

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Rimactane® 300 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient is 3-(4-Methyl-1-piperazinyloxy) rifamycin SV.

One capsule contains 300 mg rifampicin Ph. Eur.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsules.

Opaque, two-piece, hard gelatine capsule, reddish-brown in colour, marked with 'NG 300'.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Rifampicin is a major drug in the management of tuberculosis (all forms) and certain opportunistic mycobacterial infections. It is effective in cases resistant to other anti-tuberculosis agents and shows no cross-resistance outside the rifampicin group of drugs. In the treatment of tuberculosis Rifampicin must always be combined with other anti-tuberculosis agents. It is effective in combination with isoniazid, streptomycin, pyrazinamide, ethambutol and the majority of second line drugs.

Prophylaxis of meningococcal meningitis in close contact adult and paediatric patients

4.2 Posology and method of administration

For the management of tuberculosis and certain opportunistic mycobacterial infections:

Rifampicin 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	10-15	5	300	20-40	15	900	20-40	15	900
PZA	30-40	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 Rifampicin and to the table for other components of the treatment).

Continuous therapy

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: Oral doses of 10-20 mg/kg body weight daily are recommended, although a total daily dose should not usually exceed 600 mg.

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

For the chemoprophylaxis of meningococcal meningitis:

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

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

Use in Children:

Children over 1 month: 10 mg per kg every 12 hours for 2 days

Children under 1 month: 5 mg per kg every 12 hours for 2 days

The maximum dose is 600 mg

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. It is recommended that Rifampicin is only given for 2 days in this indication since resistance to this class of antibacterial agent may develop.

4.3 Contraindications

Rifampicin is contraindicated in patients who:

- are hypersensitive to any of the rifamycins or to any of the excipients listed in section 6.1;
- have jaundice;
- are concurrently receiving saquinavir/ritonavir therapy (see section 4.5 Interactions with other medicinal products and other forms of interaction).

Rifampicin is contraindicated with medicines strongly affected by its potential to induce drug metabolizing enzymes and transporters such as: lurasidone, sofosbuvir, antiretrovirals: cabotegravir, fostemsavir and lenacapavir (see section 4.5).

4.4 Special warnings and precautions for use

Rifampicin should be given under the supervision of a respiratory or other suitably qualified physician.

Cautions should be taken in case of renal impairment if dose > 600 mg/day.

All tuberculosis patients should have pre-treatment measurements of liver function.

Adults treated for tuberculosis with rifampicin should have baseline measurements of hepatic enzymes, bilirubin, serum creatinine, a complete blood count, and a platelet count (or estimate).

Baseline tests are unnecessary in children unless a complicating condition is known or clinically suspected.

Patients with impaired liver function should only be given rifampicin in cases of necessity, and then with caution and under close medical supervision. In these patients, lower doses of rifampicin are recommended and careful monitoring of liver function, especially serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) should initially be carried out prior to therapy, weekly for two weeks, then every two weeks for the next six weeks. If signs of hepatocellular damage occur, rifampicin should be withdrawn.

Rifampicin should also be withdrawn if clinically significant changes in hepatic function occur. The need for other forms of antituberculosis therapy and a different regimen should be considered. Urgent advice should be obtained from a specialist in the management of tuberculosis. If rifampicin is re-introduced after liver function has returned to normal, liver function should be monitored daily.

In patients with impaired liver function, elderly patients, malnourished patients, and possibly, children under two years of age, caution is particularly recommended when instituting therapeutic regimens in which isoniazid is to be used concurrently with rifampicin. If the patient has no evidence of pre-existing liver disease and normal pre-treatment liver function, liver function tests need only be repeated if fever, vomiting, jaundice or other deterioration in the patient's condition occur.

Patients should be seen at least monthly during therapy and should be specifically questioned concerning symptoms associated with adverse reactions.

In some patients hyperbilirubinaemia can occur in the early days of treatment. This results from competition between rifampicin and bilirubin for hepatic excretion. An isolated 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 tests, noting trends in the levels and considering them in conjunction with the patient's clinical condition.

