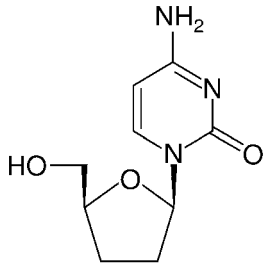
HIVID®
(zalcitabine)

CAS Registry Number: 7481-89-2



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.

DESCRIPTION

Zalcitabine [formerly called dideoxycytidine (ddC)] is a synthetic pyrimidine nucleoside analogue active against the human immunodeficiency virus (HIV).

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

HIVID is available as film-coated tablets for oral administration in strengths of 0.375 mg or 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 oxide, and titanium dioxide; 0.750 mg tablet - synthetic black iron oxide and titanium dioxide.

PHARMACOLOGY

Mechanism of Action

Zalcitabine is a synthetic nucleoside analogue of the naturally occurring nucleoside 2'-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 cellular enzymes. ddCTP serves as an alternative substrate to deoxycytidine triphosphate (dCTP) for HIV-reverse transcriptase and inhibits the *in vitro* replication of HIV-1 by inhibition of viral DNA synthesis. This inhibition has been demonstrated *in vitro* in human primary cell cultures and in established cell lines. In DNA biosynthesis, DNA chain extension occurs through the formation of a phosphodiester bridge between the 3'-hydroxyl group of the growing end of a DNA chain and the 5'-phosphate group of the incoming deoxynucleotide. Because ddCTP lacks the 3'-hydroxyl group required for chain elongation, its incorporation into a growing DNA chain leads to premature chain termination. ddCTP serves as a competitive inhibitor of the natural substrate, dCTP, for the active site of the viral-reverse transcriptase and thus further inhibits viral DNA synthesis.

The active metabolite, ddCTP, also has a high affinity for cellular mitochondrial DNA polymerase gamma and has been reported to be incorporated into the DNA of cells in culture. However, DNA chain termination with cellular DNA polymerases has not been demonstrated.

The half-life of ddCTP in established cell lines and in human peripheral blood mononuclear cells in culture has been determined to be in the range of 2.6 to 10 hours.

Microbiology

The anti-HIV activity of zalcitabine was determined in a variety of human T-cell lines infected with different strains of HIV. The *in vitro* anti-HIV activity of zalcitabine varied greatly depending upon the time between virus infection and zalcitabine treatment of cell cultures, the ratio of the number of infectious virus particles to the number of cells, the kind of assay and the cell type used. When established cell lines were infected with a large excess of virus per cell and drug added soon after infection, the concentration of zalcitabine required to inhibit HIV-1 replication by 50% (ID_{50}) was generally in the range of 30 to 500 nM (1 nM = 0.21 ng/mL). In these cell lines, >95% inhibition of viral replication was achieved with 100 to 1000 nM zalcitabine. Zalcitabine blocked virus-induced cytopathic effects in cell lines in culture at a concentration of 30 nM to 300 nM. In assays measuring the inhibition of p24 viral antigen, the ID_{50} of zalcitabine was in the range of 1 nM to 500 nM, and the 90% inhibitory concentration (ID_{90}) was in the range of 500 to 1000 nM. In peripheral blood mononuclear cell cultures infected with HIV-1 (LAV strain) at a low ratio of virus to cells and assayed for HIV-reverse transcriptase, ID_{50} and ID_{90} values for zalcitabine were determined to be 11 nM and 100 nM, respectively. In monocyte/macrophage cultures infected with HIV (Ba-L strain) and treated with zalcitabine, the ID_{90} value was <10 nM when assayed for viral p24 antigen. However, viral replication in monocyte/macrophage cultures infected with a lymphotropic isolate of HIV (LAV-1 strain) was not inhibited at 100,000 nM. Comparative studies of the antiviral activity of zalcitabine against HIV-1 and HIV-2 *in vitro* revealed no significant difference in sensitivity between the two viruses when activity was determined by measuring viral cytopathic effect.

The results of cytotoxicity studies in various cell lines demonstrated that the concentration of the drug necessary to inhibit the cell growth by 50% (EC_{50}) was in the range of 5000 to >100,000 nM. *In vitro* combination studies have demonstrated that zalcitabine and zidovudine have an additive or synergistic antiviral effect, depending on the cell line used, without increased cytotoxicity over that observed for either agent alone.

The potential for development of clinically significant zalcitabine-resistant virus in patients with HIV infection who received HIVID has not been adequately studied. Reduced zalcitabine sensitivity *in vitro* was reported in hybrid virus constructs made with portions of the HIV genome obtained from a patient who received intermittent HIVID therapy for over 18 months. Combination therapy of HIVID plus zidovudine does not appear to prevent the emergence of zidovudine-resistant isolates. However, studies with zidovudine-resistant virus isolates indicate zidovudine-resistant strains remain sensitive to zalcitabine.

Current evidence demonstrates that the incidence of resistance to zalcitabine is an infrequent event. In patients receiving combination therapies no mutations associated with zalcitabine or didanosine were detected out to 112 weeks in one study involving 173 subjects. Time to zidovudine resistance at codon 70 was significantly shorter in the zidovudine alone group than in the combination therapy groups. Combination therapy of zidovudine with zalcitabine does not appear to prevent the emergence of resistant isolates associated with mutation at codon 215.

Specific phenotype resistance to zalcitabine is usually associated with the appearance of a point mutation at codon 69. This mutation is not associated with cross-resistance to other nucleoside

analogues. Other phenotypic resistance to zalcitabine that have emerged during combination therapy are at codon 65, 74 and 184.

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 mutlidrug resistance.

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 143%, 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 eightfold increase in time to achieve maximum plasma concentrations from a mean of 0.5 hours under fasting conditions to 4 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.

***Distribution in Adults*:** The steady-state volume of distribution following IV administration of a 1.5-mg dose of zalcitabine averaged 0.534 (± 0.127) L/kg (24% CV, range 0.304 - 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 IV 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 metabolism in humans has not been fully evaluated. Zalcitabine does not appear to 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 urine and faeces. Renal excretion appears to be the primary route of elimination, and accounted for approximately 70% of an orally-administered, radiolabelled dose (i.e., total radioactivity) within 24 hours after dosing (n=6). The mean elimination half-life is 2 hours and generally ranges from 1 to 3 hours in individual patients. Total body clearance following an intravenous dose averages 285 mL/min (29% CV, range 165 to 447 mL/min). Less than 10% of a radiolabelled dose of zalcitabine appears in the faeces.

In patients with normal renal function, the pharmacokinetics of zalcitabine was not altered during three 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*). In patients with impaired kidney function, prolonged elimination of zalcitabine may be expected (see 'DOSAGE AND ADMINISTRATION').

Special Populations

Renal Impairment

Results from patients with renal impairment (estimated CrCl <55 mL/min) after single dose indicate that the average half-life ($t_{½}$) was increased to 10.73 hours in these patients compared to those with normal renal function (2.26h). Also average maximum plasma concentrations were increased up to 17.27 mg/mL (38%) of those patients after single dose compared to 12.5 mg/mL in subjects with normal renal function. Dosage adjustment may be warranted in such patients, especially in those with severe renal impairment (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Paediatric patients

In children (mean age 4.2 years) zalcitabine mean plasma concentration is 9.3 ng/mL [range 3.2-14.1]. The mean half-life is 1.4h [range 1.0-3.5]. Area under the concentration-time curve (AUC_{0-10}) is 25 ng/mL/h [range 11-37] (see PRECAUTIONS).

Clinical Trials

Monotherapy And Combination Studies Of HIVID:

1. Combination Trials

The combined use of HIVID and zidovudine is based on limited data from two small studies which extended over 3 to 6 months and a large multi-centre study ACTG 175. The first study was a Phase I/II, open-label, dose-ranging study (N3447/ACTG 106) that evaluated several dose combinations of HIVID and zidovudine. The second study was a randomised Phase II study (BW 34,225-02) designed to evaluate the virologic and immunologic effects of the combined administration of two nucleoside analogues (zidovudine combined with either HIVID or didanosine). These two studies used an experimental regimen of zidovudine administered three times daily, and neither was designed to assess the clinical efficacy of the combination.

