OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VIDEX safely and effectively. See full prescribing information for VIDEX.

VIDEX (didanosine, USP) Pediatric Powder for Oral Solution
Initial U.S. Approval: 1991

WARNING: PANCREATITIS, LACTIC ACIDOSIS and HEPATOMEGALY with STEATOSIS

See full prescribing information for complete boxed warning.

- **Fatal and nonfatal pancreatitis. VIDEX should be suspended in patients with suspected pancreatitis and discontinued in patients with confirmed pancreatitis. (5.1)**
- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases. Fatal lactic acidosis has been reported in pregnant women who received the combination of didanosine and stavudine. (5.2)**

----------RECENT MAJOR CHANGES----------

Dosage and Administration	
Dosage Adjustment (2.3)	06/2009
Contraindications	
Allopurinol (4.1)	06/2009
Ribavirin (4.2)	06/2009
Warnings and Precautions	
Non-cirrhotic Portal Hypertension (5.4)	01/2010

----------INDICATIONS AND USAGE----------

VIDEX (didanosine, USP) is a nucleoside reverse transcriptase inhibitor for use in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV)-1 infection. (1)

----------DOSAGE AND ADMINISTRATION----------

- Adult patients: Administered on an empty stomach at least 30 minutes before or 2 hours after eating. Dosing is based on body weight. (2.1)

	at least 60 kg	**less than 60 kg**
Preferred dosing	200 mg twice daily	125 mg twice daily
Dosing for patients whose management requires once-daily frequency	400 mg once daily	250 mg once daily

- Pediatric patients (2 weeks old to 18 years old): Administered on an empty stomach at least 30 minutes before or 2 hours after eating.
  - Between 2 weeks and 8 months old, dosing is 100 mg/m^2 twice daily.
  - For those greater than 8 months old, dosing is 120 mg/m^2 twice daily but not to exceed the adult dosing recommendation. (2.1)
- Renal impairment: Dose reduction is recommended. (2.2)
- Coadministration with tenofovir: Dose reduction is recommended. Patients should be monitored closely for didanosine-associated adverse reactions. (2.3, 7.1)

----------DOSAGE FORMS AND STRENGTHS----------

- 4-ounce glass bottle containing 2 g of VIDEX (3)
- 8-ounce glass bottle containing 4 g of VIDEX (3)

----------CONTRAINDICATIONS----------

Coadministration with allopurinol or ribavirin is contraindicated. (4.1 and 4.2)

----------WARNINGS AND PRECAUTIONS----------

- Pancreatitis: Suspension or discontinuation of didanosine may be necessary. (5.1)
- Lactic acidosis and severe hepatomegaly with steatosis: Suspend didanosine in patients who develop clinical symptoms or signs with or without laboratory findings. (5.2)
- Hepatic toxicity: Interruption or discontinuation of didanosine must be considered upon worsening of liver disease. (5.3)
- Non-cirrhotic portal hypertension: Discontinue didanosine in patients with evidence of non-cirrhotic portal hypertension. (5.4)
- Patients may develop peripheral neuropathy (5.5), retinal changes and optic neuritis (5.6), immune reconstitution syndrome (5.7), and redistribution/accumulation of body fat (5.8).

----------ADVERSE REACTIONS----------

- In adults, the most common adverse reactions (greater than 10%, all grades) are diarrhea, peripheral neurologic symptoms/neuropathy, abdominal pain, nausea, headache, rash, and vomiting. (6.1)
- Adverse reactions in pediatric patients were consistent with those in adults. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

Coadministration of VIDEX can alter the concentration of other drugs and other drugs may alter the concentration of didanosine. The potential drug-drug interactions must be considered prior to and during therapy. (4, 7, 12.3)

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: Fatal lactic acidosis has been reported in pregnant women who received both didanosine and stavudine with other agents. This combination should be used with caution during pregnancy and only if the potential benefit clearly outweighs the potential risk. (5.2, 8.1) Physicians are encouraged to register patients in the Antiretroviral Pregnancy Registry by calling 1-800-258-4263.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 01/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

*****Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: PANCREATITIS, LACTIC ACIDOSIS and HEPATOMEGALY with STEATOSIS

Fatal and nonfatal pancreatitis has occurred during therapy with VIDEX used alone or in combination regimens in both treatment-naive and treatment-experienced patients, regardless of degree of immunosuppression. VIDEX should be suspended in patients with suspected pancreatitis and discontinued in patients with confirmed pancreatitis [*see Warnings and Precautions (5.1)*].

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. Fatal lactic acidosis has been reported in pregnant women who received the combination of didanosine and stavudine with other antiretroviral agents. The combination of didanosine and stavudine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk [*see Warnings and Precautions (5.2)*].

1 INDICATIONS AND USAGE

VIDEX® (didanosine, USP), also known as ddI, in combination with other antiretroviral agents is indicated for the treatment of human immunodeficiency virus (HIV)-1 infection [*see Clinical Studies (14)*].

2 DOSAGE AND ADMINISTRATION

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

2.1 Recommended Dosage (Adult and Pediatric Patients)

The preferred dosing frequency of VIDEX is twice daily because there is more evidence to support the effectiveness of this dosing regimen. Once-daily dosing should be considered only for patients whose management requires once-daily dosing of VIDEX [*see Clinical Studies (14)*]. The recommended adult total daily dose is based on body weight (kg) (see Table 1).

Table 1: Recommended Dosage (Adult)

	at least 60 kg	less than 60 kg
Preferred dosing	200 mg twice daily	125 mg twice daily
Dosing for patients whose management requires once-daily frequency	400 mg once daily	250 mg once daily

Pediatric Patients (2 weeks old to 18 years old): The recommended dose of VIDEX (didanosine) in pediatric patients between 2 weeks old and 8 months old is 100 mg/m^2 twice daily, and the recommended VIDEX dose for pediatric patients greater than 8 months old is 120 mg/m^2 twice daily but not to exceed the adult dosing recommendation.

Dosing recommendations in patients less than 2 weeks of age cannot be made because the pharmacokinetics of didanosine in these children are too variable to determine an appropriate dose. There are no data on once-daily dosing of VIDEX in pediatric patients.

2.2 Renal Impairment

Adult Patients

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 2.

