Ribavirin

Brand Name: Virazole, Rebetol, Copegus
Drug Class: Opportunistic Infection and Other Drugs

Drug Description

Ribavirin is a synthetic nucleoside agent that has a broad spectrum of antiviral activity against both DNA and RNA viruses. [1] Ribavirin is structurally related to pyrazofurin (pyrazomycin), guanosine, and xanthosine. [2]

HIV/AIDS-Related Uses

HIV infected patients are commonly coinfected with hepatitis C virus (HCV). Interferon alfa-2b, peginterferon alfa-2a, or peginterferon alfa-2b, in conjunction with oral ribavirin, are regimens often prescribed for the treatment of chronic HCV infection with compensated liver disease in patients who have not previously received interferon therapy. Although therapy with oral ribavirin alone is not effective for the treatment of chronic HCV infection, use of the drug in conjunction with an interferon alfa preparation has been shown to increase the rate of sustained response by two- to threefold and decrease the rate of relapse following discontinuance of therapy. The highest rates of sustained virologic response and the lowest rates of relapse have been achieved with concomitant use of peginterferon alfa and oral ribavirin. Interferon monotherapy generally is reserved for use in patients in whom ribavirin is contraindicated or not tolerated.[3]

Oral ribavirin monotherapy has been investigated for use in the management of HIV infection; however, the results of several limited studies in patients with HIV infection have failed to show evidence of beneficial effects.[4]

Non-HIV/AIDS-Related Uses

Ribavirin is indicated in combination with interferon alfa-2a or -2b or peginterferon alfa-2a or -2b for the treatment of chronic HCV infection in patients who have compensated liver disease, have not been previously treated with interferon alfa, and are at least 18 years of age who have relapsed after interferon alfa therapy.[5]

Ribavirin inhalation solution is indicated as a primary agent in the treatment of lower respiratory tract disease (including bronchiolitis and pneumonia) caused by respiratory syncytial virus (RSV) in hospitalized infants and young children who are at high risk for severe or complicated RSV infection. This category includes premature infants and infants with structural or physiologic cardiopulmonary disorders, bronchopulmonary dysplasia, immunodeficiency, or imminent respiratory failure. Ribavirin is also indicated in the treatment of RSV infections in infants requiring mechanical ventilator assistance.[6] Ribavirin is used via nasal or oral inhalation in the treatment of these severe lower respiratory tract infections.[7]

Orally ingested ribavirin has been used with some success for the treatment of various strains of influenza A and B virus. Inhalation therapy with ribavirin is currently being studied for the treatment of these viruses. However, ribavirin is not considered the drug of choice for the treatment or prevention of influenza A or B infections.[8]

Ribavirin has been used for the treatment of a variety of viral hemorrhagic fevers, including Lassa fever, Hantavirus infections, and Crimean-Congo hemorrhagic fever. Viral hemorrhagic fevers are a diverse group of infections caused by RNA viruses from several viral families. Ribavirin is the only antiviral agent identified to date that exhibits potential efficacy for the management of some viral hemorrhagic fevers.[9]

Pharmacology

The mechanism of action of ribavirin's antiviral activity has not been fully elucidated, but the drug appears to interfere with RNA and DNA synthesis and subsequently inhibit protein synthesis and viral replication. The drug's antiviral activity results principally in an intracellular virustatic effect in cells infected with ribavirin-sensitive RNA or DNA viruses; however, its specific mechanisms of action may vary depending on the virus. The antiviral activity of ribavirin appears to depend principally on intracellular conversion of the drug to ribavirin-5'-triphosphate (RTP) and -monophosphate. Ribavirin is phosphorylated to ribavirin-5'-monophosphate, -diphosphate, and -triphosphate. Phosphorylation of ribavirin occurs

Pharmacology (cont.)

principally in virus-infected cells but also occurs in uninfected cells. Formulation of ribavirin-5'-monophosphate appears to be the rate-limiting step in the formation of ribavirin-5'-triphosphate. RTP competes with adenosine-5'-triphosphate and guanosine-5'-triphosphate for viral RNA polymerase.[10] RTP is a potent competitive inhibitor of inosine monophosphate dehydrogenase, influenza virus RNA polymerase, and messenger RNA (mRNA) guanylyltransferase, the latter resulting in inhibition of the capping of mRNA. These diverse effects markedly reduce intracellular guanosine triphosphate pools and inhibit viral RNA and protein synthesis.[11]

