin B_6 is not administered concurrently. Similar treatment care should be exercised in

elderly or malnourished patients. Vitamin B_6 in a dose of 15 to 50 mg per day should be administered with isoniazid therapy to minimise adverse reactions in malnourished patients and those predisposed to neuropathy e.g. the elderly, pregnant women, diabetics, alcoholics and uraemics.

Various haematological disturbances have been identified during treatment with isoniazid, including eosinophilia, agranulocytosis, thrombocytopenia and various anaemias. High doses of isoniazid can cause convulsions. The possibility that the frequency of fits may increase in patients with epilepsy should be borne in mind. Other neurological side effects include psychotic reactions.

Other side effects of isoniazid are skin reactions, pellagra, hyperglycaemia, lupus-like reactions, a rheumatic syndrome, gynaecomastia, urinary retention, gastrointestinal disturbances, vomiting, nausea and metabolic acidosis.

Hypersensitivity reactions occur infrequently and include various skin eruptions, fever, lymphadenopathy and vasculitis.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Rifampicin:

Acute overdosage with rifampicin has produced a characteristic bright-red discolouration of the skin and mucous membranes, sometimes referred to as “the red-man syndrome”, mental obtundation, periorbital or facial oedema and generalised pruritus.

Isoniazid:

Symptoms are more likely to be related to isoniazid. These include hyperglycaemia and metabolic acidosis, slurred speech, convulsions, coma, hallucinations, respiratory distress, central nervous system depression, fatalities can occur.

General:

In cases of overdosage with RIMACTAZID 150/75 gastric lavage should be performed as soon as possible.

Intensive supportive measures should be instituted and individual symptoms treated as they arise.

Further treatment is symptomatic and supportive.

IDENTIFICATION:

Round, biconvex, dark pink film-coated tablet, plain on both sides.

PRESENTATIONS:

Securitainers of 20, 50, 56, 60, 84, 100, 150, 200, 500 or 1 000 tablets

Blisters of 20, 40, 50, 56, 60, 84, 100, 150, 200, 500 or 1 000 tablets.

STORAGE INSTRUCTIONS:

Store at or below 25 °C. Keep the container tightly closed in order to protect from light and moisture.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBER:

35/20.2.3/0280

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

Sandoz SA (Pty) Ltd[1]

72 Steel Road

Spartan

Kempton Park, 1619

South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

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Additional country registration details:

Country	*Product name*	*Scheduling status (or Category of distribution)*	*Registration number*
Namibia	Rimactazid 150/75	NS2	04/20.2.3/0677

Name and address of manufacturer:

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