AUSTRALIAN PRODUCT INFORMATION

RIMYCIN®

(rifampicin) capsules

1 NAME OF THE MEDICINE

Rifampicin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each RIMYCIN capsule contains 150 mg or 300 mg of rifampicin as the active ingredient.

Excipients with known effect: lactose and sulfites.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

RIMYCIN 150 capsules are a size 3 hard gelatin capsule, maroon body with black cap.

RIMYCIN 300 capsules are a size 1 hard gelatin capsule with maroon body and cap.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Tuberculosis

In the initial treatment and in retreatment of patients with tuberculosis, rifampicin must be used in conjunction with at least one other anti-tuberculosis drug.

Leprosy

- In the management of lepromatous leprosy and dimorphous leprosy to effect speedy conversion of the infectious state to the non-infectious state, which may be expected to occur in three to four months of treatment
- As an alternative drug in lepromatous, dimorphous, indeterminate and tuberculoid leprosy resistant to sulfones and other anti-leprosy drugs
- As an alternative drug in all those patients having true drug allergy to the more commonly used anti-leprosy drugs

Meningococcal Disease

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

Haemophilus Influenzae

Prophylaxis of household contacts of patients with Haemophilus influenzae type B.

Buruli Ulcer

For the treatment of Mycobacterium ulcerans infections (Buruli ulcer). Rifampicin must be used in combination with another anti-Mycobacterium ulcerans antibiotic.

4.2 DOSE AND METHOD OF ADMINISTRATION

It is recommended that rifampicin be administered once daily, 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)

Dosage for contacts and carriers:

Adults: 600 mg daily for 4 days.

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

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

Prophylaxis for Household Contacts of Patients with H. influenzae Type B Infection

The National Health and Medical Research Council (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 600 mg per day) for 4 days
- Neonates (less than one month): 10 mg/kg once daily for 4 days

Buruli Ulcer

Rifampicin 10 mg/kg/day to a maximum of 600 mg/day

PLUS

Clarithromycin 500 mg (child 7.5 mg/kg up to 500 mg) orally, 12-hourly.

Other regimes that have been used are rifampicin plus either moxifloxacin or ciprofloxacin.

The recommended duration of therapy is 8 weeks; longer courses may be needed for more complicated Buruli ulcer infection, including osteomyelitis.

Other Information

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

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

Continuous daily treatment with rifampicin 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.

4.3 CONTRAINDICATIONS

- Jaundice

- Known hypersensitivity to rifampicin or any of the rifamycins
- Rifampicin 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 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)
    - daclatasvir, sofosbuvir and telaprevir for treatment of Hepatitis C Virus infections (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)
    - lurasidone (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.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics, including rifampicin. 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 moderate to severe cases, appropriate therapy with a suitable oral antibacterial agent effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

For the treatment of tuberculosis, rifampicin is usually administered on a daily basis. High doses of rifampicin (greater than 600 mg) given once or twice weekly have resulted in a high incidence of adverse reactions, including the "flu syndrome" (fever, chills and malaise), haematopoietic reactions (leucopenia, thrombocytopenia, or acute haemolytic anaemia), cutaneous, gastrointestinal and hepatic reactions, shortness of breath, shock and renal failure. Recent studies indicate that regimens using twice-weekly doses of rifampicin 600 mg plus isoniazid 15 mg/kg are much better tolerated. Intermittent therapy may be used if the patient cannot or will not self-administer drugs on a daily basis. Patients on intermittent therapy should be closely monitored for compliance and cautioned against intentional or accidental interruption of prescribed therapy because of the risk of serious adverse reactions (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Rifampicin should be used very carefully in patients with a known history of porphyria cutanea tarda or acute intermittent porphyria.

Rifampicin may precipitate acute renal crisis in patients with adrenal insufficiency. It may be necessary to increase the dose of adrenal steroids in patients with impaired adrenal function who are to receive rifampicin.

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 withdrawn. 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.

Rifampicin 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, has 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

Rifampicin 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 rifampicin should be stopped immediately and not reinstituted at any subsequent time.

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 rifampicin 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, rifampicin should be permanently discontinued in case of severe manifestations (respiratory failure and acute respiratory distress syndrome) and appropriate treatment as necessary.

Paradoxical Drug Reaction

After initial improvement of tuberculosis under therapy with rifampicin, 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 rifampicin 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 rifampicin 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 rifampicin in cases of necessity and under strict medical supervision (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – 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 rifampicin 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.

Positive direct Coombs' test may show a false positive during rifampicin therapy.

In the metyrapone test, rifampicin, by hepatic enzyme induction, may decrease the response to metyrapone.

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 elevation 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.

Rifampicin may interfere with urinalysis based on spectrophotometry or colour reaction due to discoloration of the urine.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

When rifampicin is given concomitantly with 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 cabotegravir, fostemsavir, or lenacapavir, significant reductions in antiretroviral exposure have been observed. Therefore, concomitant use of rifampicin 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 including cytochrome P450 (CYP) enzymes 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 reduce the activity of certain co-administered 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.