Cases of drug-induced liver injury, including fatal cases (especially when used in combination with other anti-tuberculosis drugs), have been reported in patients treated with rifampicin with an onset of a few days to a few months following treatment initiation. Signs and symptoms include elevated serum hepatic enzymes, cholestatic jaundice, hepatitis, hepatotoxicity, hepatocellular injury, and mixed liver injury. Most patients recovered on discontinuation of rifampicin treatment; nevertheless, progression to acute liver failure requiring liver transplantation can occur. The mechanism of rifampicin-induced liver injury is not clearly elucidated, but data indicate either an immuno-allergic mechanism or direct toxicity of metabolic products. Patients should be instructed to contact their physician in case symptoms suggestive of liver injury occur. In such patients rifampicin should be discontinued and liver function should be assessed. Rifampicin should not be re-introduced in patients with an episode of hepatic injury during treatment with rifampicin for which no other cause of liver injury has been determined.

Because of the possibility of immunological reaction including anaphylaxis (see section 4.8 Undesirable effects) occurring with intermittent therapy (less than 2 to 3 times per week) patients should be closely monitored. Patients should be cautioned against interrupting treatment since these reactions may occur.

Rifampicin has enzyme induction properties that can enhance the metabolism of endogenous substrates including adrenal hormones, thyroid hormones and vitamin D. Isolated reports have associated porphyria exacerbation with rifampicin administration.

Cases of thrombotic microangiopathy (TMA), manifested as thrombotic thrombocytopenic purpura (TTP) or haemolytic uremic syndrome (HUS), including fatal cases, have been reported with Rimactane capsules use. If laboratory or clinical findings associated with TMA occur in a patient receiving Rimactane capsules, treatment should be discontinued and thorough evaluation for TMA performed, including platelet levels, renal function, serum lactate dehydrogenase (LDH) and a blood film for schistocytes (erythrocyte fragmentation). ADAMTS13 activity and anti-ADAMTS13-antibody determination should be completed. If anti-ADAMTS13-antibody is elevated in conjunction with low ADAMTS13 activity, treatment with Rimactane capsules should not be resumed and patients should be treated accordingly (consider plasma exchange).

Severe, systemic hypersensitivity reactions, including fatal cases, such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome have been observed during treatment with anti-tuberculosis therapy (See section 4.8).

It is important to note that early manifestations of hypersensitivity, such as fever, lymphadenopathy or biological abnormalities (including eosinophilia, liver abnormalities) may be present even though rash is not evident. If such signs or symptoms are present, the patient should be advised to consult immediately their physician.

Rifampicin infusion should be discontinued if an alternative etiology for the signs and symptoms cannot be established.

After initial improvement of tuberculosis under therapy with Rimactane capsules, the symptoms may worsen again. In affected patients, clinical or radiological deterioration of existing tuberculous lesions or the development of new lesions have been detected. Such reactions have been observed within the first few weeks or months of initiation of tuberculosis therapy. Cultures are usually negative, and such reactions do not usually indicate treatment failure.

The cause of this paradoxical reaction is still unclear, but an exaggerated immune reaction is suspected as a possible cause. In case a paradoxical reaction is suspected, symptomatic therapy to suppress the exaggerated immune reaction should be initiated if necessary. Furthermore, continuation of the planned tuberculosis combination therapy is recommended.

Patients should be advised to seek medical advice immediately if their symptoms worsen. The symptoms that occur are usually specific to the affected tissues. Possible general symptoms include cough, fever, tiredness, breathlessness, headache, loss of appetite, weight loss or weakness (see section 4.8).

Severe cutaneous adverse reactions (SCARs) including Steven-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported with a not known frequency in association with Rimactane capsules treatment.

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, Rimactane capsules should be withdrawn immediately, and an alternative treatment considered (as appropriate).

Most of these reactions occurred within 2 days to 2 months after treatment initiation; the time to onset can vary depending on the conditions.

