AUSTRALIAN PRODUCT INFORMATION – RIFADIN® (RIFAMPICIN)

1 NAME OF THE MEDICINE

Rifampicin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Rifadin 150 mg capsules contain 150 mg of rifampicin per capsule.
Rifadin 300 mg capsules contain 300 mg of rifampicin per capsule.

Rifadin syrup contains 100 mg of rifampicin per 5 mL of syrup.

Rifadin IV infusion contains 600 mg rifampicin per vial.

Excipients with known effect

Capsules: contain sulfites

Syrup: contains methyl hydroxybenzoate, propyl hydroxybenzoate, potassium sorbate, sodium metabisulfite and saccharin.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Capsules:
150 mg (blue/red, marked R-150)
300 mg (red, marked R-300)

Syrup:
100 mg/5 mL (red, raspberry flavoured)

IV infusion:
600 mg (spongy, fragile amorphous red powder) with 10 mL sterile water for injection solvent

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Tuberculosis

In the initial treatment and in re-treatment of patients with tuberculosis, Rifadin must be used in conjunction with at least one other antituberculosis drug.

Leprosy

In the management of lepromatous leprosy and dimorphous leprosy to effect speedy conversion of the infectious state to the noninfectious state, which may be expected to occur in 3 to 4 months of treatment.

As an alternative drug in lepromatous, dimorphous, indeterminate and tuberculoid leprosy resistant to sulfones and other antileprosy drugs.

As an alternative drug in all those patients having true drug allergy to the more commonly used antileprosy drugs.

Meningococcal Disease*

Prophylaxis of meningococcal disease in close contacts of known cases and in carriers (Rifadin is not indicated for the treatment of meningococcal infections).

Haemophilus Influenzae*

Prophylaxis of household contacts of patients with *H. influenzae* type B.

*Rifadin syrup should be prescribed in exceptional cases only when all other available alternatives are exhausted (see Section 4.4 Special Warnings and Precautions for Use (Rifampicin syrup)).

4.2 DOSE AND METHOD OF ADMINISTRATION

Oral

It is recommended that oral Rifadin be administered once daily, on an empty stomach either 30 minutes before or two hours after a meal.

Pulmonary Tuberculosis

Adults: 600 mg in a single daily administration.

Children: 10 to 20 mg/kg, not to exceed 600 mg/day.

Leprosy

Adults: 450 to 600 mg in a single daily administration.

Prophylaxis of Meningococcal Disease (see Section 4.1 Therapeutic indications).

Adults: 600 mg/day for 4 days.

Children, over 5 years: 10 mg/kg/day for 4 days, not to exceed 600 mg/day.

Data are not available for determination of dosage for children under 5 years.

The NHMRC recommend that in any household in which a case of *H. influenzae* type B infection has occurred and in which another child less than 4 years resides, all members of

the family, including adults, should receive rifampicin in a dose of 20 mg/kg per dose once daily (maximum dose 600 mg/day) for 4 days; the dose for neonates (less than 1 month) is 10 mg/kg once daily for 4 days.

In the treatment of pulmonary tuberculosis, Rifadin must be used in conjunction with at least one other antituberculous agent. Similarly, in the treatment of leprosy, rifampicin should always be used in conjunction with at least one other antileprosy drug.

In general, therapy should be continued until bacterial conversion and maximal improvement have occurred.

Continuous daily treatment with Rifadin is usually better tolerated than intermittent medication (see Section 4.4 Special warnings and precautions for use). The termination of long-term therapy with rifampicin and a subsequent resumption of medication may lead to immunopathological effects (see Section 4.8 Adverse effects (Undesirable effects)). Intermittent therapy should be avoided but if this alternative is not possible therapy should be initiated with small incremental (150 mg/day) doses. Renal function should be monitored and corticosteroids may be useful.

Intravenous infusion

Rifadin IV infusion is indicated in patients who are unable to tolerate oral therapy, e.g. postoperative or comatose patients, or patients in whom gastrointestinal absorption is impaired. Serum concentrations following single daily administration of 600 mg rifampicin given in an intravenous infusion drip over 1 to 3 hours are similar to those obtained after 600 mg by mouth.

Adults: Usual dose is 600 mg infused daily.

Children: 10 to 20 mg/kg/day, up to 600 mg/day.

In general, therapy should be continued until bacterial conversion and maximal improvement have occurred.