ACTG 175 was a randomised, double-blind trial in 2467 patients who had no previous AIDS defining events. The study was designed to evaluate the efficacy and safety of monotherapy vs combination therapy with antiretroviral nucleosides. There was a significant decrease in the proportion of patients experiencing the combined endpoint of progression to AIDS or death or experiencing a 50% decline in CD4 count, in the combination ddC/AZT arms compared to the AZT monotherapy arms.

Data from a study of HIVID alternating with zidovudine at doses of HIVID higher than currently recommended (ACTG 047) have shown results comparable to those observed in N3447/ACTG 106 in zidovudine-naive patients. A parallel study in patients who were previously haematologically intolerant to zidovudine monotherapy but then changed to an alternating HIVID and zidovudine regimen (ACTG 050) showed greater toxicity and less CD4 response. The applicability of the results from the two studies using alternating regimens to the recommended combination regimen is uncertain.

1. a) N3447/ACTG 106

HIVID GIVEN IN COMBINATION WITH ZIDOVUDINE IN ADULT ZIDOVUDINE-NAIVE PATIENTS WITH ADVANCED HIV INFECTION (CD4 CELL COUNT ≤200 CELLS/MM^3):

This Phase I/II study of therapy with concomitant HIVID and zidovudine is a six-arm, open-label, dose-escalating study with randomisation with blocks of two arms. Doses studied were HIVID 0.005 and 0.01 mg/kg q8h administered concomitantly with zidovudine 100 or 200 mg q8h, as well as zidovudine 50 mg q8h alone or combined with HIVID 0.005 mg/kg q8h. No control arm of zidovudine monotherapy at the currently approved regimen was included in this study. A total of 56 zidovudine-naive patients with advanced HIV infection (CD4 cell count ≤200 cells/mm^3) were entered. Patients treated for a median duration varying across groups from 36 to 72 weeks; median CD4 cell counts at entry were 75 cells/mm^3. An earlier analysis of this study has been published.[2]

Treatment regimens with 150 mg/day zidovudine showed less activity than those with ≥ 300 mg/day of zidovudine; therefore, the four treatment regimens that included ≥300 mg/day zidovudine were pooled for CD4 and weight analyses. For safety analyses, data from all five combination arms were pooled. Although the clinical outcomes were monitored while subjects were on therapy, the study was not designed to evaluate clinical outcome as an efficacy parameter.

There were eight deaths during the study. Twenty of the 56 patients who entered developed an AIDS-defining opportunistic infection, neoplasm or condition. These AIDS-defining events were equally distributed among the six treatment arms.

A total of 37 patients prematurely withdrew from the study. Nine patients discontinued therapy because of adverse events. Of these 9 patients, 2 were discontinued for peripheral neuropathy, 5 for haematologic abnormalities, 1 for nausea and vomiting, 1 for myositis.

The effect of study therapy on CD4 cell counts is presented later in this section. A mean peak increase in weight of 4.5 kg for the pool of the four combination regimens was observed. The weight was sustained above baseline for >1 year.

1. b) BW 34,225-02

HIVID GIVEN IN COMBINATION WITH ZIDOVUDINE IN PATIENTS WITH HIV INFECTION, ≤4 WEEKS PRIOR ZIDOVUDINE AND CD4 CELL COUNTS ≤300 CELLS/mm^3 :

An unscheduled analysis of CD4 changes for patients administered either combined HIVID and zidovudine therapy, or zidovudine monotherapy, was obtained from this double-blind, randomised, Phase ll controlled trial. The trial was designed to compare the antiviral and immunologic effects of zidovudine monotherapy administered three times daily to that of combination therapy with either HIVID and zidovudine or didanosine and zidovudine. Subjects were HIV-infected patients with CD4 cell counts at entry ≤300 cells/mm^3 who had received <4 weeks of prior zidovudine.

The unscheduled analysis of CD4 cell count changes in this study included only the group receiving zidovudine alone (200 mg q8h, a currently experimental regimen) and the HIVID plus zidovudine group. At the time of this analysis, 45 patients were randomised to the combination of HIVID and zidovudine and 47 patients to the zidovudine-monotherapy arm. Median duration of treatment was 13 weeks for the zidovudine-monotherapy group and 14 weeks for the group receiving HIVID and zidovudine; median CD4 cell counts at entry were 153 cells/mm^3 and 125 cells/mm^3, respectively. The primary end point of this study is emergence of viral resistance. Data on viral resistance, clinical outcome (survival, incidence of opportunistic infection) or the incidence of adverse events are not currently available. Change in CD4 cell count was the only outcome variable analysed from this study.

ANALYSIS OF CD4 CELL COUNTS IN COMBINATION TRIALS: The activity of combination HIVID and zidovudine was assessed using CD4 cell counts as a marker of biologic activity. In controlled trials, zidovudine monotherapy has been associated with clinical benefit (improved survival and decreased incidence of opportunistic infection) and transient increases in CD4 cell counts.

Definitions of outcome were applied to data from patients receiving HIVID in combination with zidovudine. Analyses included the following:

1. Mean change from baseline in CD4 cell counts at various time points during therapy;

2. Longitudinal changes during study: time-weighted average of serial CD4 cell counts adjusted (normalised) for baseline CD4 cell counts (NAUC). (NAUC = Cumulative AUC of CD4 cell count up to time t/ baseline CD4 count x t.) NAUCs that exceed a value of 1 indicate that the average CD4 level during therapy is increased over the baseline CD4 cell count;

3. Presence of a "response" where response was defined as one of the following:
   a) the greater of either a 75-cell or 75% increase over baseline CD4 cell count maintained for a minimum of two consecutive visits at least 21 days apart (75:75 response), or
   b) the greater of either a 50-cell or 50% increase over baseline CD4 cell count maintained for a minimum of two consecutive visits at least 21 days apart (50:50 response).

Definitions of outcome measures 2 and 3 were not specified in the two study protocols but were applied post hoc and have not been previously correlated with clinical outcome. In the discussion below, the outcomes for the control group referred to as N3300/ACTG 114 are results for subjects in the zidovudine arm of a large, prospective study comparing zidovudine to HIVID monotherapy. The figures cited are for those patients with no previous zidovudine exposure. Comparisons across clinical studies must be interpreted cautiously due to possible differences in study population, selection bias between studies, and different methodologies for measuring CD4 cell counts.

Table 1. Baseline Characteristics

	BW 34,225-02		N3300/ACTG 114	N3447/ACTG 106
STUDY	COMBINATION HIVID + ZDV	ZDV	ZDV (no prior ZDV)	(Four Pooled Combination Arms)
n	45	47	262	36
Accrual Date	5/91 - 11/91	5/91 - 11/91	8/89 - 9/90	7/89 - 5/90
Baseline median CD4 (cells/mm^3)	125	153	85	70
CD4 Range (cells/mm^3)	1 - 301	11 - 288	5 - 289	3 - 188
% Male	89%	92%	93%	97%
% Caucasian	60%	66%	79%	89%
% Homosexual	51%	55%	77%	69%
% AIDS	22%	15%	26%	44%

Figure 1 displays the CD4 cell response for those patients receiving HIVID in combination with zidovudine in BW 34,225-02 and in N3447/ACTG 106 (pooled response for the combination regimens of HIVID with $\geq$300 mg/day of zidovudine). It also depicts the CD4 cell response for the zidovudine-monotherapy arm from BW 34,225-02 and for those zidovudine patients in N3300/ACTG 114 who were zidovudine-naive at entry. Table 1 describes the characteristics of those populations whose CD4 data were analysed as presented in Figure 1 and Table 2. Table 2 lists the NAUC response at weeks 12 and 24 for BW 34,225-02, N3447/ACTG 106 and N3300/ACTG 114.

