

NEW ZEALAND DATA SHEET

1 RIFADIN 150 MG, 300 MG CAPSULES, 600 MG TABLETS, 100 MG/5ML SYRUP, AND 600 MG INFUSION

Rifadin 150 mg capsules

Rifadin 300 mg capsules

Rifadin 600 mg tablets*

Rifadin 100 mg/5 mL syrup

Rifadin IV 600 mg infusion

* Not Marketed

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Rifadin tablets* contain 600 mg of rifampicin per tablet.

Rifadin IV infusion contains 600 mg rifampicin per vial.

Excipients with known effect:

Syrup: Methyl hydroxybenzoate, propyl hydroxybenzoate, potassium sorbate, saccharin, sodium metabisulfite.

Tablet: Lactose monohydrate and sucrose.

For the full list of excipients, see section 6.1 List of Excipients.

*Not marketed in New Zealand

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)

Tablets:

600 mg (cyclamen red)

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

Rifampicin is indicated in the treatment of all forms of tuberculosis, including fresh, advanced, chronic and drug resistant cases. Rifampicin should be used in conjunction with at least one other antituberculosis medicine.

Leprosy

Rifampicin is indicated in the treatment of multibacillary and paucibacillary leprosy to effect a conversion of the infectious state to a non-infectious state. Rifampicin should be used in conjunction with at least one other anti-leprosy drug.

Methicillin-resistant Staphylococcal infections (MRSA)

Rifampicin can be used as an alternative to vancomycin in the treatment of MRSA. In such circumstances an appropriate companion antibiotic (e.g. fusidic acid) should always be employed.

Serious Staphylococcal Infections

Rifampicin has been used for the treatment of both life-threatening and serious staphylococcal infections. In such circumstances an appropriate companion antibiotic should be employed (see Section 4.2).

Brucellosis

Rifampicin may be used for the treatment of brucellosis. In such circumstances doxycycline should also be used.

Meningococcal Carriers

Rifampicin is indicated for the treatment of asymptomatic carriers of *N. meningitidis* to eliminate meningococci from the nasopharynx. (Rifampicin is not indicated for the treatment of meningococcal infection because of the possibility of the rapid emergence of resistant organisms).

Haemophilus Influenzae

Rifampicin is indicated for the treatment of asymptomatic carriers of *H. influenzae* and as chemoprophylaxis of exposed children of 4 years of age or younger.

Other infections

Infections caused by rifampicin-sensitive microorganisms such as staphylococci, streptococci, *N. gonorrhoeae*, *Proteus sp.*, *H. influenzae*, *E. coli* and *Legionella sp.* To prevent emergence of resistant organisms, rifampicin should be given with another antibacterial agent to which the organism has been shown to be susceptible.

4.2 DOSE AND METHOD OF ADMINISTRATION

Rifampicin can be administered by the oral route or by intravenous infusion.

Oral Administration

Oral dosage should be taken on an empty stomach at least 30 minutes before a meal or 2 hours after a meal.

Tuberculosis

In the treatment of tuberculosis, rifampicin should always be administered with at least one other antituberculosis medicine.

The recommended single daily dose is 10 mg/kg, and is not to exceed 600 mg/day.

Adult:

Patients weighing less than 50 kg:	450 mg
Patients weighing 50 kg or more:	600 mg

Infants and Children:

The recommended daily dose is 10-20 mg/kg body weight, and is not to exceed 600 mg/day. Under age of 1 month, the dosage is not established.

Short Course Chemotherapy:

In general, therapy for tuberculosis should be continued for 6 to 9 months or until at least 6 months have elapsed from conversion of specimen to negative culture. In patients who cannot be relied on for compliance, intermittent therapy with 600 mg/day two or three times/week under

close supervision may be prescribed and substituted for the daily regimen after 1-2 months of an initial phase of daily therapy.

The 6-Month regimen ordinarily consists of an initial 2-month phase of rifampicin, isoniazid and pyrazinamide. If resistant organisms are suspected or proven initially, a fourth medicine, streptomycin or ethambutol, should be added in the initial 2-month phase of the 6-month regimen.

