

Rifampin

Brand Name: Rifadin, Rifadin IV, Rimactane
Drug Class: Opportunistic Infection and Other Drugs

Drug Description

Rifampin is a semisynthetic, broad-spectrum antibiotic derivative of rifamycin B, which was derived from *Streptomyces mediterranei*. [1]

HIV/AIDS-Related Uses

Rifampin is used alone or in combination as an alternative to rifabutin or other rifamycins in the treatment of latent tuberculosis (TB) infection. The combination regimen of rifampin/pyrazinamide also has been used to treat latent TB infection in HIV infected patients. However, studies indicate that this drug combination can cause severe, sometimes fatal, liver damage. Risk factors associated with toxicity include a history of liver disease, alcohol use, or isoniazid-induced liver damage. Rifampin/pyrazinamide is contraindicated in patients with these risk factors. The Centers for Disease Control and Prevention (CDC) and the American Thoracic Society recommend considering the regimen for latent TB infection only in carefully selected individuals, under the care of a clinician with expertise in the treatment of latent TB infection, if the potential benefits of the regimen outweigh the risk for severe liver injury and death, and when the preferred or alternative regimens are judged unlikely to be completed. The combination regimen may be used to treat active TB because the risks from the active disease are much greater than those posed by the latent disease.[2]

The use of rifampin to treat active TB was previously contraindicated in patients taking protease inhibitors (PIs) or nonnucleoside reverse transcriptase inhibitors (NNRTIs). However, the CDC has indicated that rifampin can be used when the antiretroviral regimen includes either efavirenz and two nucleoside reverse transcriptase inhibitors (NRTIs); ritonavir and one or more NRTIs; or the combination of two PIs (ritonavir and either saquinavir hard-gel capsule or saquinavir soft-gel capsule).[3]

Rifampin is also used in conjunction with other medications to treat *Mycobacterium avium* complex (MAC) in HIV infected individuals. [4]

Non-HIV/AIDS-Related Uses

Rifampin is used in conjunction with other antituberculosis agents for treatment of active TB. It is used alone and in combination with other drugs for treatment of latent TB infection and for treatment of atypical mycobacterial infections, including MAC and leprosy.[5]

Rifampin is used for prevention of *Neisseria meningitidis* infections, including chemoprophylaxis for individuals in close contact with people with invasive meningococcal disease or for outbreak control in small populations. It is also used to prevent *Haemophilus influenzae* type b infection of individuals in close contact with patients infected by this organism. Rifampin is used in combination with other medications to treat serious infections caused by *Streptococcus* and *Staphylococcus* species, including methicillin- and multidrug-resistant strains. [6]

Rifampin is used as part of a multidrug parenteral regimen for treatment of inhalational anthrax. It is also used as an adjunct to other anti-infective agents for treatment of brucellosis, *Legionella*, and *Rhodococcus* infections. [7]

Pharmacology

Rifampin suppresses the initiation of RNA chain formation in susceptible bacteria by inhibiting DNA-dependent RNA polymerase. The site of action appears to be the beta subunit of the enzyme. Rifampin is most active during bacteria cell division, although it retains some effect when bacteria are in the metabolic resting state. [8]

Rifampin is well absorbed from the gastrointestinal tract. Following an oral dose of rifampin 600 mg in fasting adults, peak plasma concentrations (C_{max}) average 7 mcg/ml and are reached within 2 to 4 hours. Following a 300 or 600 mg dose of rifampin given via IV infusion over 30 minutes, C_{max} averages 9 or 17.5 mcg/ml, respectively, and plasma concentrations remain detectable for 8 or 12 hours, respectively. In children given an oral dose of rifampin 10 mg/kg, peak serum concentrations range from 3.5 to 15 mcg/ml. Rifampin C_{max} may range from 4 to 32 mcg/ml, depending on

Rifampin

Pharmacology (cont.)

interpatient variation. Individuals with hepatic impairment experience higher and more prolonged rifampin plasma concentrations. [9]

Rifampin is distributed into most body tissues and fluids, including ascitic fluid, bile, bone, cerebrospinal fluid (CSF), the liver, the lungs, pleural fluid, the prostate, saliva, seminal fluid, and tears. CSF concentrations of rifampin in patients with inflamed meninges are reported to be 10% to 20% of concurrent plasma concentrations. [10]

Rifampin is in FDA Pregnancy Category C. It crosses the placenta and in rare cases has caused postnatal hemorrhage in the mother and infant when given in the last few weeks of pregnancy. Congenital malformations have been reported in rodents at doses greatly exceeding the usual daily human dose. Rifampin is distributed into breast milk; however, no problems have been documented in humans. [11]

