HIGHLIGHTS OF PRESCRIBING INFORMATION

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

VIDEX EC (didanosine, USP) Delayed-Release Capsules
Enteric-Coated Beadlets

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 EC 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----------

Warnings and Precautions,
Immune Reconstitution Syndrome (5.7) 11/2011

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

VIDEX EC (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. Dosing is based on body weight. (2.1)
- Pediatric patients: Ages 6 to 18 years, can safely swallow capsules and body weight at least 20 kg. Administered on an empty stomach, dosing is based on body weight. (2.1)

Body Weight	Dose
20 kg to less than 25 kg	200 mg once daily
25 kg to less than 60 kg	250 mg once daily
at least 60 kg	400 mg once daily

- 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----------

Capsules: 125 mg, 200 mg, 250 mg, 400 mg (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, 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 EC 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: November 2011

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 didanosine used alone or in combination regimens in both treatment-naive and treatment-experienced patients, regardless of degree of immunosuppression. VIDEX EC 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® EC (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 EC should be administered on an empty stomach. VIDEX EC Delayed-Release Capsules should be swallowed intact.

2.1 Recommended Dosage (Adult and Pediatric Patients)

The recommended total daily dose is based on body weight and is administered as one capsule given on a once-daily schedule as outlined in Table 1.

The recommended total daily dose to be administered once daily to pediatric patients weighing at least 20 kg who can swallow capsules is based on body weight (kg), consistent with the recommended adult dosing guidelines (see Table 1). Please consult the complete prescribing information for VIDEX (didanosine) Pediatric Powder for Oral Solution for dosage and administration of didanosine to pediatric patients weighing less than 20 kg or who can not swallow capsules.

Table 1: Recommended Dosage (Adult and Pediatric Patients)

Body Weight	Dose
20 kg to less than 25 kg	200 mg once daily
25 kg to less than 60 kg	250 mg once daily
at least 60 kg	400 mg once daily

2.2 Renal Impairment

Dosing recommendations for VIDEX EC and VIDEX Pediatric Powder for Oral Solution are different for patients with renal impairment. Please consult the complete prescribing information on administration of VIDEX (didanosine) Pediatric Powder for Oral Solution to patients with renal impairment.

Adult Patients

In adult patients with impaired renal function, the dose of VIDEX EC should be adjusted to compensate for the slower rate of elimination. The recommended doses and dosing intervals of VIDEX EC in adult patients with renal insufficiency are presented in Table 2.

Table 2: Recommended Dosage in Patients with Renal Impairment by Body Weight[a]

Creatinine Clearance (mL/min)	Dosage (mg)	
	at least 60 kg	less than 60 kg
at least 60	400 once daily	250 once daily
30-59	200 once daily	125 once daily
10-29	125 once daily	125 once daily
less than 10	125 once daily	[b]

[a] Based on studies using a buffered formulation of didanosine.

[b] Not suitable for use in patients less than 60 kg with CL_{cr} less than 10 mL/min. An alternate formulation of didanosine should be used.

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 EC 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 didanosine following hemodialysis.

2.3 Dose Adjustment

Concomitant Therapy with Tenofovir Disoproxil Fumarate

In patients who are also taking tenofovir disoproxil fumarate, a dose reduction of VIDEX EC 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 taken together with tenofovir disoproxil fumarate and a light meal (400 kcalories or less, 20% fat or less) or in the fasted state is recommended. The appropriate dose of VIDEX EC

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)*].

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 EC (didanosine, USP) Delayed-Release Capsules are white, opaque capsules as described below:

- 125 mg capsule imprinted with “BMS 125 mg 6671” in Tan
- 200 mg capsule imprinted with “BMS 200 mg 6672” in Green
- 250 mg capsule imprinted with “BMS 250 mg 6673” in Blue
- 400 mg capsule imprinted with “BMS 400 mg 6674” in Red

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 didanosine used alone or in combination regimens in both treatment-naive and treatment-experienced patients, regardless of degree of immunosuppression. VIDEX EC should be suspended in patients with signs or symptoms of pancreatitis and discontinued in patients with confirmed pancreatitis. Patients treated with VIDEX EC 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 EC (didanosine) therapy is recommended. In patients with risk factors for pancreatitis, VIDEX EC 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 EC 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 EC 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 EC 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 EC 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 EC 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 didanosine 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 EC 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 patients taking didanosine. Periodic retinal examinations should be considered for patients receiving VIDEX EC [*see Adverse Reactions (6)*].

