

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-154 / S-009

20-155 / S-007

20-156 / S-007

Trade Name: Videx

Generic Name: (didanosine)

Sponsor: Bristol Meyer Squibb Company

Approval Date: April 27, 1997

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APPROVAL LETTER

30

APR 27 1994

NDA 20-154 -S009
NDA 20-155 -S007
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Bristol-Myers Squibb Company
Attention: Sue Behling
Regulatory Affairs
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

Dear Ms. Behling:

Reference is made to your supplemental New Drug Application (NDA) dated June 25, 1993, submitted pursuant to section 505 (b) of the Federal Food, Drug, and Cosmetic Act for the product VIDEX® (didanosine) chewable/dispersible buffered tablets, buffered powder for oral solution, pediatric powder for oral solution.

We also acknowledge receipt of your additional communications dated September 10, 1993, November 22, 1993, December 21, 1993, and March 18, 1994.

We have completed the review of this supplemental application, and have concluded that it is approvable. Before the application may be approved, however, it will be necessary for you to submit final printed labeling.

Please submit twelve copies of the final printed labels and other labeling, seven of which are individually mounted on heavy-weight paper or similar material.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of the promotional material and the package insert directly to:

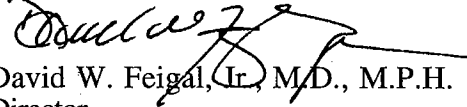
Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

Within ten days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

We remind you that you must comply with the requirements for an approved NDA as set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Mr. John Mahoney, Consumer Safety Officer, at (301) 443-9553.

Sincerely yours,



David W. Feigal, Jr., M.D., M.P.H.
Director

Division of Antiviral Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

4-22-94

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LABELING

P9691-02

Rx only

VIDEX® (didanosine)

VIDEX® (didanosine) Chewable/Dispersible Buffered Tablets

VIDEX® (didanosine) Buffered Powder for Oral Solution

VIDEX® (didanosine) Pediatric Powder for Oral Solution

WARNING

PANCREATITIS, WHICH HAS BEEN FATAL IN SOME CASES, HAS OCCURRED DURING THERAPY WITH VIDEX. VIDEX USE SHOULD BE SUSPENDED IN PATIENTS WITH SIGNS OR SYMPTOMS OF PANCREATITIS AND DISCONTINUED IN PATIENTS WITH CONFIRMED PANCREATITIS (SEE WARNINGS).

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

DESCRIPTION

VIDEX is the brand name for didanosine (ddl), a synthetic purine nucleoside analogue active against the Human Immunodeficiency Virus (HIV). VIDEX Chewable/Dispersible Buffered Tablets are available for oral administration in strengths of 25, 50, 100, or 150 mg of didanosine. Each tablet is buffered with calcium carbonate and magnesium hydroxide. VIDEX tablets also contain aspartame, sorbitol, microcrystalline cellulose, polyplasdone, mandarin-orange flavor and magnesium stearate.

VIDEX (didanosine) Buffered Powder for Oral Solution is supplied for oral administration in single-dose packets containing 100, 167, or 250 mg of didanosine. Packets of each product strength also contain a citrate-phosphate buffer (composed of dibasic sodium phosphate, sodium citrate, and citric acid) and sucrose.

VIDEX Pediatric Powder for Oral Solution is supplied for oral administration in 4- or 8-ounce glass bottles containing 2 or 4 grams of didanosine, respectively.

The chemical name for didanosine is 2',3'-dideoxyinosine. The structural formula is:

Didanosine is a white crystalline powder with the molecular formula $C_{10}H_{12}N_4O_3$ and a molecular weight of 236.2. The aqueous solubility of didanosine at 25°C and pH of approximately 6 is 27.3 mg/mL. Didanosine is unstable in acidic solutions. For example, at pH < 3 and 37°C, 10% of didanosine decomposes to hypoxanthine in less than 2 minutes.

MICROBIOLOGY

Mechanism of Action

Didanosine is a synthetic nucleoside analogue of the naturally occurring nucleoside deoxyadenosine in which the 3'-hydroxyl group is replaced by hydrogen. Intracellularly, didanosine is converted by cellular enzymes to the active metabolite, dideoxyadenosine 5'-triphosphate. Dideoxyadenosine 5'-triphosphate inhibits the activity of HIV-1 reverse transcriptase both by competing with the natural substrate, deoxyadenosine 5'-triphosphate, and by its incorporation into viral DNA causing termination of viral DNA chain elongation.

***In Vitro* HIV Susceptibility**

The *in vitro* anti-HIV-1 activity of didanosine was evaluated in a variety of HIV-1.

infected lymphoblastic cell lines and monocyte/macrophage cell cultures. The concentration of drug necessary to inhibit viral replication by 50% (IC_{50}) ranged from 2.5 to 10 μM ($1 \mu M = 0.24 \mu g/mL$) in lymphoblastic cell lines and 0.01 to 0.1 μM in monocyte/macrophage cell cultures. The relationship between *in vitro* susceptibility of HIV to didanosine and the inhibition of HIV replication in humans has not been established.