Rifampicin infusion is for intravenous infusion only and must not be administered by intramuscular or subcutaneous route. Avoid extravasation during injection; local irritation and inflammation due to extravascular infiltration of the infusion have been observed. If these occur, the infusion should be discontinued and restarted at another site.

Rifampicin infusion may produce a discoloration (yellow, orange, red, brown) of the teeth, urine, sweat, sputum and tears, and the patient should be forewarned of this. Soft contact lenses have been permanently stained (see section 4.8).

Rimactane capsules are a well characterized and potent inducer of drug metabolizing enzymes and transporters and might therefore decrease or increase

concomitant drug exposure, safety and efficacy (see section 4.5). Therefore, potential drug interactions should be considered whenever beginning or discontinuing rifampicin treatment.

Rifampicin may cause vitamin K dependent coagulopathy and severe bleeding (see Section 4.8). Monitoring of occurrence of coagulopathy is recommended for patients at particular bleeding risk. Supplemental vitamin K administration should be considered when appropriate (vitamin K deficiency, hypoprothrombinemia).

There have been reports of interstitial lung disease (ILD) or pneumonitis in patients receiving Rimactane Capsules for treatment of tuberculosis (see section 4.8). ILD/pneumonitis is a potentially fatal disorder. Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea accompanied by dry cough) and fever should be performed to confirm the diagnosis of ILD/pneumonitis. If ILD/pneumonitis is diagnosed, Rimactane Capsules should be permanently discontinued in case of severe manifestations (respiratory failure and acute respiratory distress syndrome) and appropriate treatment initiated as necessary.

All patients with abnormalities should have follow up examinations, including laboratory testing, if necessary.

Excipients

This medicine contains Lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Interference with laboratory and diagnostic tests

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 BSP and serum bilirubin has been reported. Rifampicin may impair biliary excretion of contrast media used for visualization of the gallbladder, due to competition for biliary excretion. Therefore, these tests should be performed before the morning dose of rifampicin.

Pharmacodynamic Interactions

When rifampicin is given concomitantly with the combination saquinavir/ritonavir, the potential for hepatotoxicity is increased. Therefore, concomitant use of Rifampicin with saquinavir/ritonavir is contraindicated (see section 4.3 Contraindications).

When rifampicin is given concomitantly with either halothane or isoniazid, the potential for hepatotoxicity is increased. The concomitant use of rifampicin and halothane should be avoided. Patients receiving both rifampicin and isoniazid should be monitored closely for hepatotoxicity.

The concomitant use of rifampicin with other antibiotics causing vitamin K dependent coagulopathy such as cefazolin (or other cephalosporins with N-methyl-thiotetrazole side chain) should be avoided as it may lead to severe coagulation disorders, which may result in fatal outcome (especially in high doses).

Effect of Rifampicin capsules on other medicinal products

Induction of Drug Metabolizing Enzymes and Transporters

Rifampicin capsules are a well characterized and potent inducer of drug metabolizing enzymes and transporters. Enzymes and transporters reported to be affected by Rifampicin capsules include cytochromes P450 (CYP) 1A2, 2B6, 2C8, 2C9, 2C19, and 3A4, UDP-glucuronyltransferases (UGT), sulfotransferases, carboxylesterases, and transporters including P-glycoprotein (P-gp) and multidrug resistance-associated protein 2 (MRP2). Most drugs are substrates for one or more of these enzyme or transporter pathways, and these pathways may be induced by Rifampicin capsules simultaneously. Therefore, Rifampicin capsules may accelerate the metabolism and reduce the activity of certain co-administered drugs, and has the potential to perpetuate clinically important drug-drug interactions against many drugs and across many drug classes (Table 1). To maintain optimum therapeutic blood levels, dosages of drugs may require adjustment when starting or stopping concomitantly administered Rifampicin capsules.