Table 2: Recommended Dosage in Patients with Renal Impairment

Creatinine Clearance (mL/min)	Recommended VIDEX Dose by Patient Weight	
	at least 60 kg	less than 60 kg
at least 60	200 mg twice daily[a]	125 mg twice daily[a]
30-59	200 mg once daily or 100 mg twice daily	150 mg once daily or 75 mg twice daily
10-29	150 mg once daily	100 mg once daily
less than 10	100 mg once daily	75 mg once daily

Table 2: Recommended Dosage in Patients with Renal Impairment

[a] 400 mg once daily (at least 60 kg) or 250 mg once daily (less than 60 kg) for patients whose management requires once-daily frequency of administration.

Pediatric Patients

Urinary excretion is also a major route of elimination of didanosine in pediatric patients, therefore the clearance of didanosine may be altered in pediatric patients 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 should be considered (see Table 2).

Patients Requiring Continuous Ambulatory Peritoneal Dialysis (CAPD) or Hemodialysis

For patients requiring CAPD or hemodialysis, follow dosing recommendations for patients with creatinine clearance of less than 10 mL/min, shown in Table 2. It is not necessary to administer a supplemental dose of VIDEX following hemodialysis.

2.3 Dosage Adjustment

Concomitant Therapy with Tenofovir Disoproxil Fumarate

In patients who are also taking tenofovir disoproxil fumarate, a dose reduction of VIDEX to 250 mg (adults weighing at least 60 kg with creatinine clearance of at least 60 mL/min) or 200 mg (adults weighing less than 60 kg with creatinine clearance of at least 60 mL/min) once daily is recommended. VIDEX and tenofovir disoproxil fumarate may be taken together in the fasted state. Alternatively, if tenofovir disoproxil fumarate is taken with food, VIDEX should be taken on an empty stomach (at least 30 minutes before food or 2 hours after food). The appropriate dose of VIDEX coadministered with tenofovir disoproxil fumarate in patients with creatinine clearance of less than 60 mL/min has not been established. ([*See Drug Interactions (7)* and *Clinical Pharmacology (12.3)*]; see the complete prescribing information for VIDEX EC (enteric-coated formulation of didanosine) for results of drug interaction studies of tenofovir disoproxil fumarate with reduced doses of the enteric-coated formulation of didanosine.)

Hepatic Impairment

No dose adjustment is required in patients with hepatic impairment [*see Warnings and Precautions (5.3)* and *Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

These recommendations are based on either drug interaction studies or observed clinical toxicities.

4.1 Allopurinol

Coadministration of didanosine and allopurinol is contraindicated because systemic exposures of didanosine are increased, which may increase didanosine-associated toxicity [*see Clinical Pharmacology (12.3)*].

4.2 Ribavirin

Coadministration of didanosine and ribavirin is contraindicated because exposures of the active metabolite of didanosine (dideoxyadenosine 5′-triphosphate) are increased. Fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in patients receiving both didanosine and ribavirin.

5 WARNINGS AND PRECAUTIONS

5.1 Pancreatitis

Fatal and nonfatal pancreatitis has occurred during therapy with VIDEX used alone or in combination regimens in both treatment-naive and treatment-experienced patients, regardless of degree of immunosuppression. VIDEX should be suspended in patients with signs or symptoms of pancreatitis and discontinued in patients with confirmed pancreatitis. Patients treated with VIDEX in combination with stavudine may be at increased risk for pancreatitis.

When treatment with life-sustaining 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-1 infection, especially the elderly, 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. [*See Adverse Reactions (6).*]

5.2 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. Fatal lactic acidosis has been reported in pregnant women who received the combination of didanosine and stavudine with other antiretroviral agents. The combination of didanosine and stavudine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk [*see Use in Specific Populations (8.1)*]. 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 signs or symptoms with or without laboratory findings consistent with symptomatic hyperlactatemia, lactic acidosis, or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

5.3 Hepatic Toxicity

The safety and efficacy of VIDEX have not been established in HIV-infected patients with significant underlying liver disease. During combination antiretroviral therapy, patients with preexisting liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities, including severe and potentially fatal hepatic adverse events, and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Hepatotoxicity and hepatic failure resulting in death were reported during postmarketing surveillance in HIV-infected patients treated with hydroxyurea and other antiretroviral agents. Fatal hepatic events were reported most often in patients treated with the combination of

hydroxyurea, didanosine, and stavudine. This combination should be avoided. [*See Adverse Reactions (6).*]

5.4 Non-cirrhotic Portal Hypertension

Postmarketing cases of non-cirrhotic portal hypertension have been reported, including cases leading to liver transplantation or death. Cases of didanosine-associated non-cirrhotic portal hypertension were confirmed by liver biopsy in patients with no evidence of viral hepatitis. Onset of signs and symptoms ranged from months to years after start of didanosine therapy. Common presenting features included elevated liver enzymes, esophageal varices, hematemesis, ascites, and splenomegaly.

Patients receiving VIDEX should be monitored for early signs of portal hypertension (eg, thrombocytopenia and splenomegaly) during routine medical visits. Appropriate laboratory testing including liver enzymes, serum bilirubin, albumin, complete blood count, and international normalized ratio (INR) and ultrasonography should be considered. VIDEX should be discontinued in patients with evidence of non-cirrhotic portal hypertension.

5.5 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. Discontinuation of VIDEX should be considered in patients who develop peripheral neuropathy. [*See Adverse Reactions (6).*]

5.6 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 (6)*].

5.7 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including VIDEX. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to

indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

5.8 Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections:

- Pancreatitis [*see Boxed Warning, Warnings and Precautions (5.1)*]
- Lactic acidosis/severe hepatomegaly with steatosis [*see Boxed Warning, Warnings and Precautions (5.2)*]
- Hepatic toxicity [*see Warnings and Precautions (5.3)*]
- Non-cirrhotic portal hypertension [*see Warnings and Precautions (5.4)*]
- Peripheral neuropathy [*see Warnings and Precautions (5.5)*]
- Retinal changes and optic neuritis [*see Warnings and Precautions (5.6)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults

Selected clinical adverse reactions that occurred in adult patients in clinical studies with VIDEX are provided in Tables 3 and 4.