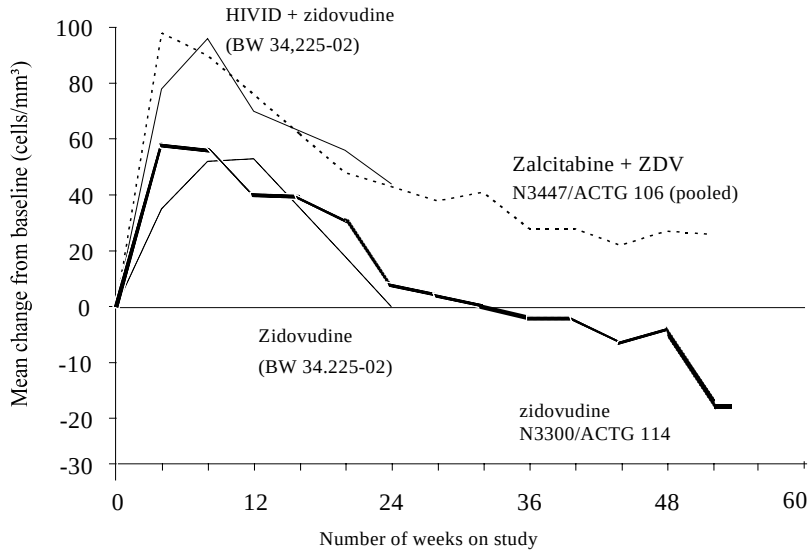
Results of the CD4 analyses are as follows:

1. *Mean Change From Baseline*: Results for changes in CD4 cell count from baseline are displayed in Figure 1 for BW 34,225-02, N3447/ACTG 106 and N3300/ACTG 114 (ZDV-monotherapy arm).

2. *Longitudinal Changes During Study*: In BW 34,225-02, 84% of patients receiving combination HIVID and zidovudine had an NAUC >1 at week 12 (89% at week 24) compared to 72% of patients receiving zidovudine monotherapy (200 mg q8h) at week 12 (68% at week 24). In a contemporary zidovudine-treated control group (N3300/ACTG 114), 87% of the zidovudine-treated patients had an NAUC >1 at week 12 (81% at week 24). In the open-label study N3447/ACTG 106, 97% of patients administered HIVID in combination with $\geq$300 mg/day of zidovudine had an NAUC >1 at weeks 12 and 24.

3. *Response*: In BW 34,225-02, 38% of patients receiving combination HIVID and zidovudine had a 50:50 response at week 24 compared to 21% of patients in the zidovudine-monotherapy group. In the zidovudine-contemporary control group (N3300/ACTG 114), 34% of patients had a 50:50 response at week 24. In N3447/ACTG 106, 70% of patients receiving HIVID combined with zidovudine ($\geq$300 mg/day) had a 50:50 response at week 24.

Figure 1- Mean change from baseline CD4



Number of patients					
Week	0	12	24	36	48
HIVID + ZDV (BW 34,225-02)	45	37	13	*	*
ZDV (BW 34,225-02)	47	37	17	*	*
ZDV (N3300)	262	220	206	176	143
HIVID + ZDV (N3447) (pooled)	36	31	29	27	23

Table 2. CD4 Response Analyses

STUDY	BW 34,225-02		N3300/ACTG 114 No Prior ZDV	N3447/ACTG 106 HIVID + ZDV
Dose	0.750mg + 200mg q8h HIVID + ZDV	200mg q8h ZDV[a]	200mg q4h ZDV[b]	Four Pooled Combination Arms[c]
Mean Peak	+94 cells mm^3	+53 cells/mm^3	+57 cells/mm^3	+97 cells/mm^3
Increase in CD4	(Week 8)	(Week 12)	(Week 4)	(Week 4)
Week 12				
NAUC >1	84%	72%	87%	97%
Median NAUC	1.4	1.2	1.50	2.37
25-25	-	-	47%	82%
50-50	-	-	29%	70%
75-75	-	-	13%	46%
Week 24				
NAUC >1	89%	68%	81%	97%
Median NAUC	1.5	1.3	1.39	2.10
25-25	51%	43%	54%	85%
50-50	38%	21%	34%	70%
75-75	31%	9%	18%	49%

a Dosage of ZDV used as not the currently approved dose and intervals of ZDV 200mg q4h for 4 weeks, followed by 100mg q4h.
b Reduced to 100mg q4h when dose was approved.
c The pooled concomitant regimens of HIVID + ZDV included:
A = HIVID 0.005mg/kg q8h + ZDV 100mg q8h
B = HIVID 0.005mg/kg q8h + ZDV 200mg q8h
D = HIVID 0.01mg/kg q8h + ZDV 100mg q8h
E = HIVID 0.01mg/kg q8h + ZDV 200mg q8h

1. c) ACTG 175

MONOTHERAPY vs COMBINATION THERAPY WITH NUCLEOSIDE ANALOGUES IN PATIENTS WITH HIV INFECTION WITH OR WITHOUT PRIOR ANTIRETROVIRAL EXPOSURE AND CD4 CELLS COUNTS ≥2 X 10^8 CELLS/L AND ≤5 X 10^8 CELLS/L

ACTG 175 was a randomised, double-blind trial in patients with no history of AIDS defining events other than minimal Kaposi's sarcoma. 2467 patients were enrolled in the study, of whom 1067 were naive to antiretroviral therapy or had received < 1 week of therapy and 1400 had received prior ZDV therapy (median >18 months). The median duration of follow-up was 135 weeks in the naive patients and 147 weeks for experienced patients. Patients were initially randomised to receive either ZDV (n=619), ddI (n=620), ZDV + ddI (n=613) or ZDV + ddC (n=615). Combined data is presented in Figure 2.

In the 1067 patients naive to prior ZDV therapy, the mean baseline CD4 count was 3.72 x 10^8 cells/L. Patients were randomised to receive either ZDV (n=269), ddI (n=268), ZDV + ddI (n=263) or ZDV + ddC (n=267). The clinical endpoints were defined as progression to AIDS or death. HIVID + ZDV was statistically superior to ZDV monotherapy ($p<0.001$) and ddI monotherapy ($p=0.043$) for the combined clinical/immunological endpoint. The use of HIVID in combination with ZDV in experienced patients is based on an analysis of 1400 patients with mean baseline CD4 counts of 3.38 x 10^8 cells/L. Patients were randomised to receive either ZDV (n=350), ddI (n=352), ZDV + ddI (n=350) or ZDV + ddC (n=348). For the combined clinical/immunological endpoint, HIVID + ZDV was significantly superior to continued ZDV monotherapy ($p=0.002$).

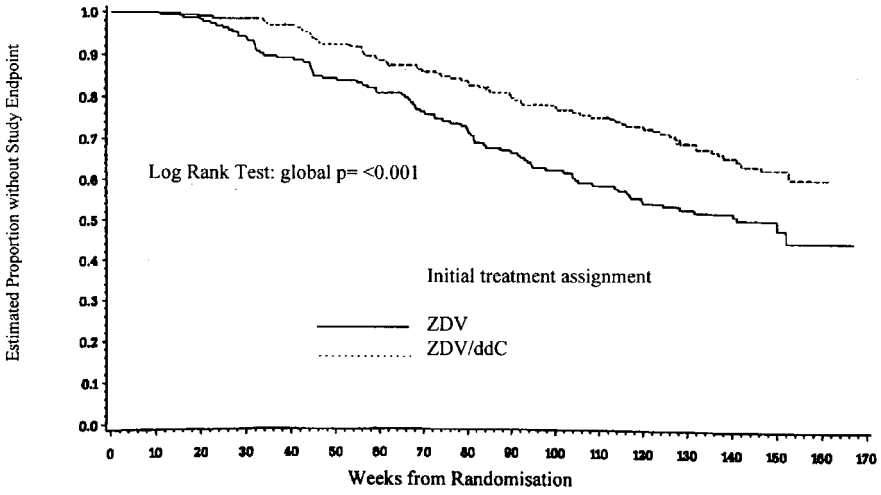
HIV RNA: Mean changes from baseline HIV RNA are summarised in Table 3.

