

VIDEX- didanosine powder, for solution
Bristol-Myers Squibb Company

HIGHLIGHTS 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. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. Fatal lactic acidosis has been reported in pregnant individuals who received the combination of VIDEX and stavudine. (5.2) Coadministration of VIDEX with stavudine is contraindicated. (4)**

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

Boxed Warning	01/2018
Contraindications (4)	01/2018
Warnings and Precautions (5.1, 5.2, 5.3, 5.5)	01/2018
Warnings and Precautions, Lipoatrophy (5.8)	01/2018
Warnings and Precautions, Fat Redistribution (5.8)	Removed 01/2018

----- **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 per m² twice daily.
 - For those greater than 8 months old, dosing is 120 mg per m² 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 stavudine, allopurinol, or ribavirin is contraindicated. (4)

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

- Pancreatitis: Suspension or discontinuation of didanosine may be necessary. (5.1) Coadministration of VIDEX with stavudine is contraindicated. (4)
- 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) Coadministration of VIDEX with stavudine is contraindicated. (4)
- 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), lipoatrophy (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 individuals who received both didanosine and stavudine with other agents. Coadministration of VIDEX with stavudine is contraindicated. (4, 5.2, 8.1)
- Lactation: Breastfeeding is not recommended due to the potential for HIV-1 transmission. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2018

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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-naïve 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 individuals who received the combination of didanosine and stavudine with other antiretroviral agents. Coadministration of VIDEX and stavudine is contraindicated because of increased risk of serious and/or life-threatening events [see *Contraindications (4)*, *Warnings and Precautions (5.2)*]. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occurs.

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 per m² twice daily, and the recommended VIDEX dose for pediatric patients greater than 8 months old is 120 mg per m² 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

^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 per 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 per min) or 200 mg (adults weighing less than 60 kg with creatinine clearance of at least 60 mL per 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 per 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)*].

2.4 Instructions for Reconstitution

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

20 mg per mL Initial Solution

Reconstitute the product to 20 mg per 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 per mL Final Admixture

1. Immediately mix one part of the 20 mg per mL initial solution with one part of any commercially available antacid that contains as active ingredients aluminum hydroxide (400 mg per 5 mL), magnesium hydroxide (400 mg per 5 mL), and simethicone (40 mg per 5 mL) 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.

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.

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

VIDEX is contraindicated when coadministered with the following medications:

- *Stavudine*- potential for serious and/or life-threatening events notably pancreatitis, lactic acidosis, hepatotoxicity, and peripheral neuropathy [see Warnings and Precautions (5.1, 5.2, 5.3, 5.5)].
- *Allopurinol*- systemic exposures of didanosine are increased, which may increase didanosine-associated toxicity [see *Clinical Pharmacology* (12.3)].
- *Ribavirin*- 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-naïve 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. Coadministration of VIDEX with stavudine is contraindicated [see Contraindications (4)].

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 individuals who received the combination of didanosine and stavudine with other antiretroviral agents. Coadministration of VIDEX and stavudine is contraindicated [see *Contraindications (4) and 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. Coadministration of VIDEX and stavudine is contraindicated; the combination of VIDEX and hydroxyurea should be avoided. [see *Contraindications (4)*, *Adverse Reactions (6)* and *Drug Interactions (7.2)*].

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. Discontinuation of VIDEX should be considered in patients who develop peripheral neuropathy [see *Contraindications (4)*, *Adverse Reactions (6)*, and *Drug Interactions (7.2)*].

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 jirovecii* 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 Lipoatrophy

Treatment with VIDEX has been associated with loss of subcutaneous fat, which is most evident in the face, limbs, and buttocks. The incidence and severity of lipoatrophy are related to cumulative exposure, and is often not reversible when VIDEX treatment is stopped. Patients receiving VIDEX should be frequently examined and questioned for signs of lipoatrophy, and if feasible therapy should be switched to an alternative regimen if there is suspicion of lipoatrophy.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in the labeling:

- Pancreatitis [see *Warnings and Precautions* (5.1)]
- Lactic acidosis/severe hepatomegaly with steatosis [see *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.

Clinical Trials Experience in 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

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.

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	*
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^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.

Pancreatitis resulting in death was observed in one patient who received VIDEX (didanosine) plus stavudine plus nelfinavir in Study AI454-148 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

Parameter	Percent of Patients			
	ACTG 116A		ACTG 116B/117	
	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)

Parameter	Percent of Patients ^a			
	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
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 ULN)	3	3	8	5
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.