5.7 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including VIDEX EC. 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.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of 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

Study AI454-152 was a 48-week, randomized, open-label study comparing VIDEX EC (400 mg once daily) plus stavudine (40 mg twice daily) plus nelfinavir (750 mg three times daily) to zidovudine (300 mg) plus lamivudine (150 mg) combination tablets twice daily plus nelfinavir (750 mg three times daily) in 511 treatment-naive patients. Selected clinical adverse reactions that occurred in combination with other antiretroviral agents are provided in Table 3.

Table 3: Selected Clinical Adverse Reactions, Study AI454-152[a]

Adverse Reactions	Percent of Patients[b,c]	
	VIDEX EC + stavudine + nelfinavir n=258	**zidovudine/lamivudine[d] +nelfinavir n=253**
Diarrhea	57	58
Peripheral Neurologic Symptoms/Neuropathy	25	11
Nausea	24	36
Headache	22	17
Rash	14	12
Vomiting	14	19
Pancreatitis (see below)	less than 1	*

[a] Median duration of treatment was 62 weeks in the VIDEX EC + stavudine + nelfinavir group and 61 weeks in the zidovudine/lamivudine + nelfinavir group.

[b] Percentages based on treated patients.

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

[d] Zidovudine/lamivudine combination tablet.

* This event was not observed in this study arm.

In clinical trials using a buffered formulation of didanosine, pancreatitis resulting in death was observed in one patient who received didanosine plus stavudine plus nelfinavir, one patient who received didanosine plus stavudine plus indinavir, and 2 of 68 patients who received didanosine plus stavudine plus indinavir plus hydroxyurea. In an early access program, pancreatitis resulting in death was observed in one patient who received VIDEX EC plus stavudine plus hydroxyurea plus ritonavir plus indinavir plus efavirenz [*see Warnings and Precautions (5)*].

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

Selected laboratory abnormalities that occurred in a study of VIDEX EC in combination with other antiretroviral agents are shown in Table 4.

Table 4: Selected Laboratory Abnormalities, Study AI454-152[a]

	Percent of Patients[b]			
	VIDEX EC + stavudine + nelfinavir n=258		zidovudine/lamivudine[c] + nelfinavir n=253	
Parameter	Grades 3-4[d]	All Grades	Grades 3-4[d]	All Grades
SGOT (AST)	5	46	5	19
SGPT (ALT)	6	44	5	22
Lipase	5	23	2	13
Bilirubin	less than 1	9	less than 1	3

[a] Median duration of treatment was 62 weeks in the VIDEX EC + stavudine + nelfinavir group and 61 weeks in the zidovudine/lamivudine + nelfinavir group.

[b] Percentages based on treated patients.

[c] Zidovudine/lamivudine combination tablet.

[d] Greater than 5 x ULN for SGOT and SGPT, at least 2.1 x ULN for lipase, and at least 2.6 x ULN for bilirubin (ULN = upper limit of normal).

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 didanosine, or a combination of these factors.

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

Body as a Whole - abdominal pain, 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 Warnings and Precautions (5.1)*], sialoadenitis, parotid gland enlargement, dry mouth, and dry eyes.

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

Metabolic Disorders - diabetes mellitus, elevated serum alkaline phosphatase level, elevated serum amylase level, elevated serum gamma-glutamyltransferase level, elevated serum uric acid level, 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 EC 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 EC 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 5. Pharmacokinetic results of drug interaction studies are shown in Tables 9-12 [*see Contraindications (4.1 and 4.2), Clinical Pharmacology (12.3)*].