When administered orally, ribavirin is rapidly absorbed from the gastrointestinal (GI) tract, with bioavailability approximately 64%.[12] A small amount of ribavirin is absorbed systemically from the respiratory tract following nasal and oral inhalation. The bioavailability of inhaled ribavirin may depend on the method of drug delivery during nebulization. At a constant flow rate, the amount of drug delivered to the respiratory tract theoretically is directly related to the concentration of nebulized drug solution and the duration of inhalation therapy. Peak plasma ribavirin concentrations (Cmax) generally occur at the end of the inhalation period, when the drug is inhaled orally and nasally using a small-particle aerosol generator, and increase with longer duration of the inhalation period.[13] Ribavirin is readily absorbed across the cellular plasma membrane, probably via a nucleoside transport mechanism. Ribavirin has two pathways of metabolism: 1) a reversible phosphorylation pathway in nucleated cells and 2) a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxylic acid metabolite.[14]

Ribavirin distributes to plasma, respiratory tract secretions, and erythrocytes (RBCs); following nasal and oral inhalation, the highest ribavirin concentrations are found in the respiratory tract and RBCs.[15] Large amounts of ribavirin triphosphate are sequestered in RBCs, reaching a plateau in approximately 4 days and remaining sequestered for weeks after administration. Cmax for intravenous (IV) doses is reached at the end of infusion; for oral doses, it is 1 to 2 hours. Therapeutically effective concentrations depend primarily on the duration of exposure and patient minute volume. Concentrations in respiratory tract secretions are much higher than corresponding plasma concentrations.[16] Following oral administration of a single 3 mg/kg dose, RBC concentrations of ribavirin have been reported to peak within approximately 4 days, exceeding concurrent plasma concentrations at 4 days by about 100-fold, then declining with a half-life of about 40 days (the half-life of RBCs). During the initial 1 to 2 hours following oral administration, RBC concentrations increase at a rate similar to plasma concentrations; thereafter, RBC concentrations continue to increase for about 4 days as plasma drug concentrations decline.[17] Significant concentrations (greater than 67%) may be found in the cerebrospinal fluid (CSF) after prolonged administration.[18] Ribavirin appears to distribute slowly into CSF. Following chronic (4 to 7 weeks) oral administration of ribavirin in patients with AIDS or AIDS-related complex, CSF concentrations of the drug were approximately 70% of concurrent plasma concentrations.[19]

Ribavirin is in FDA Pregnancy Category X. No studies have been done in pregnant women; however, ribavirin is contraindicated during pregnancy. Ribavirin crosses the placenta and studies in other animals have shown that it is teratogenic and/or embryocidal in nearly all species tested, with effects including reduced survival of fetuses and offspring and malformation of the skull, palate, eye, jaw, skeleton, and GI tract. Health care workers and visitors who spend time at the patient's bedside may become environmentally exposed to ribavirin. Female health care workers and visitors who are pregnant or may become pregnant should be advised of the potential risks of exposure. It is not known if ribavirin is excreted into human breast milk. It does distribute into the breast milk of other species and has been shown to harm lactating animals and their offspring.[20]

Plasma protein binding of ribavirin is insignificant.[21] The elimination half-life of an IV or oral dose is approximately 0.5 to 2 hours; for inhaled ribavirin, the elimination half-life is 9.5 hours. The terminal half-life of a single dose of IV

Pharmacology (cont.)

or oral ribavirin is 27 to 36 hours, reaching steady state at approximately 151 hours. Ribavirin is excreted principally in urine. For ribavirin administered for inhalation, renal elimination is approximately 30% to 55% excreted as the 1,2,4-triazole carboxamide metabolite in urine within 72 to 80 hours.[22] In healthy adults with normal renal function, approximately 53% of a single oral dose is excreted in urine within 72 to 80 hours, with about 33% excreted in the first 24 hours. Approximately 37%, 30%, and 30% of the fraction excreted in urine appears as unchanged drug, 1,2,4-triazole-3-carboxamide, and 1,2,4-triazole-3-carboxylic acid, respectively, within 1.5 to 2 hours, and approximately 17%, 50%, and 22%, respectively, within 24 hours.[23] Significant amounts of ribavirin are not removed by hemodialysis. Approximately 15% of an inhaled dose of ribavirin is excreted in feces within 72 hours. Approximately 19% of IV ribavirin is excreted unchanged in 24 hours; approximately 24% is excreted unchanged in 48 hours. Approximately 7% of an oral dose of ribavirin is excreted unchanged in 24 hours; approximately 10% is excreted unchanged in 48 hours.[24] Plasma concentrations of ribavirin appear to decline in a manner dependent on the route of administration.[25]

