

**OF PRESCRIBING INFORMATION**

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

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

**WARNING: PANCREATITIS, LACTIC ACIDOSIS and HEPATOMEGALY with STEATOSIS**  
*See full prescribing information for complete boxed warning.*

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

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

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

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

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

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

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

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

- Pediatric patients (2 weeks old to 18 years old): Administered on an empty stomach at least 30 minutes before or 2 hours after eating.
  - Between 2 weeks and 8 months old, dosing is 100 mg/m<sup>2</sup> twice daily.
  - For those greater than 8 months old, dosing is 120 mg/m<sup>2</sup> twice daily but not to exceed the adult dosing recommendation. (2.1)
- Renal impairment: Dose reduction is recommended. (2.2)

- Coadministration with tenofovir: Dose reduction is recommended. Patients should be monitored closely for didanosine-associated adverse reactions. (2.3, 7.1)

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

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

-----CONTRAINDICATIONS-----

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

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

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

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

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

**To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**

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

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

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

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

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

**Revised: 01/2010**

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are not listed

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## 1 FULL PRESCRIBING INFORMATION

### **WARNING: PANCREATITIS, LACTIC ACIDOSIS and HEPATOMEGALY with STEATOSIS**

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

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including didanosine and other antiretrovirals. Fatal lactic acidosis has been reported in pregnant women who received the combination of didanosine and stavudine with other antiretroviral agents. The combination of didanosine and stavudine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk [*see Warnings and Precautions (5.2)*].

## 2 1 INDICATIONS AND USAGE

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

## 6 2 DOSAGE AND ADMINISTRATION

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

### 9 2.1 Recommended Dosage (Adult and Pediatric Patients)

10 The preferred dosing frequency of VIDEX is twice daily because there is more evidence to  
11 support the effectiveness of this dosing regimen. Once-daily dosing should be considered only  
12 for patients whose management requires once-daily dosing of VIDEX [*see Clinical Studies (14)*].  
13 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

14 **Pediatric Patients (2 weeks old to 18 years old):** The recommended dose of VIDEX  
 15 (didanosine) in pediatric patients between 2 weeks old and 8 months old is 100 mg/m<sup>2</sup> twice  
 16 daily, and the recommended VIDEX dose for pediatric patients greater than 8 months old is  
 17 120 mg/m<sup>2</sup> twice daily but not to exceed the adult dosing recommendation.

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

## 21 **2.2 Renal Impairment**

### 22 **Adult Patients**

23 In adult patients with impaired renal function, the dose of VIDEX should be adjusted to  
 24 compensate for the slower rate of elimination. The recommended doses and dosing intervals of  
 25 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 <sup>a</sup>	125 mg twice daily <sup>a</sup>
30-59	200 mg once daily or 100 mg twice daily	150 mg once daily or 75 mg twice daily
10-29	150 mg once daily	100 mg once daily
less than 10	100 mg once daily	75 mg once daily

**Table 2: Recommended Dosage in Patients with Renal Impairment**

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<sup>a</sup> 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.

26 **Pediatric Patients**

27 Urinary excretion is also a major route of elimination of didanosine in pediatric patients,  
28 therefore the clearance of didanosine may be altered in pediatric patients with renal impairment.  
29 Although there are insufficient data to recommend a specific dose adjustment of VIDEX in this  
30 patient population, a reduction in the dose should be considered (see Table 2).

31 **Patients Requiring Continuous Ambulatory Peritoneal Dialysis (CAPD) or**  
32 **Hemodialysis**