Table 5: Established Drug Interactions Based on Studies with VIDEX EC or Studies with Buffered Formulations of Didanosine and Expected to Occur with VIDEX EC

Drug	Effect	Clinical Comment
ganciclovir	↑ didanosine concentration	If there is no suitable alternative to ganciclovir, then use in combination with VIDEX EC with caution. Monitor for didanosine-associated toxicity.
methadone	↓ didanosine concentration	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 for changes in HIV RNA viral load. Do not coadminister methadone with VIDEX pediatric powder due to significant decreases in didanosine concentrations.
nelfinavir	No interaction 1 hour after didanosine	Administer nelfinavir 1 hour after VIDEX EC.

Table 5: Established Drug Interactions Based on Studies with VIDEX EC or Studies with Buffered Formulations of Didanosine and Expected to Occur with VIDEX EC

Drug	Effect	Clinical Comment
tenofovir disoproxil fumarate	↑ didanosine concentration	A dose reduction of VIDEX EC to the following dosage once daily taken together with tenofovir disoproxil fumarate and a light meal (400 kcalories or less and 20% fat or less) or in the fasted state 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) Patients should be monitored for didanosine-associated toxicities and clinical response.

↑ Indicates increase.
↓ Indicates decrease.
[a] Coadministration of didanosine with food decreases didanosine concentrations. Thus, although not studied, it is possible that coadministration with heavier meals could reduce didanosine concentrations further.

Exposure to didanosine is increased when coadministered with tenofovir disoproxil fumarate [Table 5 and *see Clinical Pharmacokinetics (12.3, Tables 9 and 10)*]. 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 EC should be undertaken with caution, and patients should be monitored closely for didanosine-related toxicities and clinical response. VIDEX EC 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 EC are listed in Table 6.

Table 6: Predicted Drug Interactions with VIDEX EC

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]

↑ Indicates increase.

[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 EC 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 breastfeed 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 breastfeed 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 didanosine in adult and pediatric patients [*see Dosage and Administration (2), Adverse Reactions (6.1), Clinical Pharmacology (12.3),* and *Clinical Studies (14)*]. Additional pharmacokinetic studies in pediatric patients support use of VIDEX EC in pediatric patients who weigh at least 20 kg.

8.5 Geriatric Use

In an Expanded Access Program using a buffered formulation of didanosine for the treatment of 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, including those for VIDEX EC, 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

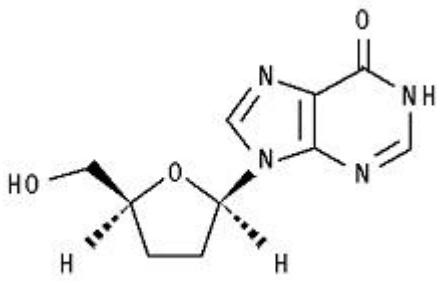
There is no known antidote for didanosine overdosage. In phase 1 studies, in which buffered formulations of didanosine were initially administered at doses ten times the currently recommended dose, toxicities included: pancreatitis, peripheral neuropathy, diarrhea, hyperuricemia, and hepatic dysfunction.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

11 DESCRIPTION

VIDEX® EC is the brand name for an enteric-coated formulation of didanosine, USP, a synthetic purine nucleoside analogue active against HIV-1. VIDEX EC Delayed-Release Capsules, containing enteric-coated beadlets, are available for oral administration in strengths of 125, 200, 250, and 400 mg of didanosine. The inactive ingredients in the beadlets include carboxymethylcellulose sodium 12, diethyl phthalate, methacrylic acid copolymer, sodium hydroxide, sodium starch glycolate, and talc. The capsule shells contain gelatin and titanium dioxide. The capsules are imprinted with edible inks.

Didanosine is also available in a powder formulation. Please consult the prescribing information for VIDEX (didanosine) Pediatric Powder for Oral Solution for additional information.

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. In VIDEX EC, an enteric coating is used to protect didanosine from degradation by stomach acid.