Table 3 - Mean Changes in Log_{10} HIV RNA From Baseline*ACTG 175, Viral Load Substudy

	All patients		Antiretroviral-naive		Antiretroviral-experienced	
Treatment (n)	ZDV (74)	ZDV + HIVID (86)	ZDV (40)	ZDV + HIVID (50)	ZDV (34)	ZDV + HIVID (43)
Week 20	- 0.1	- 0.7	- 0.3	- 0.9	+ 0.1	- 0.5
Week 56	+ 0.1	- 0.6	- 0.2	- 0.8	+ 0.3	- 0.3

* The clinical significance of changes in HIV RNA during therapy is unknown.

Figure 2-
ACTG 175 : Estimated Proportion of Patients Surviving Without Progression to AIDS or 50% Decline in CD4 Count (All Patients)



2. Monotherapy Trials

HIVID was studied in two controlled comparative trials (N3300/ACTG 114 and N3492/ACTG 119) of patients with AIDS or advanced ARC (CD4 cell count ≤200 cells/mm^3), and a randomised, dose-comparison, expanded-access safety study (N3544) of HIVID in patients with advanced HIV disease who were intolerant to zidovudine or who showed evidence of clinical progression while on zidovudine therapy. Information from these monotherapy studies is included to describe the safety profile of HIVID (see ADVERSE REACTIONS).

The parameters of efficacy evaluated in the controlled comparative studies of HIVID included the clinical end points of survival and opportunistic infection. The expanded-access safety program (N3544) was designed primarily as a dose-comparison safety study.

2.a) N3300/ACTG 114
HIVID MONOTHERAPY IN ADULT PATIENTS WITH AIDS OR ADVANCED ARC AND ≤3 MONTHS OF PRIOR ZIDOVUDINE THERAPY: This study was a randomised, double-blind, parallel, controlled trial. Patients received either HIVID 0.750 mg q8h or zidovudine 200 mg q4h, later reduced to 100 mg q4h. 320 patients were randomised to receive HIVID and 315 to zidovudine. Median duration of treatment was 44 weeks (range: 1.1 to 96) and 53 weeks (range: 0.3 to 96), respectively. Median CD4 cell count at entry was 98.7 cells/mm^3 and 96.8 cells/mm^3 for the HIVID- and zidovudine-treatment groups, respectively.

This study was terminated on the basis of 1-year survival results that showed a significant difference in survival favouring the zidovudine group, with 59 deaths in the HIVID group versus 33 deaths in the zidovudine group (p=0.007, stratified Cox analysis). One hundred and thirty patients (41%) in the HIVID group and 95 patients (30%) in the zidovudine group progressed to a critical event at the time of the 1-year analysis (i.e., death or first occurrence of an AIDS-defining opportunistic infection or neoplasm or condition, p = 0.02).

2. b) N3492/ACTG 119

HIVID MONOTHERAPY IN ADULTS WITH AIDS OR ADVANCED ARC AND ≥48 WEEKS OF PRIOR ZIDOVUDINE THERAPY: This was a nine centre, randomised, open-label, parallel, controlled trial of HIVID. This trial enrolled patients whose CD4 cell counts were ≤200 cells/mm^3 at the time zidovudine was first started. Full enrolment was not achieved. Fifty-nine patients were randomised to receive HIVID 0.750 mg q8h and 52 patients to receive zidovudine 100 mg q4h. The median duration of treatment was 40 weeks for HIVID (range: 2.3 to 64) and 25 weeks for zidovudine (range: 1.1 to 57) at the time of the unscheduled analysis. Median CD4 cell counts at entry for the HIVID- and zidovudine-treatment groups were 103.7 cells/mm^3 and 85.5 cells/mm^3.

At the time of this analysis, there were 10 (17%) deaths in the HIVID-treatment group and 13 (25%) deaths in the zidovudine group (p= 0.52, stratified Cox analysis). Nineteen (33%) patients in the HIVID group and 17 (33%) patients in the zidovudine group progressed to a critical event (i.e., death or first occurrence of an AIDS-defining opportunistic infection, neoplasm or condition, p=0.95, stratified Cox analysis). Due to the small number of patients enrolled in this study, definitive conclusions cannot be reached**.**

Twelve (20%) patients in the HIVID group (including 7 patients with peripheral neuropathy) and 5 (10%) patients in the zidovudine group discontinued treatment due to adverse events (see PRECAUTIONS and ADVERSE REACTIONS).

2. c) N3544

EXPANDED-ACCESS SAFETY STUDY OF HIVID THERAPY IN ADULT PATIENTS WITH ADVANCED HIV DISEASE WHO ARE INTOLERANT TO ZIDOVUDINE OR HAD FAILED ZIDOVUDINE THERAPY: A randomised, open-label, dose-comparison safety study was initiated in patients with advanced HIV disease (CD4 cell count ≤200 cells/mm^3). An interim analysis was performed for 3479 patients, 1757 in the HIVID 0.375 mg q8h and 1722 in the HIVID 0.750 mg q8h groups, with a median duration of treatment of 16 weeks (range: 0.1 to 61). Mean CD4 cell counts at entry were similar for the 0.375 mg (83 cells/mm^3) and 0.750 mg (79 cells/mm^3) HIVID groups.

Two hundred seventy-nine patients discontinued for an adverse event, including 164 (5%) with peripheral neuropathy (97 in the high-dose group and 67 in the low-dose group) and 11 (0.3%) with pancreatitis (7 in the high-dose group and 4 in the low-dose group - see ADVERSE REACTIONS).

No statistically significant difference in survival was found for the deaths reported at the interim analysis. Subsequently, to better define survival in the two-dose groups, survival data on 3920 patients with follow-up information as of February 1, 1992**,** were validated by telephone survey. There was a total of 556 deaths, 296 in the low-dose group and 260 in the high-dose group (p= 0.59, Cox regression analysis).

INDICATIONS

HIVID is indicated for the treatment of HIV/AIDS.

Clinical studies indicate that zalcitabine can be used in combination with other anti-retroviral therapies (see **Clinical Trials**). There are no clinical data on the use of zalcitabine, either as monotherapy or in combination with other anti-retrovirals, in children younger than 12 years.

CONTRAINDICATIONS

HIVID is contraindicated in patients with clinically significant hypersensitivity to zalcitabine or to any of the excipients contained in the tablets.

HIVID is contraindicated in patients with severe hepatic impairment.

PRECAUTIONS

Information regarding the safety of combined HIVID and zidovudine therapy is limited; the safety profile of HIVID has been characterised primarily in monotherapy trials. The safety profile of HIVID in children younger than 13 years of age and in asymptomatic HIV-infected individuals has not been established.

Patients receiving HIVID or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore, should remain under close clinical observation by physicians experienced in the treatment of patients with HIV-associated diseases.

1. *PERIPHERAL NEUROPATHY*:
   THE MAJOR CLINICAL TOXICITY OF HIVID IS PERIPHERAL NEUROPATHY, WHICH OCCURRED IN 17% TO 31% OF SUBJECTS TREATED IN PHASE II/III MONOTHERAPY STUDIES DEPENDING ON SEVERITY AND PRESUMED RELATIONSHIP TO DRUG. BY COMPARISON, NEUROPATHY OCCURRED IN 0% TO 12% OF ZIDOVUDINE-TREATED PATIENTS. THESE DATA ARE SUMMARISED BELOW IN TABLES 3 AND 5. DATA ARE VERY LIMITED ON THE OCCURRENCE OF PERIPHERAL NEUROPATHY WITH THE COMBINED USE OF HIVID AND ZIDOVUDINE.

