

1. NAME OF THE MEDICINAL PRODUCT

Rifampicin 300 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 300 mg rifampicin.

Excipients with known effect:

Each capsule contains 31 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard

Size no.1 hard gelatin capsules with a pink body and maroon cap, printed in black ink "RN300" on the body and "G" on the cap (The capsule contents are brick red).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tuberculosis: Rifampicin, used in combination with other active anti-tuberculosis drugs, is indicated in the treatment of all forms of tuberculosis, including fresh, advanced, chronic and drug-resistant cases. Rifampicin is also effective against most atypical strains of mycobacteria.

Prophylaxis of meningococcal meningitis: Prophylaxis of meningococcal meningitis in close contact adult and paediatric patients.

Leprosy: Rifampicin is indicated in the combination treatment of multibacillary and paucibacillary leprosy in patients of all age groups.

Haemophilus influenzae: Prophylaxis of *Haemophilus influenzae type b* disease in close contacts.

Other infections: Rifampicin is indicated in the treatment of brucellosis, legionnaires disease, and serious staphylococcal infections. Rifampicin should be used in combination with another appropriate antibiotic to prevent emergence of resistant strains of the infecting organism.

4.2 Posology and method of administration

Posology

Tuberculosis

Rifampicin should be given with other effective anti-tuberculosis drugs to prevent the possible emergence of rifampicin resistant strains of mycobacteria.

Adults: The recommended single daily dose in tuberculosis is 8-12mg/kg.

Usual daily dose:

Patients weighing less than 50kg – 450mg

Patients weighing 50kg or more – 600mg

Paediatric patients:

Children above 3 months: Oral doses of 15 (10-20) mg/kg body weight daily are recommended, although a total daily dose should not usually exceed 600mg.

Prophylaxis of Meningococcal Meningitis

Adults: 600mg twice daily for 2 days.

Paediatric patients:

Meningococcal Carriers: Dose must not exceed 600 mg/ dose.

For children ≥ 1 month of age the recommended dose is 10 mg/kg every 12 hours for 2 days.

For children < 1 month of age, the recommended dose is 5 mg/kg every 12 hours for 2 days.

Leprosy

Rifampicin should always be used in conjunction with at least one other anti-leprosy drug to treat the disease.

Adults: 600mg of rifampicin should be given once per month. If a daily dose regime is indicated then the recommended single dose is 10mg/kg. The usual daily dose for patients less than 50kg is 450mg and for patients 50kg or more, the usual daily dose is 600mg.

Paediatric patients:

Rifampicin should always be administered with dapsones in case of paucibacillary forms and with dapsones and clofazimine in case of multibacillary forms.

For children over 10 years, the recommended dose for rifampicin is 450 mg once a month.

For children less than 10 years, the recommended dose for rifampicin is 10 to 20 mg/kg rifampicin once a month.

The duration of treatment is 6 months for paucibacillary and 12 months multibacillary forms.

Prophylaxis of Haemophilus Influenzae

Adults and children ≥ 1 month of age: For members of a household exposed to H. Influenzae B disease when the household contains a child 4 years old or younger, it is recommended that all members (including the child) receive 20mg/kg once daily (maximum daily dose of 600mg) for 4 days.

Index cases should be treated prior to discharge from hospital.

For children < 1 month of age: 10mg/kg once daily for 4 days

Brucellosis, Legionnaires Disease or Serious Staphylococcal Infections

Adults: The recommended daily dose is 600mg to 1200mg given in 2 to 4 divided doses, together with another appropriate antibiotic to prevent the emergence of resistant strains of the infecting organism.

Patients with impaired liver function

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

Use in the Elderly

In elderly patients, the renal excretion of rifampicin is decreased proportionally with physiological decrease of renal function; due to compensatory increase of liver excretion, the serum terminal half-life is similar to that of younger patients. However, as increased blood levels have been noted in one study of rifampicin in elderly patients, caution should be exercised in using rifampicin in such patients, especially if there is evidence of liver function impairment.

Method of administration

For oral administration only.

The daily dose of rifampicin, calculated from the patient's body weight, should preferably be taken on an empty stomach or at least 30 minutes before a meal or 2 hours after a meal to ensure rapid and complete absorption.

4.3 Contraindications

Rifampicin is contra-indicated in the presence of jaundice, and in patients who are hypersensitive to the active substance, rifampicin or any of the excipients listed in section 6.1.

Rifampicin is contraindicated when given concurrently with the combination of saquinavir/ ritonavir (see section 4.5).