Drug Resistance

HIV-1 isolates with reduced sensitivity to didanosine have been selected *in vitro* and were also obtained from patients treated with didanosine. Genetic analysis of isolates from didanosine-treated patients showed mutations in the reverse transcriptase gene that resulted in the amino acid substitutions K65R, L74V, and M184V. The L74V mutation was most frequently observed in clinical isolates. Phenotypic analysis of HIV-1 isolates from 60 patients (some with prior zidovudine treatment) receiving 6 to 24 months of didanosine monotherapy showed that isolates from 10 of 60 patients exhibited an average of a 10-fold decrease in susceptibility to didanosine *in vitro* compared to baseline isolates. Clinical isolates that exhibited a decrease in didanosine susceptibility harbored one or more didanosine-associated mutations. The clinical relevance of genotypic and phenotypic changes associated with didanosine therapy has not been established.

Cross-resistance

HIV-1 isolates from 2 of 39 patients receiving combination therapy for up to 2 years with zidovudine and didanosine exhibited decreased susceptibility to zidovudine, didanosine, zalcitabine, stavudine, and lamivudine *in vitro*. These isolates harbored five mutations (A62V, V75I, F77L, F116Y, and Q151M) in the reverse transcriptase gene. The clinical relevance of these observations has not been established.

CLINICAL PHARMACOLOGY

Animal Toxicology

Evidence of a dose-limiting skeletal muscle toxicity has been observed in mice and rats (but not in dogs) following long-term (greater than 90 days) dosing with didanosine at doses that were approximately 1.2 to 12 times the estimated human exposure. The relationship of this finding to the potential of VIDEX (didanosine) to

cause myopathy in humans is unclear. However, human myopathy has been associated with administration of VIDEX and other nucleoside analogues.

Pharmacokinetics

The pharmacokinetic parameters of didanosine are summarized in Table 1. Didanosine is rapidly absorbed, with peak plasma concentrations generally observed from 0.25 to 1.50 hours following oral dosing. Increases in plasma didanosine concentrations were dose proportional over the range of oral doses administered in clinical practice. Steady-state pharmacokinetic parameters did not differ significantly from values obtained after a single dose. Binding of didanosine to plasma proteins *in vitro* was low (<5%). Based on data from *in vitro* and animal studies, it is presumed that the metabolism of didanosine in man occurs by the same pathways responsible for the elimination of endogenous purines.

Table 1				
Mean $\pm$ SD Pharmacokinetic Parameters for Didanosine in Adult and Pediatric Patients				
Parameter	Adult Patients	n	Pediatric Patients	n
Oral bioavailability	42 $\pm$ 12%	6	25 $\pm$ 20%	46
Apparent volume of distribution ^a	1.08 $\pm$ 0.22 L/kg	6	28 $\pm$ 15 L/m ²	49
CSF-plasma ratio ^b	21 $\pm$ 0.03% ^c	5	46% (range 12-85%)	7
Systemic clearance ^a	13.0 $\pm$ 1.6 mL/min/kg	6	516 $\pm$ 184 mL/min/m ²	49
Renal clearance ^d	5.5 $\pm$ 2.1 mL/min/kg	6	240 $\pm$ 90 mL/min/m ²	15
Elimination half-life ^d	1.5 $\pm$ 0.4 hr	6	0.8 $\pm$ 0.3 hr	60
Urinary recovery of didanosine ^d	18 $\pm$ 8%	6	18 $\pm$ 10%	15
CSF = cerebrospinal fluid				
^a following IV administration				
^b following IV administration in adults and IV or oral administration in pediatric patients				
^c mean $\pm$ SE				
^d following oral administration				

Effect of Food on Absorption of Didanosine: Didanosine peak plasma concentrations (C_{MAX}) and area under the plasma concentration time curve (AUC) were decreased by approximately 55% when VIDEX tablets were administered up to

2 hours after a meal. Administration of VIDEX tablets up to 30 minutes before a meal did not result in any significant changes in bioavailability. VIDEX should be taken on an empty stomach, at least 30 minutes before or 2 hours after eating. (See **DOSAGE AND ADMINISTRATION**.)

Special Populations

Renal Insufficiency: It is recommended that the VIDEX (didanosine) dose be modified in patients with reduced creatinine clearance and in patients receiving maintenance hemodialysis (see **DOSAGE AND ADMINISTRATION**). Data from two studies indicated that the apparent oral clearance of didanosine decreased and the terminal elimination half-life increased as creatinine clearance decreased (see Table 2). Following oral administration, didanosine was not detectable in peritoneal dialysate fluid (n=6); recovery in hemodialysate (n=5) ranged from 0.6% to 7.4% of the dose over a 3-4 hour dialysis period. The absolute bioavailability of didanosine was not affected in patients requiring dialysis.