Protein binding is high (89%). Rifampin is rapidly metabolized by hepatic microsomal oxidases to an active metabolite, 25-O-desacetyl-rifampin, and also to inactive metabolites. Elimination half-life is initially 3 to 5 hours and decreases to 2 to 3 hours with repeated administration. The half-life in patients with renal impairment may increase from 5 to 11 hours. Rifampin is enterohepatically recirculated, but the active deacetylated metabolite is not. Approximately 6% to 15% of the unchanged drug and 15% of the active deacetylated metabolite is excreted in urine. Approximately 60% to 65% of a dose is excreted in feces via biliary elimination. Plasma concentrations are not appreciably affected by hemodialysis or peritoneal dialysis. [12] [13]

Adverse Events/Toxicity

The most common adverse effects of rifampin include abdominal cramping, diarrhea, anorexia, flatulence, heartburn, nausea, and vomiting. [14] Rifampin has been associated with a flu-like syndrome of chills, difficult breathing, dizziness, fever, headache, muscle and bone pain, and shivering. Intermittent use of rifampin may increase the chance of developing the flu-like syndrome, acute hemolysis, or renal failure. [15] A reversible,

lupus-like syndrome characterized by arthritis, malaise, myalgias, and peripheral edema has been reported in some patients receiving concomitant therapy of rifampin and either clarithromycin or ciprofloxacin, as a result of inhibited hepatic metabolism of rifampin. [16]

Rarely, blood dyscrasias, hepatitis, hepatitis prodromal symptoms, and interstitial nephritis have been reported with rifampin use. [17] Jaundice-associated fatalities and hepatitis have occurred in patients with pre-existing liver disease or who were receiving other hepatotoxic medications. [18]

Hypersensitivity (itching, redness, and rash) and fungal overgrowth of the mouth or tongue have also been reported. In addition, rifampin may discolor body fluids, giving a red-orange or red-brown color to urine, feces, saliva, skin, sweat, and tears. Discolored tears may permanently stain soft contact lenses. [19]

Drug and Food Interactions

If rifampin is administered with food, C_{max} may be slightly reduced (approximately 30%) and delayed. [20] To ensure maximum absorption, rifampin should be taken on an empty stomach, at least 1 hour before or 2 hours after a meal. [21]

Rifampin and other rifamycin derivatives markedly induce cytochrome P-450 (CYP) oxidases, accelerating the metabolism of HIV PIs (e.g., amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, saquinavir) and NNRTIs (e.g., delavirdine, nevirapine, efavirenz), resulting in subtherapeutic plasma concentrations of these antiretroviral agents. Nevirapine and efavirenz, despite diminished plasma concentrations, may be used successfully with rifampin when absolutely necessary. [22]

Rifampin can also affect the metabolism of certain NRTIs, including zidovudine. In addition, PIs and some NNRTIs (e.g., delavirdine) may reduce the metabolism of rifamycins, leading to increased plasma concentrations and increased toxicity of the rifamycins. Because these drug interactions are complex, experts in the management of mycobacterial infections in HIV infected patients

Rifampin

Drug and Food Interactions (cont.)

should be consulted.[23]

Administration of rifampin with other medications metabolized by hepatic enzymes alters the metabolism of these other drugs. Rifampin induces CYP metabolism, thus decreasing the plasma concentration and efficacy of theophylline, azole antifungals, antiarrhythmic agents (e.g., disopyramide, mexiletine, propafenone, quinidine, tocainide), antidiabetic agents (e.g. chlorpropamide, glyburide, tolbutamide), chloramphenicol, coumarin anticoagulants, digoxin, corticosteroids, methadone, phenytoin, and verapamil. Rifampin also induces the metabolism and decreases the enterohepatic cycling of estrogen-containing oral contraceptives, causing a decrease in hormone levels and contraceptive efficacy.[24]

Concomitant use of aluminum or magnesium hydroxide antacids with rifampin may decrease absorption of rifampin, requiring rifampin administration one hour prior to the antacid.[25]

Concurrent use of rifampin and other hepatotoxic substances, including but not limited to isoniazid and alcohol, increases the potential for hepatotoxicity.[26] Daily regimens of rifampin/pyrazinamide used to treat latent TB infection appear to cause severe liver injury and fatality.[27]

Contraindications

Rifampin is contraindicated in patients with hepatic function impairment and in those with a history of hypersensitivity reaction to rifampin or to any of the rifamycins.[28]