Table 3: Selected Clinical Adverse Reactions from Monotherapy Studies

	Percent of Patients*

Table 3: Selected Clinical Adverse Reactions from Monotherapy Studies

Adverse Reactions	Percent of Patients*			
	ACTG 116A		ACTG 116B/117	
	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
Abdominal Pain	13	8	7	8
Rash/Pruritus	7	8	9	5
Pancreatitis	7	3	6	2

* The incidences reported included all severity grades and all reactions regardless of causality.

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Table 4: Selected Clinical Adverse Reactions from Combination Studies

Adverse Reactions	Percent of Patients[a,c]			
	AI454-148[b]		START 2[b]	
	VIDEX + stavudine + nelfinavir n=482	zidovudine + lamivudine + nelfinavir n=248	VIDEX + stavudine + indinavir n=102	zidovudine + lamivudine + indinavir n=103
Diarrhea	70	60	45	39
Nausea	28	40	53	67
Peripheral Neurologic Symptoms/Neuropathy	26	6	21	10
Headache	21	30	46	37
Rash	13	16	30	18
Vomiting	12	14	30	35
Pancreatitis (see below)	1	*	less than 1	*

[a] Percentages based on treated subjects.

[b] Median duration of treatment 48 weeks.

[c] The incidences reported included all severity grades and all reactions regardless of causality.

* This event was not observed in this study arm.

162 Pancreatitis resulting in death was observed in one patient who received VIDEX (didanosine)
163 plus stavudine plus nelfinavir in Study Al454-148 and in one patient who received VIDEX plus

stavudine plus indinavir in the START 2 study. In addition, pancreatitis resulting in death was observed in 2 of 68 patients who received VIDEX plus stavudine plus indinavir plus hydroxyurea in an ACTG clinical trial [*see Warnings and Precautions (5)*].

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

Selected laboratory abnormalities in clinical studies with VIDEX are shown in Tables 5-7.

Table 5: Selected Laboratory Abnormalities from Monotherapy Studies

	Percent of Patients			
	ACTG 116A		ACTG 116B/117	
Parameter	**VIDEX n=197**	**zidovudine n=212**	**VIDEX n=298**	**zidovudine n=304**
SGOT (AST) (greater than 5 x ULN)	9	4	7	6
SGPT (ALT) (greater than 5 x ULN)	9	6	6	6
Alkaline phosphatase (greater than 5 x ULN)	4	1	1	1
Amylase (at least 1.4 x ULN)	17	12	15	5
Uric acid (greater than 12 mg/dL)	3	1	2	1

ULN = upper limit of normal.

Table 6: Selected Laboratory Abnormalities from Combination Studies (Grades 3-4)

	Percent of Patients[a]			
	AI454-148[b]		START 2[b]	
Parameter	**VIDEX + stavudine + nelfinavir n=482**	**zidovudine + lamivudine + nelfinavir n=248**	**VIDEX + stavudine + indinavir n=102**	**zidovudine + lamivudine + indinavir n=103**
Bilirubin (greater than 2.6 x ULN)	less than 1	less than 1	16	8
SGOT (AST) (greater than 5 x ULN)	3	2	7	7
SGPT (ALT) (greater than 5 x	3	3	8	5

Table 6: Selected Laboratory Abnormalities from Combination Studies (Grades 3-4)

	Percent of Patients[a]			
	AI454-148[b]		START 2[b]	
Parameter	VIDEX + stavudine + nelfinavir n=482	zidovudine + lamivudine + nelfinavir n=248	VIDEX + stavudine + indinavir n=102	zidovudine + lamivudine + indinavir n=103
ULN)				
GGT (greater than 5 x ULN)	NC	NC	5	2
Lipase (greater than 2 x ULN)	7	2	5	5
Amylase (greater than 2 x ULN)	NC	NC	8	2

ULN = upper limit of normal.

NC = Not Collected.

[a] Percentages based on treated subjects.

[b] Median duration of treatment 48 weeks.

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Table 7: Selected Laboratory Abnormalities from Combination Studies (All Grades)

	Percent of Patients[a]			
	AI454-148[b]		START 2[b]	
Parameter	VIDEX + stavudine + nelfinavir n=482	zidovudine + lamivudine + nelfinavir n=248	VIDEX + stavudine + indinavir n=102	zidovudine + lamivudine + indinavir n=103
Bilirubin	7	3	68	55
SGOT (AST)	42	23	53	20
SGPT (ALT)	37	24	50	18
GGT	NC	NC	28	12
Lipase	17	11	26	19
Amylase	NC	NC	31	17

NC = Not Collected.

[a] Percentages based on treated subjects.

[b] Median duration of treatment 48 weeks.

Pediatric Patients

In clinical trials, 743 pediatric patients between 2 weeks and 18 years of age have been treated with didanosine. Adverse reactions and laboratory abnormalities reported to occur in these patients were generally consistent with the safety profile of didanosine in adults.

In pediatric phase 1 studies, pancreatitis occurred in 2 of 60 (3%) patients treated at entry doses below 300 mg/m^2/day and in 5 of 38 (13%) patients treated at higher doses. In study ACTG 152, pancreatitis occurred in none of the 281 pediatric patients who received didanosine 120 mg/m^2 every 12 hours and in less than 1% of the 274 pediatric patients who received didanosine 90 mg/m^2 every 12 hours in combination with zidovudine [*see Clinical Studies (14)*].

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

6.2 Postmarketing Experience

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

Blood and Lymphatic System Disorders – anemia, leukopenia, and thrombocytopenia.

Body as a Whole – alopecia, anaphylactoid reaction, asthenia, chills/fever, pain, and redistribution/accumulation of body fat [*see Warnings and Precautions (5.8)*].

Digestive Disorders – anorexia, dyspepsia, and flatulence.

Exocrine Gland Disorders – pancreatitis (including fatal cases) [*see Boxed Warning, Warnings and Precautions (5.1)*], sialoadenitis, parotid gland enlargement, dry mouth, and dry eyes.

Hepatobiliary Disorders – symptomatic hyperlactatemia/lactic acidosis and hepatic steatosis [*see Boxed Warning, Warnings and Precautions (5.2)*]; non-cirrhotic portal hypertension [*see Warnings and Precautions (5.4)*]; hepatitis and liver failure.