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.

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

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 and 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. It is rarely necessary, in the absence of clinical findings, to increase the frequency of performing routine liver function tests in patients with normal pretreatment liver unless fever, vomiting, jaundice or other deterioration in the patients 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 resulting from competition between rifampicin and bilirubin for excretory pathways of the liver at the cell level, can occur in early days of treatment. 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) occurring with intermittent therapy (less than 2 to 3 times per week) patients should be closely monitored. Patients should be cautioned against interruption of dosage regimens 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 Rifampicin capsules use. If laboratory or clinical findings associated with TMA occur in a patient receiving Rifampicin 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 Rifampicin 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 capsules should be discontinued if an alternative etiology for the signs and symptoms cannot be established.

Paradoxical drug reaction

After initial improvement of tuberculosis under therapy with Rifampicin 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 Rifampicin 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, Rifampicin 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 capsules 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).

Rifampicin may cause vitamin K dependent coagulation and severe bleeding (see section 4.8). Monitoring of occurrence of coagulation 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 Rifampicin 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, Rifampicin Capsules should be permanently discontinued in case of severe manifestations (respiratory failure and acute respiratory distress syndrome) and appropriate treatment initiated as necessary.

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).

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.

Examples of drugs or drug classes affected by rifampicin:

- Antiarrhythmics (e.g. disopyramide, mexiletine, quinidine, propafenone, tocainide)

- Antiepileptics (e.g. phenytoin)
- Hormone antagonist (anti-oestrogens e.g. tamoxifen, toremifene, gestrone)
- Antipsychotics (e.g. haloperidol, aripiprazole)
- Anticoagulants (e.g. coumarins)
- Antivirals (e.g. saquinavir, indinavir, efavirenz, amprenavir, nelfinavir, atazanavir, lopinavir, nevirapine)
- Antiretrovirals (e.g. cabotegravir, fostemsavir and lenacapavir)
- Barbiturates
- Beta-blockers (e.g. bisoprolol, propranolol)
- Anxiolytics and hypnotics (e.g. diazepam, benzodiazepines, zopiclone, zolpidem),
- Calcium channel blockers (e.g. diltiazem, nifedipine, verapamil, nimodipine, isradipine, nifedipine, nisoldipine)
- Anti-bacterials (e.g. chloramphenicol, clarithromycin, dapsone, doxycycline, fluoroquinolones, telithromycin)
- Corticosteroids
- Cardiac glycosides (digitoxin, digoxin)
- Clofibrate
- 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)

Lurasidone: Rifampicin 600 mg was shown to decrease lurasidone AUC by 81%. Therefore, markedly reduced exposure of lurasidone can be expected when lurasidone is given concomitantly with a CYP3A4 inducer such as rifampicin (see section 4.3).

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 concentration 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.

Clopidogrel: Increases active metabolite exposure. Rifampicin strongly induces CYP2C19, resulting in both an increased level of clopidogrel active metabolite and platelet inhibition, which in particular might potentiate the risk of bleeding. As a precaution, concomitant use of clopidogrel and rifampicin should be discouraged.

Dapsone: Rifampicin has also been shown to increase the clearance of dapsone and the production of the hydroxylamine metabolite of dapsone which could increase the risk of methaemoglobinaemia, haemolytic anaemia, agranulocytosis, and haemolysis.

Systemic hormonal contraceptives including oestrogens and progestogens: 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.

Implant contraceptives:

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.

Mifepristone: Rifampicin was shown to decrease mifepristone AUC by 6.3-fold and its metabolites 22-hydroxy mifepristone and N-demethyl mifepristone by 20-fold and 5.9-fold, respectively. Therefore, reduced efficacy can be expected when mifepristone is given concomitantly with a potent CYP inducer such as rifampicin.

Antidiabetic (e.g. chlorpropamide, tolbutamide, sulfonylureas, rosiglitazone): Diabetes may become more difficult to control.

Antifungals (e.g. fluconazole, itraconazole, ketoconazole, voriconazole, caspofungin): Concurrent use of ketoconazole and rifampicin has resulted in decreased serum concentrations of both drugs. After

two weeks of repeated administration of rifampicin, trough levels of caspofungin were 30% lower than in adult subjects who received caspofungin alone.

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.

Antacids: 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.

Paracetamol: Concomitant use of paracetamol with rifampicin may increase the risk of hepatotoxicity.

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 the 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.

