

Data Sheet

Rifadin

Name of Medicine

Rifampicin - 150 mg and 300 mg capsules, 600 mg tablets, 100 mg/5 mL suspension, and lyophilized 600 mg for intravenous infusion.

Presentation

Capsules

150 mg rifampicin - No. 2 capsule, (half blue/half red) marked "R-150"

300 mg rifampicin - No. 1 capsule, (red) marked "R-300"

Tablets

600 mg rifampicin, cyclamen-red, flat, capsule-shaped 21.2 x 10.2 x 7.4 mm.

Suspension

Red, raspberry flavoured suspension 100 mg rifampicin/5 mL.

Vials for IV infusion

Spongy, fragile amorphous red powder containing 600 mg lyophilized rifampicin.

Solvent: 10 mL sterile water for injections.

Uses

Actions

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.

Pharmacokinetics

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.

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 **Dosage and Administration**).

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.

Dosage and 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.

Contraindications

Jaundice.

History of hypersensitivity to any of the rifamycins.

Rifadin use is contraindicated when given concurrently with the combination of saquinavir / ritonavir (see **INTERACTIONS**).

Warnings and Precautions

Liver

Patients with impaired liver function should only be given rifampicin in cases of necessity and then with caution and under strict medical supervision. In these patients, careful monitoring of liver function, especially alanine aminotransferase (ALT) and aspartate aminotransferase (AST) should be carried out prior to therapy and then every two to four weeks during therapy. If signs of hepatocellular damage occur, rifampicin should be withdrawn.

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.

Immunological Reactions/Anaphylaxis

Because of the possibility of immunological reaction (occurring with intermittent therapy (less than 2 to 3 times per week) patients should be closely monitored. Patients should be cautioned against interruption of dosage regimens since these reactions may occur.

Rifampicin Syrup

Rifampicin Syrup contains sodium metabisulphite 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 sulphite sensitivity in the general population is unknown and probably low. Sulphite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

Precautions

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 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 may produce a reddish coloration of the urine, sweat, sputum, and tears and the patient should be forewarned of this. Soft contact lenses may be permanently stained.

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

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.

Carcinogenicity and Mutagenicity

There are no known human data on long-term potential for carcinogenicity or mutagenicity. 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 was no evidence of mutagenicity in bacteria, *Drosophila melanogaster* or mice. 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.

Pregnancy and Lactation

Category C.

There are no well-controlled studies with rifampicin in pregnant women.

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.

When administered during the last few weeks of pregnancy, rifampicin can cause post-natal haemorrhages in the mother and infant, for which treatment with vitamin K may be indicated.

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.

Rifampicin is excreted in breast milk. Rifampicin should not be used in a nursing mother unless in the physician's judgment the potential benefit to the patient outweighs the potential risk to the infant.

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

Adverse Effects

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

- 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 or without a rash. Urticaria and more serious hypersensitivity cutaneous reactions have occurred but are uncommon. Pemphigoid reaction, erythema multiforme including Stevens-Johnson syndrome, toxic epidermal necrolysis and vasculitis have been reported rarely.
- Gastrointestinal reactions consist of anorexia, nausea, vomiting, abdominal discomfort, and diarrhoea. Pseudomembranous colitis has been reported with rifampicin therapy.
- Hepatitis may be caused by rifampicin and liver function tests should be monitored (see **Warnings and Precautions**)
- Thrombocytopenia with or without purpura may occur, usually associated with intermittent therapy, but is reversible if 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.
- Central Nervous System: Psychoses has been rarely reported.
- Disseminated intravascular coagulation has also been rarely reported.
- Eosinophilia, leukopenia, 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.
- Adrenal insufficiency in patients with compromised adrenal function has been reported rarely.
- Occasional disturbances of the menstrual cycle have been reported in women receiving long-term antituberculosis therapy with regimens containing rifampicin.

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.
- Shortness of breath and wheezing.
- Decrease in blood pressure and shock
- Anaphylaxis
- Acute haemolytic anaemia.
- Acute renal failure usually due to acute tubular necrosis or to acute interstitial nephritis.

Interactions

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 **CONTRAINDICATIONS**).

Rifampicin is a potent inducer of certain cytochrome P-450 enzymes.

Coadministration of rifampicin with medicines that undergo biotransformation through these metabolic pathways may accelerate elimination. Dosages of medicines metabolised by these enzymes may require adjustment when starting or stopping concomitantly administered rifampicin to maintain optimum therapeutic blood levels.

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)
- Antiretroviral drugs (eg zidovudine, saquinavir, indinavir, efavirenz)
- Barbiturates
- Beta-blockers
- Benzodiazepines (eg diazepam)
- Benzodiazepine-related drugs (eg zolpiclone, zolpidem)
- Calcium channel blockers (eg diltiazem, nifedipine, verapamil)
- Chloramphenicol
- Clarithromycin
- Corticosteroids
- Cardiac glycoside preparations
- Clofibrate
- Systemic hormonal contraceptives
- Dapsone
- Doxycycline
- Estrogens
- Fluoroquinolones
- Gestrinone
- Oral hypoglycaemic agents (sulfonylureas)
- Immunosuppressive agents (eg cyclosporine, 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)

Patients using systemic hormonal contraceptives should be advised to change to non-hormonal methods of birth control during rifampicin therapy.

When the two medicines 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.

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.

Drug/Laboratory Test Interactions

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.

Overdosage

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.

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, gastric lavage should be performed as soon as possible. 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. Hemodialysis 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.

Pharmaceutical Precautions

Instructions for Use/Handling

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 24 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 4 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.

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.

Medicine Classification

Prescription Medicine

Package Quantities

Bottles of 100 x 150 mg capsules

Bottles of 100 x 300 mg capsules

Bottles of 30 x 600 mg tablets

Bottles of 60 mL suspension

Vial of 600 mg IV infusion and a 10 mL Water for Injection ampoule

Further Information

Nil

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Date of Preparation

27 May 2010