The 9-month regimen ordinarily consists of rifampicin and isoniazid. If resistant organisms are suspected or proven initially, a third drug, ethambutol, should be added during the initial 2-3 months of the 9-month regimen.

Long-Term Therapy:

Patients with drug-resistant organisms may require longer treatment with other anti-tuberculous regimens.

Leprosy

To treat leprosy rifampicin should only be administered on one day each month.

For patients weighing 50 kg or more: 10 mg/kg once a month (up to a maximum of 600 mg).

For patients weighing less than 50 kg: 10 mg/kg once a month (up to a maximum of 450 mg).

In the treatment of leprosy, rifampicin should always be used in conjunction with at least one other antileprosy drug.

Methicillin-resistant Staphylococcal Infections

The recommended dose is 600-1200 mg daily in 2 to 4 divided doses.

Rifampicin should always be administered with at least one other antibiotic.

Serious Staphylococcal Infections

The recommended dose is 600-1200 mg daily given every 12 hours.

For sepsis and endocarditis, rifampicin should be administered with vancomycin (0.5-1.0 grams intravenously every 8 hours).

For severe (but not life-threatening), deep-seated staphylococcal infections, rifampicin should be administered with at least one other antibiotic.

Brucellosis

The recommended dose is 900 mg daily, taken each day at noon.

Rifampicin should always be administered with doxycycline (200 mg daily, taken with the evening meal) for 45 days.

Meningococcal Carriers

Adults:

It is recommended that 600 mg rifampicin be administered twice daily for 2 days (600 mg every 12 hours) or once daily for 4 consecutive days (600 mg daily).

Infants and Children:

Children 1 month of age or older:

10 mg/kg every 12 hours for 2 days or once daily for 4 consecutive days.

Children under 1 month of age:

5 mg/kg every 12 hours for 2 days or once daily for 4 consecutive days.

Haemophilus Influenza Carriers

For members of households exposed to H. influenza B disease and who are in contact with a child 4 years of age or younger, it is recommended that all members (including the child) receive rifampicin 20 mg/kg once daily (maximum daily dose 600 mg) for 4 days; neonates (less than 1 month) should receive 10 mg/kg daily for 4 days.

Other Infections

Daily dosage of 600-1200 mg given in 2 to 4 divided doses.

Rifampicin should be given with another antibacterial agent with similar properties to prevent emergence of resistant strains.

Intravenous Administration

Rifampicin for infusion is indicated at the above doses when in the physician's judgment oral therapy is impractical.

FOR INTRAVENOUS INFUSION ONLY. Must not be administered by intramuscular or subcutaneous route.

For instructions on reconstitution or dilution of the medicine before administration, see section 6.6.

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).

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 not generally 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-inducing properties that can enhance the metabolism of endogenous substrates including adrenal hormones, thyroid hormone and Vitamin D. Isolated reports have associated porphyria exacerbation with rifampicin administration as a result of induction of delta amino levulinic acid synthetase.

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

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

Rifampicin IV 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.

The following risk factors may predispose patients to adverse effects: alcoholism, age, renal disease and immunocompromised patients.

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.

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 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 reinstated at any subsequent time.

Rifampicin Syrup

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

The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

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). 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 generalized 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.

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 (eg Abuscreen Online 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, alternative assay methods should be considered.

Transient elevations of bromsulphalein (BSP) and serum bilirubin have been reported. Rifampicin may impair biliary excretion of contrast media used for visualisation of the gallbladder, due to competition for biliary excretion. Therefore, these tests should be performed before the morning dose of rifampicin.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

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

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.

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 medicines metabolised by enzyme and transporters reported to be affected by rifampicin, including cytochrome P-450.