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

36 **2.3 Dosage Adjustment**

37 **Concomitant Therapy with Tenofovir Disoproxil Fumarate**

38 In patients who are also taking tenofovir disoproxil fumarate, a dose reduction of VIDEX to  
39 250 mg (adults weighing at least 60 kg with creatinine clearance of at least 60 mL/min) or  
40 200 mg (adults weighing less than 60 kg with creatinine clearance of at least 60 mL/min) once  
41 daily is recommended. VIDEX and tenofovir disoproxil fumarate may be taken together in the  
42 fasted state. Alternatively, if tenofovir disoproxil fumarate is taken with food, VIDEX should be  
43 taken on an empty stomach (at least 30 minutes before food or 2 hours after food). The  
44 appropriate dose of VIDEX coadministered with tenofovir disoproxil fumarate in patients with  
45 creatinine clearance of less than 60 mL/min has not been established. ([See *Drug Interactions* (7)  
46 and *Clinical Pharmacology* (12.3)]; see the complete prescribing information for VIDEX EC  
47 (enteric-coated formulation of didanosine) for results of drug interaction studies of tenofovir  
48 disoproxil fumarate with reduced doses of the enteric-coated formulation of didanosine.)

49 **Hepatic Impairment**

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

52 **3 DOSAGE FORMS AND STRENGTHS**

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

55 **4 CONTRAINDICATIONS**

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

58 **4.1 Allopurinol**

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

62 **4.2 Ribavirin**

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

67 **5 WARNINGS AND PRECAUTIONS**

68 **5.1 Pancreatitis**

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

75 When treatment with life-sustaining drugs known to cause pancreatic toxicity is required,  
76 suspension of VIDEX (didanosine) therapy is recommended. In patients with risk factors for  
77 pancreatitis, VIDEX should be used with extreme caution and only if clearly indicated. Patients  
78 with advanced HIV-1 infection, especially the elderly, are at increased risk of pancreatitis and  
79 should be followed closely. Patients with renal impairment may be at greater risk for pancreatitis  
80 if treated without dose adjustment. The frequency of pancreatitis is dose related. [*See Adverse*  
81 *Reactions (6).*]

## 82 **5.2 Lactic Acidosis/Severe Hepatomegaly with Steatosis**

83 **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been**  
84 **reported with the use of nucleoside analogues alone or in combination, including**  
85 **didanosine and other antiretrovirals.** A majority of these cases have been in women. Obesity  
86 and prolonged nucleoside exposure may be risk factors. Fatal lactic acidosis has been reported in  
87 pregnant women who received the combination of didanosine and stavudine with other  
88 antiretroviral agents. The combination of didanosine and stavudine should be used with caution  
89 during pregnancy and is recommended only if the potential benefit clearly outweighs the  
90 potential risk [*see Use in Specific Populations (8.1)*]. Particular caution should be exercised  
91 when administering VIDEX to any patient with known risk factors for liver disease; however,  
92 cases have also been reported in patients with no known risk factors. Treatment with VIDEX  
93 should be suspended in any patient who develops clinical signs or symptoms with or without  
94 laboratory findings consistent with symptomatic hyperlactatemia, lactic acidosis, or pronounced  
95 hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked  
96 transaminase elevations).

## 97 **5.3 Hepatic Toxicity**

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

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

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

#### 109 **5.4 Non-cirrhotic Portal Hypertension**

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

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

#### 121 **5.5 Peripheral Neuropathy**

122 Peripheral neuropathy, manifested by numbness, tingling, or pain in the hands or feet, has been  
123 reported in patients receiving VIDEX therapy. Peripheral neuropathy has occurred more  
124 frequently in patients with advanced HIV disease, in patients with a history of neuropathy, or in  
125 patients being treated with neurotoxic drug therapy, including stavudine. Discontinuation of  
126 VIDEX should be considered in patients who develop peripheral neuropathy. [*See Adverse*  
127 *Reactions (6).*]

#### 128 **5.6 Retinal Changes and Optic Neuritis**

129 Retinal changes and optic neuritis have been reported in adult and pediatric patients. Periodic  
130 retinal examinations should be considered for patients receiving VIDEX [*see Adverse Reactions*  
131 *(6)*].

#### 132 **5.7 Immune Reconstitution Syndrome**

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

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

## 139 **5.8 Fat Redistribution**

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

## 145 **6 ADVERSE REACTIONS**

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

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

### 154 **6.1 Clinical Trials Experience**

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

#### 158 **Adults**

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

**Table 3: Selected Clinical Adverse Reactions from Monotherapy Studies**

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Percent of Patients\*

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**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.