Rifampicin is contraindicated with medicines strongly affected by its potential to induce drug metabolizing enzymes and transporters such as: lurasidone, sofosbuvir, antiretrovirals: cabotegravir, fostemsavir and lenacapavir. Significant decrease in their plasma concentrations is observed because of potent induction of CYP 3A4, P-gp, UGT1A1 by rifampicin which is likely to result in loss of their therapeutic effectiveness.

Examples of drugs or drug classes affected by rifampicin:

- Antiarrhythmics (e.g. disopyramide, mexiletine, quinidine, propafenone, tocainide),
- Antiepileptics (e.g. phenytoin),
- Hormone antagonist (antiestrogens e.g. tamoxifen, toremifene, gestrinone),
- Antipsychotics (e.g. haloperidol, aripiprazole),
- Anticoagulants (e.g. coumarins),
- Antifungals (e.g. fluconazole, itraconazole, ketoconazole, voriconazole),
- Antivirals (e.g. saquinavir, indinavir, efavirenz, amprenavir, nelfinavir, atazanavir, lopinavir, nevirapine),
- Barbiturates
- Beta-blockers (e.g. bisoprolol, propranolol),

- Anxiolytics and hypnotics (e.g. diazepam, benzodiazepines, zolpidem),
- Calcium channel blockers (e.g. diltiazem, nifedipine, verapamil, nimodipine, isradipine, nicardipine, nisoldipine),
- Antibacterials (e.g. chloramphenicol, clarithromycin, dapsone, doxycycline, fluoroquinolones, telithromycin),
- Corticosteroids
- Cardiac glycosides (digitoxin, digoxin),
- Clofibrate,
- Systemic hormonal contraceptives including estrogens and progestogens,
- Antidiabetic (e.g. chlorpropamide, tolbutamide, sulfonylureas, rosiglitazone),
- Immunosuppressive agents (e.g. ciclosporin, sirolimus, tacrolimus)
- Irinotecan,
- Thyroid hormone (e.g. levothyroxine),
- Losartan,
- Analgesics (e.g. methadone, narcotic analgesics),
- Praziquantel,
- Quinine,
- Riluzole,
- Selective 5-HT₃ receptor antagonists (e.g. ondansetron)
- Statins metabolised by CYP 3A4 (e.g. simvastatin),
- Theophylline,
- Tricyclic antidepressants (e.g. amitriptyline, nortriptyline),
- Cytotoxics (e.g. imatinib),
- Diuretics (e.g. eplerenone)
- Enalapril: decrease enalapril active metabolite exposure. Dosage adjustments should be made if indicated by the patient's clinical condition
- Hepatitis-C antiviral drugs (eg, daclatasvir, simeprevir, sofosbuvir, telaprevir): Concurrent use of treatment of hepatitis-C antiviral drugs and rifampicin should be avoided.
- Morphine: Plasma concentrations of morphine may be reduced by rifampicin. The analgesic effect of morphine should be monitored and doses of morphine adjusted during and after treatment with rifampicin.
- fesoterodine - used for overactive bladder
- tadalafil - used for impotence
- cimetidine - used for ulcer-healing drugs.

Rifampicin treatment reduces the systemic exposure of oral contraceptives. Patients on oral contraceptives should be advised to use alternative, non-hormonal methods of birth control during Rifampicin therapy. Also diabetes may become more difficult to control.

Short-term treatment

Women on treatment with Rifampicin or herbal products should be advised that the efficacy of contraceptives may be reduced. An additional barrier

contraceptive method should be used. The barrier method must be used during the whole time of Rifampicin treatment and for 28 days after discontinuation.

Long-term treatment

For women on long-term Rifampicin treatment, an additional alternative method of contraception unaffected by enzyme-inducing medicinal products should be considered.

Concurrent use of ketoconazole and rifampicin has resulted in decreased serum concentrations of both drugs.

If *p*-aminosalicylic acid and rifampicin are both included in the treatment regimen, they should be given not less than eight hours apart to ensure satisfactory blood levels.

Effect of other medicinal products on Rifampicin capsules

Concomitant antacid administration may reduce the absorption of rifampicin. Daily doses of rifampicin should be given at least 1 hour before the ingestion of antacids.