Rifampicin may accelerate the metabolism and may reduce activity of medicines such as:

- Anticonvulsants (eg phenytoin)

- Antiarrhythmics (eg disopyramide, mexiletine, quinidine, propafenone, tocainide)
- Antiestrogens (eg tamoxifen, toremifen)
- Antipsychotics (eg haloperidol)
- Oral anticoagulants (eg warfarin)
- Antifungals (eg fluconazole, itraconazole, ketoconazole) (see below)
- Antiretroviral drugs (eg zidovudine, saquinavir, indinavir, efavirenz)
- Barbiturates
- Beta-blockers
- Benzodiazepines (eg diazepam)
- Benzodiazepine-related drugs (eg zopiclone, zolpidem)
- Calcium channel blockers (eg 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 (eg ciclosporin, tacrolimus)
- Irinotecan
- Levothyroxine
- Losartan
- Narcotic analgesics
- Methadone
- Praziquantel
- Progestins

- Quinine
- Riluzole
- Selective 5-HT₃ receptor antagonists (eg ondansetron)
- Statins metabolized by CYP 3A4
- Theophylline
- Tricyclic antidepressants (eg amitriptyline, nortriptyline)
- Telithromycin
- Thiazolidinediones (eg rosiglitazone)

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.

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

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.

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.

When rifampicin is given concomitantly with either halothane or isoniazid the potential for hepatotoxicity is increased for both medicines. 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).

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

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 child bearing potential only if the potential benefit justifies the potential risk to the foetus.

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

Rifampicin has been shown to be teratogenic in rodents when given in large doses.

Although rifampicin has been reported to cross the placental barrier and appear in cord blood, the effect of rifampicin, alone or in combination with other antituberculosis drugs, on the human foetus is not known.

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.

Breast-feeding

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

Fertility

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

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 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)

Rifampicin is a well tolerated medicine which rarely causes serious toxicity. Reactions occurring with either daily or intermittent dosage regimens include:

Infections and infestations:

Not known: Pseudomembranous colitis, influenza consisting of episodes of pyrexia, chills, headache and dizziness has been reported with rifampicin therapy.

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.

Very rarely: agranulocytosis

Not known: Disseminated intravascular coagulation, eosinophilia, haemolytic anaemia and vitamin K dependent coagulation disorders have been reported.

Immune system disorders:

Not known: Anaphylactic reactions have been reported.

Endocrine disorders:

Not known: Adrenal insufficiency in patients with compromised adrenal function has been reported rarely.

Elevations in BUN and serum uric acid have occurred.

Metabolism and nutritional disorders:

Not known: Decreased appetite has been reported.

Psychiatric disorders:

Not known: Psychoses (psychotic disorder) have been rarely reported.

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.

Drowsiness, fatigue, ataxia, inability to concentrate, mental confusion, visual disturbances, pains in the extremities and generalised numbness have also been noted.

Eye disorders:

Not known: Tear discoloration and exudative conjunctivitis has been reported.

Vascular disorders:

Not known: Shock, flushing, vasculitis and bleeding have been reported.

Respiratory, thoracic and mediastinal disorders:

Not known: Dyspnoea, wheezing and discoloured sputum have been observed.

Gastrointestinal disorders:

Common: Nausea, vomiting

Uncommon: Diarrhoea

Not known: Gastrointestinal disorder such as heartburn, epigastric distress, abdominal discomfort, anorexia, decreased appetite, nausea, vomiting, gas, cramps and diarrhoea have been noted in some patients, anorexia and abdominal discomfort, sore throat, and sore tongue have been reported. Tooth discolouration (which may be permanent) has also been reported.

Hepatobiliary disorders:

Rarely: Hepatitis or a shock-like syndrome with hepatic involvement and abnormal liver function tests (e.g. elevations in serum bilirubin, bromsulphophthalein, alkaline phosphatase, serum transaminases) have also been observed. Liver function tests should be monitored (see Section 4.4). Elevations in blood bilirubin, aspartate aminotransferase and alanine aminotransferase have been commonly reported. Cholestasis has also been reported.

Skin and subcutaneous tissue disorders:

Not known: Hypersensitivity reactions have been reported. Cutaneous reactions which are mild and self-limiting may occur and do not appear to be hypersensitivity reactions. Typically they consist of flushing and itching with, (pruritic rash) or without a rash, (pruritis). Urticaria and more serious hypersensitivity cutaneous reactions, (allergic dermatitis), have occurred but are uncommon. Pemphigus, pemphigoid, acneiform lesions, erythema multiforme including Stevens-Johnson syndrome, toxic epidermal necrolysis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome and acute generalized exanthematous pustulosis (AGEP) 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).