Development of resistance to the antiviral activity of ribavirin has not been fully evaluated. Unlike the viral response to some other currently available antiviral agents (e.g., acyclovir, amantadine), most susceptible viruses do not appear to develop resistance to ribavirin despite repeated exposure; this may be due to ribavirin's multiple mechanisms of action.[26]

Adverse Events/Toxicity

The primary toxicity of ribavirin is hemolytic anemia, which was observed in approximately 13% of patients treated with ribavirin and peginterferon alfa-2a[27] and 10% of patients treated with ribavirin and interferon alfa-2b.[28] [29] The anemia associated with ribavirin occurs within the first 1 to 2 weeks of oral therapy. Because the initial drop in hemoglobin may be significant, it is advised that hemoglobin or hematocrit be obtained pretreatment and at Weeks 2 and 4 of therapy or more frequently if clinically indicated. Patients should then be followed as clinically appropriate.[30] [31]

Fatal and nonfatal myocardial infarctions have been reported in patients with anemia caused by ribavirin. Patients should be assessed for underlying cardiac disease before initiation of ribavirin therapy. Patients with pre-existing cardiac disease should have electrocardiograms administered before treatment and should be monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued. Because cardiac disease may be worsened by drug-induced anemia, patients with a history of significant or unstable cardiac disease should not use ribavirin.[32] [33]

Sudden deterioration of respiratory function has been associated with aerosolized ribavirin use in infants; respiratory function should be carefully monitored during treatment. If initiated aerosolized ribavirin treatment appears to produce sudden deterioration of respiratory function, treatment should be stopped and reinstated only with extreme caution, continuous monitoring, and consideration of concomitant administration of bronchodilators.[34]

Some common adverse effects observed with IV and oral ribavirin are central nervous system effects (fatigue, headache, insomnia) and GI effects (anorexia, nausea). Skin irritation due to prolonged drug contact and skin rash is observed in patients who receive ribavirin via inhalation, and health care workers who help in the administration of inhaled doses sometime exhibit headache and itching, redness, or swelling of the eyes.[35]

Drug and Food Interactions

The manufacturer of ribavirin states that concomitant use of ribavirin and nucleoside analogues should be undertaken with caution and only if the potential benefits outweigh the potential risks. Use of ribavirin and nucleoside reverse transcriptase inhibitors may increase the risk of mitochondrial dysfunction and other associated toxicities.[36] In addition, in vitro studies have

Ribavirin

Drug and Food Interactions (cont.)

shown that when combined, ribavirin and zidovudine are reproducibly antagonistic and should not be used concurrently.[37] Ribavirin inhibits the phosphorylation of zidovudine and stavudine to its active triphosphate form, which could lead to decreased antiretroviral activity. Exposure to didanosine or its active metabolite (didoxyadenosine 5'-triphosphate) is increased when didanosine is coadministered with ribavirin, which could cause or worsen clinical toxicities.[38] Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactactemia/lactic acidosis have been reported in clinical trials.[39]

Both area under the plasma concentration-time curve (AUC) and Cmax increased by 70% when ribavirin capsules were administered with a high-fat meal in a single-dose pharmacokinetic study. There are insufficient data to address the clinical relevance of these results. Ribavirin capsules taken with an antacid containing magnesium, aluminum, and simethicone resulted in a 14% decrease in mean ribavirin AUC.[40] [41]

The manufacturer of ribavirin for nasal and oral inhalation states that the potential for drug interactions has not been evaluated in patients receiving ribavirin concomitantly with digoxin, diuretics, respiratory smooth muscle relaxants (e.g., theophylline), anti-infective agents, antimetabolites, or other antiviral agents. However, some data indicate that the in vitro and in vivo antiviral activity of ribavirin against some viruses (e.g., influenza virus) may be enhanced by other antiviral agents (e.g., amantadine, rimantadine).[42]