Table 2 Mean $\pm$ SD Pharmacokinetic Parameters for Didanosine Following a Single Oral Dose					
	Creatinine Clearance (mL/min)				
Parameter	≥ 90 (n=12)	60-90 (n=6)	30-59 (n=6)	10-29 (n=3)	Dialysis Patients (n=11)
CL _{cr} (mL/min)	112 $\pm$ 22	68 $\pm$ 8	46 $\pm$ 8	13 $\pm$ 5	ND ^a
CL/F (mL/min)	2164 $\pm$ 638	1566 $\pm$ 833	1023 $\pm$ 378	628 $\pm$ 104	543 $\pm$ 174
CL _R (mL/min)	458 $\pm$ 164	247 $\pm$ 153	100 $\pm$ 44	20 $\pm$ 8	<10
T _{1/2} (hr)	1.42 $\pm$ 0.33	1.59 $\pm$ 0.13	1.75 $\pm$ 0.43	2.0 $\pm$ 0.3	4.1 $\pm$ 1.2
^a ND = not determined due to anuria CL _{cr} = creatinine clearance CL/F = apparent oral clearance CL _R = renal clearance					

Pediatric Patients: The pharmacokinetics of didanosine have been evaluated in HIV-infected pediatric patients from 0.7 to 18.9 years of age (see Table 1). Overall,

the pharmacokinetics of didanosine in pediatric patients greater than 0.7 years of age are similar to those of didanosine in adults. Didanosine plasma concentrations increased in proportion to oral doses ranging from 80 to 180 mg/m². For information on controlled clinical studies in pediatric patients, see **PRECAUTIONS, Pediatric Use and Clinical Studies**.

Geriatric Patients: Didanosine pharmacokinetics have not been studied in patients over 65 years of age.

Gender: The effects of gender on didanosine pharmacokinetics have not been studied.

Drug Interactions: Drug interaction studies have demonstrated that there are no clinically significant pharmacokinetic interactions between VIDEX and the following: dapsone, loperamide, metoclopramide, nevirapine, ranitidine, rifabutin, ritonavir, stavudine, sulfamethoxazole, trimethoprim, and zidovudine. Studies with dapsone, nevirapine, rifabutin, ritonavir, stavudine, and zidovudine were multiple-dose studies. Studies with loperamide, metoclopramide, ranitidine, sulfamethoxazole, and trimethoprim were single-dose studies, and effects on pharmacokinetics at steady-state are not known. (See also **PRECAUTIONS: Drug Interactions**.)

INDICATIONS AND USAGE

VIDEX in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection (see Clinical Studies).

Clinical Studies

Combination Therapy

The combination use of VIDEX is based on the results of clinical studies in HIV-infected patients in double-and triple-combination regimens with other antiretroviral agents.

One of these studies (START 2) was a multicenter, randomized, open-label study comparing VIDEX (200 mg BID) plus stavudine plus indinavir to zidovudine plus lamivudine plus indinavir in 205 treatment-naïve patients. Both regimens resulted in a similar magnitude of inhibition of HIV RNA levels and increases in CD4 cell counts through 48 weeks.

Monotherapy

The efficacy of VIDEX was demonstrated in two randomized, double-blind studies comparing VIDEX with zidovudine in 617 (ACTG 116A, conducted 1989-1992) and 913 (ACTG 116B/117, conducted 1989-1991) patients with symptomatic HIV infection or AIDS who were treated for more than one year. In treatment-naïve patients (ACTG 116A), the rate of HIV disease progression or death was similar between the treatment groups; mortality rates were 26% for patients receiving VIDEX and 21% for patients receiving zidovudine. Of the patients who had received previous zidovudine treatment (ACTG 116B/117), those treated with VIDEX had a lower rate of HIV disease progression or death (32%) compared to those treated with zidovudine (41%); however, survival rates were similar between the treatment groups.

Efficacy in pediatric patients was demonstrated in a randomized, double-blind, controlled study (ACTG 152, conducted 1991-1995) involving 831 patients treated for more than 1.5 years with zidovudine (180 mg/m² q6h), VIDEX (120 mg/m² q12h), or zidovudine (120 mg/m² q6h) plus VIDEX (90 mg/m² q12h). Patients treated with VIDEX or VIDEX plus zidovudine had lower rates of HIV disease progression or death compared with those treated with zidovudine alone.

CONTRAINDICATION

VIDEX (didanosine) is contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the formulations.

WARNINGS**1. Pancreatitis**

PANCREATITIS, WHICH HAS BEEN FATAL IN SOME CASES, HAS OCCURRED DURING THERAPY WITH VIDEX. VIDEX USE SHOULD BE SUSPENDED IN PATIENTS WITH SIGNS OR SYMPTOMS OF PANCREATITIS AND DISCONTINUED IN PATIENTS WITH CONFIRMED PANCREATITIS. When treatment with other drugs known to cause pancreatic toxicity is required, suspension of VIDEX (didanosine) therapy is recommended. In patients with risk factors for pancreatitis, VIDEX should be used with extreme caution and only if clearly indicated. Patients with advanced HIV infection are at increased risk of

pancreatitis and should be followed closely. Patients with renal impairment may be at greater risk for pancreatitis if treated without dose adjustment.

The frequency of pancreatitis is dose related. In phase 3 studies, incidence ranged from 1% to 10% with high dose and 1% to 7% with recommended dose.

In pediatric studies, pancreatitis occurred in 3% (2/60) of patients treated at entry doses below 300 mg/m²/day and in 13% (5/38) of patients treated at higher doses. VIDEX use should be suspended in pediatric patients with signs or symptoms of pancreatitis and discontinued in pediatric patients with confirmed pancreatitis.

2. Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including didanosine and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering VIDEX to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with VIDEX 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).

