Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rimactazid 300 tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient of rifampicin is 3-[4-methyl-1-piperazinyl)-imino]-methyl]-
Rifamycin SV (=rifampicin) 300 mg.
The active ingredient for isoniazid is isonicotinic acid hydrazide (=isoniazid, INH) 150 mg.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Rimactane and isoniazid are both major drugs in the management of tuberculosis and in certain opportunist mycobacterial infections. Rifampicin is effective in cases resistant to other anti-tuberculous agents and shows no cross-resistance outside the rifamycin group of drugs. Rimactazid must always be used in combination with other anti-tuberculous agents, e.g. streptomycin, pyrazinamide, ethambutol and the majority of second-line drugs.

4.2 Posology and method of administration

Rimactazid should be given as a single dose, preferably on an empty stomach, at least 30 minutes before breakfast to ensure a high peak serum concentration.

***Adults*:**

Continuous therapy

Body weight less than 50kg:	3 tablets Rimactazid 150 (= 450mg rifampicin + 300mg INH) once daily.
Body weight 50kg or more:	2 tablets Rimactazid 300 (= 600mg rifampicin + 300mg INH) once daily.

Intermittent therapy

Body weight less than 50kg:	3 tablets rimactazid 150 (= 450mg rifampicin + 300mg INH) twice or 3 times weekly.
Body weight 50kg or more:	2 tablets rimactazid 300 (= 600mg rifampicin + 300mg INH) twice or 3 times weekly.

Rimactazid has to be supplemented with 150mg isoniazid for every 10kg body weight above 20kg (i.e. body weight 60kg: 150 x 4 = 600mg additional isoniazid needed).

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

The dosages recommended by the Centres for Disease Control and Prevention are as follows:

	Daily		Twice a week		3 times a week	
Drug	mg/kg	max. mg	mg/kg	max. mg	mg/kg	max. mg
RMP	10	600	10	600	10	600
INH	5	300	15	900	15	900
PZA	15-30	2,000	50-70	4,000	50-70	3,000
EMB	5-25	2,500	50	2,500	25-30	2,500
STM	15	1,000	25-30	1,500	25-30	1,000

For the treatment of sputum-positive pulmonary tuberculosis, preference is given to the following regimens: (For dosages please refer to the text above for rifampicin and isoniazid, and to the table for advice on the other components of the treatment).

Continuous therapy (7 times a week)

Daily for a total of 9 months
Initial phase for 2 months: RMP + INH + PZA + EMB or STM.

Continuation phase for 7 months: RMP + INH.

A total duration of 9 months is recommended for tuberculosis with HIV infection and for tuberculous meningitis, disseminated tuberculosis, or spinal involvement with neurological complications.

Daily for a total of 6 months:
Initial phase for 2 months: RMP + INH + PZA + EMB or STM.
Continuation phase for 4 months: RMP + INH.

Partially intermittent therapy

Total duration 6 months:
Initial phase for 2 months: RMP + INH + PZA + EMB or STM daily.
Continuation phase for 4 months: RMP + INH twice or 3 times a week.

Fully intermittent therapy

Total duration 6 months: RMP + INH + PZA + EMB or STM 3 times a week.

DOTS strategy (directly observed treatment, short course, i.e. administration of the antituberculous agents under supervision) should be considered for all patients, irrespective of the treatment regimen they are receiving.

Use in Children: The ratios of Rimactane and isoniazid present in Rimactazid 300 make it difficult for both components to be administered in a dosage suitable for children. Rimactazid tablets are therefore not recommended for paediatric use.

Use in Elderly: No special dosage regime is necessary but concurrent hepatic insufficiency should be taken into account (see Pharmacokinetics).

4.3 Contraindications

Known or suspected hypersensitivity to rifamycins and/or to isoniazid and/or to any of the excipients, including, a history of drug induced hepatitis, acute liver diseases regardless of their origin, peripheral neuritis.

