Lamivudine

Brand Name: Epivir
Drug Class: Nucleoside Reverse Transcriptase Inhibitors

Drug Description

Lamivudine, a synthetic antiretroviral agent, is a dideoxynucleoside reverse transcriptase inhibitor. Lamivudine is the negative enantiomer of a dideoxy analogue of cytidine and is structurally similar to zalcitabine (2',3'-dideoxycytidine, ddC). Lamivudine differs structurally from zalcitabine in that the 3'-carbon of the ribose ring is replaced with sulfur, forming an oxathiolane ring. The absence of a free 3'-hydroxy group on the oxathiolane ring results in the inability of lamivudine to form phosphodiester linkages at this position. Both the positive and negative enantiomers of 2',3'-dideoxy,3'-thiacytidine exhibit antiviral activity in vitro, but lamivudine appears to exhibit greater antiviral activity and to be considerably less cytotoxic than the positive enantiomer. [1]

HIV/AIDS-Related Uses

Lamivudine was approved by the FDA on November 17, 1995, for use in combination with other antiretroviral agents for the treatment of HIV infection in adults and in pediatric patients 3 months of age and older.[2] [3] Lamivudine should always be used in conjunction with other antiretroviral agents and should not be used alone in the management of HIV infection. Lamivudine usually is used in three- or four-drug regimens that include another nucleoside reverse transcriptase inhibitor (NRTI) and either one or two protease inhibitors (PIs) or a non-nucleoside reverse transcriptase inhibitor (NNRTI).[4]

Lamivudine has been used in combination with zidovudine for prevention of mother-to-child transmission of HIV. Although the safety and efficacy of this two-drug regimen has not been established, it is considered one of several options used in HIV infected women in labor who have received no prior antiretroviral therapy. Lamivudine is also used in conjunction with zidovudine or, alternatively, with stavudine for postexposure prophylaxis of HIV infection in health care workers and other individuals exposed occupationally to blood, body fluids, or tissues associated with a risk for transmission of HIV.[5]

Non-HIV/AIDS-Related Uses

Lamivudine is used to treat chronic hepatitis B virus (HBV) infection associated with evidence of hepatitis B viral replication and active liver inflammation.[6] For HBV therapy, it is administered in doses lower than those used to treat HIV infection. The formulation and dosage of lamivudine used in HBV therapy are not appropriate for patients coinfected with HIV and HBV.[7] Patients with HIV infection should receive only dosing forms appropriate for treatment of HIV. The safety and efficacy of lamivudine have not been established for treatment of chronic HBV in patients coinfected with HIV and HBV.[8]

Pharmacology

Lamivudine exerts a virustatic effect against retroviruses by acting as a reverse transcriptase inhibitor. Lamivudine is phosphorylated intracellularly to its active 5'-triphosphate metabolite, lamivudine triphosphate (L-TP, also known as 3TC-TP), which inhibits HIV reverse transcription and HBV polymerase activity via viral DNA chain termination.[9] The principal mode of action of L-TP is inhibition of HIV reverse transcription via viral DNA chain termination after incorporation of the nucleoside analogue. L-TP is a weak inhibitor of mitochondrial DNA polymerase and mammalian DNA polymerases alpha and beta.[10] 3TC-LP is a structural analogue of deoxycytidine triphosphate (dC-TP), the natural substrate for reverse transcriptase. 3TC-TP appears to compete with naturally occurring dC-TP for incorporation into viral DNA by reverse transcriptase. Following incorporation of 3TC-TP into the viral DNA chain instead of dC-TP, viral DNA synthesis is terminated prematurely because the absence of a 3'-hydroxyl group on the oxathiolane ring prevents further 5' to 3' phosphodiester linkages. Lamivudine has in vitro virustatic activity against HIV-1, HIV-2, and HBV, but it appears to be inactive against other common human viruses (e.g., cytomegalovirus, Epstein-Barr virus, influenza virus, herpes simplex virus types 1 and 2, respiratory syncytial virus, varicella-zoster virus).[11]

Lamivudine

Pharmacology (cont.)