Contraindications

Because ribavirin may cause birth defects or death of the exposed fetus, it is contraindicated for use in women who are pregnant or in men whose female partners are pregnant. Ribavirin is also contraindicated in patients with a hypersensitivity to the drug or any of its components and in patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia).[43] [44] Patients who have autoimmune hepatitis or hepatic decompensation (Child-Pugh class B and C) must not be treated with ribavirin combination therapy that includes interferon alfa.[45]

IV and oral ribavirin may cause anemia that is reversible when the drug is discontinued.[46]

Clinical Trials

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

Dosing Information

Mode of Delivery: Oral.[47] [48] [49]

Inhalation.[50]

Dosage Form: Capsules and tablets containing ribavirin 200 mg.[51] [52]

Glass vials containing ribavirin 6 g of lyophilized powder per 100 ml for reconstitution into solution for inhalation.[53]

Storage: Store capsules or tablets at 25 C (77 F); excursions are permitted between 15 C to 30 C (59 F to 86 F).[54] [55] Keep bottle tightly closed.[56] Store ribavirin oral solution between 2 C and 8 C (36 F and 46 F) or at 25 C (77 F); excursions are permitted between 15 C to 30 C (59 F to 86 F).[57]

Vials containing lyophilized ribavirin for reconstitution for inhalation should be stored in a dry place at 25 C (77 F); excursions are permitted between 15 C to 30 C (59 F to 86 F).[58]

Chemistry

CAS Name: 1-beta-D-Ribofuranosyl-1H-1,2,4-triazole-3-carboxamide[59]

CAS Number: 36791-04-5[60]

Molecular formula: C8-H12-N4-O5[61]

C39.35%, H4.95%, N22.94%, O32.76%[62]

Molecular weight: 244.20[63]

Ribavirin

Chemistry (cont.)

Melting point: 166 C to 168 C (aqueous ethanol); 174 C to 176 C (ethanol)[64]

Physical Description: White crystalline powder.[65]

Stability: Reconstituted solutions of ribavirin for inhalation may be stored for up to 24 hours at room temperature, 20 C to 30 C (68 F to 86 F).[66]

Solubility: 142 mg/ml at 25 C in water; only a slight solubility in ethanol.[67] Slightly soluble in anhydrous alcohol.[68]

Other Names

Ribamide[69]

Viramide[70]

Ribamidil[71]

Ribamidyl[72]

Ribavirina[73]

Ribovirin[74]

Tribavirin[75]

Further Reading

Adeyemi OM. Hepatitis C in HIV-positive Patients-Treatment and Liver Disease Outcomes. J Clin Gastroenterol. 2007 Jan;41(1):75-87.

Brennan C. Treatment of hepatitis C virus in the coinfected patient. J Assoc Nurses AIDS Care. 2003 Sep-Oct;14(5 Suppl):52S-79S. Review.

Laguno M, Larrousse M, Murillas J, Blanco JL, Leon A, Milinkovic A, Lonca M, Martinez E, Sanchez-Tapias JM, de Lazzari E, Gatell JM, Costa J, Mallolas J. Predictive Value of Early Virologic Response in HIV/Hepatitis C Virus-Coinfected Patients Treated With an Interferon-Based Regimen Plus Ribavirin. J Acquir Immune Defic Syndr. 2006 Nov 9 [Epub ahead of print].

Rodriguez-Torres M, Rodriguez-Orengo JF, Rios-Bedoya CF, Fernandez-Carbia A, Gonzalez-Lassalle E, Salgado-Mercado R, Marxuach-Cuetara AM. Efficacy and safety of peg-IFN alfa-2a with ribavirin for the treatment of HCV/HIV coinfected patients who failed previous IFN based therapy. J Clin Virol. 2007 Jan;38(1):32-8. Epub 2006 Oct 24.

Romero M, Perez-Olmeda M, Garcia-Samaniego J, Soriano V. Management of chronic hepatitis C in patients co-infected with HIV: focus on safety considerations. Drug Saf. 2004;27(1):7-24.