Other drug interactions with Rifampicin capsules

When the two drugs were taken concomitantly, decreased concentrations of atovaquone and increased concentrations of rifampicin were observed.

4.6 Fertility, pregnancy and lactation

Pregnancy

At very high doses in animals rifampicin has been shown to have teratogenic effects. There are no well controlled studies with rifampicin in pregnant women. Although rifampicin has been reported to cross the placental barrier and appear in cord blood, the effect of rifampicin, alone or in combination with other antituberculosis drugs, on the human foetus is not known. Therefore, Rifampicin should be used in pregnant women or in women of child bearing potential only if the potential benefit justifies the potential risk to the foetus. When Rifampicin is administered during the last few weeks of pregnancy it may cause post-natal haemorrhages in the mother and infant for which treatment with Vitamin K1 may be indicated.

Lactation

Rifampicin is excreted in breast milk, patients receiving rifampicin should not breast feed unless in the physician's judgement the potential benefit to the patient outweighs the potential risk to the infant.

4.7. Effects on ability to drive or use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable:
 Very common $\geq 10\%$; Common ≥ 1 and $<10\%$; Uncommon ≥ 0.1 and $<1\%$;
 Rare ≥ 0.01 and $<0.1\%$; Very rare $<0.01\%$, Not known (cannot be estimated from available data).

Reactions occurring with either daily or intermittent dosage regimens include:

System organ class	Frequency	Preferred Term
Infections and infestations	Not known	Pseudomembranous colitis Influenza
Blood and lymphatic system disorders	Common	Thrombocytopenia with or without purpura, usually associated with intermittent therapy, but is reversible if drug is discontinued as soon as purpura occurs.
	Uncommon	Leukopenia
	Not known	Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uremic syndrome Disseminated intravascular coagulation Eosinophilia Agranulocytosis Hemolytic anemia Vitamin K dependent coagulation disorders
Immune system disorders	Not known	Anaphylactic reaction
Endocrine disorders	Not known	Adrenal insufficiency in patients with compromised adrenal function have been observed
Metabolism and nutritional disorders	Not known	Decreased appetite
Psychiatric disorders	Not known	Psychotic disorder
Nervous system disorders	Common	Headache Dizziness
	Not known	Cerebral hemorrhage and fatalities have been reported when rifampicin administration has been continued or resumed after the appearance of purpura
Eye disorders	Not known	Tear discoloration

Vascular disorders	Not known	Shock Flushing Vasculitis Bleeding
Respiratory, thoracic and mediastinal disorders	Not known	Dyspnoea Wheezing Sputum discoloured Interstitial lung disease (including pneumonitis)
Gastrointestinal disorders	Common	Nausea Vomiting
	Uncommon	Diarrhea
	Not known	Gastrointestinal disorder Abdominal discomfort Tooth discolouration (which may be permanent)
Hepatobiliary disorders	Not known	Drug-induced liver injury (including fatal cases especially when used in combination with other anti-tuberculosis drugs) Hepatitis Hyperbilirubinaemia (see section 4.4)
Skin and subcutaneous tissue disorders	Not known	Erythema multiforme Stevens-Johnson syndrome (SJS) Toxic epidermal necrolysis (TEN) Drug reaction with eosinophilia and systemic symptoms (DRESS) Acute generalized exanthematous pustulosis (AGEP) (see section 4.4) Skin reaction Pruritus Rash pruritic Urticaria Dermatitis allergic Pemphigoid Sweat discoloration
Musculoskeletal and connective tissue disorders	Not known	Muscle weakness Myopathy Bone pain
Renal and urinary disorders	Not known	Acute kidney injury usually due to renal tubular necrosis or tubulointerstitial nephritis Chromaturia
Pregnancy, puerperium and perinatal conditions	Not known	Post-partum haemorrhage Fetal-maternal haemorrhage
Reproductive system and breast disorders	Not known	Menstrual disorder
Congenital, familial and genetic disorders	Not known	Porphyria