Preparation of intravenous infusion

Rifadin IV is only intended to be administered via intravenous infusion and must not be administered by intramuscular or subcutaneous route. It should be freshly prepared by aseptically adding the solvent to the vial of rifampicin powder and swirling gently and continuously until the powder has completely dissolved. When the powder has completely dissolved, the solution is stable for up to 30 hours.

The solution should be diluted in 500mL of 5% glucose solution or normal saline. It is suggested that the infusion is administered over a period of 1 to 3 hours.

Dilutions in glucose 5% for injections are stable for up to 8 hours at room temperature and should be prepared and used within this time. Precipitation of rifampicin from the infusion solution may occur beyond this time.

Rifadin IV infusion is compatible with normal saline for up to 6 hours. Other infusion solutions are not recommended.

4.3 CONTRAINDICATIONS

Jaundice.

History of hypersensitivity to any of the rifamycins.

Rifadin use is contraindicated when given concurrently with:

- the combination of saquinavir / ritonavir (see Section 4.5 Interactions with other medicines and other forms of interactions).
- cabotegravir, fostemsavir and lenacapavir (see Section 4.5 Interaction with other medicines and other forms of interaction).

Concomitant administration with lurasidone as it markedly decreases the exposure of lurasidone compared to the use of lurasidone alone (see Section 4.5 Interactions with other medicines and other forms of interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 should be seen at least monthly during therapy and should be specifically questioned concerning symptoms associated with adverse reactions. All patients with abnormalities should have follow-up, including laboratory testing, if necessary. Routine laboratory monitoring for toxicity in people with normal baseline is generally not necessary.

Rifampicin has been observed to increase the requirement for anticoagulant drugs of the coumarin type. The cause of this phenomenon is unknown. In patients receiving anticoagulants and rifampicin concurrently, it is recommended that the prothrombin time be performed daily or as frequently as necessary to establish and maintain the required dose of anticoagulant.

Urine, faeces, saliva, sputum, sweat, tears and teeth may be coloured red-orange, yellow or brown by rifampicin and its metabolites. Soft contact lenses may be permanently stained. Individuals to be treated should be made aware of these possibilities in order to prevent undue anxiety.

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 as a result of induction of delta amino levulinic acid synthetase.

Rifampicin may cause vitamin K dependent coagulopathy and severe bleeding (see Section 4.8 Adverse effects (Undesirable effects)). 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, hypoprothrombinaemia).

Rifampicin is a well characterised and potent inducer of drug metabolising enzymes and transporters and might therefore decrease or increase concomitant drug exposure, safety and efficacy (see Section 4.5 Interactions with other medicines and other forms of interactions).

Therefore, patients should be advised not to take any other medication without medical advice.

I.V. preparation 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.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in severe cases, appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement therapy should be provided when indicated.

Hepatotoxicity

Rifampicin has been shown to produce liver dysfunction. There have been fatalities associated with jaundice in patients with liver disease or receiving rifampicin concomitantly with other hepatotoxic agents. Since an increased risk may exist for individuals with liver disease, rifampicin should only be given to these patients in cases of necessity and under strict medical supervision. Periodic liver function monitoring in these patients, especially ALT and AST, should be carried out prior to therapy and then every 2 to 4 weeks during therapy. Dosage adjustment may be necessary. If signs of hepatocellular damage occur, rifampicin should be discontinued. Similar precautions are recommended for undernourished patients.

Cases of mild to severe cholestasis have been reported with rifampicin therapy. Patients should be instructed to contact their physician immediately if they experience symptoms such as itching, weakness, loss of appetite, nausea, vomiting, abdominal pain, yellowing of the eyes or skin or dark urine. If cholestasis is confirmed, rifampicin should be discontinued.

In some cases, hyperbilirubinaemia resulting from competition between rifampicin and bilirubin for excretory pathways of the liver at the cell level can occur in the 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.

Drug Resistance

Both in the treatment of tuberculosis and in meningococcal prophylaxis, small numbers of resistant cells, present within large populations of susceptible cells, can rapidly become the predominating type. Since rapid emergence of resistance can occur, culture and susceptibility tests should be performed in the event of persistent positive cultures.

Rifadin should not be used for the treatment of meningococcal disease. In the treatment of asymptomatic carriers, it should be reserved for situations where the risk of meningococcal meningitis is high.