Manufacturer Information

Ribavirin
Valeant Pharmaceuticals International
Valeant Plaza
3300 Hyland Avenue
Costa Mesa, CA 92626
(800) 548-5100

Virazole
Valeant Pharmaceuticals International
Valeant Plaza
3300 Hyland Avenue
Costa Mesa, CA 92626
(800) 548-5100

Rebetol
Schering - Plough Corp
2000 Galloping Hill Rd
Kenilworth, NJ 07033-0530
(800) 526-4099

Copegus
Roche Laboratories
340 Kingsland Street
Nutley, NJ 07110
(973) 235-5000

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

For More Information (cont.)

• 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 - 2005; p. 800

2. AHFS Drug Information - 2005; p. 811

3. AHFS Drug Information - 2005; p. 801

4. AHFS Drug Information - 2005; p. 802

5. Schering Plough - Rebetol Prescribing Information, July 2004, p. 1. Available at: http://www.spfiles.com/pirebetol.pdf. Accessed 02/01/07.

6. USP DI - 2005; p. 2537

7. AHFS Drug Information - 2005; p. 800

8. AHFS Drug Information - 2005; p. 802

9. AHFS Drug Information - 2005; p. 801

10. AHFS Drug Information - 2005; p. 809

11. USP DI - 2005; p. 2538

12. USP DI - 2005; p. 2538

13. AHFS Drug Information - 2005; p. 810

14. Schering Plough - Rebetol Prescribing Information, July 2004, p. 1. Available at: http://www.spfiles.com/pirebetol.pdf. Accessed 02/01/07.

15. AHFS Drug Information - 2005; p. 811

16. USP DI - 2005; p. 2538

17. AHFS Drug Information - 2005; p. 811

18. USP DI - 2005; p. 2538

19. AHFS Drug Information - 2005; p. 811

20. USP DI - 2005; p. 2539

21. AHFS Drug Information - 2005; p. 811

22. USP DI - 2005; p. 2538

23. AHFS Drug Information - 2005; p. 811

24. USP DI - 2005; p. 2538

25. AHFS Drug Information - 2005; p. 811

26. AHFS Drug Information - 2005; p. 810

27. Roche Laboratories - Copegus Prescribing Information, June 2005, p. 9. Available at: http://www.rocheusa.com/products/copegus/pi.pdf. Accessed 01/25/07.

28. Schering Plough - Rebetol Prescribing Information, July 2004, p. 2. Available at http://www.spfiles.com/pirebetol.pdf. Accessed 01/25/07.

29. AHFS Drug Information - 2005; p. 805

30. Roche Laboratories - Copegus Prescribing Information, June 2005, p. 9. Available at: http://www.rocheusa.com/products/copegus/pi.pdf. Accessed 01/25/07.

31. Schering Plough - Rebetol Prescribing Information, July 2004, p. 1. Available at http://www.spfiles.com/pirebetol.pdf. Accessed 01/25/07.

32. Schering Plough - Rebetol Prescribing Information, July 2004, p. 2. Available at http://www.spfiles.com/pirebetol.pdf. Accessed 01/25/07.

33. Roche Laboratories - Copegus Prescribing Information, June 2005, p. 9. Available at: http://www.rocheusa.com/products/copegus/pi.pdf. Accessed 01/25/07.

34. Valeant Pharmaceuticals International - Virazole Prescribing Information, April 2002, p. 1. Available at http://www.valeant.com/fileRepository/products/PI/Virazole_Inhalation%20Solution%206gm_PI_Apr02.pdf. Accessed 01/25/07.

35. USP DI - 2005; p. 2540

36. AHFS Drug Information - 2005; p. 808

37. USP DI - 2005; p. 2539

38. Roche Laboratories - Copegus Prescribing Information, June 2005, p. 3. Available at: http://www.rocheusa.com/products/copegus/pi.pdf. Accessed 01/25/07.

39. Schering Plough - Rebetol Prescribing Information, July 2004, p. 3. Available at: http://www.spfiles.com/pirebetol.pdf. Accessed 02/01/07.

40. AHFS Drug Information - 2005; pp. 808, 811

41. Schering Plough - Rebetol Prescribing Information, July 2004, p. 1. Available at: http://www.spfiles.com/pirebetol.pdf. Accessed 02/01/07.

42. AHFS Drug Information - 2005; p. 808

43. Schering Plough - Rebetol Prescribing Information, July 2004, p. 2. Available at: http://www.spfiles.com/pirebetol.pdf. Accessed 02/01/07.