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 in HIV-infected adult and pediatric patients are summarized in Table 7, by weight ranges that correspond to recommended doses (Table 1). Didanosine is rapidly absorbed, with peak plasma concentrations generally observed from 0.25 to 1.50 hours following oral dosing with a buffered formulation. Increases in plasma didanosine concentrations were dose proportional over the range of 50 to 400 mg. In adults, the mean (± standard deviation) oral bioavailability following single oral dosing with a buffered formulation is 42 (±12)%. After oral administration, the urinary recovery of didanosine is approximately 18 (±8)% of the dose. The CSF-plasma ratio following IV administration is 21 (±0.03)%. 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 7: Pharmacokinetic Parameters for Didanosine in HIV-infected Patients

	Pediatrics			Adults
Parameter[a]	**20 kg to less than 25 kg n=10**	**25 kg to less than 60 kg n=17**	**At least 60 kg n=7**	**At least 60 kg n=44**
Apparent clearance (L/h)	89.5 ± 21.6	116.2 ± 38.6	196.0 ± 55.8	174.5 ± 69.7
Apparent volume of distribution (L)	98.1 ± 30.2	154.7 ± 55.0	363 ± 137.7	308.3 ± 164.3
Elimination half-life (h)	0.75 ± 0.13	0.92 ± 0.09	1.26 ± 0.19	1.19 ± 0.21
Steady-state AUC (mg•h/L)	2.38 ± 0.66	2.36 ± 0.70	2.25 ± 0.89	2.65 ± 1.07

[a] The pharmacokinetic parameters (mean ± standard deviation) of didanosine were determined by a population pharmacokinetic model based on combined clinical studies.

Comparison of Didanosine Formulations

In VIDEX EC, the active ingredient, didanosine, is protected against degradation by stomach acid by the use of an enteric coating on the beadlets in the capsule. The enteric coating dissolves when the beadlets empty into the small intestine, the site of drug absorption. With buffered formulations of didanosine, administration with antacid provides protection from degradation by stomach acid.

In healthy volunteers, as well as subjects infected with HIV-1, the AUC is equivalent for didanosine administered as the VIDEX EC formulation relative to a buffered tablet formulation. The peak plasma concentration (C_{max}) of didanosine, administered as VIDEX EC, is reduced approximately 40% relative to didanosine buffered tablets. The time to the peak concentration (T_{max}) increases from approximately 0.67 hours for didanosine buffered tablets to 2.0 hours for VIDEX EC.

Effect of Food

In the presence of food, the C_{max} and AUC for VIDEX EC were reduced by approximately 46% and 19%, respectively, compared to the fasting state [*see Dosage and Administration (2)*]. VIDEX EC should be taken on an empty stomach.

Special Populations

Renal Insufficiency: Data from two studies using a buffered formulation of didanosine indicated that the apparent oral clearance of didanosine decreased and the terminal elimination half-life increased as creatinine clearance decreased (see Table 8). 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 8: Mean ± SD Pharmacokinetic Parameters for Didanosine Following a Single Oral Dose of a Buffered Formulation

	Creatinine Clearance (mL/min)				Dialysis Patients n=11
Parameter	at least 90 n=12	60-90 n=6	30-59 n=6	10-29 n=3	
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.

A population pharmacokinetic analysis was conducted on pooled didanosine plasma concentration data from 9 clinical trials in 106 pediatric (neonate to 18 years of age) and 45 adult patients (greater than 18 years of age). Results showed that body weight is the primary factor associated with oral clearance. Based on the data analyzed, dosing schedule (once versus twice daily) and formulation (powder for oral solution, tablet, and delayed-release capsule) did not have an effect on oral clearance. Didanosine exposure similar to that at recommended adult doses can be achieved in pediatric patients with a weight-based dosing scheme [*see Dosage and Administration (2)*].

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 9 and 10 summarize the effects on AUC and C_{max}, with a 90% confidence interval (CI) when available, following coadministration of VIDEX EC with a variety of drugs. For clinical recommendations based on drug interaction studies for drugs in bold font, see *Dosage and Administration (2.3)* and *Drug Interactions (7.1)*.