Concomitant use of rifampin with unboosted saquinavir or saquinavir mesylate results in reduced plasma concentrations of saquinavir and is contraindicated.[29]

Recent data from a 28-day Phase I clinical trial of rifampin 600 mg once-daily and twice-daily saquinavir/ritonavir 1000 mg/100 mg showed significant hepatocellular toxicity in nearly 40% of patients. Transaminase elevations of up to 20 times the upper limit of normal were noted. Following

drug discontinuation, clinical symptoms abated and liver function tests began returning to normal in all affected patients. Based on this data, the saquinavir manufacturer recommends that rifampin not be administered to patients taking ritonavir-boosted saquinavir as part of combination antiretroviral therapy.[30]

Clinical Trials

For information on clinical trials that involve Rifampin, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Rifampin AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[31]

Intravenous.[32]

Dosage Form: Capsules containing rifampin 150 mg or 300 mg. [33]

Powder for injection with preservative containing rifampin 600 mg per vial, with preservative, and reconstituted with 10 ml sterile water for injection. [34]

Capsules in fixed-dose combination with isoniazid (rifampin 300 mg and isoniazid 150 mg). [35]

Tablets in fixed-dose combination with isoniazid and pyrazinamide (rifampin 120 mg, isoniazid 50 mg, and pyrazinamide 300 mg).[36]

Oral compounded suspension containing rifampin 10 mg/ml in simple syrup. [37]

Contents of rifampin capsules may be mixed with applesauce or jelly or used to compound a suspension for oral use. [38]

Storage: Store capsules in a tight, light-resistant container between 15 C and 30 C (59 F to 86 F). Store injection below 40 C (104 F) in a tight, light-resistant container. Store compounded suspension in a tight, light-resistant, amber glass or plastic prescription bottle at controlled room temperature between 22 C and 28 C (71.6 F to 82.4 F) or under refrigeration between 2 C and 8 C (35.6

Rifampin

Dosing Information (cont.)

F to 46.4 F). [39] [40]

Chemistry

CAS Name: Rifamycin,
3-[[[(4-methyl-1-piperazinyl)imino]methyl]-[41]

CAS Number: 13292-46-1[42]

Molecular formula: C43-H58-N4-O12[43]

C62.76%, H7.10%, N6.81%, O23.33%[44]

Molecular weight: 822.94[45]

Physical Description: Red-brown crystalline powder.[46]

Stability: Compounded oral rifampin suspension should be discarded 30 days after the day of compounding.[47]

Oral suspension must be shaken well prior to administration.[48]

After reconstitution with sterile water for injection, the parenteral solution of 60 mg/ml is stable at room temperature for 24 hours. After rifampin dilution in 100 or 500 ml normal saline, the solution may be stable at room temperature for up to 24 hours. After a similar dilution in 5% dextrose in water, the solution is stable at room temperature for up to 4 hours.[49] [50]

Solubility: Very slightly soluble in water and slightly soluble in alcohol.[51]

Other Names

Rifampicina[52]

Rifamycin AMP[53]

Rifampicin[54]

Further Reading

Gordin FM, Cohn DL, Matts JP, Chaisson RE, O'Brien RJ; Terry Bein Community Programs for

Clinical Research on AIDS; Adult AIDS Clinical Trials Group; Centers for Disease Control and Prevention. Hepatotoxicity of rifampin and pyrazinamide in the treatment of latent tuberculosis infection in HIV-infected persons: is it different than in HIV-uninfected persons? *Clin Infect Dis.* 2004 Aug 15;39(4):561-5. Epub 2004 Jul 30.

Korenromp EL, Scano F, Williams BG, Dye C, Nunn P. Effects of human immunodeficiency virus infection on recurrence of tuberculosis after rifampin-based treatment: an analytical review. *Clin Infect Dis.* 2003 Jul 1;37(1):101-12. Epub 2003 Jun 23.

Lim HJ, Okwera A, Mayanja-Kizza H, Ellner JJ, Mugerwa RD, Whalen CC. Effect of tuberculosis preventive therapy on HIV disease progression and survival in HIV-infected adults. *HIV Clin Trials.* 2006 Jul-Aug;7(4):172-83.

Page KR, Sifakis F, Montes de Oca R, Cronin WA, Doherty MC, Federline L, Bur S, Walsh T, Karney W, Milman J, Baruch N, Adelakun A, Dorman SE. Improved adherence and less toxicity with rifampin vs isoniazid for treatment of latent tuberculosis: a retrospective study. *Arch Intern Med.* 2006 Sep 25;166(17):1863-70.

