HIVID® (zalcitabine) Tablets - PACKAGE INSERT
09/21/2001

HIVID®
(zalcitabine)
TABLETS

WARNING:

THE USE OF HIVID HAS BEEN ASSOCIATED WITH SIGNIFICANT CLINICAL ADVERSE REACTIONS, SOME OF WHICH ARE POTENTIALLY FATAL. HIVID CAN CAUSE SEVERE PERIPHERAL NEUROPATHY AND BECAUSE OF THIS SHOULD BE USED WITH EXTREME CAUTION IN PATIENTS WITH PREEXISTING NEUROPATHY. HIVID MAY ALSO RARELY CAUSE PANCREATITIS AND PATIENTS WHO DEVELOP ANY SYMPTOMS SUGGESTIVE OF PANCREATITIS WHILE USING HIVID SHOULD HAVE THERAPY SUSPENDED IMMEDIATELY UNTIL THIS DIAGNOSIS IS EXCLUDED.

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF ANTIRETROVIRAL NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING HIVID (SEE WARNINGS).

IN ADDITION, RARE CASES OF HEPATIC FAILURE AND DEATH CONSIDERED POSSIBLY RELATED TO UNDERLYING HEPATITIS B AND HIVID HAVE BEEN REPORTED (SEE WARNINGS AND PRECAUTIONS).

DESCRIPTION

HIVID is the Hoffmann-La Roche brand of zalcitabine [formerly called 2',3'-dideoxycytidine (ddC)], a synthetic pyrimidine nucleoside analogue active against the human immunodeficiency virus (HIV). HIVID is available as film-coated tablets for oral administration in strengths of 0.375 mg and 0.750 mg. Each tablet also contains the inactive ingredients lactose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, and polysorbate 80 along with the following colorant system: 0.375 mg tablet — synthetic brown, black, red and yellow iron oxides, and titanium dioxide; 0.750 mg tablet — synthetic black iron oxide and titanium dioxide. The chemical name for zalcitabine is 4-amino-1-beta-D-2', 3'-dideoxyribofuranosyl-2-(1H)-pyrimidone or 2',3'-dideoxycytidine with the molecular formula $C_9H_{13}N_3O_3$ and a molecular weight of 211.22. Zalcitabine has the following structural formula:

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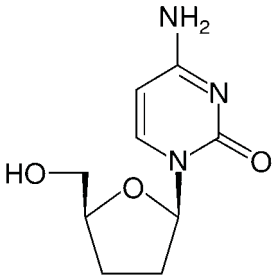

Zalcitabine is a white to off-white crystalline powder with an aqueous solubility of 76.4 mg/mL at 25°C.

MICROBIOLOGY

Mechanism of Action: Zalcitabine is a synthetic nucleoside analogue of the naturally occurring nucleoside deoxycytidine, in which the 3'-hydroxyl group is replaced by hydrogen. Within cells, zalcitabine is converted to the active metabolite, dideoxycytidine 5'-triphosphate (ddCTP), by the sequential action of cellular enzymes. Dideoxycytidine 5'-triphosphate inhibits the activity of the HIV-reverse transcriptase both by competing for utilization of the natural substrate, deoxycytidine 5'-triphosphate (dCTP), and by its incorporation into viral DNA. The lack of a 3'-OH group in the incorporated nucleoside analogue prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation and, therefore, the viral DNA growth is terminated. The active metabolite, ddCTP, is also an inhibitor of cellular DNA polymerase-beta and mitochondrial DNA polymerase-gamma and has been reported to be incorporated into the DNA of cells in culture.

In Vitro HIV Susceptibility: The in vitro anti-HIV activity of zalcitabine was assessed by infecting cell lines of lymphoblastic and monocytic origin and peripheral blood lymphocytes with laboratory and clinical isolates of HIV. The IC_{50} and IC_{95} values (50% and 95% inhibitory concentration) were in the range of 30 to 500 nM and 100 to 1000 nM, respectively (1 nM = 0.21 ng/mL). Zalcitabine showed antiviral activity in all acute infections; however, activity was substantially less in chronically infected cells. In drug combination studies with zidovudine (ZDV) or saquinavir, zalcitabine showed additive to synergistic activity in cell culture. The relationship between the in vitro susceptibility of HIV to reverse-transcriptase inhibitors and the inhibition of HIV replication in humans has not been established.

Drug Resistance: HIV isolates with a reduction in sensitivity to zalcitabine (ddC) have been isolated from a small number of patients treated with HIVID by 1 year of therapy. Genetic analysis of these isolates showed point mutations (Lys 65 Arg or Asn, Thr 69 Asp, Leu 74 Val, Val 75 Thr or Ala, Met 184 Val or Tyr 215 Cys) in the pol gene that encodes for the reverse transcriptase. Combination therapy with HIVID and ZDV does not appear to prevent the emergence of zidovudine-resistant isolates.