Table 9: Results of Drug Interaction Studies with VIDEX EC: 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 (90% CI)**	**C_{max} of Didanosine (90% CI)**
tenofovir,[b,c] 300 mg once daily with a light meal[d]	400 mg single dose fasting 2 hours before tenofovir	26	↑ 48% (31, 67%)	↑ 48% (25, 76%)
tenofovir,[b,c] 300 mg once daily with a light meal[d]	400 mg single dose with tenofovir and a light meal	25	↑ 60% (44, 79%)	↑ 64% (41, 89%)
tenofovir,[b,c] 300 mg once daily with a light meal[d]	200 mg single dose with tenofovir and a light meal	33	↑ 16% (6, 27%)[e]	↓ 12% (-25, 3%)[e]
	250 mg single dose with tenofovir and a light meal	33	↔ (-13, 5%)[f]	↓ 20% (-32, -7%)[f]

Table 9: Results of Drug Interaction Studies with VIDEX EC: 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 (90% CI)**	**C_{max} of Didanosine (90% CI)**
	325 mg single dose with tenofovir and a light meal	33	↑ 13% (3, 24%)[f]	↓ 11% (-24, 4%)[f]
methadone, chronic maintenance dose	400 mg single dose	15, 16[g]	↓ 17% (-29, -2%)	↓ 16% (-33, 4%)

↑ Indicates increase.

↓ Indicates decrease.

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

[a] The 90% confidence intervals for the percent change in the pharmacokinetic parameter are displayed.

[b] All studies conducted in healthy volunteers at least 60 kg with creatinine clearance of at least 60 mL/min.

[c] Tenofovir disoproxil fumarate.

[d] 373 kcalories, 8.2 grams fat.

[e] Compared with VIDEX EC 250 mg administered alone under fasting conditions.

[f] Compared with VIDEX EC 400 mg administered alone under fasting conditions.

[g] Comparisons are made to historical controls (n=148, pooled from 5 studies) conducted in healthy subjects. The number of subjects evaluated for AUC and C_{max} is 15 and 16, respectively.

Table 10: Results of Drug Interaction Studies with VIDEX EC: Effects of Didanosine on Coadministered Drug Plasma AUC and C_{max} Values

			% Change of Coadministered Drug Pharmacokinetic Parameters[a,b]	
Drug	**Didanosine Dosage**	**n**	**AUC of Coadministered Drug (90% CI)**	**C_{max} of Coadministered Drug (90% CI)**
ciprofloxacin, 750 mg single dose	400 mg single dose	16	↔	↔
indinavir, 800 mg single dose	400 mg single dose	23	↔	↔

Table 10: Results of Drug Interaction Studies with VIDEX EC: Effects of Didanosine on Coadministered Drug Plasma AUC and C_{max} Values

Drug	Didanosine Dosage	n	% Change of Coadministered Drug Pharmacokinetic Parameters[a,b]	
			AUC of Coadministered Drug (90% CI)	C_{max} of Coadministered Drug (90% CI)
ketoconazole, 200 mg single dose	400 mg single dose	21	↔	↔
tenofovir,[c] 300 mg once daily with a light meal[d]	400 mg single dose fasting 2 hours before tenofovir	25	↔	↔
tenofovir,[c] 300 mg once daily with a light meal[d]	400 mg single dose with tenofovir and a light meal	25	↔	↔

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

[a] The 90% confidence intervals for the percent change in the pharmacokinetic parameter are displayed.

[b] All studies conducted in healthy volunteers at least 60 kg with creatinine clearance of at least 60 mL/min.

[c] Tenofovir disoproxil fumarate.

[d] 373 kcalories, 8.2 grams fat.

Didanosine Buffered Formulations: Tables 11 and 12 summarize the effects on AUC and C_{max}, with a 90% or 95% CI when available, following coadministration of buffered formulations of didanosine with a variety of drugs. The results of these studies may be expected to apply to VIDEX EC. For most of the listed drugs, no clinically significant pharmacokinetic interactions were noted. 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).*