The risks of drug resistance with rifampicin, when used in leprosy, have not been adequately evaluated and, therefore, a second drug should be added to the treatment regimen as is done in the case of tuberculosis.

It is necessary to exclude concomitant tuberculosis in any patient with leprosy who is to be given rifampicin. If tuberculosis exists concurrently, combined chemotherapy must be used.

Immunological Reactions/Anaphylaxis

Rifadin is not recommended for intermittent therapy (less frequently than 2 to 3 times/week) because of the possibility of immunological reactions including anaphylaxis (see Section 4.8 Adverse effects (Undesirable effects)). The patient should be cautioned against intentional or accidental interruption of the daily dosage regimen since rare renal hypersensitivity reactions have been reported when therapy was resumed in such cases. If, as may happen in rare cases, a patient develops thrombocytopenia, purpura, haemolytic anaemia or renal failure, treatment with Rifadin should be stopped at once and not reinstituted at any subsequent time.

Rifampicin syrup

Rifampicin syrup contains sodium metabisulfite which may cause allergic reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people.

For Meningococcal carriers and Haemophilus Influenzae carriers, Rifadin syrup should be prescribed in exceptional cases only when all other available alternatives are exhausted, due to the potential carcinogenic risk from combined exposure of nitrosamine impurity and the excipient diethanolamine (see Section 5.3 Preclinical Safety Data).

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome

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 Adverse effects (Undesirable effects)). 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 their physician immediately.

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

Severe bullous reactions

Cases of severe bullous skin reactions such as Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalised exanthematous pustulosis (AGEP) have been reported with rifampicin. If symptoms or signs of AGEP, SJS or TEN are present, rifampicin treatment must immediately be discontinued.

Interstitial Lung Disease (ILD)/Pneumonitis

There have been reports of ILD or pneumonitis in patients receiving Rifadin for treatment of tuberculosis. 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, Rifadin should be permanently discontinued in case of severe manifestations (respiratory failure and acute respiratory distress syndrome) and appropriate treatment initiated as necessary.

Paradoxical Drug Reaction

After initial improvement of tuberculosis under therapy with Rifadin, 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.

The cause of this paradoxical reaction is still unclear, but an exaggerated immune reaction is suspected as a possible cause. When 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 Adverse Effects (Undesirable Effects)).

Thrombotic microangiopathy

Cases of thrombotic microangiopathy (TMA), manifested as thrombotic thrombocytopenic purpura (TTP) or haemolytic uremic syndrome (HUS), including fatal cases, have been reported with rifampicin use. If laboratory or clinical findings associated with TMA occur in a patient receiving rifampicin, 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

should not be resumed and patients should be treated accordingly (consider plasma exchange).

Contraception in males and females

Males should be warned not to father a child and to use effective contraceptive measures during treatment with Rifadin and for 3 months following completion of treatment.

Females of childbearing potential should be warned not to become pregnant and to use effective contraceptive measures during treatment with Rifadin and for 6 months following completion of treatment. (See Section 5.3 Preclinical Safety Data and Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

Use in hepatic impairment

Patients with impaired liver function should only be given Rifadin in cases of necessity and under strict medical supervision (see Hepatotoxicity).

Use in the elderly

No data available.

Paediatric use

Use in Premature and Newborn Infants

As liver enzymes are not fully developed in this age group, treatment with Rifadin should be considered only in the most grave emergencies.

Effects on laboratory tests

Cross-reactivity and false-positive urine screening tests for opiates have been reported in patients receiving rifampicin when using the KIMS (Kinetic Interaction of Microparticles in Solution) method (e.g. Abuscreen On-Line opiates assay; Roche Diagnostic Systems). Confirmatory tests, such as gas chromatography / mass spectrometry, will distinguish rifampicin from opiates.

Therapeutic levels of rifampicin have been shown to inhibit standard microbiological assays for serum folate and vitamin B12. Thus, alternate assay methods should be considered.

Transient elevations of bromsulfophthalein and serum bilirubin have 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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

When Rifadin is given concomitantly with cabotegravir, fostemsavir, or lenacapavir, significant reductions in antiretroviral exposure have been observed. Therefore, concomitant use of Rifadin with cabotegravir, fostemsavir, or lenacapavir is contraindicated (see Section 4.3 Contraindications).

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

Concomitant use of paracetamol with rifampicin may increase the known risk of hepatotoxicity seen in relation to each drug.