3. Retinal Changes and Optic Neuritis

Retinal changes and optic neuritis have been reported in adult and pediatric patients. Periodic retinal examinations should be considered for patients receiving VIDEX. (See ADVERSE REACTIONS.)

PRECAUTIONS

Peripheral Neuropathy

Peripheral neuropathy, manifested by numbness, tingling, or pain in the hands or feet, has been reported in patients receiving VIDEX therapy. Peripheral neuropathy has occurred more frequently in patients with advanced HIV disease, in patients with a history of neuropathy, or in patients being treated with neurotoxic drug therapy, including stavudine (see ADVERSE REACTIONS).

General

VIDEX should be taken on an empty stomach, at least 30 minutes before or 2 hours after eating.

Patients with Phenylketonuria: VIDEX Chewable/Dispersible Buffered Tablets contain the following quantities of phenylalanine:

Table 3	
All Strengths	
Phenylalanine per 2-tablet dose	73 mg
Phenylalanine per tablet	36.5 mg

Patients on Sodium-Restricted Diets: VIDEX Buffered Powder for Oral Solution: Each single-dose packet of VIDEX Buffered Powder for Oral Solution contains 1380 mg sodium.

Patients with Renal Impairment: Patients with renal impairment (creatinine clearance <60 mL/min) may be at greater risk of toxicity from VIDEX due to decreased drug clearance (see **CLINICAL PHARMACOLOGY** section). A dose reduction is recommended in these patients (see **DOSAGE AND ADMINISTRATION** section). The magnesium content of each buffered tablet of VIDEX is 8.6 mEq. This may present an excessive load of magnesium to patients with significant renal impairment, particularly after prolonged dosing.

Patients with Hepatic Impairment: It is unknown if hepatic impairment significantly affects didanosine pharmacokinetics. Therefore, these patients should be monitored closely for evidence of didanosine toxicity.

Hyperuricemia: VIDEX has been associated with asymptomatic hyperuricemia; treatment suspension may be necessary if clinical measures aimed at reducing uric acid levels fail.

Information for Patients

Patients should be informed that a serious toxicity of VIDEX is pancreatitis, which has been fatal in some patients.

Patients should also be aware that peripheral neuropathy, manifested by numbness, tingling, or pain in hands or feet, may develop during therapy with VIDEX. Patients should be counseled that peripheral neuropathy occurs with

greatest frequency in patients with advanced HIV disease or a history of peripheral neuropathy, and that dose modification and/or discontinuation of VIDEX may be required if toxicity develops.

Patients should be informed that when VIDEX is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when VIDEX is used alone. These patients should be followed closely.

Patients should be cautioned about the use of medications or other substances, including alcohol, that may exacerbate VIDEX toxicities.

VIDEX (didanosine) is not a cure for HIV infection, and patients may continue to develop HIV-associated illnesses, including opportunistic infection. Therefore, patients should remain under the care of a physician when using VIDEX. Patients should be advised that VIDEX therapy has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination. Patients should be informed that the long-term effects of VIDEX are unknown at this time.

Drug Interactions (see also CLINICAL PHARMACOLOGY, Drug Interactions)

Coadministration of VIDEX with drugs that are known to cause pancreatitis may increase the risk of this toxicity (see WARNINGS) and should be done with extreme caution and only if clearly indicated. Neuropathy has occurred more frequently in patients with a history of neuropathy or neurotoxic drug therapy, including stavudine, and these patients may be at increased risk of neuropathy during VIDEX therapy (see ADVERSE REACTIONS).

Allopurinol: The AUC of didanosine was increased about 4-fold when allopurinol at 300 mg/day was coadministered with a single 200-mg dose of VIDEX to two patients with renal impairment (CL_{cr} =15 and 18 mL/min). The effects of allopurinol on didanosine pharmacokinetics in subjects with normal renal function are not known.

Antacids: Concomitant administration of antacids containing magnesium or aluminum with VIDEX Chewable/Dispersible Buffered Tablets or Pediatric Powder for Oral Solution may potentiate adverse events associated with the antacid components.

Drugs Whose Absorption Can Be Affected by the Level of Acidity in the Stomach: Drugs such as ketoconazole and itraconazole should be administered at least 2 hours prior to dosing with VIDEX.

Ganciclovir: Administration of VIDEX 2 hours prior to or concurrent with oral ganciclovir was associated with a 111 (± 114)% increase in the steady-state AUC of didanosine ($n = 12$). A 21 (± 17)% decrease in the steady-state AUC of ganciclovir was observed when VIDEX was administered 2 hours prior to ganciclovir, but not when the two drugs were administered simultaneously ($n = 12$).

Quinolone Antibiotics: VIDEX should be administered at least 2 hours after or 6 hours before dosing with ciprofloxacin because plasma concentrations of ciprofloxacin are decreased when administered with antacids containing magnesium, calcium, or aluminum. In eight HIV-infected patients, the steady-state AUC of ciprofloxacin was decreased an average of 26% (95% CI = 14%, 37%) when ciprofloxacin was administered 2 hours prior to a marketed chewable/dispersible tablet formulation of VIDEX. The AUC of ciprofloxacin was decreased an average of 15-fold in 12 healthy subjects given ciprofloxacin and didanosine-placebo tablets concurrently. In a single subject given one dose of ciprofloxacin 2 hours after a dose of didanosine-placebo tablets, a greater than 50% reduction in the AUC of ciprofloxacin was observed.