Table 11: Results of Drug Interaction Studies with Buffered Formulations of Didanosine: 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)	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%
ganciclovir, 1000 mg every 8 hours, 2 hours after didanosine	200 mg every 12 hours	12	↑ 111%	NA
ciprofloxacin, 750 mg every 12 hours for 3 days, 2 hours before didanosine	200 mg every 12 hours for 3 days	8[c]	↓ 16%	↓ 28%
indinavir, 800 mg single dose simultaneous	200 mg single dose	16	↔	↔
1 hour before didanosine	200 mg single dose	16	↓ 17% (-27, -7%)[b]	↓ 13% (-28, 5%)[b]
ketoconazole, 200 mg/day for 4 days, 2 hours before didanosine	375 mg every 12 hours for 4 days	12[c]	↔	↓ 12%
loperamide, 4 mg every 6 hours for 1 day	300 mg single dose	12[c]	↔	↓ 23%
metoclopramide, 10 mg single dose	300 mg single dose	12[c]	↔	↑ 13%
ranitidine, 150 mg single dose, 2 hours before didanosine	375 mg single dose	12[c]	↑ 14%	↑ 13%
rifabutin, 300 mg 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[c]	↔	↔
trimethoprim, 200 mg single dose	200 mg single dose	8[c]	↔	↑ 17% (-23, 77%)
zidovudine, 200 mg every 8 hours for 3 days	200 mg every 12 hours for 3 days	6[c]	↔	↔

Table 11: Results of Drug Interaction Studies with Buffered Formulations of Didanosine: Effects of Coadministered Drug on Didanosine Plasma AUC and C_{max} Values

↑ 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] 90% CI.

[c] HIV-infected patients.

NA = Not available.

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

			% Change of Coadministered Drug Pharmacokinetic Parameters[a]	
Drug	**Didanosine Dosage**	**n**	**AUC of Coadministered Drug (95% CI)**	**C_{max} of Coadministered Drug (95% CI)**
dapsone, 100 mg single dose	200 mg every 12 hours for 14 days	6[b]	↔	↔
ganciclovir, 1000 mg every 8 hours, 2 hours after didanosine	200 mg every 12 hours	12[b]	↓ 21%	NA
nelfinavir, 750 mg single dose, 1 hour after didanosine	200 mg single dose	10[b]	↑ 12%	↔
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%)
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%)

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

↑ 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.

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 (A62V, V75I, F77L, F116Y, and Q151M) in the reverse transcriptase gene. 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 didanosine to cause myopathy in humans is unclear. However, human myopathy has been associated with administration of didanosine and other nucleoside analogues.

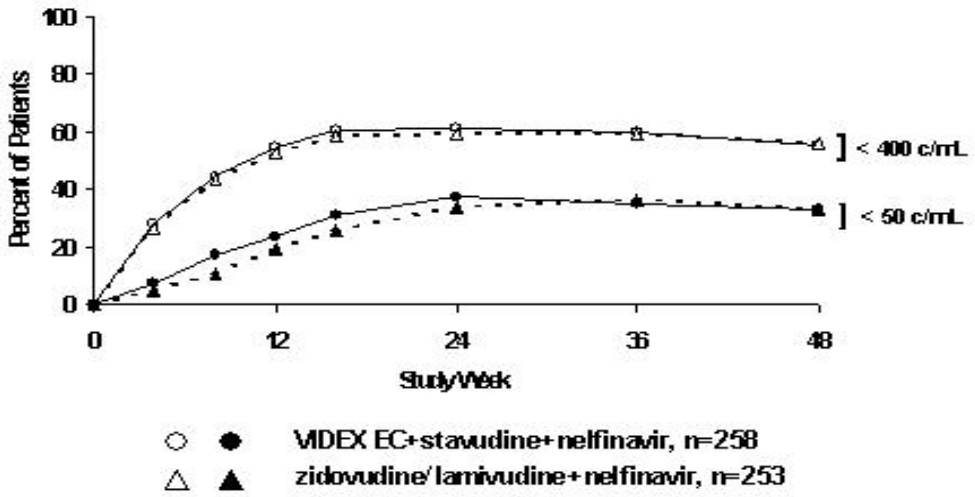
14 CLINICAL STUDIES

14.1 Adult Patients

Study AI454-152 was a 48-week, randomized, open-label study comparing VIDEX EC (400 mg once daily) plus stavudine (40 mg twice daily) plus nelfinavir (750 mg three times daily) to zidovudine (300 mg) plus lamivudine (150 mg) combination tablets twice daily plus nelfinavir (750 mg three times daily) in 511 treatment-naive patients, with a mean CD4 cell count of 411 cells/mm^3 (range 39 to 1105 cells/mm^3) and a mean plasma HIV-1 RNA of 4.71 $\log_{10}$ copies/mL (range 2.8 to 5.9 $\log_{10}$ copies/mL) at baseline. Patients were primarily males (72%) and Caucasian (53%) with a mean age of 35 years (range 18 to 73 years). The percentages of patients with HIV-1 RNA less than 400 and less than 50 copies/mL and outcomes of patients through 48 weeks are summarized in Figure 1 and Table 13, respectively.