Rifampicin is a well characterised and potent inducer of drug metabolising enzymes and transporters. Enzymes and transporters reported to be affected by rifampicin 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 simultaneously. Therefore, rifampicin may accelerate the metabolism and decrease the activity of certain coadministered drugs or increase the activity of a coadministered pro-drug (where metabolic activation is required), and has the potential to perpetuate clinically important drug-drug interactions against many drugs and across many drug classes. To maintain optimum therapeutic blood levels dosages of drugs may require adjustment when starting or stopping concomitantly administered rifampicin.

Caution should be used when prescribing rifampicin with drugs metabolised by enzyme and transporters reported to be affected by rifampicin, including cytochrome P-450.

Examples of drugs metabolised by cytochrome P-450 enzymes include: oral anticoagulants (e.g. warfarin), anticonvulsants (e.g. phenytoin), antiarrhythmics (e.g. disopyramide, mexiletine, quinidine, tocainide and propafenone), antioestrogens (e.g. tamoxifen, toremifen), antipsychotics (e.g. haloperidol), antifungals (e.g. fluconazole, itraconazole, ketoconazole - see below), caspofungin, antiretroviral drugs (e.g. zidovudine, saquinavir, indinavir, efavirenz, cabotegravir, fostemsavir and lenacapavir), barbiturates, beta-blockers, benzodiazepines (e.g. diazepam), benzodiazepine-related drugs (e.g. zopiclone, zolpidem), calcium channel blockers (e.g. diltiazem, nifedipine, verapamil), chloramphenicol, clarithromycin, corticosteroids, cardiac glycoside preparations, clofibrate, systemic hormonal contraceptives (see below), dapsone, doxycycline, oestrogens, fluoroquinolones, gestrinone, oral hypoglycaemic agents (sulfonylureas), immunosuppressive agents (e.g. ciclosporin, tacrolimus), irinotecan, levothyroxine, narcotic analgesics, methadone, praziquantel, progestins, quinine, riluzole, selective 5-HT_3 receptor antagonists (e.g. ondansetron), statins metabolized by CYP 3A4, telithromycin, theophylline, thiazolidinediones (e.g. rosiglitazone), tricyclic antidepressants (e.g. amitriptyline, nortriptyline) and losartan. It may be necessary to adjust the dosage of these drugs if they are given concurrently with rifampicin.

Concurrent use of hepatitis C antiviral drugs (e.g. daclatasvir, simeprevir, sofosbuvir, telaprevir) and rifampicin should be avoided.

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

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

Concurrent use of rifampicin and enalapril has resulted in decreased concentrations of enalaprilat, the active metabolite of enalapril. Dosage adjustments should be made if indicated by the patient's clinical condition.

When rifampicin is taken with p-aminosalicylic acid (PAS), rifampicin levels in the serum may decrease. Therefore, the drugs should be taken at least 4 hours apart.

Rifampicin treatment reduces the systemic exposure of oral contraceptives. Patients using oral contraceptives should be advised to change to non-hormonal methods of birth control during rifampicin therapy. Diabetes may become more difficult to control in patients treated with rifampicin.

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.

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 methemoglobinemia.

Combined administration of either halothane or isoniazid and rifampicin may give rise to more frequent and marked disorders of liver function than treatment with rifampicin alone. 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 with high doses).

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

Rifampicin 600mg 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 Contraindications).

Rifadin 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Contraception in males and females

Due to the genotoxic potential of rifampicin (see section 5.3 Preclinical Safety Data), males should be warned not to father a child and to use effective contraceptive measures for the duration of treatment and for 3 months following completion of treatment.

Females of childbearing potential should be warned not to become pregnant and to use effective contraceptive measures (using non-hormonal methods of birth control, see section 4.5 Interactions with Other Medicines and Other Forms of Interactions) during treatment and for 6 months following completion of treatment.

Effects on fertility

There is no known human data on the long-term potential for impairment of fertility.

Rifampicin has a genotoxic potential in animals, which is a risk factor for impairment of human fertility (see section 5.3 Preclinical Safety Data).

Use in pregnancy – Pregnancy Category C

There are no well-controlled studies with rifampicin in pregnant women. Therefore, rifampicin should be used in pregnant women or in women of childbearing potential only if the potential benefit justifies the potential risk to the fetus.

In animal experiments, rifampicin, given during organ development, has caused skeletal malformations.

Although rifampicin has been reported to cross the placental barrier and appear in cord blood, the effect of rifampicin on the human fetus is not known.