Lamivudine is rapidly absorbed, with bioavailability from 80% to 88% in adults and adolescents and from 66% to 68% in children. Food delays the peak serum concentration; however, there is no significant difference in bioavailability when lamivudine is taken with food. Time to peak concentration (Tmax) is approximately 0.5 to 2 hours after a single 100 mg dose; with food, it increases to approximately 3.2 hours; with fasting, Tmax is about 1 hour.[12]

Lamivudine is widely distributed after administration. Lamivudine crosses the blood-brain barrier and is distributed into the cerebrospinal fluid (CSF) to a limited extent. In children, CSF concentrations have ranged from 10% to 17% of the corresponding non-steady-state serum concentration.[13] Apparent volume of distribution after intravenous (IV) administration in 20 patients was 1.3 +/- 0.4 l/kg, suggesting that lamivudine distributes into extravascular spaces. The volume of distribution was independent of dose and did not correlate with body weight.[14]

Plasma protein binding is low (36%).[15] Metabolism is a minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite. Within 12 hours after a single oral dose in six HIV infected adults, 5.2% +/- 1.4% was excreted as the trans-sulfoxide metabolite in the urine. Serum concentrations of this metabolite have not been determined.[16] The majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion. In 20 HIV-infected patients given a single IV dose, renal clearance was 280.4 +/- 75.2 ml/min, representing 71% +/- 16% of total clearance of the drug. In most single-dose studies in infected patients, the mean elimination half-life ranged from 5 to 7 hours. Oral clearance and elimination half-life were independent of dose and body weight over an oral dosing range of 0.25 mg/kg to 10 mg/kg.[17] The half-life of intracellular lamivudine triphosphate is 11 to 15 hours; serum half-life of lamivudine is about 2.6 hours in adults and 1.7 to 2 hours in children. The renal clearance of lamivudine is greater than the glomerular filtration rate, implying active secretion into the renal tubules.[18] Hemodialysis increases lamivudine clearance by a range of 64 to 88 ml/min, but the length of dialysis treatment (i.e., 4 hours) may not be long enough to alter mean lamivudine exposure. It is not known if lamivudine is removed by continuous (24 hour) hemodialysis.[19]

Resistance to lamivudine can be produced in vitro by serial passage of HIV-1 in the presence of increasing concentrations of the drug, and strains of HIV-1 with in vitro resistance to lamivudine have emerged during therapy with the drug. Primary infection with lamivudine-resistant HIV-1 has been reported rarely in adults who were treatment naive. While some strains of zidovudine-resistant HIV-1 may be susceptible to lamivudine, strains resistant to both zidovudine and lamivudine have been isolated. HIV isolates resistant to zalcitabine, zidovudine, didanosine, lamivudine, and stavudine have been isolated from a limited number of patients who received zidovudine in conjunction with zalcitabine or didanosine for 1 year or longer. Mutations identified in these multidrug-resistant isolates were Ala62 to Val, Val75 to Ile, Phe77 to Leu, Phe116 to Tyr, and Gln151 to Met; the mutation at position 151 appears to play an important role in the development of multidrug resistance. The possibility of cross resistance among lamivudine, didanosine, and zalcitabine based on reverse transcriptase codon 184 mutations also is of concern.[20]

Adverse Events/Toxicity

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including lamivudine and other antiretrovirals. Female gender, obesity, and prolonged exposure to antiretroviral nucleoside analogues may be risk factors. Such cases have occurred in patients with and without known risk factors for liver disease. Treatment with lamivudine should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis, even in the absence of marked transaminase elevations).[21] [22]

Post-treatment exacerbations of HBV infection have been reported in HIV uninfected patients

Lamivudine

Adverse Events/Toxicity (cont.)

treated with lamivudine for chronic HBV infection when lamivudine therapy was discontinued. Similar exacerbations of HBV infection have been reported in patients infected with both HIV and HBV when lamivudine therapy was switched to a regimen not containing lamivudine. The causal relationship between discontinuation of lamivudine therapy and exacerbation of HBV infection is unknown. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. There is insufficient evidence to determine whether reinitiation of lamivudine alters the course of post-treatment exacerbations of hepatitis.[23]

