Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rimactane Capsules 150mg.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Rifampicin 150mg.

For list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsules, hard.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the treatment of tuberculosis and certain other mycobacterial infections.

Non-mycobacterial infections:
In these infections, e.g. *staphylococcal* infections, Rimactane should only be employed:
- if the pathogens are resistant to the first-line antibiotics that normally prove effective,
- if the pathogens are demonstrably sensitive to rifampicin,
- if given in combination with other antibiotics/chemotherapeutic agents to which the pathogens are sensitive,
- if a diagnosis of tuberculosis or leprosy has first been excluded.

Prevention of meningococcal meningitis:
Rimactane is also indicated for the chemoprophylaxis of *meningococcal meningitis.*

4.2 Posology and method of administration

For the management of tuberculosis and certain opportunistic mycobacterial infections:

Rimactane must always be given in association with other anti-tuberculosis drugs, to prevent emergence of resistant strains.

Use in Adults: 450-600mg daily as a single dose (based on approximately 10mg per kg body weight). (Those patients 50kg (8 stone) and over should take 600mg rifampicin daily, whilst patients under 50kg should take 450mg).

The following chemotherapeutic agents are employed today as combined therapy for tuberculosis: 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:

Drug	Daily			Twice a week			3 times a week		
	mg/kg		max. mg	mg/kg		max. mg	mg/kg		max. mg
	Children	Adults		Children	Adults		Children	Adults	
RMP	10-20	10	600	10-20	10	600	10-20	10	600
INH	10-20	5	300	20-40	15	900	20-40	15	900
PZA	15-30	15-30	2,000	50-70	50-70	4,000	50-70	50-70	3,000
EMB	15-25	5-25	2,500	50	50	2,500	25-30	25-30	2,500
STM	20-30	15	1,000	25-30	25-30	1,500	25-30	25-30	1,000

For the treatment of sputum-positive pulmonary tuberculosis, preference is given to the following regimens: (For dosage information please refer to the text above for Rimactane and to the table for 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 anti-tuberculosis agents under supervision) should be considered for all patients, irrespective of the treatment regimen they are receiving.

Use in Children: Up to 20mg per kg body weight daily to a maximum of 600mg as a single dose.

Use in Premature and New-born infants: 10mg/kg once daily. Premature and new-born infants should be treated only in cases of emergency and with extreme caution since their liver enzyme system may not be fully developed.

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

Non-mycobacterial infections:

In combination with other antibiotic/chemotherapeutic agents.

Adults: 600-1200mg daily in two doses

Infants and children: 10-20mg/kg daily

For the chemoprophylaxis of meningococcal meningitis:

Note: Rimactane should not be used to treat overt *meningococcal meningitis*.

Use in Adults: 600mg twice daily (12 hourly) for 2 days.

Use in Children (aged 1-12 years): 10mg/kg twice daily (12 hourly) for 2 days. Children at the lower end of this age range may metabolise rifampicin more rapidly and produce significantly lower serum levels than new-borns or adults. In such cases doses up to 15mg/kg 12 hourly may be required.

Use in Infants (up to 1 year): 5mg/kg twice daily (12 hourly) for 2 days.

Use in the Elderly: There is no evidence to suggest that dose adjustments are necessary.

This prophylactic administration should be started as soon as possible.

Method of administration
To ensure optimum absorption, Rimactane should preferably be taken on an empty stomach i.e. at least a half an hour before a meal.

4.3 Contraindications

Known or suspected hypersensitivity to rifamycins or to any of the excipients of Rimactane (such as parabens or sodium metabisulphite in the oral suspension).

Use in patients with jaundice.

4.4 Special warnings and precautions for use

Special warnings for use:

Prevention of *meningococcal meningitis*

Patients receiving Rimactane for the chemoprophylaxis of *meningococcal meningitis* should be kept under close surveillance. Special attention should be paid to signs of overt infection.

Rimactane should not be used to treat an overt *meningococcal* infection.

Resistance

To prevent the emergence of resistant bacteria, Rimactane must always be combined with other antibiotics/chemotherapeutic agents when used to treat infections.

Intermittent therapy

The "flu syndrome" (*See section 4.8, Undesirable effects*) is chiefly encountered during intermittent therapy and may be a prelude to serious complications such as thrombocytopenia, purpura, haemolytic anaemia, dyspnoea and asthma-like attacks, shock and renal failure. In the event of its onset, therefore, one should consider the possibility of switching to daily medication. Such a switch must always be made where the "flu syndrome" assumes a relatively severe form and if the aforementioned serious complications occur, the medication must be withdrawn at once and never reinstituted.

When changing over from intermittent to daily therapy, an incremental dosage must be employed, starting with approx. 75-150mg on the first day. The desired therapeutic dose should be reached within 3-4 days. During this time the patient's renal function should be closely monitored. Corticosteroids may prove useful in attenuating possible immunopathological reactions.

Resumption of therapy after its interruption

Since severe reactions such as shock and renal failure may occur in rare cases upon resumption of therapy, incremental dosing under close surveillance is mandatory (see "intermittent therapy").

