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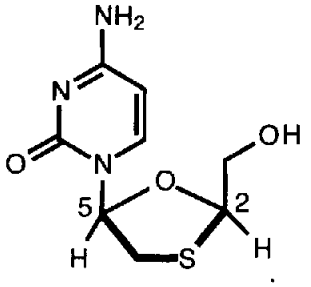
New Drugs—Reports of New Drugs Recently Approved by the FDA

Lamivudine



Structure

$C_8H_{11}N_3O_3S$

(−)-(2′*R*,5′*S*)-1-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine: (2*R*,*cis*)-4-amino-1-(2-hydroxymethyl)-1,3-oxathiolan-5-yl-(1H)-pyrimidine-2-one

[CAS 134678-17-4]

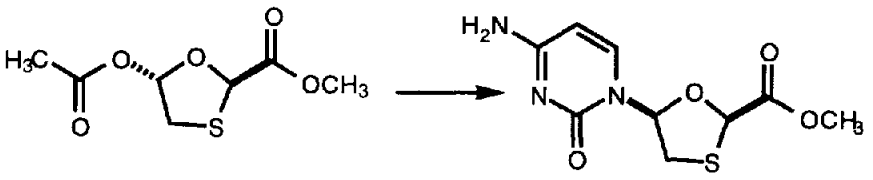
Supply: a white to off-white crystalline solid

Epivir™, 3TC, BC-189, BCH-189, BCH-790, GR-109714X, NGPB-21

Mechanism of action: Lamivudine is a synthetic nucleoside analogue. In vitro studies have shown that, intracellularly, lamivudine is phosphorylated to its active 5′-triphosphate metabolite (L-TP), which has an intracellular half-life of 10.5–15.5 h. The principal mode of action of L-TP is inhibition of HIV reverse transcription via viral DNA chain termination. L-TP also inhibits the RNA- and DNA-dependent DNA polymerase activities of reverse transcriptase (RT). L-TP is a weak inhibitor of mammalian α-, β- and γ-DNA polymerases.

Therapeutic category: Antiviral agent

Synthesis: Lamivudine can be synthesized by utilizing racemic oxathiolane which is obtained from the reaction of benzoyl-oxyacetaldehyde with mercaptoacetaldehyde dimethylacetal in the presence of a Lewis acid. Treatment of the oxathiolane with silylated cytosine in the presence of TMS-triflate affords a 1:1 mixture of β- and α-anomers from which the required β-anomer may be obtained by crystallization. The second approach to synthesis of lamivudine does not involve intermediacy of the racemic nucleoside. The chiral oxathiolane intermediate which may be coupled to the cytosine base under appropriate conditions where the chirality of the oxathiolane is maintained.



Summary: Several 2′,3′-dideoxynucleosides are potential inhibitors of HIV. In vitro activity of lamivudine against HIV-1 was assessed in a number of cell lines using standard susceptibility assays. IC_{50} values were in the range of

2 nM to 15 μM. Lamivudine has anti HIV-1 activity in all acute virus-cell infections tested. Lamivudine was rapidly absorbed after oral administration in HIV-infected patients. Absolute bioavailability in adult patients was ~86% for the tablet and ~87% for the oral solution. After oral administration of 2 mg/kg twice a day, the peak serum lamivudine concentration was ~1.5 μg/mL. The AUC and C_{max} increased in proportion to oral dose over the range 0.25–10 mg/kg. Lamivudine is also active against zidovudine-resistant clinical isolates of HIV. In patients receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-isolates from most patients became phenotypically and genotypically resistant to lamivudine within 12 weeks. Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine. The lamivudine distributes into extravascular spaces. Volume of distribution was independent of dose and did not correlate with body weight. Metabolism of lamivudine is a minor route of elimination. In man, the only known metabolism of lamivudine is the *trans*-sulfoxide metabolite in the urine. The majority of lamivudine is eliminated unchanged in urine. The recommended oral dose of lamivudine for adult is 150 mg twice a day administered in combination with zidovudine. In genetic toxicology tests, lamivudine, like many other nucleoside analogue, has shown evidence of weak activity in in vitro cytogenic assays and the mouse lymphoma assay. However, no evidence of genotoxic activity was seen when the racemate was examined in the rat bone marrow micronucleus test and the rat liver UDS test using doses of up to 600 mg/kg by the iv route. Negative results have also been obtained in an in vitro cell transformation assay using Balb/3T3 cells. Epivir™ tablets are for oral administration. Each tablet contains 150 mg of lamivudine and the inactive ingredients magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. Epivir™ Oral Solution is for oral administration. One milliliter of Epivir™ Oral Solution contains 10 mg of lamivudine (6% v/v), methylparaben, propylene glycol, propylparaben, and sucrose.

Manufacturer: Glaxo Wellcome Inc. and Biochem Pharma Inc.

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