Metabolic Disorders – diabetes mellitus, hypoglycemia, and hyperglycemia.

Musculoskeletal Disorders – myalgia (with or without increases in creatine kinase), rhabdomyolysis including acute renal failure and hemodialysis, arthralgia, and myopathy.

Ophthalmologic Disorders – retinal depigmentation and optic neuritis [*see Warnings and Precautions (5.6)*].

Use with Stavudine- and Hydroxyurea-Based Regimens

When didanosine is used in combination with other agents with similar toxicities, the incidence of these toxicities may be higher than when didanosine is used alone. Thus, patients treated with VIDEX in combination with stavudine, with or without hydroxyurea, may be at increased risk for pancreatitis and hepatotoxicity, which may be fatal, and severe peripheral neuropathy [*see Warnings and Precautions (5)*]. The combination of VIDEX and hydroxyurea, with or without stavudine, should be avoided.

7 DRUG INTERACTIONS

7.1 Established Drug Interactions

Clinical recommendations based on the results of drug interaction studies are listed in Table 8. Pharmacokinetic results of drug interactions studies are shown in Tables 12 and 13 [*see Contraindications (4.1 and 4.2), Clinical Pharmacology (12.3)*].

Table 8: Established Drug Interactions with VIDEX

Drug	Effect	Clinical Comment
ciprofloxacin	↓ ciprofloxacin concentration	Administer VIDEX at least 2 hours after or 6 hours before ciprofloxacin.
delavirdine	↓ delavirdine concentration	Administer VIDEX 1 hour after delavirdine.
ganciclovir	↑ didanosine concentration	If there is no suitable alternative to ganciclovir, then use in combination with VIDEX with caution. Monitor for didanosine-associated toxicity.
indinavir	↓ indinavir concentration	Administer VIDEX 1 hour after indinavir.
methadone	↓ didanosine concentration	Do not coadminister methadone with VIDEX pediatric powder due to significant decreases in didanosine concentrations. If coadministration of methadone and didanosine is necessary, the recommended formulation of didanosine is VIDEX EC. Patients should be closely monitored for adequate clinical response when VIDEX EC is coadministered with methadone, including monitoring

Table 8: Established Drug Interactions with VIDEX

Drug	Effect	Clinical Comment
		for changes in HIV RNA viral load.
nelfinavir	No interaction 1 hour after didanosine	Administer nelfinavir 1 hour after VIDEX.
tenofovir disoproxil fumarate	↑ didanosine concentration	A dose reduction of VIDEX to the following dosage once daily is recommended.[a] • 250 mg (adults weighing at least 60 kg with creatinine clearance of at least 60 mL/min) • 200 mg (adults weighing less than 60 kg with creatinine clearance of at least 60 mL/min) VIDEX and tenofovir disoproxil fumarate may be taken together in the fasted state. If tenofovir disoproxil fumarate is taken with food, VIDEX should be taken on an empty stomach (at least 30 minutes before food or 2 hours after food). Patients should be monitored for didanosine-associated toxicities and clinical response.

↑ Indicates increase.

↓ Indicates decrease.

[a] The dosing recommendation for coadministration of VIDEX EC and tenofovir disoproxil fumarate with respect to meal consumption differs from that of VIDEX. See the complete prescribing information for VIDEX EC.

Exposure to didanosine is increased when coadministered with tenofovir disoproxil fumarate [Table 8 and *see Clinical Pharmacokinetics (12.3, Table 12)*]. Increased exposure may cause or worsen didanosine-related clinical toxicities, including pancreatitis, symptomatic hyperlactatemia/lactic acidosis, and peripheral neuropathy. Coadministration of tenofovir disoproxil fumarate with VIDEX should be undertaken with caution, and patients should be monitored closely for didanosine-related toxicities and clinical response. VIDEX should be suspended if signs or symptoms of pancreatitis, symptomatic hyperlactatemia, or lactic acidosis develop [*see Dosage and Administration (2.3), Warnings and Precautions (5)*]. Suppression of CD4 cell counts has been observed in patients receiving tenofovir disoproxil fumarate with didanosine at a dose of 400 mg daily.

7.2 Predicted Drug Interactions

Predicted drug interactions with VIDEX are listed in Table 9.

Table 9: Predicted Drug Interactions with VIDEX

Drug or Drug Class	Effect	Clinical Comment
Drugs that may cause pancreatic toxicity	↑ risk of pancreatitis	Use only with extreme caution[a]
Neurotoxic drugs	↑ risk of neuropathy	Use with caution[b]
Antacids containing magnesium or aluminum	↑ side effects associated with antacid components	Use caution with VIDEX Pediatric Powder for Oral Solution
Azole antifungals	↓ ketoconazole or itraconazole concentration	Administer drugs such as ketoconazole or itraconazole at least 2 hours before VIDEX.
Quinolone antibiotics (see also ciprofloxacin in Table 8)	↓ quinolone concentration	Consult package insert of the quinolone.
Tetracycline antibiotics	↓ antibiotic concentration	Consult package insert of the tetracycline.

↑ Indicates increase.

↓ Indicates decrease.

[a] Only if other drugs are not available and if clearly indicated. If treatment with life-sustaining drugs that cause pancreatic toxicity is required, suspension of VIDEX is recommended [*see Warnings and Precautions (5.1)*].

[b] [*See Warnings and Precautions (5.6).*]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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. Animal reproduction studies are not always predictive of human response.

There are no adequate and well-controlled studies of didanosine in pregnant women. Didanosine should be used during pregnancy only if the potential benefit justifies the potential risk.

Fatal lactic acidosis has been reported in pregnant women who received the combination of didanosine and stavudine with other antiretroviral agents. It is unclear if pregnancy augments the risk of lactic acidosis/hepatic steatosis syndrome reported in nonpregnant individuals receiving nucleoside analogues [*see Warnings and Precautions (5.2)*]. **The combination of didanosine and stavudine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk.** Healthcare providers caring for HIV-infected pregnant women receiving didanosine should be alert for early diagnosis of lactic acidosis/hepatic steatosis syndrome.

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 1-800-258-4263.

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. A study in rats showed that following oral administration, didanosine and/or its metabolites were excreted into the milk of lactating rats. It is not known if didanosine is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving didanosine**.