Rifampicin is contraindicated with medicines strongly affected by its potential to induce drug metabolising enzymes and transporters such as lurasidone, sofosbuvir, daclatasvir, telaprevir, cabotegravir, fostemsavir and lenacapavir.

To maintain optimum therapeutic blood levels, dosages of drugs metabolised by these enzymes 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, toremifene), 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 metabolised by CYP3A4, 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 daily use of alcohol may result in increased incidence of rifampicin induced hepatotoxicity and increased metabolism of rifampicin; dosage adjustments of rifampicin may be necessary and patient monitoring for hepatotoxicity.

Concurrent use of simeprevir and rifampicin should be avoided. (For daclatasvir, sofosbuvir and telaprevir, see Section 4.3 CONTRAINDICATIONS).

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 isoniazid and rifampicin 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 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 CONTRAINDICATIONS).

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.

Probenecid may increase rifampicin serum concentration and/or toxicity due to competition for hepatic uptake, however the effect on blood levels is inconsistent and concurrent use of probenecid to increase rifampicin serum concentration is not recommended.

Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

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 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

Rifampicin 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 reported rarely.

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 (blood urea nitrogen), serum urea and serum uric acid and hyperuricaemia have occurred. Rarely, haemolysis, haemoglobinuria, haematuria, renal insufficiency or acute renal 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 renal injury usually due to renal tubular necrosis or tubulointerstitial nephritis, but cortical necrosis has been reported.

During the treatment of leprosy with rifampicin, a lepromatous reaction may occur. Mild reactions do not require a cessation of rifampicin 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 hepatic 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 placental barrier. Serum levels in the fetus equal 15 to 96% of the maternal serum levels. Rifampicin also appears in the breast milk of nursing mothers.

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 vitro* 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 have immunosuppressive potential in rabbits, mice, rats, guinea pigs, human lymphocytes *in vitro*, and humans.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The capsules contain ascorbic acid, brilliant blue FCF, colloidal anhydrous silica, erythrosine, gelatin, lactose monohydrate, magnesium stearate, purified talc, purified water, sodium lauryl sulfate and titanium dioxide. The 150 mg capsules also contain iron oxide yellow and iron oxide red.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

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.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

RIMYCIN 150:

HDPE bottle with PP screw cap closure containing 10 capsules or HDPE bottle with PP child resistant closure containing 100 capsules.

RIMYCIN 300:

HDPE bottle with PP screw cap closure containing 10 capsules or HDPE bottle with PP child resistant closure containing 100 capsules.

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 48230 – RIMYCIN 150 rifampicin 150 mg capsule bottle

AUST R 48231 – RIMYCIN 300 rifampicin 300 mg capsule bottle

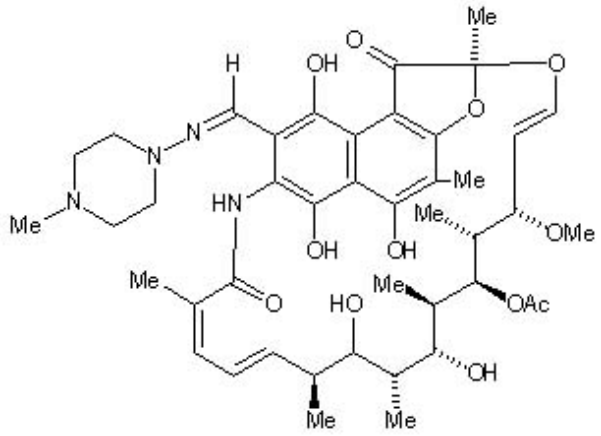
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

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



Chemical name: Rifamycin,3-[[(4-methyl-1-piperazinyl)imino]methyl]-.5,6,9,17,19,21-Hexahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-8-[N-(4-methyl-1-piperazinyl)formimidoyl]-2,7-(epoxypentadeca[1,11,13]trienimino)naphtho[2,1-b]furan-1,11-(2H)-dione 21-acetate

Molecular formula: $C_{43}H_{58}N_4O_{12}$

Molecular weight: 822.94 g/mol

CAS Number

13292-46-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

10/03/1994

10 DATE OF REVISION

26/11/2026

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
4.3	Revision of contraindications pertaining to concomitant use of daclatasvir, sofosbuvir, telaprevir and lurasidone
4.4	Inclusion of warning statements regarding contraception for males and females
4.5	Addition of contraindication statement related to drug interactions with lurasidone, sofosbuvir, daclatasvir, telaprevir, cabotegravir, fostemsavir and lenacapavir Amendment to reference of simeprevir in place of hepatitis C antiviral drugs
4.6	Addition of statements pertaining to contraception for males and females and genotoxic potential in animals
5.3	Revision of wording regarding availability of human data and inclusion of mutagenic potential in mice

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