   HIVID-related peripheral neuropathy is a sensorimotor neuropathy characterised initially by numbness and burning dysesthesia involving the distal extremities. These symptoms may be followed by sharp shooting pains or severe continuous burning pain if the drug is not withdrawn. The neuropathy may progress to severe pain requiring narcotic analgesics and persist for months, especially if HIVID is not stopped promptly. In some patients, symptoms of neuropathy may initially progress despite discontinuation of HIVID. With prompt discontinuation of HIVID, the neuropathy is usually slowly reversible.

   HIVID should be used with particular caution in individuals with pre-existing peripheral neuropathy of any aetiology or in patients with low CD4 cell counts (CD4 <50 cells/mm^3) for whom the risk of developing peripheral neuropathy while on HIVID therapy is greater. Careful monitoring is strongly recommended for these individuals. Individuals with moderate or severe peripheral neuropathy, as evidenced by symptoms accompanied by objective findings, are advised to avoid HIVID.

   HIVID should be stopped promptly when moderate discomfort from numbness, tingling, burning or pain of the extremities progresses, or any related symptoms occur that are accompanied by an objective finding. In a large clinical trial, moderate peripheral neuropathy requiring HIVID interruption was defined as discomfort of the lower extremities (requiring non-narcotic analgesics) that was bilateral and persisted for $\geq$3 days, or mild symptoms accompanied by the loss of a previously present Achilles reflex. Once symptoms resolved to mild intensity, rechallenge with half-dosage was permitted.

Severe peripheral neuropathy requiring permanent discontinuation of HIVID has been defined in clinical trials as any severe discomfort of the extremities requiring narcotic analgesics or moderate discomfort progressing for ≥ 1 week.

2. *PANCREATITIS:*

DOCUMENTED FATAL PANCREATITIS HAS BEEN OBSERVED WITH THE ADMINISTRATION OF HIVID ALONE OR THE COMBINATION OF HIVID WITH ZIDOVUDINE. PANCREATITIS IS AN UNCOMMON COMPLICATION OF HIVID MONOTHERAPY, OCCURRING IN <1% OF PATIENTS. The occurrence of asymptomatic elevated serum amylase of any aetiology while on HIVID monotherapy was also <1%. Of 633 patients treated with HIVID in the expanded-access safety study (N3544) who had a history of prior pancreatitis or increased amylase, 10 (1.6%) developed pancreatitis and an additional 10 (1.6%) developed asymptomatic elevated serum amylase. There was no apparent difference in the occurrence of pancreatitis between the two doses of HIVID in the expanded-access trial N3544.

Caution should be exercised when administering HIVID to any patient with a history of pancreatitis or known risk factor for the development of pancreatitis. To date, in an ongoing, blinded, combination study, one patient has died of fulminant pancreatitis possibly related to HIVID and/or zidovudine. Another patient who received concomitant intravenous pentamidine and HIVID died of fulminant pancreatitis possibly related to the concomitant use of HIVID and intravenous pentamidine.

Patients with a history of pancreatitis or history of elevated serum amylase should be followed more closely while on HIVID therapy. The significance of an asymptomatic increase in serum amylase levels in HIV-infected patients prior to starting HIVID or while on HIVID is unclear. Treatment with HIVID should be interrupted in the setting of a rising serum amylase level associated with dysglycemia, rising triglyceride level, decreasing serum calcium or other parameters or symptoms suggestive of impending pancreatitis, until a clinical diagnosis is reached. Treatment with HIVID should also be interrupted if treatment with another drug known to cause pancreatitis (e.g., intravenous pentamidine) is required (see *Drug Interactions*).

Treatment with HIVID should be stopped immediately if nausea, vomiting, abdominal pain or other symptoms suggestive of pancreatitis develop, until a definitive diagnosis can be established. HIVID should be restarted only after pancreatitis has been ruled out. If clinical pancreatitis develops during HIVID administration, it is recommended that HIVID be permanently discontinued.

3. *LIPODYSTROPHY:*

Combination antiretroviral therapy is associated with redistribution of body fat in some patients. It has also been associated with metabolic abnormalities such as hypertriglyceridemia, hypercholesterolaemia, insulin resistance, and hyperglycemia. The severity of these metabolic abnormalities differ within and between the three classes of antiretrovirals (PIs, NRTIs, and NNRTIs).

A higher risk of lipodystrophy has been associated with older age, longer duration of antiretroviral treatment, stavudine use, hypertriglyceridemia, and hyperlactaemia. Clinical examination should include evaluation for physical signs of fat redistribution.

Measurement of serum lipids and blood glucose is recommended. In case of such metabolic abnormalities, a switch in antiretroviral therapy may be considered, and/or the addition of treatments designed to directly correct these abnormalities (e.g. lipid lowering agents). The

mechanisms of these events and long-term consequences, such as an increased risk of cardiovascular disease, are currently unknown (see ADVERSE REACTIONS).

4. OTHER SERIOUS TOXICITIES:

a) *Oesophageal Ulcers*: Infrequent cases of oesophageal ulcers have been attributed to HIVID therapy. Interruption of HIVID should be considered in patients who develop oesophageal ulcers that do not respond to specific treatment for opportunistic pathogens in order to assess a possible relationship to HIVID.

b) *Cardiomyopathy/Congestive Heart Failure*: Cardiomyopathy and congestive heart failure in patients with AIDS have been associated with the use of nucleoside antiretroviral agents. Infrequent cases have been reported in patients receiving HIVID. In one case, the investigator considered that the exacerbation of pre-existing cardiomyopathy was possibly related to HIVID. Treatment with HIVID in patients with baseline cardiomyopathy or history of congestive heart failure should be approached with caution.

c) *Anaphylactoid Reaction:* There has been one report of an anaphylactoid reaction occurring in a patient receiving both HIVID and zidovudine in an alternating regimen. In addition, there have been reports of several cases of urticaria without other signs of anaphylaxis.

d) Rare occurrences of lactic acidosis in the absence of hypoxemia, and severe hepatomegaly with steatosis have been reported with the use of nucleoside analogues, including zidovudine and HIVID, and are potentially life-threatening. In addition, cases of hepatic failure in association with underlying Hepatitis B and HIVID monotherapy have been reported. Treatment with HIVID in patients with pre-existing liver disease, liver enzyme abnormalities, a history of ethanol abuse or hepatitis, should be approached with caution. HIVID should be interrupted or discontinued in the setting of deterioration of liver function tests, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis.

e) Severe oral ulcers occurred in approximately 3% of patients receiving HIVID in two studies; less severe oral ulcerations have occurred at higher frequencies in other clinical trials.

BECAUSE SEVERE ADVERSE EFFECTS MAY BE ATTRIBUTABLE TO EITHER THE HIVID OR THE ZIDOVUDINE COMPONENTS OF COMBINATION THERAPY, OR TO THEIR COMBINATION, THE COMPLETE PRODUCT INFORMATION FOR ZIDOVUDINE SHOULD BE CONSULTED BEFORE INITIATION OF COMBINATION THERAPY OR REINSTITUTION OF MONOTHERAPY WITH ZIDOVUDINE FOLLOWING AN ADVERSE REACTION.

Use in Patients with Renal Impairment

Patients with renal impairment (estimated creatinine clearance <55 mL/min) may be at a greater risk of toxicity from HIVID due to decreased drug clearance (see DOSAGE AND ADMINISTRATION).

Use in Patients with Hepatic Impairment

The use of HIVID by patients with hepatic impairment has not been studied. In the absence of such studies, caution should be exercised in patients with mild to moderate impairment, as increases in liver enzymes may occur (see CONTRAINDICATIONS). The use of HIVID may be associated with exacerbation of hepatic dysfunction, especially in individuals with pre-existing liver disease or with a history of ethanol abuse. Of 85 patients in the expanded-access safety study N3544 with a prior history of liver function test (LFT) elevation before starting HIVID, 10 (12%) developed increases in LFTs >5 times the upper limit of normal while on HIVID. Cases of hepatic failure in association with underlying hepatitis B and HIVID monotherapy have been reported. Treatment with HIVID in patients with pre-existing liver disease, liver enzyme abnormalities, a history of ethanol abuse or

hepatitis, should be approached with caution. Such patients should be closely monitored by their physician for signs and symptoms of liver toxicity. Zidovudine use has also been associated with increases in liver function tests. HIVID should be interrupted or discontinued in the setting of deterioration of liver function tests, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis.