8.4 Pediatric Use

Use of didanosine in pediatric patients from 2 weeks of age through adolescence is supported by evidence from adequate and well-controlled studies of VIDEX in adult and pediatric patients [*see Dosage and Administration (2), Adverse Reactions (6.1), Clinical Pharmacology (12.3),* and *Clinical Studies (14)*].

8.5 Geriatric Use

In an Expanded Access Program for patients with advanced HIV infection, patients aged 65 years and older had a higher frequency of pancreatitis (10%) than younger patients (5%) [*see*

Warnings and Precautions (5.1)]. Clinical studies of didanosine did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently than younger subjects. Didanosine is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. In addition, renal function should be monitored and dosage adjustments should be made accordingly [*see Dosage and Administration (2.2)*].

8.6 Renal Impairment

Patients with renal impairment (creatinine clearance of less than 60 mL/min) may be at greater risk of toxicity from didanosine due to decreased drug clearance [*see Clinical Pharmacology (12.3)*]. A dose reduction is recommended for these patients [*see Dosage and Administration (2)*].

10 OVERDOSAGE

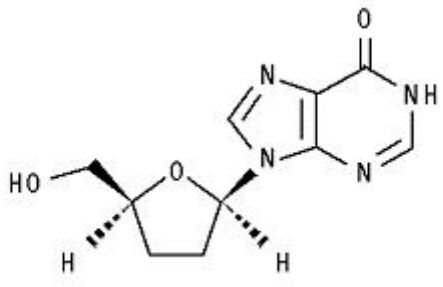
There is no known antidote for VIDEX (didanosine) overdosage. In phase 1 studies, in which VIDEX was initially administered at doses ten times the currently recommended dose, toxicities included: pancreatitis, peripheral neuropathy, diarrhea, hyperuricemia, and hepatic dysfunction. Didanosine is not dialyzable by peritoneal dialysis, although there is some clearance by hemodialysis [*see Clinical Pharmacology (12.3)*].

11 DESCRIPTION

VIDEX® is a brand name for didanosine, USP, a synthetic purine nucleoside analogue active against HIV-1.

Didanosine is available as VIDEX, a Pediatric Powder for Oral Solution [*see How Supplied/Storage and Handling (16)*] and as VIDEX® EC Delayed-Release Capsules, containing enteric-coated beadlets [consult prescribing information for VIDEX EC (didanosine)].

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 less than 3 and 37° C, 10% of didanosine decomposes to hypoxanthine in less than 2 minutes.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Didanosine is an antiviral agent [*see Clinical Pharmacology (12.4)*].

12.3 Pharmacokinetics

The pharmacokinetic parameters of didanosine are summarized in Table 10. 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 50 to 400 mg. 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 (less than 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 10: Mean ± SD Pharmacokinetic Parameters for Didanosine in Adult and Pediatric Patients

			Pediatric Patients[b]			
Parameter	**Adult Patients[a]**	**n**	**8 months to 19 years**	**n**	**2 weeks to 4 months**	**n**
Oral bioavailability (%)	42 ± 12	6	25 ± 20	46	ND	
Apparent volume of distribution[c] (L/m^2)	43.70 ± 8.90	6	28 ± 15	49	ND	
CSF-plasma ratio[d]	21 ± 0.03%[e]	5	46% (range 12-85%)	7	ND	
Systemic clearance[c] ($mL/min/m^2$)	526 ± 64.7	6	516 ± 184	49	ND	
Renal clearance[f] ($mL/min/m^2$)	223 ± 85.0	6	240 ± 90	15	ND	
Apparent oral clearance[g] ($mL/min/m^2$)	1252 ± 154	6	2064 ± 736	48	1353 ± 759	41
Elimination half-life[f] (h)	1.5 ± 0.4	6	0.8 ± 0.3	60	1.2 ± 0.3	21
Urinary recovery of didanosine[f] (%)	18 ± 8	6	18 ± 10	15	ND	

CSF = cerebrospinal fluid, ND = not determined.

[a] Parameter units for adults were converted to the same units in pediatric patients to facilitate comparisons among populations: mean adult body weight = 70 kg and mean adult body surface area = 1.73 m^2.

[b] In 1-day old infants (n=10), the mean ± SD apparent oral clearance was 1523 ± 1176 $mL/min/m^2$ and half-life was 2.0 ± 0.7 h.

[c] Following IV administration.

[d] Following IV administration in adults and IV or oral administration in pediatric patients.

[e] Mean ± SE.

[f] Following oral administration.

[g] Apparent oral clearance estimate was determined as the ratio of the mean systemic clearance and the mean oral bioavailability estimate.

Effect of Food

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 [*see Dosage and Administration (2)*]. VIDEX should be taken on an empty stomach.

Special Populations

Renal Insufficiency: Data from two studies in adults indicated that the apparent oral clearance of didanosine decreased and the terminal elimination half-life increased as creatinine clearance decreased (see Table 11). 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. [*See Dosage and Administration (2.2).*]

Table 11: Mean ± SD Pharmacokinetic Parameters for Didanosine Following a Single Oral Dose

	Creatinine Clearance (mL/min)				
Parameter	**at least 90 n=12**	**60-90 n=6**	**30-59 n=6**	**10-29 n=3**	**Dialysis Patients n=11**
CL_{cr} (mL/min)	112 ± 22	68 ± 8	46 ± 8	13 ± 5	ND
CL/F (mL/min)	2164 ± 638	1566 ± 833	1023 ± 378	628 ± 104	543 ± 174
CL_R (mL/min)	458 ± 164	247 ± 153	100 ± 44	20 ± 8	less than 10
$T_{½}$ (h)	1.42 ± 0.33	1.59 ± 0.13	1.75 ± 0.43	2.0 ± 0.3	4.1 ± 1.2

ND = not determined due to anuria.

CL_{cr} = creatinine clearance.

CL/F = apparent oral clearance.

CL_R = renal clearance.