4.4 Special warnings and precautions for use

4.4.1. Warnings

Intermittent therapy, resumption of therapy after its interruption

The presence of rifampicin means that, if treatment with Rimactazid is withdrawn for a while and then resumed again, or if the medication is not taken regularly, potentially serious side effects can occur (see under rifampicin in "Undesirable effects"). For this reason, both temporary interruption of treatment and non-compliance should if possible be avoided. Where temporary withdrawal of the medication is unavoidable, the two components rifampicin and INH should be administered separately when resuming the treatment, because rifampicin should then be given in an incremental dosage. A start should be made with approx. 75-150mg rifampicin on the first day, and the desired therapeutic dose should be reached within 3-4 days. During this time the patient's renal function should be close monitored. Corticosteroids may prove useful in attenuating possible immunopathological reactions. Isoniazid should be given in its normal dosage from the first day onwards.

If severe acute hypersensitivity reactions set in, such as thrombocytopenia, purpura, haemolytic anaemia, dyspnoea and asthma-like attacks, shock, or renal failure (these being side effects which rifampicin may provoke in exceptional cases), Rimactazid should be withdrawn at once. Patients developing such complications should never again be treated with rifampicin.

If other signs of hypersensitivity appear, such as fever or skin reactions, Rimactazid should be withdrawn For safety reasons, treatment should not be continued with rifampicin. Where isoniazid is considered essential, treatment should be resumed in low doses and under strict surveillance.

4.4.2. Precautions

As rifampicin and isoniazid are metabolised in the liver, patients with impaired liver function should be treated with caution.
The occurrence of liver function abnormalities is more common when rifampicin and isoniazid are used in combination and special care is therefore required in patients with pre-existing liver impairment or malnourished patients.

Liver diseases, undernourishment, alcoholism
In patients with chronic liver disease, as well as in chronic alcoholics and undernourished patients, the therapeutic benefits of treatment with Rimactazid must be weighed against the possible risks. If the treatment is considered necessary, the dosage of both components must be correspondingly reduced. In such cases it is only possible to adapt the dosage by administering rifampicin and isoniazid separately.

Porphyria
Owing 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 the porphyria.

Contraception
To preclude the possibility of pregnancy during treatment with rifampicin, additional non-hormonal means of contraception must be employed (see interactions).

Patients with epilepsy
Owing to the neurotoxic action of isoniazid, patients suffering from convulsive disorders must be kept under special observation during treatment with Rimactazid.

Neuropathy
Pyridoxine may be useful in preventing the occurrence of peripheral neuritis and should be given in a dose of 10mg daily from the start of treatment with Rimactazid.

Alcohol

Patients should abstain from alcohol while under treatment with Rimactazid.

Tests to be performed
Blood counts and liver function tests should be performed periodically, and at baseline if possible.

4.5 Interaction with other medicinal products and other forms of interaction

Rifampicin
Antacids, opiates, and anticholinergic drugs and **ketoconazole** reduce the bioavailability of rifampicin when given concomitantly by mouth. The same applies to PAS preparations containing bentonite.

To avoid this interaction, rifampicin must be administered a few hours before these preparations.
Owing to its enzyme-inducing effect, rifampicin accelerates the metabolism of many concomitantly administered drugs shoes activity may thus be reduced and the success of treatment with them jeopardised.
Rifampicin is a potent inducer of endothelial excretory proteins and liver enzymes which may either reduce the intestinal absorption and/or increase the metabolism of concomitantly administered drugs such as those listed below. The activity of the following drugs may be impaired and their dosage must be reassessed during and after treatment with Rifampicin.