Laboratory Tests
Complete blood counts and clinical chemistry tests should be performed prior to initiating combination therapy with HIVID and zidovudine and at appropriate intervals thereafter. Baseline testing of serum amylase and triglyceride levels should be performed in individuals with a prior history of pancreatitis, increased amylase, those on parenteral nutrition or with a history of ethanol abuse.

Carcinogenesis, Mutagenesis and Impairment of Fertility:
Carcinogenesis: Zalcitabine was administered in the diet to CRL:CD-1®(ICR)Br mice (0, 3, 83, 250 mg/kg/day) and CDF®(F-344)/CrlBR rats (3, 28, 83, 250 mg/kg/day) for 2 years. Plasma zalcitabine $AUC_{0\text{-}24h}$ values at the respective high-doses were 704x (mice) and 833x (rats) the clinical $AUC_{0\text{-}24h}$. The incidence of thymic lymphoma was significantly increased in female CD-1 mice after 2 years of treatment. No increases in tumour incidences were observed in male mice or in rats of either sex. Independent published studies showed that gavage administration of zalcitabine 1000 mg/kg/day to B6C3F1 mice for 3 months or to NIH Swiss mice for 3 or 6 months induced increased incidences of thymic lymphoma. Although the relevance of these findings to humans receiving therapeutic doses of zalcitabine is questionable, the currently available evidence does not permit them to be entirely dismissed.

Mutagenesis: Ames tests using seven different tester strains, were performed with no evidence of mutagenicity. Chinese hamster lung cell tests and mouse lymphoma cell tests were performed and there was no evidence of mutagenicity. However, it is unknown whether zalcitabine was phosphorylated to its active form in these systems which use standard methods of metabolic activation. An unscheduled DNA synthesis assay was performed in rat hepatocytes with no increases in DNA repair. Human peripheral blood lymphocytes were exposed to zalcitabine in the absence and in the presence of metabolic activation, and at doses of 1.5 mcg/mL and higher, dose-related increases in chromosomal aberration were seen. Oral doses of zalcitabine at 2500 and 4500 mg/kg were clastogenic in the mouse micronucleus assay.

Impairment of Fertility: Fertility and reproductive performance were assessed in rats at plasma concentrations up to 2142 times those achieved with the maximum recommended human dose (MRHD) based on AUC measurements. No adverse effects on rate of conception or general reproductive performance were observed. The highest dose was associated with embryolethality and evidence of teratogenicity. The next lower dose studied (plasma concentrations equivalent to 485 times the MRHD) was associated with a lower frequency of embryotoxicity but no teratogenicity.

Use in Pregnancy (Category D).
Zalcitabine was teratogenic in rats at oral doses of 2000mg/kg (and possibly at 400mg/kg). In mice, zalcitabine administered orally on days 6-15 of gestation was teratogenic at doses of 1000mg/kg (and possibly 400mg/kg). In both species, teratogenic effects were observed at doses which did not produce overt maternal toxicity. In another study, no adverse effects were observed on the fertility of male and female rats treated with oral doses of up to 2000mg/kg/day of zalcitabine.

Safe use in human pregnancy has not been established in adequate and well controlled studies. Fertile women should not receive zalcitabine unless they are using effective contraception during the therapy

period. Zalcitabine should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Nonteratogenic Effects: Increased embryolethality was observed in pregnant mice at doses 2730 times the MRHD and in rats above 485 times the MRHD (based on AUC measurements). Average foetal body weight was significantly decreased in mice at doses of 1365 times the MRHD and in rats at 2142 times the MRHD.

Use in Lactation
It is not known whether zalcitabine is excreted in human milk. Because many drugs are excreted in human milk and the potential exists for serious adverse reactions from HIVID in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. It is currently recommended practice that HIV-infected women do not breastfeed infants regardless of the use of anti-retroviral agents.

Use in Paediatrics
Safety and effectiveness of HIVID in combination with zidovudine or as monotherapy in HIV-infected children younger than 13 years of age has not been established.

Use in the Elderly
Specific information about the use of zalcitabine in the elderly is not available. In such patients special attention should be paid to renal and hepatic function information.

Effects on Ability to Drive and Use Machines
There is no clinical evidence that HIVID may alter the patient's ability to drive or use machines. However, the adverse event profile should be taken into account (see ADVERSE REACTIONS).

Drug Interactions

Lamivudine: *In vitro* studies in peripheral blood mononuclear cells, U-937 and Molt-4 cells revealed that lamivudine significantly inhibited zalcitabine phosphorylation in a dose dependent manner. Effects were already seen with doses corresponding to relevant plasma levels in humans, and the intracellular phosphorylation of zalcitabine to its three metabolites (including the active zalcitabine triphosphate metabolite) was significantly inhibited. Zalcitabine inhibited lamivudine phosphorylation at high concentration ratios (10 and 100), however, it is considered to be unlikely that this decrease of phosphorylated lamivudine concentration is of clinical significance, as lamivudine is a more efficient substrate for deoxycytidine kinase than zalcitabine. These *in vitro* studies suggest that concomitant administration of zalcitabine and lamivudine in humans may result in sub-therapeutic concentrations of active phosphorylated zalcitabine, which may lead to a decreased antiretroviral effect of zalcitabine. It is unknown how the effect seen in these *in vitro* studies translates into clinical consequences. Concomitant use of HIVID with lamivudine is not recommended.

Drugs associated with peripheral neuropathy: The concomitant use of HIVID with drugs that have the potential to cause peripheral neuropathy should be avoided where possible. Drugs which have been associated with peripheral neuropathy include chloramphenicol, cisplatinum, dapsone, disulfiram, ethionamide, glutethimide, gold, hydralazine, iodoquinol, isoniazid, metronidazole, nitrofurantoin, phenytoin, ribavirin and vincristine. Concomitant use of HIVID with didanosine is not recommended.
Amphotericin, Foscarnet and Aminoglycosides: Drugs such as amphotericin, foscarnet and aminoglycosides, may increase the risk of developing peripheral neuropathy or other HIVID toxicities by interfering with the renal clearance of zalcitabine (and thereby raising systemic exposure). Patients

who require the use of one of these drugs with HIVID and zidovudine should have frequent clinical and laboratory monitoring with dosage adjustment for any significant change in renal function.

Intravenous Pentamidine: Treatment with HIVID should be interrupted when the use of a drug that has the potential to cause pancreatitis is required. One death due to fulminant pancreatitis possibly related to HIVID and intravenous pentamidine was reported. If intravenous pentamidine is required to treat Pneumocystis carinii pneumonia, treatment with HIVID should be interrupted (see PRECAUTIONS).

Probenecid or Cimetidine: Concomitant administration of probenecid or cimetidine decreases the elimination of zalcitabine. Patients receiving these drugs in combination with HIVID should be monitored for signs of toxicity and the dose of HIVID reduced if required.

Magnesium/Aluminium- containing antacids: Co-administered magnesium/aluminium antacids reduce absorption of HIVID by approximately 25%. Antacids should not be administered within 2 hours of a dose of HIVID.

Metoclopramide: Bioavailability is mildly reduced (approximately 10%) when zalcitabine and metoclopramide are coadministered.

Doxorubicin: Doxorubicin caused a decrease in zalcitabine phosphorylation (>50% inhibition of total phosphate formation) in U937/Molt-4 cells with the implication of decreased zalcitabine activity because of lessened active metabolite formation.