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

Parameter	Percent of Patients ^a			
	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
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.

Clinical Trials Experience in 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 per m² per 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 per m² every 12 hours and in less than 1% of the 274 pediatric patients who received didanosine 90 mg per m² 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, it is not always possible to reliably estimate their frequency. 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.

Digestive Disorders – anorexia, dyspepsia, and flatulence.

Exocrine Gland Disorders – pancreatitis (including fatal cases) [see Warnings and Precautions (5.1)], sialadenitis, 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, 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)].

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 interaction studies are shown in Tables 12 and 13 [see *Contraindications (4)*, *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 for changes in HIV RNA viral load.
nelfinavir	No interaction 1 hour after didanosine	Administer nelfinavir 1 hour after VIDEX. A dose reduction of VIDEX to the following dosage once daily is recommended. ^a <ul style="list-style-type: none">• 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)
tenofovir disoproxil fumarate	↑ didanosine concentration	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 [see *Clinical Pharmacology (12.3)*]. 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.
Hydroxyurea	↑ risk of pancreatitis, fatal hepatotoxicity, and severe peripheral neuropathy	Use should be avoided.

↑ 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 Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to VIDEX during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

Fatal lactic acidosis has been reported in pregnant individuals 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 VIDEX and stavudine is

contraindicated [see Contraindications (4)]

Based on APR reports, congenital malformations were reported when administered during pregnancy. The prevalence of birth defects was 4.7% in the first trimester compared with 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) and 4.2% in the Texas Birth Defects Registry (TBDR) (see Data). No pattern of defects was identified by the APR. Based on these findings, the clinical relevance is uncertain.

The rate of miscarriage is not reported in the APR. In the U.S. general population, the estimated background risks of miscarriage in clinically recognized pregnancies is 15 to 20%.

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with didanosine at systemic exposures (AUC) up to 12 (rats) and 14 (rabbits) times the exposure in humans at the recommended daily human dose of VIDEX (see Data)

Clinical Considerations

Maternal Adverse Reactions

Cases of lactic acidosis syndrome, sometimes fatal have occurred in pregnant individuals using VIDEX in combination with stavudine. VIDEX is associated with an increased risk of lactic acidosis syndrome/hepatic steatosis syndrome [see Warnings and Precautions (5.2)]

Data

Human Data

Based on prospective reports to the APR exposure to didanosine-containing regimens during pregnancy (including 427 exposed in the first trimester and 462 exposed in the second/third trimester), the prevalence of birth defects in live births was 4.7 % (95% CI: 2.9% to 7.1%) with first trimester exposure to didanosine-containing regimens and 4.3% (95% CI: 2.7% to 6.6%) with the second/third trimester exposure to didanosine-containing regimens compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP and 4.2% in the TBDR.□□

Prospective reports from the APR of overall major birth defects in pregnancies exposed to VIDEX is compared with a U.S. background major birth defect rate. Methodological limitations of the APR include the use of MACDP and TBDR as the external comparator groups. Limitations of using external comparators include differences in methodology and populations, as well as confounding due to the underlying disease.

Animal Data

Didanosine was administered orally at up to 1000 mg per kg daily to pregnant rats and at up to 600 mg per kg daily to pregnant rabbits on gestation Days 7 to 17 and 6 to 18, respectively, and also to rats 14 days before mating through weaning. No adverse effects on embryo-fetal development (rats and rabbits) were observed up to the highest dose tested. During organogenesis, systemic exposures (AUC) to didanosine were up to 12 (rats) and 14.2 (rabbits) times the estimated human exposure at the recommended daily human dose. Didanosine and/or its metabolites are transferred to the fetus through the placenta. In the rat pre/postnatal development study, reduced food intake and body weight gain was observed in the offspring of females administered didanosine at a maternally toxic exposure (approximately 12 times the exposure at the recommended human dose).

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. It is not known whether VIDEX is present in human breast milk, affects human milk production, or has effects on the breastfed infant. When administered to lactating rats, didanosine was present in milk (see *Data*).

Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants) and (3) adverse reactions in breastfed infants similar to those seen in adults, instruct mothers not to breastfeed if they are receiving VIDEX.