Oral anticoagulants; oral antidiabetic agents (glimepiride, glibenclamide, repaglinide, glipizide, digitalis preparations, antiarrhythmic agents (disopyramide, quinidine, mexiletine, tocainide, lorcainide, propafenone), methadone (withdrawal signs may set in), hydantoins (phenytoin), hexobarbital, nortriptyline, benzodiazepines, corticosteroids (Addison patients may develop a crisis; exacerbation of pemphigus may occur; treatment for corticoid-dependent asthma patients may become more difficult or impossible); sex hormones (menstrual disorders may appear); oral contraceptives (their effect can no longer be relied upon); theophyllines, dapsone, chloramphenicol, azole antifungal agents (ketoconazole; itraconazole), cyclosporin A; azathioprine (transplants may be rejected); beta blockers, calcium-channel blockers (nifedipine, verapamil); enalapril, cimetidine, simvastatin, fexofenadine.
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.
Microbiological techniques for assaying folic acid and vitamin B_{12} in the serum are unsuitable for use during treatment with Rimactane.
Rifampicin 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 Rimactazid.

Isoniazid
The absorption of isoniazid is reduced by antacids. Isoniazid retards the metabolism of various concomitantly administered drugs, including hydantoins (phenytoin), carbamazepine, primidone, and valproic acid. The dosages of these drugs may have to be reduced. It is not advisable to administer disulfiram concomitantly with isoniazid as this may lead to mental disturbances, the mechanism of this interaction is not known.
Concomitant use of halothane and isoniazid (and possibly rifampicin) may increase the risk of hepatotoxic reactions.
As alcohol tolerance is decreased under isoniazid, the consumption of alcoholic beverages should be avoided. The metabolism of isoniazid is increased in chronic alcoholics.

4.6 Pregnancy and lactation

Rifampicin:
In mice and rats, rifampicin proved teratogenic in daily doses of over 150 mg/kg, insofar as an increased occurrence of spina bifida and cleft palate was observed. In rabbits it had no teratogenic effect. In all three animal; species, unspecific embryotoxic effects occurred after doses > 150 mg/kg.
In studies of over 300 women exposed to rifampicin during pregnancy, no significant increase in the rate of malformations in their offspring, over and above the background level was observed. Rimactane should not be given during pregnancy unless the potential benefit justifies the potential risk to the foetus.
Administration of rifampicin during the last few weeks of pregnancy can cause post-natal haemorrhage in the mother and new-born infant. This may necessitate treatment with vitamin K preparations.

Isoniazid:
Isoniazid, besides having weak direct genotoxic activity, is a promutagen in the sense that the formation of the toxic metabolites, hydrazine and acetylhydrazine, is the first step in metabolic activation. In lymphocytes of patients treated with isoniazid no chromosomal alterations could be detected whereas in a study comparing the effects of combination treatment an increased frequency of chromosomal alterations was observed.
Nevertheless isoniazid has been found to entail relatively little risk during pregnancy in humans. Congenital malformations have not been observed to be any greater than those expected for the normal population. Since it is theoretically possible that the drug might exert neurotoxic effects on the child, it is recommended that the mother should take pyridoxine during her pregnancy.
Rimactazid should not be given during pregnancy unless the potential benefit justifies the potential risk to the foetus.
Although rifampicin and isoniazid pass into the breast milk, no adverse effects on breast-fed infants have been observed. It is therefore not absolutely necessary to wean the infant. However, in view of the theoretical possibility of neurotoxic effects due to isoniazid, breast-fed infants should be kept under careful surveillance. Prophylactic administration of pyridoxine to mother and child is recommended.

4.7 Effects on ability to drive and use machines

Doses of 10 mg/kg or more of isoniazid may adversely affect the reactions of the nervous system, e.g. peripheral neuropathy and thus impair the patients ability to drive or operate machinery.

4.8 Undesirable effects

Rifampicin may cause reddish discolouration of body fluids and commonly other body secretions, e.g. urine, sputum, lacrimal fluid, faeces, saliva, sweat. It may permanently discolour soft contact-lenses.

Unwanted effects which may occur during continuous daily or intermittent therapy.