Plasma concentrations of quinolone antibiotics are decreased when administered with antacids containing magnesium, calcium, or aluminum. The optimal dosing interval for coadministration with VIDEX should be determined by consulting the appropriate quinolone package insert.

Interactions with Other Antiretroviral Drugs: Significant decreases in the AUC of delavirdine (20%) and indinavir (84%) occurred following simultaneous administration of these agents with VIDEX. To avoid this interaction, delavirdine or indinavir should be given 1 hour prior to dosing with VIDEX. The pharmacokinetics of nelfinavir are not altered to a clinically significant degree when it is administered with a light meal 1 hour after VIDEX.

Carcinogenesis and Mutagenesis

Lifetime carcinogenicity studies were conducted in mice and rats for 22 and 24 months, respectively. In the mouse study, initial doses of 120, 800 and 1200 mg/kg/day for each sex, were lowered after 8 months, to 120, 210 and 210 mg/kg/day for females and 120, 300 and 600 mg/kg/day for males. The two higher

doses exceeded the maximally tolerated dose in females and the high dose exceeded the maximally tolerated dose in males. The low dose in females represented 0.68-fold maximum human exposure and the intermediate dose in males represented 1.7-fold maximum human exposure. In the rat study, initial doses were 100, 250 and 1000 mg/kg/day, and the high dose was lowered to 500 mg/kg/day after 18 months. The upper dose in male and female rats represented 3-fold maximum human exposure.

Didanosine induced no significant increase in neoplastic lesions in mice or rats at maximally tolerated doses.

No evidence of mutagenicity (with or without metabolic activation) was observed in Ames *Salmonella* mutagenicity assays or in a mutagenicity assay conducted with *Escherichia coli* tester strain WP2 uvrA where only a slight increase in revertants was observed with didanosine. In a mammalian cell gene mutation assay conducted in L5178Y/TK+/- mouse lymphoma cells, didanosine was weakly positive both in the absence and presence of metabolic activation at concentrations of approximately 2000 µg/mL and above. In an *in vitro* cytogenic study performed in cultured human peripheral lymphocytes, high concentrations of didanosine (≥ 500 µg/mL) elevated the frequency of cells bearing chromosome aberrations. Another *in vitro* mammalian cell chromosome aberration study using Chinese Hamster Lung cells revealed that didanosine produces chromosome aberrations at ≥ 500 µg/mL after 48 hours of exposure. However, no significant elevations in the frequency of cells with chromosome aberrations were seen at didanosine concentrations up to 250 µg/mL. In a BALB/c 3T3 *in vitro* transformation assay, didanosine was considered positive only at concentrations of 3000 µg/mL and above. No evidence of genotoxicity was observed in rat and mouse micronucleus assays.

The results from the genotoxicity studies suggest that didanosine is not mutagenic at biologically and pharmacologically relevant doses. At significantly elevated doses *in vitro*, the genotoxic effects of didanosine are similar in magnitude to those seen with natural DNA nucleosides.

Pregnancy, Reproduction and Fertility

Pregnancy Category B. Reproduction studies have been performed in rats and rabbits at doses up to 12 and 14.2 times the estimated human exposure (based upon plasma levels), respectively, and have revealed no evidence of impaired fertility or harm to the fetus due to didanosine. At approximately 12 times the

estimated human exposure, didanosine was slightly toxic to female rats and their pups during mid and late lactation. These rats showed reduced food intake and body weight gains but the physical and functional development of the offspring was not impaired and there were no major changes in the F2 generation. A study in rats showed that didanosine and/or its metabolites are transferred to the fetus through the placenta. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to didanosine and other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling (800) 258-4263.

Nursing Mothers

A study in rats showed that following oral administration, didanosine and/or its metabolites were excreted into the milk of lactating rats. Although it is not known if didanosine is excreted in human milk, there is the potential for adverse effects from didanosine in nursing infants. Mothers should be instructed to discontinue nursing if they are receiving didanosine. This instruction is consistent with the Centers for Disease Control recommendation that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV infection.

Pediatric Use

Use of VIDEX in pediatric patients is supported by evidence from adequate and well-controlled studies of VIDEX in adults and pediatric patients (see **Clinical Studies, CLINICAL PHARMACOLOGY, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

A SERIOUS TOXICITY OF VIDEX (didanosine) IS PANCREATITIS. OTHER IMPORTANT TOXICITIES INCLUDE LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS; RETINAL CHANGES AND OPTIC NEURITIS; AND PERIPHERAL NEUROPATHY (see **WARNINGS and PRECAUTIONS**).

When VIDEX is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when VIDEX is used alone. Patients treated with VIDEX in combination with stavudine may be at increased risk for adverse events such as pancreatitis, peripheral neuropathy, and liver function abnormalities (see **WARNINGS** and **PRECAUTIONS**).

Adults: Selected clinical adverse events that occurred in adult patients in clinical studies with VIDEX are provided in Table 4 and Table 5.