Bleeding attributable to hypoprothrombinaemia has been reported in newborn infants and in mothers after the use of rifampicin during late pregnancy. If rifampicin is used during the last few weeks of pregnancy, vitamin K should be given to the mother and the newborn infant.

Use in lactation

Rifampicin is excreted in breast milk and infants should not be breastfed by a patient receiving rifampicin.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Rifadin may cause undesirable effects which may reduce the capacity for the completion of certain tasks. Patients should be informed of the potential for these undesirable effects and if they experience these symptoms, consideration should be given not to drive or operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Gastrointestinal disturbances such as heartburn, epigastric distress, abdominal discomfort, anorexia, decreased appetite, nausea, vomiting, gas, cramps and diarrhoea have been noted in some patients. Pseudomembranous colitis has been reported (see Section 4.4 Special warnings and precautions for use).

Headache, drowsiness, fatigue, menstrual disturbances (in women receiving long-term antituberculosis therapy with regimens containing rifampicin), post-partum haemorrhage, fetal-maternal haemorrhage, ataxia, dizziness, inability to concentrate, mental confusion, visual disturbances, muscular weakness, fever, pains in the extremities and generalised numbness have also been noted. Psychoses have been rarely reported.

Encountered occasionally have been flushing, pruritus, urticarial rash, allergic dermatitis, pemphigus, pemphigoid, acneform lesions, sore mouth, sore tongue and exudative conjunctivitis. Rarely, hepatitis or a shock-like syndrome with hepatic involvement and abnormal liver function tests (e.g. elevations in serum bilirubin, bromsulfophthalein, alkaline phosphatase, serum transaminases) have also been observed. Elevations in blood bilirubin, aspartate aminotransferase and alanine aminotransferase have been commonly reported. An increase in blood creatinine and hepatic enzymes have also been reported. Cholestasis has also been reported.

Drug-induced liver injury (including fatal cases especially when used in combination with other anti-tuberculosis drugs) has been reported.

Hypersensitivity reactions have been reported. Erythema multiforme including Stevens-Johnson syndrome, toxic epidermal necrolysis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome, acute generalised exanthematous pustulosis (AGEP), and vasculitis have been reported rarely.

Rifampicin can cause certain bodily fluids such as sputum, urine, sweat and tears to become red-orange, yellow or brown in colour (see Section 4.4 Special warnings and precautions for use). Tooth discolouration (which may be permanent) has also been reported.

Thrombocytopenia with or without purpura may occur, usually associated with intermittent therapy, but is reversible if the drug is discontinued as soon as purpura occurs. Cerebral haemorrhage and fatalities have been reported when rifampicin administration has been continued or resumed after the appearance of purpura. Eosinophilia, leucopenia, oedema, muscle weakness and myopathy have been reported to occur in a small percentage of patients treated with rifampicin. Agranulocytosis has been reported very rarely. Disseminated intravascular coagulation has been rarely reported. Vitamin K dependent coagulation disorders and bleeding have been reported. Porphyria has been reported. Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uremic syndrome have been reported.

Elevations in BUN, serum uric acid and hyperuricaemia have occurred. Rarely, haemolysis, haemoglobinuria, haematuria, renal insufficiency or acute kidney injury have been reported and are generally considered to be hypersensitivity reactions. These have usually occurred during intermittent therapy or when treatment was resumed following intentional or accidental interruption of a daily dosage regimen and were reversible when rifampicin was discontinued and appropriate therapy instituted.

Rare reports of adrenal insufficiency have been observed in patients with compromised adrenal function.

Reactions usually occurring with intermittent dosage regimens and most probably of immunological origin include the following:

- "Flu-like syndrome" consisting of episodes of fever, chills, headache, dizziness and bone pain appearing most commonly during the third to the sixth month of therapy. The frequency of the syndrome varies but may occur in up to 50% of patients given once weekly regimens with a dose of rifampicin of 25 mg/kg or more. These symptoms may be a prelude to more serious complications such as renal hypersensitivity reactions. It is preferable in such cases to change to daily medication.
- Shortness of breath/dyspnoea and wheezing.
- Anaphylaxis/anaphylactic reaction.
- Decrease in blood pressure and shock.
- Haemolytic anaemia.

Paradoxical drug reaction: Recurrence or appearance of fresh symptoms, 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.

Interstitial lung disease (including pneumonitis) has been reported.