Rolla VC, da Silva Vieira MA, Pereira Pinto D, Lourenco MC, de Jesus Cda S, Goncalves Morgado M, Ferreira Filho M, Werneck-Barroso E. Safety, efficacy and pharmacokinetics of ritonavir 400mg/saquinavir 400mg twice daily plus rifampicin combined therapy in HIV patients with tuberculosis. *Clin Drug Investig.* 2006;26(8):469-79.

Manufacturer Information

Rifadin
Aventis Pharmaceuticals (HMR)
P.O. Box 9627 / 10236 Marion Park Dr
Kansas City, MO 64134-0627
(888) 242-9321

Rifadin IV
Aventis Pharmaceuticals (HMR)
P.O. Box 9627 / 10236 Marion Park Dr
Kansas City, MO 64134-0627
(888) 242-9321

Rifampin



Manufacturer Information (cont.)

Rimactane
Novartis Pharmaceuticals Corp
59 Route 10
East Hanover, NJ 07936
(888) 669-6682

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

References

1. AHFS Drug Information - 2007; p. 577
2. AHFS Drug Information - 2007; pp. 566-7
3. USP DI - 2005; p. 2555
4. AHFS Drug Information - 2007; p. 568
5. AHFS Drug Information - 2007; pp. 566-9
6. AHFS Drug Information - 2007; pp. 568-71
7. AHFS Drug Information - 2007; p. 570
8. AHFS Drug Information - 2007; pp. 575-6
9. AHFS Drug Information - 2007; p. 576
10. AHFS Drug Information - 2007; p. 577
11. USP DI - 2005; p. 2551
12. USP DI - 2005; pp. 2550-1
13. AHFS Drug Information - 2007; p. 577
14. AHFS Drug Information - 2007; p. 572
15. USP DI - 2005; p. 2553
16. AHFS Drug Information - 2007; p. 573

Rifampin



17. USP DI - 2005; p. 2553
18. AHFS Drug Information - 2007; p. 572
19. USP DI - 2005; p. 2553
20. AHFS Drug Information - 2007; p. 576
21. AHFS Drug Information - 2007; p. 572
22. AHFS Drug Information - 2007; p. 574
23. AHFS Drug Information - 2007; p. 574
24. USP DI - 2005; pp. 2552-3
25. AHFS Drug Information - 2007; p. 575
26. USP DI - 2005; pp. 2551-2
27. AHFS Drug Information - 2007; p. 575
28. USP DI - 2005; pp. 2553-4
29. FDA - Invirase Prescribing Information, September 2005, p. 14. Available at: <http://www.fda.gov/cder/foi/label/2005/021785s001,002,020828s019,020,020628s022,023lbl.pdf>. Accessed 04/23/07.
30. Hoffmann-LaRoche, Inc. - Saquinavir-Rifampin Interaction [Dear Health Care Provider Letter]. New Jersey: Hoffman-La Roche; February 2005. Available at: http://www.rocheusa.com/products/invirase/Invirase_DrLetter.pdf. Accessed 04/23/07.
31. USP DI - 2005; pp. 2557-8
32. USP DI - 2005; pp. 2557-8
33. USP DI - 2005; p. 2557
34. USP DI - 2005; p. 2558
35. AHFS Drug Information - 2007; p. 577
36. AHFS Drug Information - 2007; p. 577
37. USP DI - 2005; p. 2557
38. AHFS Drug Information - 2007; p. 571
39. AHFS Drug Information - 2007; pp. 571, 577
40. USP DI - 2005; pp. 2557-8
41. ChemIDplus - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp>. Accessed 04/23/07.
42. ChemIDplus - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp>. Accessed 04/23/07.
43. Merck Index - 2006; p. 1417
44. Merck Index - 2006; p. 1417
45. Merck Index - 2006; p. 1417
46. AHFS Drug Information - 2007; p. 577

Rifampin



47. USP DI - 2005; p. 2557

48. AHFS Drug Information - 2007; p. 571

49. AHFS Drug Information - 2007; p. 577

50. FDA - Rifadin Prescribing Information, January 2004, p. 13. Available at: <http://www.fda.gov/cder/foi/label/2004/50420s072,50627s0081bl.pdf>. Accessed 04/23/07.

51. AHFS Drug Information - 2007; p. 577

52. ChemIDplus - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp>. Accessed 04/23/07.

53. ChemIDplus - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp>. Accessed 04/23/07.

54. ChemIDplus - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp>. Accessed 04/23/07.