Cross-resistance: The potential for cross-resistance between HIV-reverse transcriptase inhibitors and HIV-protease inhibitors is low because of the different enzyme targets involved. The point

mutation at position 69 appears to be specific to ddC in its selection and effect. Additionally, the point mutations at positions 65, 74, 75, and 184 are associated with resistance to didanosine (ddI), that at position 75 with resistance to stavudine (d4T), and those at positions 65 (Lys to Arg), and 184 (Met to Val) with resistance to lamivudine (3TC). HIV isolates with multidrug resistance to ZDV, ddI, ddC, d4T, and 3TC were recovered from a small number of patients treated for 1 year with the combination of ZDV, ddI or ddC. The pattern of resistance mutations in the combination therapy was different (Ala 62 Val, Val 75 Ile, Phe 77 Leu, Phe 116 Tyr and Gln 151 Met) from monotherapy with mutation 151 being most significant for multidrug resistance.

CLINICAL PHARMACOLOGY

Pharmacokinetics: The pharmacokinetics of zalcitabine has been evaluated in studies in HIV-infected patients following 0.01 mg/kg, 0.03 mg/kg, and 1.5 mg oral doses, and a 1.5 mg intravenous dose administered as a 1-hour infusion.

Absorption and Bioavailability in Adults: Following oral administration to HIV-infected patients, the mean absolute bioavailability of zalcitabine was >80% (30% CV, range 23% to 124%, n=19). The absorption rate of a 1.5 mg oral dose of zalcitabine (n=20) was reduced when administered with food. This resulted in a 39% decrease in mean maximum plasma concentrations (C_{max}) from 25.2 ng/mL (35% CV, range 11.6 to 37.5 ng/mL) to 15.5 ng/mL (24% CV, range 9.1 to 23.7 ng/mL), and a twofold increase in time to achieve maximum plasma concentrations from a mean of 0.8 hours under fasting conditions to 1.6 hours when the drug was given with food. The extent of absorption (as reflected by AUC) was decreased by 14%, from 72 ng·hr/mL (28% CV, range 43 to 119 ng·hr/mL) to 62 ng·hr/mL (23% CV, range 42 to 91 ng·hr/mL). The clinical relevance of these decreases is unknown. Absorption of zalcitabine does not appear to be reduced in patients with diarrhea not caused by an identified pathogen.

Distribution in Adults: The steady-state volume of distribution following intravenous administration of a 1.5 mg dose of zalcitabine averaged 0.534 (± 0.127) L/kg (24% CV, range 0.304 to 0.734 L/kg, n=20). Cerebrospinal fluid obtained from 9 patients at 2 to 3.5 hours following 0.06 mg/kg or 0.09 mg/kg intravenous infusion showed measurable concentrations of zalcitabine. The CSF: plasma concentration ratio ranged from 9% to 37% (mean 20%), demonstrating penetration of the drug through the blood-brain barrier. The clinical relevance of these ratios has not been evaluated.

Metabolism and Elimination in Adults: Zalcitabine is phosphorylated intracellularly to zalcitabine triphosphate, the active substrate for HIV-reverse transcriptase. Concentrations of zalcitabine triphosphate are too low for quantitation following administration of therapeutic doses to humans.

Zalcitabine does not undergo a significant degree of metabolism by the liver. The primary metabolite of zalcitabine that has been identified is dideoxyuridine (ddU), which accounts for less than 15% of an oral dose in both urine and feces (n=4). Approximately 10% of an orally administered radiolabeled dose of zalcitabine appears in the feces (n=10), comprised primarily of

unchanged drug and ddU. Renal excretion of unchanged drug appears to be the primary route of elimination, accounting for approximately 80% of an intravenous dose and 60% of an orally administered dose within 24 hours after dosing (n=19). The mean elimination half-life is 2 hours and generally ranges from 1 to 3 hours in individual patients. Total clearance following an intravenous dose averaged 285 mL/min (29% CV, range 165 to 447 mL/min, n=20). Renal clearance averaged approximately 235 mL/min or about 80% of total clearance (30% CV, range 129 to 348 mL/min, n=20). Renal clearance exceeds glomerular filtration rate suggesting renal tubular secretion contributes to the elimination of zalcitabine by the kidneys.

In patients with impaired kidney function, prolonged elimination of zalcitabine may be expected. Preliminary results from 7 patients with renal impairment (estimated creatinine clearance <55 mL/min) indicate that the half-life was prolonged (up to 8.5 hours) in these patients compared to those with normal renal function. Maximum plasma concentrations were higher in some patients after a single dose (see PRECAUTIONS).