Trimethoprim: Trimethoprim significantly increases the AUC (37%) and decreases the Clr/F (36%) of zalcitabine because of inhibition of renal tubular excretion of zalcitabine by trimethoprim (zalcitabine does not affect the disposition of trimethoprim).

Drugs having potentially no significant interactions

Zidovudine: No significant pharmacokinetic interaction betweemn ZDV and zalcitabine was observed when administered as single doses of 1.5 mg and 200 mg, respectively. Zalcitabine also has no significant effect on the intracellular phosphorylation of ZDV, as shown *in vitro* in peripheral blood mononuclear cells or in two other cell lines (U937 and Molt-4). In the same study it was shown that didanosine and stavudine had no significant effect on the intracellular phosphorylation of zalcitabine in peripheral blood mononuclear cells.

No significant pharmacokinetic interactions were observed during two clinical trials in which HIVID was administered in combination with ZDV+saquinavir, or ZDV alone.

Possible interactions of HIVID with other concomitant medications have not been formally investigated.

ADVERSE REACTIONS

The following data on adverse reactions are based primarily on the administration of HIVID at the recommended dose, as a single agent, to patients with AIDS or advanced ARC (CD4 cell count ≤200 cells/mm^3). The majority of adverse events were mild to moderate in intensity. Individual undesirable effects are unchanged during combination therapy. The major undesirable effect of HIVID is peripheral neuropathy.

The percentage of the 320 patients taking HIVID as monotherapy in the double-blind study N3300 that experienced adverse drug reactions (considered to be at least remotely related to HIVID by the investigator) is compared to the frequency of adverse reactions that were reported in the patients taking zidovudine monotherapy in the same study. Only adverse events with a frequency of equal to or higher than 1% in the zalcitabine monotherapy arm are listed in Table 4 below.

Table 4. Adverse reactions that occurred in ≥1% of patients taking zalcitabine in N3300

Body system Adverse event	**Zalcitabine arm** N=320	**Zidovudine arm** N=318
Central and peripheral nervous system disorders		
Peripheral neuropathy (see PRECAUTIONS)	41.6%	22.6%
Hypoesthesia in lower and upper extremities	30.6%	12.9%
Paresthesia in lower and upper extremities	30.7%	13.2%
Pain in lower and upper extremities	25.1%	9.1%
Weakness in lower and upper extremities	13.5%	7.5%
Reflexes decreased	3.4%	1.9%
Neuropathy	2.8%	0
Decreased sensation	2.8%	1.3%
Hypoesthesia	2.8%	0.9%
Gait abnormal	1.9%	0
Sensory disturbance	1.9%	1.6%
Absent Achilles tendon reflex	1.3%	0
Headache	17.8%	19.8%
Dizziness	5.0%	4.7%
Gastrointestinal system disorders		
Nausea	13.1%	24.5%
Stomatitis ulcerative	12.8%	6.3%
Anorexia	8.4%	7.2%
Diarrhoea	7.5%	7.9%
Mouth dry	5.0%	1.6%
Vomiting	6.9%	7.5%
Dysphagia	4.7%	0.3%
Abdominal pain	5.9%	6.0%
Stomatitis aphthous	3.8%	1.3%
Constipation	1.9%	0.9%
Dyspepsia	1.9%	2.2%
Glossitis	1.9%	0
Oesophageal pain	1.9%	0
Oesophageal ulcer (see PRECAUTIONS)	1.9%	0
Stomatitis	1.6%	0.6%
Skin and appendages disorders		
Rash	15.6%	10.4%
Pruritus	9.4%	9.4%
Night sweats	3.4%	2.8%
Dermatitis	2.2%	2.2%
Musculoskeletal system disorders		
Myalgia	12.2%	10.1%
Arthralgia	3.8%	1.3%
Pain feet	1.6%	0
Stiff neck	1.6%	0

Body system Adverse event	**Zalcitabine arm** N=320	**Zidovudine arm** N=318
Body as a whole		
Fatigue	15.0%	16.7%
Weight decrease	6.6%	3.1%
Fever	6.5%	5.0%
Pain	2.5%	0.3%
Rigors	2.5%	3.5%
Chest pain	1.9%	0.6%
Back pain	1.3%	0.3%
Respiratory disorders		
Pharyngitis	5.3%	1.6%
Coughing	4.1%	2.5%
Dyspnea	2.2%	1.9%
Psychiatric disorders		
Confusion	2.8%	0.3%
Concentration impaired	1.6%	2.2%
Depression	1.3%	0.6%
Insomnia	1.3%	1.9%
Vision disorders		
Hypoesthesia	2.8%	0.9%
Xerophthalmia	1.3%	0.6%
Heart rate and rhythm disorders		
Heart racing	1.3%	1.3%

Marked laboratory abnormalities (grade III and IV) that occurred in more than 2% of the patients in the zalcitabine arm of study N3300 are presented in Table 5 below.

Table 5. Laboratory abnormalities

Laboratory abnormality	**Zalcitabine arm** N=320	**Zidovudine arm** N=318
SGPT increased	8.2%	6.8%
Low absolute neutrophil count	5.8%	15.5%
High absolute eosinophil count	5.8%	2.3%
SGOT increased	5.6%	4.9%
Low haemoglobin	3.8%	12.4%
Low platelets	3.8%	1.9%
Low white blood cell count	3.1%	5.1%
Alkaline phosphatase increased	2.8%	2.3%
Total bilirubin increased	2.2%	1.0%

Clinical adverse events in the HIVID and zidovudine concomitant combination Protocol N3447/ACTG 106 are included in Table 6.

Table 6. Percentage of Patients with Clinical Adverse Experiences Considered Possibly or Probably Related to Study Drug Occurring in >3% of Patients

	HIVID + ZDV Combination Trial Pooled Concomitant Regimens[a]	N3447/ACTG 106[b] No Prior ZDV n=47
Body System/Adverse Event	mild/mod/sev	mod/sev
Peripheral Neuropathy	See Table 4	
Gastrointestinal		
Nausea	36.2%	8.5%
Oral Ulcers	27.7%	4.3%
Abdominal Pain	21.3%	8.5%
Diarrhoea	14.9%	10.6%
Vomiting	14.9%	2.1%
Anorexia	12.8%	6.4%
Constipation	6.4%	2.1%
Skin and Appendages		
Pruritus	14.9%	4.3%
Rash	14.9%	2.1%
Erythematous Rash	6.4%	2.1%
Night Sweats	6.4%	2.1%
Maculopapular Rash	4.3%	2.1%
Follicular Rash	4.3%	0.0%
Central and Periph NS		
Headache	38.3%	8.5%
Musculoskeletal		
Myalgia	14.9%	2.1%
Arthralgia	8.5%	2.1%
Body as a Whole		
Fatigue	34.0%	8.5%
Fever	14.9%	2.1%
Rigours	8.5%	2.1%
Chest Pain	6.4%	2.1%
Weight Decrease	6.4%	4.3%
Respiratory		
Pharyngitis	8.5%	2.1%

a Excluded are 9 patients who received ZDV alone for the greater part of the study. Only 8 patients were treated with the recommended combination regimen; all other patients were treated at lower doses of HIVID and/or ZDV.

b Median duration of treatment ranged from 22 to 92 weeks among the arms.

Other additional relevant adverse events that have been reported from studies, in which HIVID was administered as mono- or combination therapy, are given below. Unless otherwise stated, all adverse events reported below occurred in < 1% of HIVID-treated patients:

Body as a whole: asthenia, cold extremities, oedema, malaise, substernal chest pain.

Cardiovascular disorders: atrial fibrillation, hypertension, palpitation, syncope, tachycardia.

Skin and appendages disorders: acne, alopecia, bullous eruptions, erythematous papules, flushing, urticaria, maculopapular rash, follicular rash, skin lesions, increased sweating.

Gastrointestinal disorders: distended abdomen, eructation, oesophagitis, flatulence, gastritis, gastrointestinal haemorrhage, glossitis, gum disorder, haemorrhoids, oral ulcers, pancreatitis, rectal haemorrhage, rectal ulcers, salivary gland enlargement, tongue ulceration, left quadrant pain.