Hepatic Impairment: The pharmacokinetics of didanosine have been studied in 12 non-HIV-infected subjects with moderate (n=8) to severe (n=4) hepatic impairment (Child-Pugh Class B or C). Mean AUC and C_{max} values following a single 400 mg dose of didanosine were approximately 13% and 19% higher, respectively, in patients with hepatic impairment compared to matched healthy subjects. No dose adjustment is needed, because a similar range and distribution of AUC and C_{max} values was observed for subjects with hepatic impairment and matched healthy controls. [*See Dosage and Administration (2.3).*]

Pediatric Patients: The pharmacokinetics of didanosine have been evaluated in HIV-exposed and HIV-infected pediatric patients from birth to adulthood. Overall, the pharmacokinetics of

didanosine in pediatric patients are similar to those of didanosine in adults. Didanosine plasma concentrations appear to increase in proportion to oral doses ranging from 25 to 120 mg/m^2 in pediatric patients less than 5 months old and from 80 to 180 mg/m^2 in children above 8 months old. For information on controlled clinical studies in pediatric patients, *see Clinical Studies (14.2)* and *Use in Specific Populations (8.4).*

Geriatric Patients: Didanosine pharmacokinetics have not been studied in patients over 65 years of age [*see Use in Specific Populations (8.5)*].

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

Drug Interactions

Tables 12 and 13 summarize the effects on AUC and C_{max}, with a 95% confidence interval (CI) when available, following coadministration of VIDEX (didanosine) with a variety of drugs. Drug-drug interactions for VIDEX buffered tablets are applicable to the VIDEX pediatric powder formulation and are noted in Tables 12 and 13. For clinical recommendations based on drug interaction studies for drugs in bold font, see *Dosage and Administration (2.3 for Concomitant Therapy with Tenofovir Disoproxil Fumarate), Contraindications (4.1),* and *Drug Interactions (7.1 and 7.2).*

Table 12: Results of Drug Interaction Studies with VIDEX: Effects of Coadministered Drug on Didanosine Plasma AUC and C_{max} Values

			% Change of Didanosine Pharmacokinetic Parameters[a]	
Drug	**Didanosine Dosage**	**n**	**AUC of Didanosine (95% CI)**	**C_{max} of Didanosine (95% CI)**
allopurinol, renally impaired, 300 mg/day	200 mg single dose	2	↑ 312%	↑ 232%
healthy volunteer, 300 mg/day for 7 days	400 mg single dose	14	↑ 113%	↑ 69%
ciprofloxacin, 750 mg every 12 hours for 3 days, 2 hours before didanosine	200 mg every 12 hours for 3 days	8[b]	↓ 16%	↓ 28%
ganciclovir, 1000 mg every 8 hours, 2 hours after didanosine	200 mg every 12 hours	12	↑ 111%	NA
indinavir, 800 mg single dose, simultaneous	200 mg single dose	16	↔	↔
1 hour before didanosine	200 mg single dose	16	↓ 17%	↓ 13%

Table 12: Results of Drug Interaction Studies with VIDEX: Effects of Coadministered Drug on Didanosine Plasma AUC and C_{max} Values

Drug	Didanosine Dosage	n	% Change of Didanosine Pharmacokinetic Parameters[a] AUC of Didanosine (95% CI)	% Change of Didanosine Pharmacokinetic Parameters[a] C_{max} of Didanosine (95% CI)
			(-27, - 7%)[c]	(-28, 5%)[c]
ketoconazole, 200 mg/day for 4 days, 2 hours before didanosine	375 mg every 12 hours for 4 days	12[b]	↔	↓ 12%
methadone, chronic maintenance dose[f]	200 mg single dose	16[d]	↓ 57%	↓ 66%
	400 mg single dose	15,16[e]	↓ 29% (-40, -16%)[c]	↓ 41% (-54, -26%)[c]
tenofovir,[g,h] 300 mg once daily, 1 hour after didanosine	250[i] mg or 400 mg once daily for 7 days	14	↑ 44% (31, 59%)[c]	↑ 28% (11, 48%)[c]
loperamide, 4 mg every 6 hours for 1 day	300 mg single dose	12[b]	↔	↓ 23%
metoclopramide, 10 mg single dose	300 mg single dose	12[b]	↔	↑ 13%
ranitidine, 150 mg single dose, 2 hours before didanosine	375 mg single dose	12[b]	↑ 14%	↑ 13%
rifabutin, 300 or 600 mg/day for 12 days	167 mg or 250 mg every 12 hours for 12 days	11	↑ 13% (-1, 27%)	↑ 17% (-4, 38%)
ritonavir, 600 mg every 12 hours for 4 days	200 mg every 12 hours for 4 days	12	↓ 13% (0, 23%)	↓ 16% (5, 26%)
stavudine, 40 mg every 12 hours for 4 days	100 mg every 12 hours for 4 days	10	↔	↔
sulfamethoxazole, 1000 mg single dose	200 mg single dose	8[b]	↔	↔
trimethoprim, 200 mg single dose	200 mg single dose	8[b]	↔	↑ 17% (-23, 77%)
zidovudine, 200 mg every 8 hours for 3 days	200 mg every 12 hours for 3 days	6[b]	↔	↔

↑ Indicates increase.

↓ Indicates decrease.

↔ Indicates no change, or mean increase or decrease of less than 10%.

[a] The 95% confidence intervals for the percent change in the pharmacokinetic parameter are displayed.

[b] HIV-infected patients.

[c] 90% CI.

[d] Comparisons are made to a parallel control group not receiving methadone (n=10).

Table 12: Results of Drug Interaction Studies with VIDEX: Effects of Coadministered Drug on Didanosine Plasma AUC and C_{max} Values

Drug	Didanosine Dosage	n	% Change of Didanosine Pharmacokinetic Parameters[a] AUC of Didanosine (95% CI)	% Change of Didanosine Pharmacokinetic Parameters[a] C_{max} of Didanosine (95% CI)

[e] Comparisons are made to historical controls (n=68, pooled from 3 studies) conducted in healthy subjects. The number of subjects evaluated for AUC and C_{max} is 15 and 16, respectively.

[f] For results of drug interaction studies between the enteric-coated formulation of didanosine (VIDEX EC) and methadone, see the complete prescribing information for VIDEX EC.

[g] Tenofovir disoproxil fumarate.

[h] For results of drug interaction studies between the enteric-coated formulation of didanosine (VIDEX EC) and tenofovir disoproxil fumarate, see the complete prescribing information for VIDEX EC.

[i] Patients less than 60 kg with creatinine clearance of at least 60 mL/min.