Frequency estimates: very common > 10%, common 1-10%, uncommon 0.1-1%, rare 0.01 – 0.1%, very rare <0.01%

Associated with Rifampicin:

Skin and appendages:
Commonly: flushing, itching with or without skin rash,urticaria and reddening of the eyes.
Very rare cases: severe signs and symptoms, such as exudative conjunctivitis or generalised hypersensitivity reactions involving the skin, e.g. exfoliative dermatitis, Lyell's syndrome and pemphigoid reactions.

Gastro-intestinal tract
Commonly: anorexia, nausea, abdominal pains, gaseous distension; uncommonly: vomiting or diarrhoea; very rare occurrences of erosive gastritis and pseudomembranous colitis.

Hepatic:
Very commonly: an asymptomatic increase in liver enzymes; uncommonly: hepatitis or jaundice including severe life threatening hepatic reactions such as hepatic failure and acute fulminant hepatitis, very rare (<0.01%) a fatal outcome was observed; here account should also be taken of the liver toxicity of chemotherapeutic agents, e.g. isoniazid or pyrazinamide, employed in combination with rifampicin. Induction of porphyria in very rare cases.

Renal reactions
Rarely: interstitial nephritis, renal insufficiency and acute renal failure have been noted. These are generally considered to be hypersensitivity reactions and are reversible when rifampicin is discontinued and appropriate therapy instituted.

Central and peripheral nervous system:
Commonly: tiredness, drowsiness, headache, light-headedness, dizziness; uncommonly: ataxia, mental confusion.
Very rare cases: muscular weakness, visual disturbances.

Blood:
Very rare cases of transient leucopenia; eosinophilia; thrombocytopenia and thrombocytopenic purpura are encountered more frequently under intermittent therapy than on continuous daily treatment, during which hey occur only in very rare cases. Agranulocytosis was reported in very rare cases.

Endocrine:
Uncommonly: disturbances in the menstrual cycle (in extreme cases amenorrhoea); induction of a crisis in Addison patients (see Interactions).

***Unwanted effects chiefly occurring during intermittent therapy or upon resumption of treatment after temporary interruption*:**
In patients taking rifampicin other than on a daily basis or in those resuming treatment with the drug after a temporary interruption, an influenza-like syndrome ("flu syndrome") may occur, this being very probably of immunopathological origin. It is characterised by fever, shivering, and possibly headache, dizziness and musculoskeletal pain. In uncommon cases the "flu syndrome" may be followed by thrombocytopenia, purpura, dyspnoea, asthma-like attacks, haemolytic anaemia, 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 a temporary interruption or when rifampicin is given only once a week in high doses (25mg/kg or more).

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

Associated with Isoniazid:

Central nervous system
Very common: peripheral neuropathy (dose dependent and more common in undernourished patients, alcoholics and diabetics).
Uncommonly: damage to the optic nerve, convulsions, psychoses, dizziness, light-headedness, headache. Isolated cases: toxic encephalopathy. High doses may increase seizure frequency in epileptics.

Gastro-intestinal
Commonly: nausea, vomiting, epigastric distress.

Hepatic
Very commonly: disturbances of liver function (usually transient).
Uncommonly: hepatitis, which in very rare instances may be severe; the frequencyof hepatitis increases with the patient's age.

Blood
Very rare cases: agranulocytosis, eosinophilia, thrombocytopenia, anaemia (haemolytic, hypoplastic) purpura, hyperglycaemia..

Allergic and miscellaneous reactions
Commonly: drug rash, fever, erythema multiforme,
Uncommonly: dryness of the mouth, heartburn, disorders of micturition, rheumatic syndrome, lupus erythematosus-like signs and symptoms, pellagra. Very rare cases: gynaecomastia, vasculitis.