Adverse effects seen with the use of lamivudine include pancreatitis, paresthesia and peripheral neuropathy, skin rash, or splenomegaly, and are more commonly observed in pediatric patients than in adults.[24]

Drug and Food Interactions

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Consequently, lamivudine should not be coadministered with zalcitabine.[25]

Lamivudine exposure was increased by 44% and lamivudine renal clearance was decreased by 30% when coadministered with sulfamethoxazole/trimethoprim. Concurrent administration of lamivudine and zidovudine in one small study resulted in a 39% increase in peak plasma concentration of zidovudine with no significant changes in the area under the concentration-time curve (AUC) or total clearance of lamivudine or zidovudine.[26]

Concurrent administration of lamivudine with indinavir and zidovudine resulted in a 6% decrease in AUC of lamivudine, no change in AUC of indinavir, and a 36% increase in AUC of zidovudine. No adjustment in dose is necessary. Concurrent administration of lamivudine with drugs associated with pancreatitis (e.g., alcohol, didanosine, IV pentamidine, sulfonamides) or with drugs associated with peripheral neuropathy (e.g., dapsone, didanosine, isoniazid, stavudine, zalcitabine) should be avoided or done with caution.[27]

The higher and lower dose formulations of lamivudine should not be used concurrently. Concurrent administration of products that also contain lamivudine should be avoided, including the coformulations of abacavir sulfate and lamivudine; lamivudine and zidovudine; and abacavir sulfate, lamivudine, and zidovudine.[28]

Contraindications

Lamivudine is contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the products.[29]

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including lamivudine and other antiretrovirals. Lamivudine for HIV (brand name Epivir) in oral solution or tablet form contains higher doses of the active ingredient (lamivudine) than the lamividune formulation used to treat chronic HBV infection (brand name Epivir-HBV). Patients with HIV infection should receive only dosing forms appropriate for treatment of HIV.[30]

In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, lamivudine should be used in caution. Treatment with lamivudine should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur.[31]

Risk-benefit should be considered in HIV infected patients with renal function impairment.[32]

Clinical Trials

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

Lamivudine

Dosing Information

Mode of Delivery: Oral.[33]

Dosage Form: Film-coated tablets that contain lamivudine 300 mg.[34] Scored, film-coated tablets, appropriate for pediatric dosing, that contain lamivudine 150 mg.[35]

Oral solution containing lamivudine 10 mg/ml in 240 ml bottles.[36]

The recommended dose of lamivudine for HIV infected adults is 300 mg once daily or 150 mg twice daily, in combination with other antiretroviral agents. The recommended dose of lamivudine for HIV infected children age 3 months to 16 years is 4 mg/kg twice daily, up to a maximum of 150 mg twice daily, in combination with other antiretroviral agents.[37]

Lamivudine dosage should be adjusted in accordance with renal function in patients with creatinine clearance below 50 ml/min. No additional dosing of lamivudine is required after routine (4-hour) hemodialysis or peritoneal dialysis.[38]

Storage: Store tablets at 25 C (77 F); excursions permitted between 15 C and 30 C (59 F and 86 F). Store oral solution at 25 C (77 F) in tightly closed bottles; oral solution need not be reconstituted.[39]

Chemistry

CAS Name: 2(1H)-Pyrimidinone, 4-amino-1-((2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-[40]

CAS Number: 134678-17-4[41]

Molecular formula: C8-H11-N3-O3-S[42]

C41.91%, H4.84%, N18.33%, O20.94%, S13.99%[43]

Molecular weight: 229.26[44]

Melting point: 160 to 162 C[45]

Physical Description: White to off-white crystalline solid.[46]

Stability: Lamivudine oral solution need not be reconstituted.[47]

Solubility: Approximately 70 mg/ml in water at 20 C.[48]

Other Names

3TC[49]

Epivir-HBV[50]

Further Reading

Lehmann C, Wyen C, Fatkenheuer G. Rapid Improvement of Liver Function in a Patient with HIV and Hepatitis B Coinfection Treated with Lamivudine and Tenofovir. Infection. 2006 Aug;34(4):234-5.