Central and peripheral nervous system disorders: abnormal coordination, ataxia, Bell's palsy, convulsions, seizures, dysphonia, hyperkinesia, hypertonia, hypokinesia, migraine, neuralgia, neuritis, stupor, tremor, twitching, vertigo.

Psychiatric disorders: agitation, amnesia, anxiety, dementia, depersonalization, emotional lability, euphoria, manic reaction, nervousness, somnolence, hallucination, abnormal thinking, abnormal crying.

Liver and biliary disorders: abnormal hepatic function, hepatitis, hepatocellular damage, jaundice.

Metabolic and nutritional disorders: amylase increased, hyperuricemia, gout, diabetes mellitus, hyperglycaemia, hypocalcaemia, impotence, hot flushes.

Endocrine disorders: epistaxis.

Respiratory disorders: cyanosis, flu-like symptoms.

Special senses and vision disorders: abnormal vision, deafness, ear blockage, eye abnormalities, eye pain, burning eyes, itching eyes, loss of taste, parosmia, taste perversion, tinnitus.

Urinary disorders: abnormal renal function, acute renal failure, micturition frequency, polyuria, renal calculus, renal cyst, toxic nephropathy.

Musculoskeletal disorders: arthritis, arthropathy, myositis, muscle weakness, musculoskeletal pain, shoulder pain, leg cramps, arm pain, wrist pain.

Post-marketing Experience

Body as a whole: hypersensitivity reactions (very rare)

Cardiovascular disorders: cardiomyopathy (very rare), congestive heart failure (very rare).

Metabolic and nutritional disorders: lactic acidosis (very rare). Redistribution of body fat including peripheral wasting, facial wasting, central obesity, dorso-cervical fat enlargement (buffalo hump), breast enlargement and "Cushingoid appearance" have been observed in patients taking antiretroviral therapy.

Liver and biliary disorders: hepatic failure (very rare), hepatomegaly (very rare), hepatic steatosis (very rare).

DOSAGE AND ADMINISTRATION

The recommended combination regimen is one 0.750 mg tablet of HIVID orally, administered concomitantly with 200 mg of zidovudine every 8 hours (2.25 mg HIVID total daily dose and 600 mg zidovudine total daily dose).

The recommended dosage of HIVID as monotherapy is one 0.750 mg tablet every eight hours.

Absorption of HIVID is decreased with food (see Pharmacokinetics). The clinical relevance of this decrease is unknown.

Renal Impairment: Dose adjustment in patients with renal impairment should be considered as follows: estimated creatinine clearance 10 to 40 mL.min- reduce the HIVID dose to 0.750 mg every 12 hours; estimated creatinine clearance <10 mL/min- reduce the HIVID dose to 0.750 mg once a day.

Monitoring of Patients: Periodic complete blood counts and clinical chemistry tests should be performed. Serum amylase levels should be monitored in those individuals who have a history of elevated amylase, pancreatitis, ethanol abuse, who are on parenteral nutrition, or who are otherwise at high risk of pancreatitis. Careful monitoring for signs or symptoms suggestive of peripheral neuropathy is recommended, particularly in individuals with pre-existing peripheral neuropathy of any aetiology or a low CD4 cell count (see PRECAUTIONS).

Dose Adjustment for Combination Therapy with HIVID and Zidovudine: For recipients of combination therapy with HIVID and zidovudine, dose adjustments for either drug should be based on the known toxicity profile of the individual drugs. For HIVID-associated toxicities (e.g., peripheral neuropathy, severe oral ulcers), HIVID should be interrupted or dose reduced (see PRECAUTIONS and PRECAUTIONS). For patients experiencing presumed zidovudine-related toxicities (e.g., anaemia, granulocytopenia), zidovudine should be interrupted or the dose reduced first. For any interruption of HIVID, and especially if HIVID is permanently discontinued, the zidovudine dosage schedule should be adjusted from 200mg q8h to 100mg q4h as recommended in the complete product information for zidovudine. FOR SEVERE TOXICITIES OR TOXICITIES IN WHICH THE CAUSATIVE DRUG IS UNCLEAR OR THOSE PERSISTING AFTER DOSE INTERRUPTION OR REDUCTION OF ONE DRUG, THE OTHER DRUG SHOULD ALSO BE INTERRUPTED OR DOSE REDUCED. PHYSICIANS SHOULD REFER TO THE COMPLETE PRODUCT INFORMATION FOR ZIDOVUDINE FOR A DESCRIPTION OF KNOWN ZIDOVUDINE-ASSOCIATED ADVERSE REACTIONS.

Patients developing moderate discomfort with signs or symptoms of peripheral neuropathy (e.g., numbness, tingling, hypaesthesia, burning or shooting pains of the lower or upper extremities, or loss of vibratory sense or ankle reflex) should stop HIVID, especially when these symptoms are bilateral and progress for >72 hours. HIVID-associated peripheral neuropathy may continue to worsen despite interruption of HIVID. HIVID should be reintroduced at 50% dose - 0.375 mg q8h only if all findings related to peripheral neuropathy have improved to mild symptoms. HIVID should be permanently discontinued when patients experience severe discomfort related to peripheral neuropathy or moderate discomfort progressing for $\geq$ 1 week. If other moderate to severe clinical adverse reactions or laboratory abnormalities (such as increased liver function tests) occur, then both HIVID and zidovudine should be interrupted until the adverse reaction abates. Either zidovudine monotherapy or HIVID and zidovudine therapy should then be carefully reintroduced at lower doses if appropriate. If adverse reactions recur at the reduced dose, therapy should be discontinued. The minimum effective dose of HIVID in combination with zidovudine for the treatment of adult patients with advanced HIV infection has not been established.

In patients with poor bone marrow reserve, particularly those patients with advanced symptomatic HIV disease, frequent monitoring of haematologic indices is recommended to detect serious anaemia or granulocytopenia (see PRECAUTIONS). Zidovudine-related toxicities, such as significant anaemia (haemoglobin of <75 g/L or reduction of >25% of baseline) and/or significant granulocytopenia (granulocyte count of $<7.5 \times 10^8$ cells/L or reduction of >50% from baseline), may require a treatment interruption of HIVID and zidovudine until evidence of marrow recovery is observed (see PRECAUTIONS). For less severe anaemia or granulocytopenia, a reduction in daily dose of zidovudine may be adequate. In patients who experience haematologic toxicity, reduction in haemoglobin may occur as early as 2 to 4 weeks after initiation of therapy, and granulocytopenia usually occurs after 6 to 8 weeks of therapy. In patients who develop significant anaemia, dose modification does not necessarily eliminate the need for transfusion. If marrow recovery occurs following dose modification, gradual increases in dose may be appropriate depending on haematologic indices and patient tolerance. For more details, refer to the complete product information for zidovudine.

OVERDOSAGE

***Acute Overdosage*:** There is little experience with acute HIVID overdosage and the sequelae are unknown. There is no known antidote for HIVID overdosage. It is not known whether zalcitabine is dialysable by peritoneal dialysis or haemodialysis.

***Chronic Overdosage*:** In an initial dose-finding study in which zalcitabine was administered at doses 25 times (0.25 mg/kg q8h) the currently recommended dose, one patient discontinued HIVID after one and one-half weeks of treatment subsequent to the development of a rash and fever.

In the early Phase I studies, all patients receiving zalcitabine at approximately 6 times the current total daily recommended dose experienced peripheral neuropathy by week 10. Eighty percent of patients who received approximately 2 times the current total daily recommended dose experienced peripheral neuropathy by week 12.

PRESENTATION

0.375 mg film-coated tablets (beige, oval, imprinted HIVID 0.375 on one side and ROCHE on the other side): 100s.

0.750 mg film-coated tablets (grey, oval imprinted HIVID 0.750 on one side and ROCHE on the other side): 100s.

SPONSOR

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