4.9 Overdose

Signs and Symptoms:
Rifampicin: Nausea, vomiting, abdominal pain, enlargement of the liver, jaundice, elevated liver enzymes, possibly acute pulmonary oedema, lethargy, clouding of consciousness, convulsions.
Isoniazid: In mild poisoning - ataxia, symptoms of polyneuritis, disturbed articulation, vertigo. In severe poisoning - hallucinations, epileptiform tonic-clonic attacks, respiratory depression, coma, severe metabolic acidosis, hyperglycaemia, acetonuria.

Treatment:
General supportive measures to maintain vital functions; intravenous administration of anti-convulsants and pyridoxine in large doses; control of metabolic acidosis, gastric lavage together with instillation of an activated charcoal suspension via a stomach tube; forced diuresis; haemodialysis, in the presence of severe liver damage, cholecystotomy if necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group
Rimactazid is a fixed combination for the treatment of tuberculosis.
Rifampicin is a rifamycin antibiotic and isoniazid is a specific antituberculous agent.

Mechanism of action
Rifampicin exerts both *in vitro* and *in vivo* bactericidal effects on *Mycobacterium tuberculosis*. It also exhibits variable activity against other atypical species of Mycobacterium.

In vivo it exerts its bactericidal effect not only on micro-organisms in the extracellular spaces but also on those located intracellularly. Of particular clinical significance in the treatment of tuberculosis is its rapid onset of action Rifampicin has a potent sterilising effect.

Rifampicin inhibits the DNA-dependent RNA polymerase of sensitive bacterial strains, but without affecting the corresponding mammalian enzyme.

Isoniazid exerts a strong bactericidal effect mainly on rapidly growing populations of *Mycobacterium tuberculosis.* Its mechanism of action is probably based chiefly on inhibition of mycolic acid synthesis, mycolic acid being an important constituent of the mycobacterial cell wall.

5.2 Pharmacokinetic properties

The bioavailability of both active ingredients, rifampicin and isoniazid, is the same when administered as a fixed combination or when given separately. Neither component interferes with the pharmacokinetic of the other when administered simultaneously

Absorption
After oral administration of the fixed combination on an empty stomach, the two active substances are well absorbed.

Rifampicin, following a single dose of 600mg, reaches mean peak plasma concentrations of 9.4 micrograms/mL after 2-3 hours.
Isoniazid, following a single dose of 300mg, reaches mean peak plasma concentrations of 6.1 micrograms/mL after 0.5-2 hours. However, plasma concentrations vary interindividually, depending on the acetylator status of the patient.

Concomitant intake of food reduces the absorption of both active components.

Distribution

Rifampicin: The apparent distribution volume is 1.6 L/kg in adults and 1.1 L/kg in children. Binding to serum proteins amounts to 84%-91%.

Isoniazid: The apparent distribution volume is 0.61L/kg. Isoniazid is not appreciably bound to serum proteins.

Rifampicin and isoniazid penetrate rapidly into various body fluids and tissues, including bone tissue (rifampicin)

and cerebrospinal fluid, **in therapeutically active** concentrations.

Rifampicin crosses the blood brain barrier in the case of inflamed meninges only, but concentrations in the cerebrospinal fluid may remain above the MIC for *Mycobacterium tuberculosis* for up to two months with continuous therapy of 600mg/day orally.

Rifampicin and isoniazid cross the human placenta and are secreted in human breast milk.

Isoniazid attains the highest levels, but it is estimated that a breast-fed infant would receive no more than 20%, and in the case of *rifampicin* less than 1%, of the usual therapeutic dose.

Biotransformation

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

Isoniazid is acetylated and hydrolysed in the liver. Acetylation is the most important metabolic pathway and is subject to genetic predisposition (fast and slow acetylators).

Elimination/Excretion

Rifampicin: The plasma elimination half-life of rifampicin increases with increasing doses and amounts to 2.5h, 3-4h and about 5h after single doses of 300mg, 600mg and 900mg respectively. After a few days of repeated daily administration, the bioavailability of rifampicin diminishes, and the half-life value following repeated doses of 600mg falls to 1-2 hours.