Musculoskeletal and connective tissue disorders:

Not known: Muscle weakness and myopathy have been reported to occur in a small percentage of patients treated with rifampicin. Bone pain has been reported.

Renal and urinary disorders:

Not known: haemolysis, haemoglobinuria, haematuria, renal insufficiency or acute kidney injury usually due to renal tubular necrosis or tubulointerstitial nephritis and chromaturia (discolouration of urine), have been reported.

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.

Pregnancy, puerperium and perinatal conditions:

Not known: Menstrual disturbances (in women receiving long-term antituberculosis therapy with

regimens containing rifampicin), post-partum haemorrhage and fetal-maternal haemorrhage have been reported.

Reproductive system and breast disorders:

Not known: Occasional disturbances of the menstrual cycle have been reported in women receiving long-term antituberculosis therapy with regimens containing rifampicin.

Congenital, familial and genetic disorders:

Not known: Cases of porphyria have been reported.

General disorders and administration site conditions:

Very common: Pyrexia and chills.

Not known: Oedema has been reported.

Investigations:

Common: Increases in blood bilirubin, aspartate aminotransferase and alanine aminotransferase.

Not known: An increase in hepatic enzymes and blood creatinine has also been reported. Blood pressure decrease has been observed.

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

- "Flu Syndrome" consisting of episodes of fever, chills, headache, dizziness, and bone pain appearing most commonly during the 3rd to the 6th 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 and wheezing.
- Decrease in blood pressure and shock
- Anaphylaxis/anaphylactic reaction
- Haemolytic anaemia.
- 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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 OVERDOSE

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 discoloration of the skin, urine, sweat, saliva, tears and faeces will occur, the discoloration being proportional to the amount of rifampicin 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 non-fatal acute overdoses have been reported with doses ranging from 9-12 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 non-fatal reports. Nonfatal overdoses in paediatric patients aged 1-4 years old of 100 mg/kg for one or two doses have been reported.

Treatment

Intensive supportive measures should be instituted and individual symptoms treated as they arise.

In cases of overdosage with rifampicin, following evacuation of the gastric contents, the instillation of activated charcoal slurry into the stomach may help absorb any remaining medicine from the gastrointestinal tract. Anti-emetic 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.

In patients with previously adequate hepatic function, reversal of liver enlargement and of impaired hepatic excretory function probably will be noted within 72 hours, with a rapid return toward normal thereafter.

Although it has not been observed in man, animal studies suggest a possible neurodepressant action associated with very high doses of rifampicin.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antimycobacterials, antibiotic, ATC code: J04AB02

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

Rifampicin is active *in vitro* against tubercle bacilli and a variety of gram-positive and gram-negative microorganisms. The sensitive organisms include *Mycobacterium tuberculosis*, *Mycobacterium leprae*, *Neisseria meningitides*, *Neisseria gonorrhoea*, *Staphylococcus aureus*, *Proteus sp.*, *Staphylococcus epidermidis*, *H. influenzae*, *E. coli*, *Pseudomonas aeruginosa*, *Legionella pneumophila*, *Brucella sp.* and *Streptococcus pyogenes*. Both penicillinase producing and non-penicillinase producing strains and Beta-lactam resistant staphylococci are susceptible to rifampicin.

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.

5.2 PHARMACOKINETIC PROPERTIES

Rifampicin is readily absorbed from the gastrointestinal tract. Peak blood levels in normal adults and children vary widely from individual to individual. Peak serum concentrations of the order of 10 mcg/mL occur about 2-4 hours after a dose of 10 mg/kg body weight on an empty stomach.

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 the half-life does not differ in patients with renal failure and, consequently, no dosage adjustment is required.

After absorption, rifampicin (oral or iv) is rapidly eliminated in the bile, and an enterohepatic circulation ensues. During this process, rifampicin undergoes progressive deacetylation, so that nearly all present in the bile is deacetylated in about 6 hours. This metabolite retains 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 rifampicin. Absorption of rifampicin is reduced when ingested with food.