Table 4				
Selected Clinical Adverse Events from Monotherapy Studies				
	Percent of Patients			
	ACTG 116A		ACTG 116B/117	
Adverse Events	VIDEX n=197	zidovudine n=212	VIDEX n=298	zidovudine n=304
Diarrhea	19	15	28	21
Peripheral Neurologic Symptoms/Neuropathy	17	14	20	12
Rash/Pruritus	7	8	9	5
Abdominal Pain	13	8	7	8
Pancreatitis	7	3	6	2

Table 5		
Selected Clinical Adverse Events from START 2 Study		
	Percent of Patients	
	VIDEX + stavudine + indinavir n=102	zidovudine + lamivudine + indinavir n=103
Adverse Events		
Nausea	53	67
Headache	46	37
Diarrhea	45	39
Rash	30	18
Vomiting	30	35
Peripheral Neurologic Symptoms/Neuropathy	21	10

Pancreatitis resulting in death was observed in one patient who received VIDEX plus stavudine plus indinavir in the START 2 study.

Selected laboratory abnormalities in clinical studies with VIDEX are shown in Tables 6-8.

Table 6				
Selected Laboratory Abnormalities from Monotherapy Studies				
Parameter	Percent of Patients			
	ACTG 116A		ACTG 116B/117	
	VIDEX n=197	zidovudine n=212	VIDEX n=298	zidovudine n=304
SGOT (AST) ($>5 \times$ ULN)	9	4	7	6
SGPT (ALT) ($>5 \times$ ULN)	9	6	6	6
Alkaline phosphatase ($>5 \times$ ULN)	4	1	1	1
Amylase ($\geq 1.4 \times$ ULN)	17	12	15	5
Uric Acid (>12 mg/dL)	3	1	2	1
ULN = upper limit of normal.				

Table 7 Selected Laboratory Abnormalities in the START 2 Study (Grades 3-4)		
Percent of Patients		
Parameter	VIDEX+ stavudine+ indinavir (n=102)	zidovudine+ lamivudine+ indinavir (n=103)
Bilirubin (>2.6xULN)	16	8
SGOT (AST) (>5xULN)	7	7
SGPT (ALT) (>5xULN)	8	5
GGT (>5xULN)	5	2
Lipase (>2xULN)	5	5
Amylase (>2xULN)	8	2
ULN = upper limit of normal.		

Table 8 Selected Laboratory Abnormalities in the START 2 Study (All Grades)		
Percent of Patients		
Parameter	VIDEX+ stavudine+ indinavir (n=102)	zidovudine+ lamivudine+ indinavir (n=103)
Bilirubin	68	55
SGOT (AST)	53	20
SGPT (ALT)	50	18
GGT	28	12
Lipase	26	19
Amylase	31	17

Observed during Clinical Practice: The following events have been identified during postapproval use of VIDEX. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to their seriousness, frequency of reporting, causal connection to VIDEX, or a combination of these factors.

Body as a Whole - alopecia, anaphylactoid reaction, asthenia, chills/fever, and pain.

Digestive Disorders- anorexia, dyspepsia, and flatulence.

0000043

Exocrine Gland Disorders- sialoadenitis, parotid gland enlargement, dry mouth and dry eyes.

Hematologic Disorders - anemia, leukopenia, and thrombocytopenia.

Liver - lactic acidosis and hepatic steatosis (see **WARNINGS**); hepatitis and liver failure.

Metabolic Disorders - diabetes mellitus, hypoglycemia, and hyperglycemia.

Musculoskeletal Disorders - myalgia (with or without increases in creatinine phosphokinase), rhabdomyolysis including acute renal failure and hemodialysis, arthralgia, and myopathy.

Ophthalmologic Disorders - Retinal depigmentation and optic neuritis (see **WARNINGS**).

Pediatric Patients: Adverse events and laboratory abnormalities reported to occur in the pediatric patients in ACTG 152 were generally similar to adverse events and laboratory abnormalities reported in adult patients.

In pediatric phase 1 studies, pancreatitis occurred in 2 of 60 (3%) patients treated at entry doses below 300 mg/m²/day and in 5 of 38 (13%) patients treated at higher doses.

Retinal changes and optic neuritis have been reported in pediatric patients.

OVERDOSAGE

There is no known antidote for VIDEX (didanosine) overdose. In phase 1 studies, in which VIDEX was initially administered at doses ten times the currently recommended dose, toxicities included: pancreatitis, peripheral neuropathy, diarrhea, hyperuricemia and hepatic dysfunction. Didanosine is not dialyzable by peritoneal dialysis, although there is some clearance by hemodialysis (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**).

DOSAGE AND ADMINISTRATION

Dosage:

Adults: The dosing interval should be 12 hours. All VIDEX formulations should be administered on an empty stomach, at least 30 minutes before or 2 hours after eating. Adult patients should take 2 tablets at each dose so that adequate buffering is provided to prevent gastric acid degradation of didanosine. The recommended dose of VIDEX in adults, in any regimen, is dependent on weight as outlined in the table below:

Table 9 Adult Dosing		
Patient Weight	VIDEX Tablets	VIDEX Buffered Powder
≥ 60 kg	200 mg BID	250 mg BID
< 60 kg	125 mg BID	167 mg BID

Pediatric Patients: The recommended dosing interval is 12 hours. All VIDEX formulations should be administered on an empty stomach, at least 30 minutes before or 2 hours after eating. The recommended dose of VIDEX (didanosine) in pediatric patients is 120 mg/m² BID.