NA = Not available.

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Table 13: Results of Drug Interaction Studies with VIDEX: Effects of Didanosine on Coadministered Drug Plasma AUC and C_{max} Values

Drug	Didanosine Dosage	n	% Change of Coadministered Drug Pharmacokinetic Parameters[a] AUC of Coadministered Drug (95% CI)	% Change of Coadministered Drug Pharmacokinetic Parameters[a] C_{max} of Coadministered Drug (95% CI)
ciprofloxacin, 750 mg every 12 hours for 3 days, 2 hours before didanosine	200 mg every 12 hours for 3 days	8[b]	↓ 26%	↓ 16%
750 mg single dose	buffered placebo tablet	12	↓ 98%	↓ 93%
delavirdine, 400 mg single dose simultaneous	125 mg or 200 mg every 12 hours	12[b]	↓ 32%	↓ 53%
1 hour before didanosine	125 mg or 200 mg every 12 hours	12[b]	↑ 20%	↑ 18%
ganciclovir, 1000 mg every 8 hours, 2 hours after didanosine	200 mg every 12 hours	12[b]	↓ 21%	NA
indinavir, 800 mg single dose simultaneous	200 mg single dose	16	↓ 84%	↓ 82%
1 hour before didanosine	200 mg single dose	16	↓ 11%	↓ 4%

Table 13: Results of Drug Interaction Studies with VIDEX: Effects of Didanosine on Coadministered Drug Plasma AUC and C_{max} Values

Drug	Didanosine Dosage	n	% Change of Coadministered Drug Pharmacokinetic Parameters[a]	
			AUC of Coadministered Drug (95% CI)	C_{max} of Coadministered Drug (95% CI)
ketoconazole, 200 mg/day for 4 days, 2 hours before didanosine	375 mg every 12 hours for 4 days	12[b]	↓ 14%	↓ 20%
nelfinavir, 750 mg single dose, 1 hour after didanosine	200 mg single dose	10[b]	↑ 12%	↔
dapsone, 100 mg single dose	200 mg every 12 hours for 14 days	6[b]	↔	↔
ranitidine, 150 mg single dose, 2 hours before didanosine	375 mg single dose	12[b]	↓ 16%	↔
ritonavir, 600 mg every 12 hours for 4 days	200 mg every 12 hours for 4 days	12	↔	↔
stavudine, 40 mg every 12 hours for 4 days	100 mg every 12 hours for 4 days	10[b]	↔	↑ 17%
sulfamethoxazole, 1000 mg single dose	200 mg single dose	8[b]	↓ 11% (-17, -4%)	↓ 12% (-28, 8%)
tenofovir,[c] 300 mg once daily 1 hour after didanosine	250[d] mg or 400 mg once daily for 7 days	14	↔	↔
trimethoprim, 200 mg single dose	200 mg single dose	8[b]	↑ 10% (-9, 34%)	↓ 22% (-59, 49%)
zidovudine, 200 mg every 8 hours for 3 days	200 mg every 12 hours for 3 days	6[b]	↓ 10% (-27, 11%)	↓ 16.5% (-53, 47%)

↑ Indicates increase.

↓ Indicates decrease.

↔ Indicates no change, or mean increase or decrease of less than 10%.

[a] The 95% confidence intervals for the percent change in the pharmacokinetic parameter are displayed.

[b] HIV-infected patients.

[c] Tenofovir disoproxil fumarate.

[d] Patients less than 60 kg with creatinine clearance of at least 60 mL/min.

NA = Not available.

12.4 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.

Antiviral Activity in Cell Culture

The 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% (EC_{50}) ranged from 2.5 to 10 µM (1 µM = 0.24 µg/mL) in lymphoblastic cell lines and 0.01 to 0.1 µM in monocyte/macrophage cell cultures.

Resistance

HIV-1 isolates with reduced sensitivity to didanosine have been selected in cell culture 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 substitution 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 cell culture compared to baseline isolates. Clinical isolates that exhibited a decrease in didanosine susceptibility harbored one or more didanosine resistance-associated substitutions.

Cross-resistance

HIV-1 isolates from 2 of 39 patients receiving combination therapy for up to 2 years with didanosine and zidovudine exhibited decreased susceptibility to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine in cell culture. These isolates harbored five substitutions

In data from clinical

studies, the presence of thymidine analogue mutations (M41L, D67N, L210W, T215Y, K219Q) has been shown to decrease the response to didanosine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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 based on relative AUC comparisons. 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.

Didanosine was positive in the following genetic toxicology assays: 1) the *Escherichia coli* tester strain WP2 uvrA bacterial mutagenicity assay; 2) the L5178Y/TK+/- mouse lymphoma mammalian cell gene mutation assay; 3) the *in vitro* chromosomal aberrations assay in cultured human peripheral lymphocytes; 4) the *in vitro* chromosomal aberrations assay in Chinese Hamster Lung cells; and 5) the BALB/c 3T3 *in vitro* transformation assay. No evidence of mutagenicity was observed in an Ames *Salmonella* bacterial mutagenicity assay or in rat and mouse *in vivo* micronucleus assays.

13.2 Animal Toxicology and/or Pharmacology

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.

14 CLINICAL STUDIES

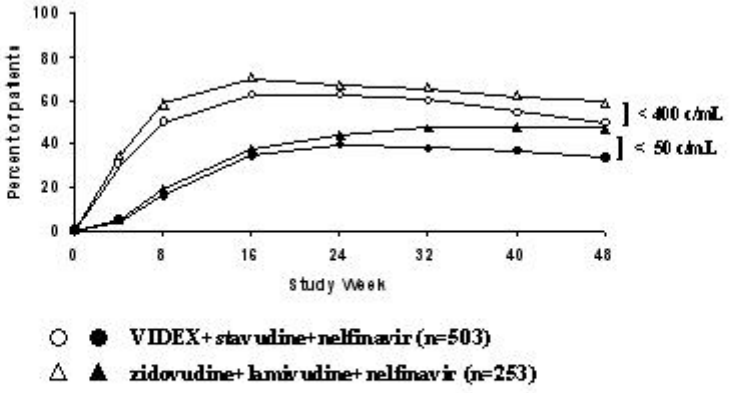
14.1 Adult Patients

Combination Therapy

START 2 was a multicenter, randomized, open-label study comparing VIDEX (200 mg twice daily)/stavudine/indinavir to zidovudine/lamivudine/indinavir in 205 treatment-naive patients. Both regimens resulted in a similar magnitude of suppression of HIV-1 RNA levels and increases in CD4 cell counts through 48 weeks.