LePrevost M, Green H, Flynn J, Head S, Clapson M, Lyall H, Novelli V, Farrelly L, Walker AS, Burger DM, Gibb DM. Pediatric European Network for the Treatment of AIDS 13 Study Group. Adherence and acceptability of once daily Lamivudine and abacavir in human immunodeficiency virus type-1 infected children. Pediatr Infect Dis J. 2006 Jun;25(6):533-7.

Levy V, Grant RM. Antiretroviral Therapy for Hepatitis B Virus-HIV-Coinfected Patients: Promises and Pitfalls.Clin Infect Dis. 2006 Oct 1;43(7):904-10. Epub 2006 Aug 23.

Manufacturer Information

Lamivudine
GlaxoSmithKline
5 Moore Drive
Research Triangle Park, NC 27709
(888) 825-5249

Epivir
GlaxoSmithKline
5 Moore Drive
Research Triangle Park, NC 27709
(888) 825-5249

Lamivudine

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 - 2008; p. 740

2. GlaxoSmithKline - Epivir Product Information, October 2006, p. 15. Available at: http://us.gsk.com/products/assets/us_epivir.pdf. Accessed 11/11/08.

3. AHFS Drug Information - 2007; p. 735

4. AHFS Drug Information - 2008; p. 735

5. AHFS Drug Information - 2008; pp. 735-6

6. AHFS Drug Information - 2008; p. 736

7. GlaxoSmithKline - Epivir-HBV Product Information, October 2007, p. 10. Available at: http://us.gsk.com/products/assets/us_epivir_hbv.pdf. Accessed 11/11/08.

8. GlaxoSmithKline - Epivir-HBV Product Information, October 2007, p. 10. Available at: http://us.gsk.com/products/assets/us_epivir_hbv.pdf. Accessed 11/11/08.

9. AHFS Drug Information - 2008; p. 740

10. GlaxoSmithKline - Epivir Product Information, October 2006, p. 2. Available at: http://us.gsk.com/products/assets/us_epivir.pdf. Accessed 11/11/08.

11. AHFS Drug Information - 2008; p. 740

12. Pharm GKB - The Pharmacogenetics and Pharmacogenomics Knowledge Base - lamivudine. Available at: http://www.pharmgkb.org/do/serve?objId=PA450163&objCls=Drug. Accessed 11/11/08.

13. Pharm GKB - The Pharmacogenetics and Pharmacogenomics Knowledge Base - lamivudine. Available at: http://www.pharmgkb.org/do/serve?objId=PA450163&objCls=Drug. Accessed 11/11/08.

14. GlaxoSmithKline - Epivir Product Information, October 2006, p. 5. Available at: http://us.gsk.com/products/assets/us_epivir.pdf. Accessed 11/11/08.

15. GlaxoSmithKline - Epivir Product Information, October 2006, p. 6. Available at: http://us.gsk.com/products/assets/us_epivir.pdf. Accessed 11/11/08.

16. GlaxoSmithKline - Epivir Product Information, October 2006, p. 6. Available at: http://us.gsk.com/products/assets/us_epivir.pdf. Accessed 11/11/08.

17. GlaxoSmithKline - Epivir Product Information, October 2006, p. 6. Available at: http://us.gsk.com/products/assets/us_epivir.pdf. Accessed 11/11/08.

18. Pharm GKB - The Pharmacogenetics and Pharmacogenomics Knowledge Base - lamivudine. Available at: http://www.pharmgkb.org/do/serve?objId=PA450163&objCls=Drug. Accessed 11/11/08.

19. GlaxoSmithKline - Epivir Product Information, October 2006, pp. 6-7. Available at: http://us.gsk.com/products/assets/us_epivir.pdf. Accessed 11/11/08.

20. AHFS Drug Information - 2008; p. 740

21. GlaxoSmithKline - Epivir Product Information, October 2006, p. 11. Available at: http://us.gsk.com/products/assets/us_epivir.pdf. Accessed 11/11/08.

22. Pharm GKB - The Pharmacogenetics and Pharmacogenomics Knowledge Base - lamivudine. Available at: http://www.pharmgkb.org/do/serve?objId=PA450163&objCls=Drug. Accessed 11/11/08.