Dose Adjustment:

Clinical and laboratory signs suggestive of pancreatitis should prompt dose suspension and careful evaluation of the possibility of pancreatitis. VIDEX use should be discontinued in patients with confirmed pancreatitis.

Patients with symptoms of peripheral neuropathy may tolerate a reduced dose of VIDEX after resolution of the symptoms of peripheral neuropathy upon drug discontinuation. If neuropathy recurs after resumption of VIDEX, permanent discontinuation of VIDEX should be considered.

In adult patients with impaired renal function, the dose of VIDEX should be adjusted to compensate for the slower rate of elimination. The recommended doses and dosing intervals of VIDEX in adult patients with renal insufficiency are presented in Table 10.

Table 10**Recommended Dose (mg) of VIDEX by Body Weight**

Creatinine Clearance (mL/min)	≥ 60 kg		< 60 kg		Interval (hr)
	Tablet ^a	Solution ^b	Tablet ^a	Solution ^b	
≥60	200	250	125	167	12
30-59	100	100	75	100	12
10-29	150	167	100	100	24
<10	100	100	75	100	24

^a VIDEX Chewable/Dispersible Buffered Tablet. Two VIDEX tablets must be taken with each dose; different strengths of tablets may be combined to yield the recommended dose.

^b VIDEX Buffered Powder for Oral Solution

Urinary excretion is also a major route of elimination of didanosine in pediatric patients; therefore, the clearance of didanosine may be altered in children with renal impairment. Although there are insufficient data to recommend a specific dose adjustment of VIDEX in this patient population, a reduction in the dose and/or increase in the interval between doses should be considered.

Patients Requiring Continuous Ambulatory Peritoneal Dialysis (CAPD) or Hemodialysis: It is recommended that one fourth of the total daily dose of VIDEX be administered once a day (see Table 10, recommended dosage for patients with $CL_{cr} < 10$ mL/min). It is not necessary to administer a supplemental dose of VIDEX following hemodialysis.

Hepatic Impairment: See PRECAUTIONS.

Method of Preparation:

VIDEX Chewable/Dispersible Buffered Tablets

Adult Dosing: Two tablets should be thoroughly chewed, manually crushed, or dispersed in at least 1 ounce of water prior to consumption. To disperse tablets, add 2 tablets to at least 1 ounce of drinking water. Stir until a uniform dispersion forms, and drink the entire dispersion immediately. If additional flavoring is desired, the dispersion may be diluted with one ounce of clear apple juice. Stir the further diluted dispersion just prior to consumption. The dispersion with clear apple juice is stable at room temperature, 62-73°F (17-23°C), for up to one hour.

VIDEX Buffered Powder for Oral Solution

1. Open packet carefully and pour contents into a container with approximately 4 ounces of drinking water. Do not mix with fruit juice or other acid-containing liquid.
2. Stir until the powder completely dissolves (approximately 2 to 3 minutes).
3. Drink the entire solution immediately.

VIDEX Pediatric Powder for Oral Solution

Prior to dispensing, the pharmacist must constitute dry powder with Purified Water, USP, to an initial concentration of 20 mg/mL and immediately mix the resulting solution with antacid to a final concentration of 10 mg/mL as follows:

20 mg/mL Initial Solution: Constitute the product to 20 mg/mL by adding 100 mL or 200 mL of Purified Water, USP, to the 2 g or 4 g of VIDEX powder, respectively, in the product bottle.

10 mg/mL Final Admixture: 1. Immediately mix one part of the 20 mg/mL initial solution with one part of either Mylanta® Double Strength Liquid (Mylanta® is a registered trademark of Stuart Pharmaceuticals, a business unit of Zeneca, Inc., Mylanta® Double Strength, formerly Mylanta® II, is distributed by Johnson & Johnson/Merck, Consumer Pharmaceuticals Company, Fort Washington, PA 19034 [USA]), Extra Strength Maalox® Plus Suspension, or Maalox® TC Suspension (Maalox® is a registered trademark of William H. Rorer Inc., Unit of Rhone-Poulenc) for a final dispensing concentration of 10 mg VIDEX per mL. For patient home use, the admixture should be dispensed in appropriately sized, flint-glass or plastic (HDPE, PET, or PETG) bottles with child-resistant closures. This admixture is stable for 30 days under refrigeration, 36° to 46° F (2° to 8° C).

2. Instruct the patient to shake the admixture thoroughly prior to use and to store the tightly closed container in the refrigerator, 36° to 46° F (2° to 8° C), up to 30 days.

HOW SUPPLIED

VIDEX® (didanosine) Chewable/Dispersible Buffered Tablets are round, off white to light orange/yellow with a mottled appearance, orange-flavored, tablets embossed with "VIDEX" on one side and the product strength on the other. The tablets are available in the following strengths of VIDEX: 25, 50, 100, or 150 mg. Sixty tablets are packaged in bottles with child-resistant closures.

The tablets should be stored in tightly closed bottles at 59° to 86° F (15° to 30° C). If dispersed in water, the dose may be held for up to 1 hour at ambient temperature.