Data

Didanosine and its metabolites were excreted into the milk of lactating rats following a single oral dose of 50 mg per kg on lactation Day 14, with milk concentrations 5 times that of maternal plasma concentrations at 8 and 24 hours post-dose.

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)*, *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 per 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

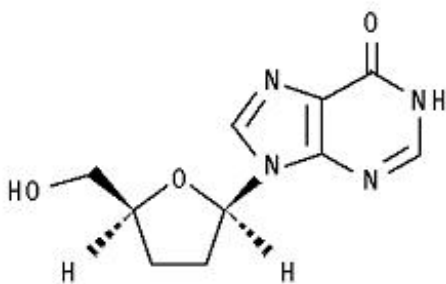
There is no known antidote for VIDEX (didanosine) overdose. In phase 1 studies, in which VIDEX was initially administered at doses ten times the currently recommended dose, toxicities included: pancreatitis, peripheral neuropathy, diarrhea, hyperuricemia, and hepatic dysfunction. Didanosine is not dialyzable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

11 DESCRIPTION

VIDEX[®] is a brand name for didanosine, 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 per 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 antiretroviral drug [see *Microbiology* (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

Parameter	Adult Patients ^a		Pediatric Patients ^b			
	Mean ± SD	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 m².

^b In 1-day old infants (n=10), the mean ± SD apparent oral clearance was 1523 ± 1176 mL/min/m² 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 \pm 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 \pm SD Pharmacokinetic Parameters for Didanosine Following a Single Oral Dose

Parameter	Creatinine Clearance (mL/min)				Dialysis Patients n=11
	at least 90 n=12	60-90 n=6	30-59 n=6	10-29 n=3	
CL _{cr} (mL/min)	112 \pm 22	68 \pm 8	46 \pm 8	13 \pm 5	ND
CL/F (mL/min)	2164 \pm 638	1566 \pm 833	1023 \pm 378	628 \pm 104	543 \pm 174
CL _R (mL/min)	458 \pm 164	247 \pm 153	100 \pm 44	20 \pm 8	less than 10
T _{1/2} (h)	1.42 \pm 0.33	1.59 \pm 0.13	1.75 \pm 0.43	2.0 \pm 0.3	4.1 \pm 1.2

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 per m² in pediatric patients less than 5 months old and from 80 to 180 mg per m² 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)*, 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

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%
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% (-27, -7%) ^c	↓ 13% (-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).

^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.

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)
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%
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% (EC₅₀) 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 amino acid substitutions K65R, L74V, and M184V in reverse transcriptase. 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, and zidovudine in cell culture. These isolates harbored five substitutions (A62V, V75I, F77L, F116Y, and Q151M) in reverse transcriptase. In data from clinical studies, the presence of thymidine analogue mutation substitutions (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 per kg per day for each sex were lowered after 8 months to 120, 210, and 210 mg per kg per day for females and 120, 300, and 600 mg per kg per 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 per kg per day, and the high dose was lowered to 500 mg per kg per 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.

Reproduction studies have been performed in rats and rabbits at doses up to 12 and 14 times the estimated human exposure at the recommended daily human dose of VIDEX, respectively, and have revealed no evidence of impaired fertility or harm to the fetus due to didanosine.