As Rimactane is excreted principally by the biliary tract, caution should be exercised in treating patients with hepatic disorders.

Liver diseases, under nourishment, alchoholism

In patients with or likely to have liver function abnormalities including those with chronic liver disease, chronic alcoholism, the elderly and the undernourished, the benefit of combined treatment with rifampicin must be weighed against the possible risks. This applies particularly to combination of isoniazid and/or pyrazinamide with rifampicin. In the presence of severely impaired liver function, the dosage may have to be reduced.

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 all possibility of pregnancy during treatment with Rimactane, non-hormonal means of contraception must be employed (*See section 4.5, Interaction with other medicinal products and other forms of interactions*).

Tests to be performed:

During prolonged treatment, blood counts and liver function tests should be performed periodically and at baseline, if possible.

Rimactan capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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.

Rifampicin is a potent inducer of endothelial excretory proteins and of 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 bromsulphtalein excretion. To guard against false positive results, the bromsulphthalein test should be performed in the morning before administration of Rimactane.

4.6 Pregnancy and lactation

In mice and rats, rifampicin proved teratogenic in daily doses of over 150mg/kg, insofar as an increased occurrence of spina bifida and cleft palate was observed. In rabbits it has no teratogenic effect. In all three animal species, unspecific embryotoxic effects occurred after doses > 150mg/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 Rimactane 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.

Rifampicin passes into the breast milk but no adverse effects on breast-fed infants have been observed. Therefore nursing mothers may continue to breast-feed their infants.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

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

<u>Unwanted effects which may occur during continuous daily or intermittent therapy.</u>

Frequency estimates: very common > 10%, common 1-10%, uncommon 0.1-1%, rare 0.01-0.1%, very rare including isolated cases < 0.01%.

Skin and appendages:
Commonly: flushing, itching with or without skin rash, urticaria and reddening of the eyes.
Very rare: 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 (<0.1%) 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 occurrences of transient leucopenia; eosinophilia; thrombocytopenia and thrombocytopenic purpura are encountered more frequently under intermittent therapy than on continuous daily treatment, during which they occur only in very rare cases. Agranulocytosis was reported in very rare cases.

Endocrine:
In common instances disturbances in the menstrual cycle (in extreme cases amenorrhoea); induction of a crisis in Addison patients (*See section 4.5, Interaction with other medicinal products and other forms of 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 commonly, its incidence then being comparable to that observed during daily medication.

4.9 Overdose

Signs and symptoms:

Nausea, vomiting, abdominal pains; enlargement of the liver, jaundice, elevated liver enzyme levels, possibly acute pulmonary oedema, lethargy, clouding of consciousness, convulsions, reddish-brown or orange discoloration of the skin, saliva, lacrimal fluid, sweat, faeces (“red man syndrome”).

Treatment:

Gastric lavage together with instillation of an activated charcoal suspension via a stomach tube; general supportive measures to maintain vital functions; forced diureses; haemodialysis; in the presence of severe liver damage, cholecystotomy if necessary. Bear in mind that other drugs used in combination with Rimactane may also have been taken in an overdosage and necessitate additional specific measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group
Rifampicin is a rifamycin antibiotic.

Mechanism of action
Rimactane 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. Rifampicin has a potent sterilising effect.

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

Since relatively rapid "one-step" selection of resistant bacteria occurs with rifampicin, the drug must not be employed as monotherapy to treat overt infections. Bacteria resistant to rifampicin display no cross-resistance to other antibiotics with the exception of the rifamycins.

5.2 Pharmacokinetic properties

Absorption
Rifampicin is rapidly and completely absorbed. Following a single dose taken on an empty stomach (600mg) the peak serum concentrations (approx. 10g/ml) are observed after about 2 hours. Ingestion with food may adversely affect the absorption of rifampicin.

Distribution
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%.

Rifampicin penetrates rapidly into various body fluids and tissues, including bone tissue. 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 600 mg/day orally.

Rifampicin crosses the human placenta and is secreted in human breast milk. However, it is estimated that a breast-fed infant would receive no more 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**.**

Elimination
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.

Characteristics in patients
In elderly patients, renal clearance is reduced, but, owing to the large scale on which the drug is eliminated via the liver, the 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. 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 severe hepatic dysfunction the dosage may have to be adjusted as plasma concentrations are raised and half-life prolonged.

5.3 Preclinical safety data

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:

Calcium stearate
Lactose monohydrate

Capsule shell:

Iron oxide red (E172)
Titanium dioxide (E171)
Gelatin

Printing Inks:

Dimethylpolysiloxane
Soya lecithin
Black iron oxide
Shellac

6.2 Incompatibilities

None known.

6.3 Shelf Life

4 years.

6.4 Special precautions for storage

Protect from heat and moisture. Store below 30°C.

6.5 Nature and contents of container

PVC/PE/PVDC blister packs of 60 (6 x 10).

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

See section 4.2, Posology and method of administration.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 0111/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 July 1997

Date of last renewal: 05 July 2002

10 DATE OF REVISION OF THE TEXT

December 2004