VIDEX Buffered Powder for Oral Solution is supplied in single-dose, child-resistant foil packets in the following strengths of VIDEX: 100, 167, or 250 mg. Each product strength provides a sweetened, buffered solution of VIDEX.

The packets should be stored at 59° to 86° F (15° to 30° C). After dissolving in water, the solution may be stored at ambient room temperature for up to 4 hours.

VIDEX Pediatric Powder for Oral Solution is supplied in 4- and 8-ounce glass bottles containing 2 g or 4 g of VIDEX, respectively.

The bottles of powder should be stored at 59° to 86° F (15° to 30° C). The VIDEX admixture may be stored up to 30 days in a refrigerator, 36° to 46° F (2° to 8° C). Discard any unused portion after 30 days.

The NDC numbers for the previously described VIDEX products are:

Table 11		
NDC NO.	Packaging Information	Product Strength
VIDEX® Chewable/Dispersible Buffered Tablets		
0087-6650-01	60 tablets/bottle	25 mg/tablet
0087-6651-01	60 tablets/bottle	50 mg/tablet
0087-6652-01	60 tablets/bottle	100 mg/tablet
0087-6653-01	60 tablets/bottle	150 mg/tablet
VIDEX® Buffered Powder for Oral Solution		
0087-6614-43	One single-dose foil packet*	100 mg/packet
0087-6615-43	One single-dose foil packet*	167 mg/packet
0087-6616-43	One single-dose foil packet*	250 mg/packet
VIDEX® Pediatric Powder for Oral Solution		
0087-6632-41	One bottle per carton	2 g/bottle
0087-6633-41	One bottle per carton	4 g/bottle
*Packaged as 30 packets per carton.		

US Patent Nos: 4,861,759 and 5,616,566.

HANDLING AND DISPOSAL

Spill, Leak and Disposal Procedure

Avoid generating dust during clean-up of powdered products; use wet mop or damp sponge. Clean surface with soap and water as necessary. Containerize larger spills.

There is no single preferred method of disposal of containerized waste. Disposal options include incineration, landfill, or sewer as dictated by specific circumstances and relevant national, state, and local regulations.

BRISTOL-MYERS SQUIBB Immunology
A Bristol-Myers Squibb Company.
Princeton, New Jersey 08543
U.S.A.

Revised May 1998

P9691-02

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-154 / S-009

20-155 / S-007

20-156 / S-007

MEDICAL REVIEW

APR - 4 1994

NDA 20,154 -S009
20,155- S007
20,156- S007

Date submitted: 3/18/94
Date received: 3/21/94
Date assigned: 3/23/94
MOR completed: 3/31/94

**Medical Officer's Review
(Final Draft Labeling)**

Title: "Phase II efficacy study comparing 2', 3' - dideoxyinosine and zidovudine therapy in patients with HIV infection who have received < 16 weeks of prior zidovudine" (ACTG 116A)

Sponsor: Bristol-Myers Squibb Pharmaceutical Research Institute
5 Research Parkway - P.O. Box 5100
Wallingford, CT 06492-7660

Drug: Chemical: 2',3'-dideoxyinosine (ddI)
Generic: didanosine
Trade: Videx®

Related documents: Memoranda of teleconferences dated November 3, 1993, November 10, 1993, and December 9, 1993
Medical Officer's review of ACTG 116B/117 dated October 8, 1992
Medical Officer's review of ACTG 116A dated January 6, 1994
Statistician's reviews of ACTG 116B/117 dated October 9, 1992, and December 2, 1992
Statistician's review of ACTG 116A dated February 15, 1994

I. Summary

This one volume submission is an amendment to the above referenced NDA supplements and contains the sponsor's final draft didanosine (ddI) label (Appendix A). The proposed ddI label incorporates the results of ACTG 116A, and are based on frequent discussions and telefacsimile exchanges between the sponsor and this division. (This trial and proposed labelling changes were previously reviewed in a Medical Officer Review, dated January 6, 1994). In these discussions, the sponsor was informed that the results of ACTG 116A do not support a change in didanosine's indication. The final draft label contains an acceptable description of the ACTG 116A trial results. Other changes in the label were initiated at the request of this division in order to shorten and update relevant safety and efficacy information. These miscellaneous changes are indicated in the appended label, and are acceptable.

II. Recommended Regulatory Action

The currently proposed draft ddi label is acceptable and the NDA supplement should be approved. An approval letter will be issued from this division to Bristol-Myers Squibb.



Heidi M. Jolson, M.D., M.P.H.
Medical Officer, DAVDP

Concurrences:

HFD-530/Division Dir/DFeigal

HFD-530/SMO/RBehrman

HFD-530/MO/HJolson

cc:

HFD-530/NDA 20-154, 155, 156

HFD-530/Division file

HFD-530/Pharm/JFarrelly

HFD-530/Micro/LMishra

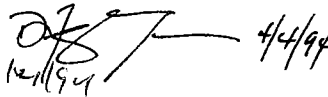
HFD-530/Chem/K-YLo

HFD-530/Stat/LKammerman/PFlyer

HFD-340

HFD-530/MO/HJolson

HFD-530/CSO/TDecicco/JMahoney



4/4/94