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

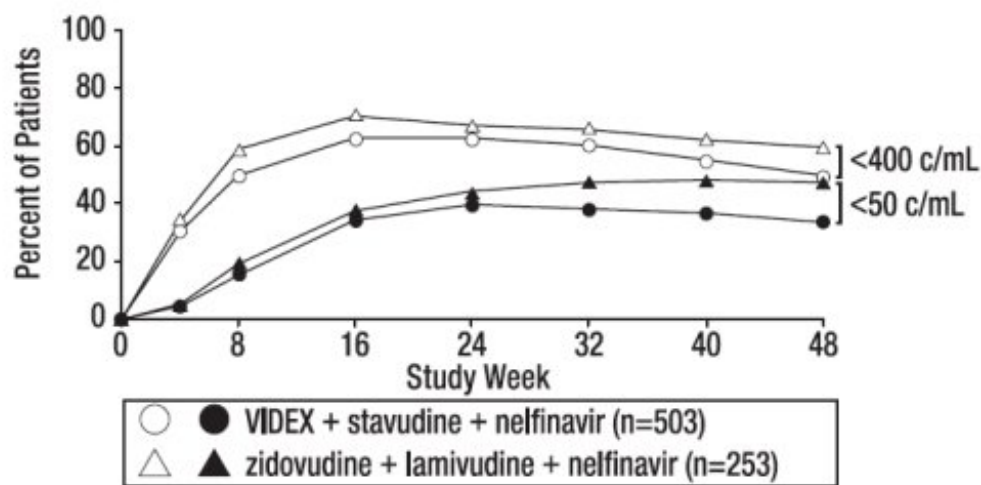
14.1 Adult Patients

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 per mm³ (range 80 to 1568 cells per mm³) and a median plasma HIV-1 RNA of 4.69 log₁₀ copies per mL (range 2.6 to 5.9 log₁₀ copies per mL) at baseline. Median CD4 cell count increases at 48 weeks were 188 cells per mm³ 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 per m² every 6 hours), VIDEX (120 mg per m² every 12 hours), or zidovudine (120 mg per m² every 6 hours) plus VIDEX (90 mg per m² 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

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.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Pancreatitis

Advise patients that a serious toxicity of VIDEX, used alone and in combination regimens, is pancreatitis, which may be fatal. VIDEX is contraindicated in combination with stavudine [see Warnings and Precautions (5.1)]. Closely monitor patients for symptoms of pancreatitis.

Lactic Acidosis and Severe Hepatomegaly with Steatosis

Advise patients 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. Advise pregnant individuals of the potential risks of lactic acidosis syndrome/hepatic steatosis syndrome [see Contraindications (4), Warnings and Precautions (5.2) and Use in Specific Populations (8.1)]

Hepatic Toxicity

Inform patients that hepatotoxicity, including fatal hepatic adverse events, has been reported. The safety and efficacy of VIDEX have not been established in HIV-infected patients with significant underlying liver disease. VIDEX is contraindicated in combination with stavudine [see Contraindications (4)]. Avoid the combination of VIDEX with hydroxyurea [see Warnings and Precautions (5.3) and Drug Interactions (7)].

Non-cirrhotic Portal Hypertension

Inform patients that non-cirrhotic portal hypertension has been reported in patients taking VIDEX, including cases leading to liver transplantation or death [see Warnings and Precautions (5.4)].

Peripheral Neuropathy

Inform patients 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 [see Warnings and Precautions (5.5)].

Retinal Changes and Optic Neuritis

Inform patients that retinal changes and optic neuritis, which may result in blurred vision, have been reported in adult and pediatric patients. Advise patients to have regular eye exams while taking VIDEX [see Warnings and Precautions (5.6)].

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any symptoms of infection, as in some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started [see Warnings and Precautions (5.7)].

Lipoatrophy

Inform patient that loss of body fat (e.g., from arms, legs, or face) may occur in individuals receiving antiretroviral therapy including VIDEX. Monitor patients receiving VIDEX to monitor for clinical signs and symptoms of lipoatrophy. Patients should be routinely questioned about body changes related to lipoatrophy [see Warnings and Precautions (5.8)].

Drug Interactions

VIDEX may interact with many drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription of non-prescription medication or herbal products, including alcohol, which may exacerbate VIDEX toxicities [see Contraindications (4), Drug Interactions (7)].

Pregnancy Registry

Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant individuals exposed to VIDEX [see Use in Specific Populations (8.1)].

Lactation

Advise mothers with HIV-1 not to breastfeed because HIV-1 can be passed to the baby in breast milk. [see Use in Specific Populations (8.2)]

Dosing Information

Instruct patients to take VIDEX on an empty stomach at least 30 minutes before or 2 hours after eating.

Instruct patients 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.

Instruct patients not to miss a dose but if they do, patients should take VIDEX as soon as possible. Inform patients that it is important to take VIDEX on a regular dosing schedule and to avoid missing doses as it can result in development of resistance.

Guide	Medication
dex)	VIDEX (VY-
USP)	(didanosine,
for oral solution	pediatric powder

What is the most important information I should know about VIDEX?