In patients with normal renal function, the pharmacokinetics of zalcitabine was not altered during 3 times daily multiple dosing (n=9). Accumulation of drug in plasma during this regimen was negligible. The drug was <4% bound to plasma proteins, indicating that drug interactions involving binding-site displacement are unlikely (see *Drug Interactions*).

Drug Interactions*: Zidovudine:* There was no significant pharmacokinetic interaction between zidovudine and zalcitabine when single doses of zalcitabine (1.5 mg) and zidovudine (200 mg) were coadministered to 12 HIV-positive patients.

Probenecid: Following administration of a single oral 1.5 mg dose of zalcitabine alone during probenecid treatment (500 mg at 8 and 2 hours before and 4 hours after zalcitabine dosing) to 12 HIV-positive patients, mean renal clearance decreased from 310 mL/min (28% CV) to 180 mL/min (22% CV) and AUC increased from 59 ng·hr/mL (27% CV) to 91 ng·hr/mL (22% CV), indicating an increase in exposure of approximately 50% to zalcitabine. Mean half-life of zalcitabine increased from 1.7 to 2.5 hours (see PRECAUTIONS).

Cimetidine: Administration of a single dose of 1.5 mg zalcitabine with a single dose of 800 mg cimetidine to 12 HIV-positive patients resulted in a decrease in renal clearance from 224 mL/min (27% CV) to 171 mL/min (39% CV) and an increase in AUC from 75 ng·hr/mL (29% CV) to 102 ng·hr/mL (35% CV) (see PRECAUTIONS) indicating an increase in exposure of approximately 36% to zalcitabine.

Maalox: Concomitant administration of Maalox® TC (30 mL) with single dose of 1.5 mg zalcitabine to 12 HIV-positive patients resulted in a decrease in mean C_{max} from 25.2 ng/mL (28% CV) to 18.4 ng/mL (34% CV) and AUC from 75 ng·hr/mL (29% CV, n=10) to 58 ng·hr/mL (36% CV, n=10) indicating a decrease in bioavailability of approximately 25% to zalcitabine (see PRECAUTIONS).

Metoclopramide: Administration of a single dose of 1.5 mg zalcitabine with 20 mg metoclopramide (10 mg 1 hour before and 10 mg 4 hours after zalcitabine dose) to 12 HIV-positive patients resulted in a decrease in AUC from 69 ng·hr/mL (16% CV) to 62 ng·hr/mL (21% CV) indicating a decrease in bioavailability of approximately 10% (see PRECAUTIONS).
Loperamide: Administration of a single dose of 1.5 mg zalcitabine during loperamide treatment (4 mg 16 hours before zalcitabine, 2 mg at 10 hours and 4 hours before zalcitabine, and 2 mg 2 hours after the zalcitabine dose) to 12 HIV-positive patients with diarrhea resulted in no significant pharmacokinetic interaction between zalcitabine and loperamide.

Pharmacokinetics in Pediatric Patients: For pharmacokinetic properties in pediatric patients, see PRECAUTIONS: *Pediatric Use*. Limited pharmacokinetic data have been reported for 5 HIV-positive pediatric patients using doses of 0.03 and 0.04 mg/kg HIVID administered orally every 6 hours.[1] The mean bioavailability of zalcitabine in these pediatric patients was 54% and mean apparent systemic clearance was 150 mL/min/m^2. Due to the small number of subjects and different analytical techniques, it is difficult to make comparisons between pediatric and adult data.

INDICATIONS AND USAGE

HIVID is indicated in combination with antiretroviral agents for the treatment of HIV infection. This indication is based on study results showing a reduction in the rate of disease progression (AIDS-defining events or death) in patients with limited prior antiretroviral therapy who were treated with the combination of HIVID and zidovudine (see *Description of Clinical Studies*). This indication is also based on a study showing a reduction in both mortality and AIDS-defining clinical events for patients who received INVIRASE® (saquinavir mesylate) in combination with HIVID compared to patients who received either HIVID or INVIRASE alone.

Description of Clinical Studies: The use of HIVID in combination with zidovudine is based on the clinical results from study ACTG 175. ACTG 175 was a randomized, double-blind, controlled trial that compared zidovudine 200 mg three times daily; didanosine 200 mg twice daily; zidovudine+didanosine; and zidovudine+HIVID 0.750 mg three times daily. A total of 2467 HIV-infected adults (mean baseline CD_4 count = 352 cells/mm^3) with no prior AIDS-defining event enrolled with the following demographics: male (82%), Caucasian (70%), mean age of 35 years, asymptomatic HIV infection (81%) and prior antiretroviral use (57%, mean duration = 89.5 weeks). The overall mean duration of study treatment was 99 weeks. The incidence of AIDS-defining events or death is shown in Table 1:

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