Figure 1

Treatment Response Through Week 48*, AI454-152



*Percent of patients at each time point who have HIV RNA <400 or <50 copies/mL and do not meet any criteria for treatment failure (eg, virologic failure or discontinuation for any reason).

Table 13: Outcomes of Randomized Treatment Through Week 48, AI454-152

	Percent of Patients with HIV-1 RNA less than 400 copies/mL (less than 50 copies/mL)	
Outcome	**VIDEX EC + stavudine + nelfinavir n=258**	**zidovudine/lamivudine[a] + nelfinavir n=253**
Responder[b,c]	55% (33%)	56% (33%)
Virologic failure[d]	22% (45%)	21% (43%)
Death or discontinued due to disease progression	1% (1%)	2% (2%)
Discontinued due to adverse event	6% (6%)	7% (7%)
Discontinued due to other reasons[e]	16% (16%)	15% (16%)

Table 13: Outcomes of Randomized Treatment Through Week 48, AI454-152

Outcome	Percent of Patients with HIV-1 RNA less than 400 copies/mL (less than 50 copies/mL)	
	VIDEX EC + stavudine + nelfinavir n=258	zidovudine/lamivudine[a] + nelfinavir n=253

[a] Zidovudine/lamivudine combination tablet.

[b] Corresponds to rates at Week 48 in Figure 1.

[c] Subjects achieved and maintained confirmed HIV-1 RNA less than 400 copies/mL (less than 50 copies/mL) through Week 48.

[d] Includes viral rebound at or before Week 48 and failure to achieve confirmed HIV-1 RNA less than 400 copies/mL (less than 50 copies/mL) through Week 48.

[e] Includes lost to follow-up, subject's withdrawal, discontinuation due to physician's decision, never treated, and other reasons.

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), didanosine (120 mg/m^2 every 12 hours), or zidovudine (120 mg/m^2 every 6 hours) plus didanosine (90 mg/m^2 every 12 hours). Patients treated with didanosine or didanosine 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 EC (didanosine, USP) Delayed-Release Capsules are white, opaque capsules that are packaged in bottles with child-resistant closures as described in Table 14.

Table 14: VIDEX EC Delayed-Release Capsules

125 mg capsule imprinted with "BMS 125 mg 6671" in Tan	
NDC No. 0087-6671-17	30 capsules/bottle
200 mg capsule imprinted with "BMS 200 mg 6672" in Green	
NDC No. 0087-6672-17	30 capsules/bottle
250 mg capsule imprinted with "BMS 250 mg 6673" in Blue	
NDC No. 0087-6673-17	30 capsules/bottle
400 mg capsule imprinted with "BMS 400 mg 6674" in Red	
NDC No. 0087-6674-17	30 capsules/bottle

Storage

The capsules should be stored in tightly closed containers at 25° C (77° F). Excursions between 15° C and 30° C (59° F and 86° F) are permitted (see USP Controlled Room Temperature).

17 PATIENT COUNSELING INFORMATION

See Medication Guide.

17.1 Pancreatitis

Patients should be informed that a serious toxicity of didanosine, 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 EC (didanosine). 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 EC 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 EC 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 EC, 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 didanosine is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when didanosine 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 EC toxicities.

17.9 General Information

VIDEX EC is not a cure for HIV-1 infection, and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Therefore, patients should remain under the care of a physician when using VIDEX EC.

Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** It is not known if VIDEX EC can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in breast milk.

Patients should be instructed to swallow the capsule as a whole and to not open the capsule.

Patients should be instructed to not miss a dose but if they do, patients should take VIDEX EC 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.