161

**Table 4: Selected Clinical Adverse Reactions from Combination Studies**

Adverse Reactions	Percent of Patients <sup>a,c</sup>			
	AI454-148 <sup>b</sup>		START 2 <sup>b</sup>	
	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	*

<sup>a</sup> Percentages based on treated subjects.

<sup>b</sup> Median duration of treatment 48 weeks.

<sup>c</sup> The incidences reported included all severity grades and all reactions regardless of causality.

\* This event was not observed in this study arm.

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

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

167 The frequency of pancreatitis is dose related. In phase 3 studies, incidence ranged from 1% to  
168 10% with doses higher than are currently recommended and from 1% to 7% with recommended  
169 dose.

170 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.

171

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

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

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

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

ULN = upper limit of normal.

NC = Not Collected.

<sup>a</sup> Percentages based on treated subjects.

<sup>b</sup> Median duration of treatment 48 weeks.

172

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

Parameter	Percent of Patients <sup>a</sup>			
	AI454-148 <sup>b</sup>		START 2 <sup>b</sup>	
	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.

<sup>a</sup> Percentages based on treated subjects.

<sup>b</sup> Median duration of treatment 48 weeks.

173 **Pediatric Patients**

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

177 In pediatric phase 1 studies, pancreatitis occurred in 2 of 60 (3%) patients treated at entry doses  
178 below 300 mg/m<sup>2</sup>/day and in 5 of 38 (13%) patients treated at higher doses. In study ACTG 152,  
179 pancreatitis occurred in none of the 281 pediatric patients who received didanosine 120 mg/m<sup>2</sup>  
180 every 12 hours and in less than 1% of the 274 pediatric patients who received didanosine  
181 90 mg/m<sup>2</sup> every 12 hours in combination with zidovudine [*see Clinical Studies (14)*].

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

183 **6.2 Postmarketing Experience**

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

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

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

191 *Digestive Disorders* – anorexia, dyspepsia, and flatulence.

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

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

198 *Metabolic Disorders* – diabetes mellitus, hypoglycemia, and hyperglycemia.

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

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

### 203 **Use with Stavudine- and Hydroxyurea-Based Regimens**

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

## 210 **7 DRUG INTERACTIONS**

### 211 **7.1 Established Drug Interactions**

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

**Table 8: Established Drug Interactions with VIDEX**

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

**Table 8: Established Drug Interactions with VIDEX**

Drug	Effect	Clinical Comment
		for changes in HIV RNA viral load.
nelfinavir	No interaction 1 hour after didanosine	Administer nelfinavir 1 hour after VIDEX.
tenofovir disoproxil fumarate	↑ didanosine concentration	<p>A dose reduction of VIDEX to the following dosage once daily is recommended.<sup>a</sup></p> <ul style="list-style-type: none"> <li>• 250 mg (adults weighing at least 60 kg with creatinine clearance of at least 60 mL/min)</li> <li>• 200 mg (adults weighing less than 60 kg with creatinine clearance of at least 60 mL/min)</li> </ul> <p>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.</p>

↑ Indicates increase.

↓ Indicates decrease.

<sup>a</sup> 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.

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

## 225 7.2 Predicted Drug Interactions

226 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 <sup>a</sup>
Neurotoxic drugs	↑ risk of neuropathy	Use with caution <sup>b</sup>
Antacids containing magnesium or aluminum	↑ side effects associated with antacid components	Use caution with VIDEX Pediatric Powder for Oral Solution
Azole antifungals	↓ ketoconazole or itraconazole concentration	Administer drugs such as ketoconazole or itraconazole at least 2 hours before VIDEX.
Quinolone antibiotics (see also ciprofloxacin in Table 8)	↓ quinolone concentration	Consult package insert of the quinolone.
Tetracycline antibiotics	↓ antibiotic concentration	Consult package insert of the tetracycline.