Acute kidney injury usually due to renal tubular necrosis or tubulointerstitial nephritis but cortical necrosis has been reported.

During the treatment of leprosy with Rifadin, a lepromatous reaction may occur. Mild reactions do not require cessation of Rifadin therapy; in other cases corticosteroid therapy may be required and withdrawal of rifampicin considered.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

Nausea, vomiting, abdominal pain, pruritus, headache and increasing lethargy will probably occur within a short time after acute ingestion; actual unconsciousness may occur with severe hepatic involvement. Transient increases in liver enzymes and/or bilirubin may occur. Brownish-red or orange discolouration of the skin, urine, sweat, saliva, tears and faeces is proportional to 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.

Liver enlargement, possibly with tenderness, can develop within a few hours after severe overdosage and jaundice may develop rapidly. Hepatic involvement may be more marked in patients with prior impairment of hepatic function. Other physical findings remain essentially normal. Direct and total bilirubin levels may increase rapidly with severe overdosage; hepatic enzyme levels may be affected, especially with prior impairment of hepatic function. A direct effect upon the haematopoietic system, electrolyte levels, or acid-base balance is unlikely.

Although it has not been observed in humans, animal studies suggest a possible neurodepressant action associated with very high doses of rifampicin. Where overdoses of other drugs, including such potentially hepatotoxic substances as isoniazid, pyrazinamide or ethionamide have occurred simultaneously, the signs and symptoms of acute poisoning may be aggravated and/or modified.

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 of rifampicin. Fatal acute overdoses in adults have been reported with doses ranging from 14 to 60 g. Alcohol or a history of alcohol abuse was involved in some of the fatal and nonfatal reports. Nonfatal overdoses in paediatric patients aged 1 to 4 years old of 100 mg/kg for one to two doses have been reported.

Treatment

Intensive supportive and symptomatic measures should be instituted. Since nausea and vomiting are likely present, activated charcoal slurry instilled into the stomach following evacuation of gastric contents could help absorb any remaining drug in the gastrointestinal tract. Antiemetic medication may be required to control severe nausea/vomiting.

Active diuresis (with measured intake and output) will help promote excretion of the drug. Bile drainage may be indicated in the presence of serious impairment of hepatic function lasting more than 24 to 48 hours; under these circumstances, extracorporeal haemodialysis may be required. In patients with previously adequate hepatic function, reversal of liver enlargement and impaired hepatic excretory function probably will be noted within 72 hours, with rapid return toward normal thereafter.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antimycobacterials, antibiotic, ATC code: J04AB02

Mechanism of action

Rifampicin is particularly active against rapidly growing extracellular organisms but it also has bactericidal activity intracellularly and against slow and intermittently growing *Mycobacterium 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.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Rifampicin is readily absorbed from the stomach and the duodenum. Peak serum concentrations of the order of 7 microgram/mL (range 6 to 32 microgram/mL) occur about 2 to 4 hours after an oral dose of 600 mg on an empty stomach.

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

Distribution

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 ionised and therefore diffuses freely in tissues.

Rifampicin crosses the placenta and serum levels in the fetus equal 15 to 96% of the maternal levels. It also appears in breast milk.

Metabolism

In normal subjects the biological half-life of rifampicin in serum averages about 3 hours after a 600 mg dose.

Excretion

After absorption, 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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Data available from literature reports have indicated that rifampicin possesses a mutagenic potential in the Ames test and is considered to be aneugenic as well as clastogenic in mice after oral administration. An increase in chromatid breaks was noted when whole-blood cell

cultures were treated with rifampicin. Increased frequency of chromosomal aberrations was observed in lymphocytes obtained from patients treated with combinations of rifampicin, isoniazid and pyrazinamide, and combinations of streptomycin, rifampicin, isoniazid and pyrazinamide. There are insufficient human data on the long-term effects of the genotoxic potential of rifampicin.

Carcinogenicity

There is insufficient human data on the long-term potential for carcinogenicity. A few cases of accelerated growth of lung carcinoma have been reported in humans, but a causal relationship with the drug has not been established.

Rifampicin was associated with an increased incidence of liver tumours in the females of one strain of mice at doses from 2 to 10 times the recommended human therapeutic doses administered for 60 weeks. In another strain of mice and in rats, no increase of tumours was found. All these studies were carried out during most of the animals' life span.