Owing to its enzyme-inducing effect in the liver, rifampicin accelerates its own metabolism, with the result that its systemic clearance, which amounts to approx. 6 L/h after the first dose, rises to approx. 9 L/h after repeated dosing.

Although the bulk of the drug is eliminated in the bile, 80% of the quantity excreted being accounted for by the deacetylrifampicin metabolite, rifampicin also appears in the urine.
In a dosage range of 150-900mg, 4-18% of a dose is excreted dose-dependently in the urine in unchanged form.

Isoniazid: The plasma elimination half-life is 0.6-1.8 hours in fast acetylators and 1.8-6.7 hours in slow acetylators.

Within 24 hours 75-95% of the dose administered is excreted in the urine, mainly as metabolites. N-acetylisoniazid is eliminated in the urine together with other metabolites. The quantity appearing in the urine as unchanged isoniazid is equivalent to 12% of the dose in fast acetylators and to 27% in slow acetylators.

Characteristics in patients

Rifampicin: In elderly patients, plasma concentrations are similar to those in young patients.

With impaired renal function, the elimination half-life becomes prolonged only at doses exceeding 600mg daily. Provided that hepatic excretory function is normal, the dosage in patients with impaired renal function does not need to be reduced below 600mg daily.

Rifampicin is eliminated by peritoneal or haemodialysis. Dosage adjustment is not necessary during dialysis. Dosage adjustment is not necessary during dialysis. Because rifampicin is dialysable it is recommended that the drug should not be administered until after the period of dialysis is complete.

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

Isoniazid
Elderly patients: In fast acetylators, old age has no significant influence on the rate at which the drug is eliminated. However, clearance and elimination half-life vary significantly in elderly slow acetylators, so that it might be necessary to adjust the dosage accordingly.

In slow acetylators with severely impaired renal function, accumulation of isoniazid may occur. In such cases, the serum concentration of isoniazid should be monitored and, if necessary, the dosage reduced.

In the presence of impaired liver function the elimination half-life of isoniazid is prolonged. To avoid unwanted effects it may therefore be necessary to adapt the dosage accordingly.

5.3 Preclinical safety data

Rifampicin:
There is limited evidence as to the carcinogenic potential of rifampicin in animals. In female mice of a strain known to be susceptible to hepatomas, a significant increase in such tumours was observed after 1 year of treatment with rifampicin in quantities equivalent to 2-10 times the maximum clinical doses.

In mice of another strain treated for 1 year, and in rats treated for 2 years, no significant increase was noted in the incidence of any type of tumour. Studies with various mammalian models, as well as with bacteria, yielded no evidence that rifampicin has a mutagenic effect.

Isoniazid:
Teratogenic effects have been noted in animal models. Limited evidence shows that isoniazid produces lung tumours in mice after various modes of administration. Available evidence of human exposure has not suggested that isoniazid is carcinogenic in man at doses applicable to the treatment and prophylaxis of tuberculosis.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium stearate
Sodium Lauryl sulphate
Maize starch
Talc
Hypromellose
Povidone
Titanium dioxide
Microcrystalline cellulose
Polyethylene glycol
Polyvinylpyrrolidone
Sucrose
Carmellose sodium
Dispersed orange (consisting of Iron oxide red, Iron oxide yellow and Titanium Dioxide)

6.2 Incompatibilities

None known.

6.3 Shelf Life

Three years.

6.4 Special precautions for storage

Do not store above 25°C.
Store in original container.

6.5 Nature and contents of container

Rimactazid 300 mg packed in PVC/PVdC blister packs of 60.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

None.

7 MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestrasse 10
6250 Kundl
Austria

8 MARKETING AUTHORISATION NUMBER

PA 111/3/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1977

Date of last renewal: 01 April 2002

10 DATE OF REVISION OF THE TEXT

November 2004