44. Roche Laboratories - Copegus Prescribing Information, June 2005, p. 8. Available at: http://www.rocheusa.com/products/copegus/pi.pdf. Accessed 02/01/07.

45. Roche Laboratories - Copegus Prescribing Information, June 2005, p. 8. Available at: http://www.rocheusa.com/products/copegus/pi.pdf. Accessed 02/01/07.

46. USP DI - 2005; p. 2539

47. USP DI - 2005; pp. 2542-3

48. Schering Plough - Rebetol Prescribing Information, July 2004, p. 4. Available at: http://www.spfiles.com/pirebetol.pdf. Accessed 02/01/07.

49. Roche Laboratories - Copegus Prescribing Information, June 2005, p. 21. Available at: http://www.rocheusa.com/products/copegus/pi.pdf. Accessed 01/25/07.

50. Valeant Pharmaceuticals International - Virazole Prescribing Information, April 2002, p. 1. Available at: http://www.valeant.com/fileRepository/products/PI.Virazole_Inhalation%20Solution%206gm_PI_Apr02.pdf. Accessed 02/01/07.

51. Roche Laboratories - Copegus Prescribing Information, June 2005, p. 21. Available at: http://www.rocheusa.com/products/copegus/pi.pdf. Accessed 01/25/07.

52. Schering Plough - Schering Plough - Rebetol Prescribing Information, July 2004, p. 4. Available at: http://www.spfiles.com/pirebetol.pdf. Accessed 02/01/07.

53. Valeant Pharmaceuticals International - Virazole Prescribing Information, April 2002, p. 2. Available at: http://www.valeant.com/fileRepository/products/PI.Virazole_Inhalation%20Solution%206gm_PI_Apr02.pdf. Accessed 02/01/07.

54. Schering Plough - Schering Plough - Rebetol Prescribing Information, July 2004, p. 4. Available at: http://www.spfiles.com/pirebetol.pdf. Accessed 02/01/07.

55. Roche Laboratories - Roche Laboratories - Copegus Prescribing Information, June 2005, p. 21. Available at: http://www.rocheusa.com/products/copegus/pi.pdf. Accessed 02/01/07.

56. Roche Laboratories - Roche Laboratories - Copegus Prescribing Information, June 2005, p. 21. Available at: http://www.rocheusa.com/products/copegus/pi.pdf. Accessed 02/01/07.

57. Schering Plough - Schering Plough - Rebetol Prescribing Information, July 2004, p. 4. Available at: http://www.spfiles.com/pirebetol.pdf. Accessed 02/01/07.

58. Valeant Pharmaceuticals International - Virazole Prescribing Information, April 2002, p. 2. Available at: http://www.valeant.com/fileRepository/products/PI.Virazole_Inhalation%20Solution%206gm_PI_Apr02.pdf. Accessed 02/01/07.

59. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 02/01/07.

60. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 02/01/07.

61. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 02/01/07.

62. Merck Index - 2006; p. 1413

63. Merck Index - 2006; p. 1413

64. Merck Index - 2006; p. 1413

65. Schering Plough - Schering Plough - Rebetol Prescribing Information, July 2004, p. 1. Available at: http://www.spfiles.com/pirebetol.pdf. Accessed 02/01/07.

66. Valeant Pharmaceuticals International - Virazole Prescribing Information, April 2002, p. 2. Available at: http://www.valeant.com/fileRepository/products/PI.Virazole_Inhalation%20Solution%206gm_PI_Apr02.pdf. Accessed 02/01/07.

67. Valeant Pharmaceuticals International - Virazole Prescribing Information, April 2002, p. 1. Available at: http://www.valeant.com/fileRepository/products/PI.Virazole_Inhalation%20Solution%206gm_PI_Apr02.pdf. Accessed 02/01/07.

68. Schering Plough - Rebetol Prescribing Information, July 2004, p. 1. Available at: http://www.spfiles.com/pirebetol.pdf. Accessed 02/01/07.

69. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 02/01/07.

70. MeSH - Available at: http://www.nlm.nih.gov/mesh/Mbrowser.html. Accessed 02/01/07.

71. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 02/01/07.

72. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 02/01/07

73. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 02/01/07.

74. MeSH - Available at: http://www.nlm.nih.gov/mesh/Mbrowser.html. Accessed 02/01/07.

75. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 02/01/07.