↑ Indicates increase.

↓ Indicates decrease.

<sup>a</sup> 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)*].

<sup>b</sup> [See *Warnings and Precautions (5.6)*.]

227 **8 USE IN SPECIFIC POPULATIONS**

228 **8.1 Pregnancy**

229 **Pregnancy Category B**

230 Reproduction studies have been performed in rats and rabbits at doses up to 12 and 14.2 times  
 231 the estimated human exposure (based upon plasma levels), respectively, and have revealed no  
 232 evidence of impaired fertility or harm to the fetus due to didanosine. At approximately 12 times  
 233 the estimated human exposure, didanosine was slightly toxic to female rats and their pups during  
 234 mid and late lactation. These rats showed reduced food intake and body weight gains but the  
 235 physical and functional development of the offspring was not impaired and there were no major  
 236 changes in the F2 generation. A study in rats showed that didanosine and/or its metabolites are  
 237 transferred to the fetus through the placenta. Animal reproduction studies are not always  
 238 predictive of human response.

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

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

### 249 **Antiretroviral Pregnancy Registry**

250 To monitor maternal-fetal outcomes of pregnant women exposed to didanosine and other  
251 antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are  
252 encouraged to register patients by calling 1-800-258-4263.

## 253 **8.3 Nursing Mothers**

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

## 260 **8.4 Pediatric Use**

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

## 265 **8.5 Geriatric Use**

266 In an Expanded Access Program for patients with advanced HIV infection, patients aged  
267 65 years and older had a higher frequency of pancreatitis (10%) than younger patients (5%) [*see*

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

## 275 **8.6 Renal Impairment**

276 Patients with renal impairment (creatinine clearance of less than 60 mL/min) may be at greater  
277 risk of toxicity from didanosine due to decreased drug clearance [*see Clinical Pharmacology*  
278 *(12.3)*]. A dose reduction is recommended for these patients [*see Dosage and Administration*  
279 *(2)*].

## 280 **10 OVERDOSAGE**

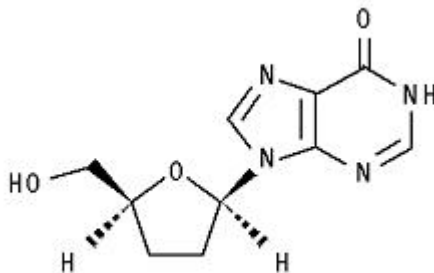
281 There is no known antidote for VIDEX (didanosine) overdose. In phase 1 studies, in which  
282 VIDEX was initially administered at doses ten times the currently recommended dose, toxicities  
283 included: pancreatitis, peripheral neuropathy, diarrhea, hyperuricemia, and hepatic dysfunction.  
284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

## 286 **11 DESCRIPTION**

287 VIDEX<sup>®</sup> is a brand name for didanosine, USP, a synthetic purine nucleoside analogue active  
288 against HIV-1.

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

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



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

## 297 **12 CLINICAL PHARMACOLOGY**

### 298 **12.1 Mechanism of Action**

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

### 300 **12.3 Pharmacokinetics**

301 The pharmacokinetic parameters of didanosine are summarized in Table 10. Didanosine is  
302 rapidly absorbed, with peak plasma concentrations generally observed from 0.25 to 1.50 hours  
303 following oral dosing. Increases in plasma didanosine concentrations were dose proportional  
304 over the range of 50 to 400 mg. Steady-state pharmacokinetic parameters did not differ  
305 significantly from values obtained after a single dose. Binding of didanosine to plasma proteins  
306 *in vitro* was low (less than 5%). Based on data from *in vitro* and animal studies, it is presumed  
307 that the metabolism of didanosine in man occurs by the same pathways responsible for the  
308 elimination of endogenous purines.