Breast-feeding

Rifampicin is excreted in breast milk, infants should not be breast fed by a patient receiving rifampicin 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 and 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 ($\geq 1/10$); Common ($\geq 1/100$ to $<1/10$); Uncommon ($\geq 1/1,000$ to $<1/100$); Rare ($\geq 1/10,000$ to $<1/1,000$); Very rare ($<1/10,000$), Not known (cannot be estimated from available data).

Reactions occurring with either daily or intermittent dosage regimens include:

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, Haemolytic anaemia, Vitamin K dependent coagulation disorders

Immune system disorders

Not known: Anaphylactic reaction

Endocrine disorders

Not known: Adrenal insufficiency in patient 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 haemorrhage and fatalities have been reported when rifampicin administration has been continued or resumed after the appearance of purpura.

Eye disorders

Not known: Tear discolouration

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: Diarrhoea

Not known: Gastrointestinal disorder, Abdominal discomfort, Tooth discoloration (which may be permanent)

Hepatobiliary disorders

Not known: Drug-induced liver injury (including fatal cases especially when used in combination with other antituberculosis drugs), Hepatitis, Hyperbilirubinaemia (see section 4.4)

Skin and subcutaneous tissue disorders

Not known: Erythema multiforme including Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome (See section 4.4), 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, Foetal-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).*

* 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).

Not known: Oedema

Investigations

Common: Blood bilirubin increased, Aspartate aminotransferase increased, Alanine aminotransferase increased

Not known: Blood pressure decreased, Blood creatinine increased, Hepatic enzyme increased.

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 the 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.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterials, antibiotics, ATC code: J04AB02

Rifampicin is an active bactericidal antituberculosis drug which is particularly active against the rapidly growing extracellular organisms and also has bactericidal activity intracellularly. Rifampicin has activity against slow and intermittently-growing *M. Tuberculosis*.

Rifampicin inhibits DNA-dependent RNA polymerase activity in susceptible cells. Specifically, it interacts with bacterial RNA polymerase but does not inhibit the mammalian enzyme. Cross-resistance to rifampicin has only been shown with other rifamycins.

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for Rifampicin and are listed here: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

5.2 Pharmacokinetic properties

Rifampicin is readily absorbed from the gastrointestinal tract. Peak serum concentrations of the order of 10 µg/ml occur about 2 to 4 hours after a dose of 10 mg/kg body weight on an empty stomach.

Absorption of rifampicin is reduced when the drug is ingested with food.

The pharmacokinetics (oral and intravenous) in children are similar to adults.

In normal subjects the biological half-life of rifampicin in serum averages about 3 hours after a 600 mg dose and increases to 5.1 hours after a 900 mg dose. With repeated administration, the half-life decreases and reaches average values of approximately 2-3 hours. At a dose of up to 600 mg/day, it does not differ in patients with renal failure and consequently, no dosage adjustment is required.

Rifampicin is rapidly eliminated in the bile and an enterohepatic circulation ensues. During this process, rifampicin undergoes progressive deacetylation, so that nearly all the drug in the bile is in this form in about 6 hours. This metabolite retains essentially complete antibacterial activity. Intestinal reabsorption is reduced by deacetylation and elimination is facilitated. Up to 30 % of a dose is excreted in the urine, with about half of this being unchanged drug.

Rifampicin is widely distributed throughout the body. It is present in effective concentrations in many organs and body fluids, including cerebrospinal fluid. Rifampicin is about 80 % protein bound. Most of the unbound fraction is not ionized and therefore is diffused freely in tissues.

5.3 Preclinical safety data

There are no preclinical safety data of relevance to the prescriber which are additional to those already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each capsule contains:

Ascorbic Acid

Lactose monohydrate

Talc

Magnesium Stearate.

The capsule cap and body contains:

Indigotine (E132)

Titanium Dioxide (E171)

Gelatin

Erythrosine (E127)

Red Iron Oxide (E172).

The capsule printing ink contains:

Shellac

Iron oxide black (E172)

Propylene glycol

Ammonium hydroxide

6.2 Incompatibilities

None known

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in a cool dry place

6.5 Nature and contents of container

Polypropylene containers with polyethylene cap (with optional polyethylene ullage filler) in packs of 5, 7, 8, 10, 14, 15, 16, 20, 21, 25, 28, 30, 56, 60, 84, 90, 100, 250 and 500 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Generics [UK] Limited t/a Mylan

Station Close

Potters Bar

Hertfordshire

EN6 1TL

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04569/0087

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/07/1986 / 05/04/2002

10 DATE OF REVISION OF THE TEXT

07/05/2026