General disorders and administration site conditions	Very common	Pyrexia Chills
	Common	Paradoxical drug reaction (Recurrence or appearance of new symptoms of tuberculosis, physical and radiological signs in a patient who had previously shown improvement with appropriate anti-tuberculosis treatment is called a paradoxical reaction, which is diagnosed after excluding poor compliance of the patient to treatment, drug resistance, side effects of antitubercular therapy, secondary bacterial/fungal infections).*
	Not known	Oedema
Investigations	Common	Blood bilirubin increased Aspartate aminotransferase increased Alanine aminotransferase increased
	Unknown	Blood pressure decreased Blood creatinine increased Hepatic enzyme increased

*Incidence of paradoxical drug reaction: Lower frequency is reported as 9.2% (53/573) (data between October 2007 and March 2010) and higher frequency is reported as 25% (19/76) (data between 2000 and 2010).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the [Google Play](#) or [Apple App Store](#).

4.9. Overdose

Human Experience

Signs and Symptoms:

Nausea, vomiting, abdominal pain, pruritus, headache and increasing lethargy will probably occur within a short time after acute ingestion; unconsciousness may occur when there is severe hepatic disease. Transient increases in liver enzymes and/or bilirubin may occur. Brownish-red or orange colouration of the skin, urine, sweat, saliva, tears and faeces will occur, and its intensity is proportional to the amount ingested. Facial or periorbital oedema has also been reported in paediatric patients. Hypotension, sinus tachycardia, ventricular arrhythmias, seizures and cardiac arrest were reported in some fatal cases.

The minimum acute lethal or toxic dose is not well established. However, nonfatal acute overdoses in adults have been reported with doses ranging from 9 to 12 g rifampicin. Fatal acute overdoses in adults have been reported with doses ranging from 14-60 g. Alcohol or a history of alcohol abuse was involved in some of the fatal and nonfatal reports.

Nonfatal overdoses in paediatric patients ages 1 to 4 years old of 100 mg/kg for one to two doses have been reported.

Management:

Intensive supportive measures should be instituted and individual symptoms treated as they arise. Since nausea and vomiting are likely to be present, gastric lavage is probably preferable to induction of emesis. Following evacuation of the gastric contents, the instillation of activated charcoal slurry into the stomach may help absorb any remaining drug from the gastrointestinal tract. Antiemetic medication may be required to control severe nausea and vomiting. Active diuresis (with measured intake and output) will help promote excretion of the drug. Haemodialysis may be of value in some patients.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-mycobacterials, antibiotic.
ATC code: J04AB02.

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. 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 (600 mg) the peak serum concentrations (approx. 10 µg/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-deacetyl rifampicin, 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 300 mg, 600 mg and 900 mg respectively. After a few days of repeated daily administration, the bioavailability of rifampicin diminishes, and the half-life value following repeated doses of 600 mg 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 deacetyl rifampicin metabolite, rifampicin also appears in the urine. In a dosage range of 150-900 mg, 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 600 mg daily. Provided that hepatic excretory function is normal, the dosage in patients with impaired renal function does not need to be reduced below 600 mg 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.

In daily doses of 150-250 mg/kg, rifampicin proved teratogenic in mice and rats, 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The capsules contain
calcium stearate
lactose
titanium dioxide (E171)
iron oxide red (E172)
iron oxide yellow (E172)
iron oxide black (E172)
gelatine
shellac glaze
propylene glycol (E1520)
ammonium hydroxide (E527).

6.2. Incompatibilities

None known.

6.3. Shelf life

Four years.

6.4. Special precautions for storage

Protect from light and heat (store below 30°C).

Medicines should be kept out of reach of children.

6.5. Nature and contents of container

The capsules are opaque, two-piece, hard gelatine capsule size 1, reddish-brown in colour, marked with the monogram NG on each half and the code 300, and come in securitainers of 100 and PVC/PE/PVdC blister packs of 60.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Sandoz GmbH
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