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

Carcinogenicity and Mutagenicity

There are no known human data on long-term potential for carcinogenicity. A few cases of accelerated growth of lung carcinoma have been reported in man, but a causal relationship with the medicine has not been established. An increase in the incidence of hepatomas in female mice (of a strain known to be particularly susceptible to the spontaneous development of hepatomas) was observed when rifampicin was administered in doses 2 to 10 times the average daily human dose for 60 weeks followed by an observation period of 46 weeks. No evidence of carcinogenicity was found in male mice of the same strain, mice of a different strain, or rats, under similar experimental conditions.

Rifampicin has been reported to possess immunosuppressive potential in rabbits, mice, rats, guinea pigs, human lymphocytes *in vitro* and humans.

Antitumour activity *in vitro* has also been shown with rifampicin.

There are no known human data on the long-term potential for mutagenicity. There was no evidence of mutagenicity in bacteria, *Drosophila melanogaster* or mice. An increase in chromatid breaks was noted when whole-blood cell cultures were treated with rifampicin. Increased frequency of chromosome 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. An increase in chromatid breaks was noted when whole-blood cell cultures were treated with rifampicin.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Capsules, 150 mg, 300 mg: maize starch and magnesium stearate.

Tablets, 600 mg: sodium lauryl sulfate, microcrystalline cellulose, lactose monohydrate, calcium stearate, carmellose sodium, maize starch, magnesium stearate, acacia, povidone, erythrosine, titanium dioxide, sucrose, purified talc, magnesium carbonate hydrate, kaolin, colloidal anhydrous silica and gelatin.

Syrup, 100 mg/5 mL: agar, diethanolamine, polysorbate 80, potassium sorbate, methyl hydroxybenzoate, sodium metabisulfite, propyl hydroxybenzoate, purified water, sucrose, saccharin and raspberry essence.

IV infusion, 600 mg: sodium formaldehyde sulfoxylate, sodium hydroxide, water for injection, and polysorbate 80.

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.

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 SHELF LIFE

3 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

For storage conditions after reconstitution or dilution of the medicine, see section 6.6.

6.5 NATURE AND CONTENTS OF CONTAINER

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

Tablets*, 600 mg: packed in Al/Al blister strip in packs of 30.

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

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

*Not marketed in New Zealand

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Any unused medicine or waste material should be disposed of in accordance with local requirements.

Preparation of solution for Intravenous Infusion

Reconstitute the lyophilized powder by transferring 10 mL of sterile water for injection to a vial containing 600 mg of rifampicin for injection. Swirl vial gently to completely dissolve the antibiotic. The resultant solution contains 60 mg rifampicin activity per mL and is stable at room temperature for 30 hours. Prior to administration withdraw from the reconstituted solution a

volume equivalent to the amount of rifampicin calculated to be administered and add to 250 or 500 mL of infusion medium. Mix well and infuse at a rate allowing for complete infusion in up to 3 hours. In some cases, the amount of rifampicin calculated to be administered may be added to 100 mL of infusion medium and infused in 30 minutes.

Dilutions in dextrose 5% for injection are stable up to 8 hours at room temperature and should be prepared and used in 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.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

sanofi-aventis new zealand limited
Level 8, 56 Cawley St
Ellerslie
Auckland, New Zealand
Freecall No: 0800 283 684
medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

Capsules, 150 mg; 300 mg: 31 December 1969

Syrup, 100 mg/5 mL: 23 November 1971

Tablets*, 600 mg: 31 December 1969

IV infusion, 600 mg: 12 May 1983

*Not marketed in New Zealand

10 DATE OF REVISION OF THE TEXT

24 August 2020

SUMMARY OF CHANGES

Section changed	Summary of new information
General	Minor editorial changes throughout for improved readability.
4.4	Addition of warnings and precautions to provide more information on potential adverse effects, drug interactions and drug resistance; to update the warning with respect to intermittent use; and to add subheadings for use in the elderly and children. Editorial changes to correct ingredient name improve readability.
4.5	Addition of information relating to drug interactions.
4.6	Revisions to pregnancy section for greater clarity and to include additional information on animal studies. Strengthening of statement relating to breastfeeding.
4.8	Addition of adverse effects