Study AI454-148 was a randomized, open-label, multicenter study comparing treatment with VIDEX (400 mg once daily) plus stavudine (40 mg twice daily) and nelfinavir (750 mg three times daily) versus zidovudine (300 mg twice daily) plus lamivudine (150 mg twice daily) and nelfinavir (750 mg three times daily) in 756 treatment-naive patients, with a median CD4 cell count of 340 cells/mm^3 (range 80 to 1568 cells/mm^3) and a median plasma HIV-1 RNA of 4.69 $\log_{10}$ copies/mL (range 2.6 to 5.9 $\log_{10}$ copies/mL) at baseline. Median CD4 cell count increases at 48 weeks were 188 cells/mm^3 in both treatment groups. Treatment response and outcomes through 48 weeks are shown in Figure 1 and Table 14.

Figure 1: Treatment Response Through Week 48*, AI454-148



* Percent of patients at each time point who have HIV RNA <400 or <50 copies/mL, are on their original study medication (except stavudine-zidovudine switches), and have not experienced an AIDS-defining event.

Table 14: Outcomes of Randomized Treatment Through Week 48, AI454-148

Week 48 Status	Percent of Patients with HIV-1 RNA less than 400 copies/mL (less than 50 copies/mL)	
	VIDEX/stavudine/nelfinavir n=503	lamivudine/zidovudine/nelfinavir n=253
Responder[a]	50* (34*)	59 (47)
Virologic failure[b]	36 (57)	32 (48)
Death or disease progression	less than 1 (less than 1)	1 (less than 1)
Discontinued due to adverse events	4 (2)	2 (less than 1)
Discontinued due to other reasons[c]	6 (3)	4 (2)
Never initiated treatment	4 (4)	2 (2)

* p less than 0.05 for the differences between treatment groups, by Cochran-Mantel-Haenszel test.

[a] Patients achieved virologic response [two consecutive viral loads less than 400 (less than 50) copies/mL] and maintained it to Week 48.

[b] Includes viral rebound and failing to achieve confirmed less than 400 (less than 50) copies/mL by Week 48.

[c] Includes lost to follow-up, noncompliance, withdrawal, and pregnancy.

Monotherapy

The efficacy of VIDEX was demonstrated in two randomized, double-blind studies comparing VIDEX, given on a twice-daily schedule, to zidovudine, given three times daily, 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-naive 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.

Studies have demonstrated that the clinical benefit of monotherapy with antiretrovirals, including VIDEX, was time limited.

14.2 Pediatric Patients

Efficacy in pediatric patients was demonstrated in a randomized, double-blind, controlled study (ACTG 152, conducted 1991-1995) involving 831 patients 3 months to 18 years of age treated for more than 1.5 years with zidovudine (180 mg/m^2 every 6 hours), VIDEX (120 mg/m^2 every 12 hours), or zidovudine (120 mg/m^2 every 6 hours) plus VIDEX (90 mg/m^2 every 12 hours). Patients treated with VIDEX or VIDEX plus zidovudine had lower rates of HIV-1 disease progression or death compared with those treated with zidovudine alone.

16 HOW SUPPLIED/STORAGE AND HANDLING

VIDEX (didanosine, USP) Pediatric Powder for Oral Solution is supplied as shown in Table 15:

Table 15: VIDEX Pediatric Powder for Oral Solution

NDC NO.	Packaging Information	Product Quantity
0087-6632-41	One, 4-ounce glass, bottle per carton	2 g/bottle
0087-6633-41	One, 8-ounce glass, bottle per carton	4 g/bottle

Prior to dispensing, the pharmacist must reconstitute 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

Reconstitute 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 Maximum Strength Mylanta® Liquid 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.

2. Instruct the patient to shake the admixture thoroughly prior to use and to store the tightly closed container in the refrigerator.

Storage

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

_____

Mylanta® is a registered trademark of Johnson & Johnson-Merck Consumer Pharmaceuticals Company.

17 PATIENT COUNSELING INFORMATION

See Medication Guide.

17.1 Pancreatitis

Patients should be informed that a serious toxicity of VIDEX, used alone and in combination regimens, is pancreatitis, which may be fatal.

17.2 Peripheral Neuropathy

Patients should be informed 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-1 disease or a history of peripheral neuropathy, and that discontinuation of VIDEX may be required if toxicity develops.

17.3 Lactic Acidosis and Severe Hepatomegaly with Steatosis

Patients should be informed that 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.

17.4 Hepatic Toxicity

Patients should be informed that hepatotoxicity including fatal hepatic adverse events were reported in patients with preexisting liver dysfunction. The safety and efficacy of VIDEX have not been established in HIV-infected patients with significant underlying liver disease.

17.5 Non-cirrhotic Portal Hypertension

Patients should be informed that non-cirrhotic portal hypertension has been reported in patients taking VIDEX, including cases leading to liver transplantation or death.

17.6 Retinal Changes and Optic Neuritis

Patients should be informed that retinal changes and optic neuritis have been reported in adult and pediatric patients.

17.7 Fat Redistribution

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

17.8 Concomitant Therapy

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, which may exacerbate VIDEX toxicities.

17.9 General Information

VIDEX (didanosine) is not a cure for HIV-1 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.

Patients should be informed that the preferred dosing frequency of VIDEX is twice daily because there is more evidence to support the effectiveness of this dosing frequency. Once-daily dosing should be considered only for patients whose management requires once-daily dosing of VIDEX.

Patients should be instructed to not miss a dose but if they do, patients should take VIDEX as soon as possible. Patients should be told that if it is almost time for the next dose, they should skip the missed dose and continue with the regular dosing schedule.

Patients should be instructed to contact a poison control center or emergency room right away in case of an overdose.

VIDEX has not been shown to prevent a patient infected with HIV from passing the virus to other people. To protect others, patients should be advised to continue to practice safer sex and take precautions to prevent others from coming in contact with infected blood and other body fluids.