Rifampicin has been reported to possess immunosuppressive potential in rabbits, mice, rats, guinea pigs, human lymphocytes *in vitro* and humans. Antitumor activity in vitro has also been shown with rifampicin.

Diethanolamine is an excipient in Rifadin oral syrup. In a mouse dermal carcinogenicity study, there was an increased incidence of hepatocellular tumours in female mice at all tested doses (≥40 mg/kg) and male mice at ≥80 mg/kg. There was also an increased incidence of renal tubule adenoma in male mice at all tested doses (≥40 mg/kg). In a rat dermal carcinogenicity study, no treatment-related increase in the incidence of tumours was seen up to the highest tested dose in either males (64 mg/kg) or females (32 mg/kg); however, estimated maximum systemic exposures in this study were significantly lower than those achieved in the mouse study.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Excipients present in the capsules are maize starch, magnesium stearate, titanium dioxide, erythrosine, indigo carmine and gelatin.

Excipients present in the injection are sodium formaldehyde sulfoxylate and sodium hydroxide, the diluent is water for injections.

Excipients present in the syrup are agar, sucrose, methyl hydroxybenzoate, propyl hydroxybenzoate, potassium sorbate, saccharin, sodium metabisulfite, polysorbate 80, Raspberry Aroma 15 D 90, diethanolamine and purified water.

6.2 INCOMPATIBILITIES

Physical incompatibility (precipitate) was observed with undiluted (5 mg/mL) and diluted (1 mg/mL in normal saline) diltiazem hydrochloride and rifampicin (6 mg/mL in normal saline) during simulated Y-site administration.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

In-use shelf life for intravenous infusion

For instructions on reconstitution or dilution of Rifadin IV before administration (see Section 4.2 Dose and method of administration).

After reconstitution with the solvent, the solution is stable for up to 30 hours.

Dilutions in glucose 5% for injections are stable for up to 8 hours at room temperature and should be prepared and used within this time. Precipitation of rifampicin from the infusion solution may occur beyond this time.

Rifadin IV infusion is compatible with normal saline for up to 6 hours.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Capsules 150 mg, 300 mg: packed in PVC/PVDC-Alu-PVDC blister strips in packs of 100.

Syrup 100 mg/5 mL: 60 mL - amber glass bottles.

IV infusion 600 mg; with 10 mL sterile water for injection solvent - glass vials.

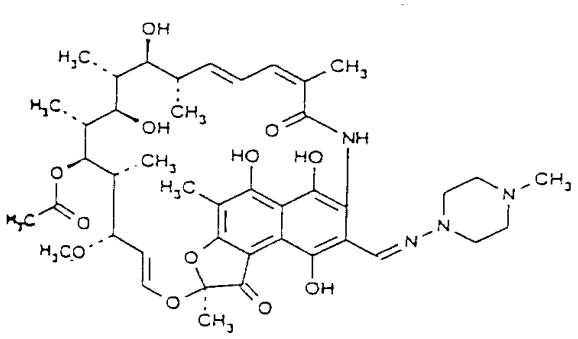
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Rifampicin is a semisynthetic antibiotic derivative of rifamycin B. Specifically, rifampicin is the hydrazone, 3-(4-methylpiperazinyliminomethyl) rifamycin SV. It is only slightly soluble in water and is rather unstable to light and moisture.

Chemical structure



$C_{43}H_{58}N_4O_{12}$

CAS number

13292-46-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 Prescription Only Medicine

8 SPONSOR

sanofi-aventis australia pty ltd
International Tower 3, Level 23
300 Barangaroo Avenue
Sydney NSW 2000
Freecall: 1800 818 806
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

22 August 1996

10 DATE OF REVISION

25 June 2026

Summary table of changes

Section changed	Summary of new information
4.1	Addition of restrictive use for Rifadin syrup Inclusion of cross-referencing to Section 4.4 for restricted indications for oral syrup formulations
4.4	Addition of restricted therapeutic indications for rifampicin oral syrup Inclusion of warning statements regarding contraception for males and females Addition of cross-referencing to Sections 4.5 and 5.3

Section changed	Summary of new information
4.6	Addition of statements pertaining to contraception for males and females and genotoxic potential in animals Correction of the spelling of 'fetus'
5.2	Correction of the spelling of 'fetus'
5.3	Revision of wording regarding availability of human data and inclusion of mutagenic potential in mice Addition of statements for carcinogenicity of diethanolamine