VIDEX can cause serious side effects, including:

- **Inflammation of your pancreas (pancreatitis)** can happen in people who take VIDEX and can lead to death. People who take VIDEX in combination with the medicine stavudine may be at an increased risk for pancreatitis. **Do not take VIDEX with stavudine.**

Call your healthcare provider right away if you have any of the following symptoms of pancreatitis:

-
- | | |
|---------------------------------|-----------------------|
| • severe stomach (abdomen) pain | • nausea and vomiting |
| • swelling of your stomach | • fever |
-

- **Build-up of an acid in your blood (lactic acidosis).** Lactic acidosis can happen in some people who take VIDEX or similar medicines (nucleoside analogues). Lactic acidosis is a serious medical emergency that can lead to death. There have been deaths reported in pregnant women who get lactic acidosis after taking VIDEX and stavudine. **Do not take VIDEX with stavudine.**

- **Call your healthcare provider right away if you have any of the following symptoms which could be signs of lactic acidosis:**

-
- feel very weak or tired
 - feel cold, especially in your arms and legs
 - have unusual (not normal) muscle pain
 - feel dizzy or light-headed
 - have trouble breathing
 - have a fast or irregular heartbeat
 - have stomach pain with nausea and vomiting
 - weight loss
-

- **Severe liver problems**, including liver failure, can happen in people who take VIDEX. Your liver may become large (hepatomegaly), you may develop fat in your liver (steatosis), or you may have high blood pressure in the large vein of your liver (portal hypertension). Severe liver problems can lead to liver transplantation or death in some people taking VIDEX. Taking VIDEX with medicines that contain hydroxyurea or stavudine may increase your risk for liver problems.

You may be more likely to get lactic acidosis or severe liver problems if you are a female, are very overweight (obese), or have been taking nucleoside analogue medicines for a long time. Call your healthcare provider right away if you have any of the following symptoms of severe liver problems:

-
- yellowing of your skin or the white of your eyes (jaundice)
 - loss of appetite
 - nausea
 - dark or "tea-colored" urine
 - pain, aching, or tenderness on the right side of your stomach area
 - light-colored stools (bowel movements)
-

For more information about side effects, see "What are the possible side effects of VIDEX?".

What is VIDEX?

VIDEX is a prescription medicine that is used with other antiretroviral medicines to treat Human Immunodeficiency Virus (HIV)-1 infection.

HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

Do not take VIDEX if you take a medicine that contains:

-
- allopurinol
 - ribavirin
 - stavudine
-

Before you take VIDEX, tell your healthcare provider about all of your medical conditions, including if you:

- have or had problems with your pancreas
- have or had kidney problems
- have or had liver problems, including hepatitis
- have or had numbness, tingling, or pain in the hands or feet (peripheral neuropathy)
- are receiving dialysis
- drink alcoholic beverages
- are pregnant or plan to become pregnant. It is not known if VIDEX will harm your unborn baby.

Pregnancy Registry: There is a pregnancy registry for women who take antiretroviral medicines, including VIDEX during pregnancy. The purpose of the registry is to collect information about the

health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.

- are breastfeeding or plan to breastfeed. **Do not breastfeed if you take VIDEX.**
 - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
 - It is not known if VIDEX can pass into your breast milk and if it could harm your baby.

Talk to your healthcare provider about the best way to feed your baby while taking VIDEX.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some medicines interact with VIDEX. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with VIDEX.
- **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take VIDEX with other medicines.

How should I take VIDEX?

- Take VIDEX exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much VIDEX to take and when to take it.
- Take VIDEX on an empty stomach at least 30 minutes before or 2 hours after you eat.
- Your healthcare provider may change your dose if you have certain side effects. Do not change your dose of VIDEX without talking to your healthcare provider.
- Shake the bottle well before taking each dose of VIDEX.
- Be sure to close the bottle tightly after each use.
- Do not miss a dose of VIDEX. If you miss a dose of VIDEX, take it as soon as possible.
- It is important to take VIDEX on a regular schedule. The virus in your blood may increase and the virus may become harder to treat if you miss doses.
- Your healthcare provider may lower your dose of VIDEX if your kidneys are not working well.
- If you take too much VIDEX, go to the nearest emergency room right away.

What are the possible side effects of VIDEX?