23. GlaxoSmithKline - Epivir Product Information, October 2006, p. 12. Available at: http://us.gsk.com/products/assets/us_epivir.pdf. Accessed 11/11/08.

24. Wolters Kluwer Health, Inc. - Lamivudine, Facts and Comparisons 4.0. Available at: http://online.factsandcomparisons.com. Accessed 11/11/08.

25. GlaxoSmithKline - Epivir Product Information, October 2006, p. 14. Available at: http://us.gsk.com/products/assets/us_epivir.pdf. Accessed 11/11/08.

26. Pharm GKB - The Pharmacogenetics and Pharmacogenomics Knowledge Base - lamivudine. Available at: http://www.pharmgkb.org/do/serve?objId=PA450163&objCls=Drug. Accessed 11/11/08.

27. Pharm GKB - The Pharmacogenetics and Pharmacogenomics Knowledge Base - lamivudine. Available at: http://www.pharmgkb.org/do/serve?objId=PA450163&objCls=Drug. Accessed 11/11/08.

28. Pharm GKB - The Pharmacogenetics and Pharmacogenomics Knowledge Base - lamivudine. Available at: http://www.pharmgkb.org/do/serve?objId=PA450163&objCls=Drug. Accessed 11/11/08.

29. GlaxoSmithKline - Epivir Product Information, October 2006, p. 11. Available at: http://us.gsk.com/products/assets/us_epivir.pdf. Accessed 11/11/08.

30. GlaxoSmithKline - Epivir Product Information, October 2006, p. 1. Available at: http://us.gsk.com/products/assets/us_epivir.pdf. Accessed 11/11/08.

31. GlaxoSmithKline - Epivir Product Information, October 2006, p. 11. Available at: http://us.gsk.com/products/assets/us_epivir.pdf. Accessed 11/11/08.

32. Pharm GKB - The Pharmacogenetics and Pharmacogenomics Knowledge Base - lamivudine. Available at: http://www.pharmgkb.org/do/serve?objId=PA450163&objCls=Drug. Accessed 11/11/08.

33. AHFS Drug Information - 2008; p. 741

34. GlaxoSmithKline - Epivir Product Information, October 2006, p. 24. Available at: http://us.gsk.com/products/assets/us_epivir.pdf. Accessed 11/11/08.

35. FDA - Epivir Prescribing Information, February 2008, p. 2. Available at: http://www.fda.gov/cder/foi/label/2008/020564s028lbl.pdf. Accessed 11/11/08.

36. GlaxoSmithKline - Epivir Product Information, October 2006, p. 23. Available at: http://us.gsk.com/products/assets/us_epivir.pdf. Accessed 11/11/08.

37. GlaxoSmithKline - Epivir Product Information, October 2006, pp. 22-3. Available at: http://us.gsk.com/products/assets/us_epivir.pdf. Accessed 11/11/08.

38. GlaxoSmithKline - Epivir Product Information, October 2006, p. 23. Available at: http://us.gsk.com/products/assets/us_epivir.pdf. Accessed 11/11/08.

39. GlaxoSmithKline - Epivir Product Information, October 2006, pp. 23-4. Available at: http://us.gsk.com/products/assets/us_epivir.pdf. Accessed 11/11/08.

40. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 11/11/08.

41. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 11/11/08.

42. Merck Index - 2001; p. 958

43. Merck Index - 2001; p. 958

44. Merck Index - 2001; p. 958

45. Merck Index - 2001; p. 959

46. GlaxoSmithKline - Epivir Product Information, October 2006, p. 2. Available at: http://us.gsk.com/products/assets/us_epivir.pdf. Accessed 11/11/08.

47. GlaxoSmithKline - Epivir Product Information, October 2006, p. 23. Available at: http://us.gsk.com/products/assets/us_epivir.pdf. Accessed 11/11/08.

48. GlaxoSmithKline - Epivir Product Information, October 2006, p. 2. Available at: http://us.gsk.com/products/assets/us_epivir.pdf. Accessed 11/11/08.

49. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 11/11/08.

50. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 11/11/08.