VIDEX can cause serious side effects, including:

- See "What is the most important information I should know about VIDEX?"
- **Numbness, tingling, or pain in your hands or feet (peripheral neuropathy).** Peripheral neuropathy is common during treatment with VIDEX and can be severe. Peripheral neuropathy happens more often in people who have advanced HIV-1 disease, have a history of peripheral neuropathy, or in people who are being treated with medicines that can cause neurologic problems.
- **Vision changes.** Call your healthcare provider if you have changes in vision, such as blurred vision. You should have regular eye exams during treatment with VIDEX.
- **Changes in your immune system (immune reconstitution syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider if you start having any new symptoms after starting your HIV-1 medicine.
- **Loss of body fat (lipoatrophy)** from the arms, legs, face, or buttocks can happen during treatment with VIDEX. Your healthcare provider will monitor you for changes in your body fat. It is important to tell your healthcare provider if you notice any changes.

The most common side effects of VIDEX include:

-
- | | |
|--------------------------|------------|
| • diarrhea | • headache |
| • stomach (abdomen) pain | • rash |

- nausea

- vomiting

These are not all the possible side effects of VIDEX.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store VIDEX?

- Store VIDEX oral solution in a tightly closed container in the refrigerator between 36 °F to 46 °F (2 °C to 8 °C) for up to 30 days.
- Safely throw away any unused VIDEX after 30 days.

Keep VIDEX and all medicines out of the reach of children.**General information about the safe and effective use of VIDEX**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use VIDEX for a condition for which it was not prescribed. Do not give VIDEX to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about VIDEX that is written for health professionals.

What are the ingredients in VIDEX?

Active ingredient: didanosine, USP

Inactive ingredients: Purified Water, USP and an antacid containing aluminum hydroxide (400 mg per 5 mL), magnesium hydroxide (400 mg per 5 mL), and simethicone (40 mg per 5 mL).

Distributed by: Bristol-Myers Squibb Company Princeton, NJ 08543 USA

VIDEX® is a registered trademarks of Bristol-Myers Squibb Company.

For more information, go to www.bms.com/products/Pages/home.aspx or call 1-800-321-1335.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: December 2018

[Print Code]

VIDEX 2 g Pediatric Powder Representative Packaging

See **How Supplied** section for a complete list of available packages of VIDEX.

NDC 0087-6632-41

VIDEX®

(didanosine, USP)

Pediatric Powder

For Oral Solution

Rx only

2 g

Detach and dispense the enclosed Medication Guide to the patient.

NDC 0087-6632-41

VIDEX[®]
(didanosine, USP)

Pediatric Powder
For Oral Solution

See enclosed package insert for indications, dosage schedule, and directions for use.
This bottle contains 2 grams of didanosine.
Store bottles of the dry product at 59° F to 86° F (15° C to 30° C).

Rx only

2g

Detach and dispense the enclosed Medication Guide to the patient.

Distributed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA
1351364A0

3923600

For Position Only
3 0000 0000 00 0

Lot: Exp:

VIDEX 4 g Pediatric Powder Representative Packaging

NDC 0087-6633-41

VIDEX[®]

(didanosine, USP)

Pediatric Powder

For Oral Solution

Rx only

4 g

Detach and dispense the enclosed Medication Guide to the patient.

NDC 0087-6633-41

VIDEX[®]
(didanosine, USP)

Pediatric Powder
For Oral Solution

See enclosed package insert for indications, dosage schedule, and directions for use.
This bottle contains 4 grams of didanosine.
Store bottles of the dry product at 59° F to 86° F (15° C to 30° C).
Do not use if inner seal of bottle is broken or missing.

Rx only

4g

Detach and dispense the enclosed Medication Guide to the patient.

Distributed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

1351359

For Position Only
0000 0000 00 0

Lot: Exp:

VIDEX

didanosine powder, for solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0087-6632
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
didanosine (UNII: K3GDH6OH08) (didanosine - UNII:K3GDH6OH08)	didanosine	10 mg in 1 mL

Product Characteristics

Color	WHITE	Score	
Shape		Size	
Flavor		Imprint Code	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0087-6632-41	1 in 1 CARTON	10/09/1991	
1		200 mL in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020156	10/09/1991	

VIDEX

didanosine powder, for solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0087-6633
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
didanosine (UNII: K3GDH6OH08) (didanosine - UNII:K3GDH6OH08)	didanosine	10 mg in 1 mL

Product Characteristics

Color	WHITE	Score	
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Shape		Size	
Flavor		Imprint Code	
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0087-6633-41	1 in 1 CARTON	10/09/1991	
1		400 mL in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020156	10/09/1991	

Labeler - Bristol-Myers Squibb Company (102826703)

Revised: 12/2018

Bristol-Myers Squibb Company