**Table 10: Mean ± SD Pharmacokinetic Parameters for Didanosine in Adult and Pediatric Patients**

Parameter	Adult Patients <sup>a</sup>	n	Pediatric Patients <sup>b</sup>			
			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 <sup>c</sup> (L/m <sup>2</sup> )	43.70 ± 8.90	6	28 ± 15	49	ND	
CSF-plasma ratio <sup>d</sup>	21 ± 0.03% <sup>e</sup>	5	46% (range 12-85%)	7	ND	
Systemic clearance <sup>c</sup> (mL/min/m <sup>2</sup> )	526 ± 64.7	6	516 ± 184	49	ND	
Renal clearance <sup>f</sup> (mL/min/m <sup>2</sup> )	223 ± 85.0	6	240 ± 90	15	ND	
Apparent oral clearance <sup>g</sup> (mL/min/m <sup>2</sup> )	1252 ± 154	6	2064 ± 736	48	1353 ± 759	41
Elimination half-life <sup>f</sup> (h)	1.5 ± 0.4	6	0.8 ± 0.3	60	1.2 ± 0.3	21
Urinary recovery of didanosine <sup>f</sup> (%)	18 ± 8	6	18 ± 10	15	ND	

CSF = cerebrospinal fluid, ND = not determined.

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

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

<sup>c</sup> Following IV administration.

<sup>d</sup> Following IV administration in adults and IV or oral administration in pediatric patients.

<sup>e</sup> Mean ± SE.

<sup>f</sup> Following oral administration.

<sup>g</sup> Apparent oral clearance estimate was determined as the ratio of the mean systemic clearance and the mean oral bioavailability estimate.

### 309 Effect of Food

310 Didanosine peak plasma concentrations (C<sub>max</sub>) and area under the plasma concentration time  
311 curve (AUC) were decreased by approximately 55% when VIDEX tablets were administered up  
312 to 2 hours after a meal. Administration of VIDEX tablets up to 30 minutes before a meal did not

313 result in any significant changes in bioavailability [see *Dosage and Administration (2)*]. VIDEX  
314 should be taken on an empty stomach.

### 315 **Special Populations**

316 *Renal Insufficiency:* Data from two studies in adults indicated that the apparent oral clearance of  
317 didanosine decreased and the terminal elimination half-life increased as creatinine clearance  
318 decreased (see Table 11). Following oral administration, didanosine was not detectable in  
319 peritoneal dialysate fluid (n=6); recovery in hemodialysate (n=5) ranged from 0.6% to 7.4% of  
320 the dose over a 3-4 hour dialysis period. The absolute bioavailability of didanosine was not  
321 affected in patients requiring dialysis. [See *Dosage and Administration (2.2)*.]

**Table 11: Mean ± 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 <sub>cr</sub> (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 <sub>R</sub> (mL/min)	458 ± 164	247 ± 153	100 ± 44	20 ± 8	less than 10
T <sub>1/2</sub> (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<sub>cr</sub> = creatinine clearance.

CL/F = apparent oral clearance.

CL<sub>R</sub> = renal clearance.

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

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

331 didanosine in pediatric patients are similar to those of didanosine in adults. Didanosine plasma  
332 concentrations appear to increase in proportion to oral doses ranging from 25 to 120 mg/m<sup>2</sup> in  
333 pediatric patients less than 5 months old and from 80 to 180 mg/m<sup>2</sup> in children above 8 months  
334 old. For information on controlled clinical studies in pediatric patients, *see Clinical Studies*  
335 *(14.2)* and *Use in Specific Populations (8.4)*.

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

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

### 339 **Drug Interactions**

340 Tables 12 and 13 summarize the effects on AUC and C<sub>max</sub>, with a 95% confidence interval (CI)  
341 when available, following coadministration of VIDEX (didanosine) with a variety of drugs.  
342 Drug-drug interactions for VIDEX buffered tablets are applicable to the VIDEX pediatric  
343 powder formulation and are noted in Tables 12 and 13. For clinical recommendations based on  
344 drug interaction studies for drugs in bold font, see *Dosage and Administration (2.3 for*  
345 *Concomitant Therapy with Tenofovir Disoproxil Fumarate)*, *Contraindications (4.1)*, and *Drug*  
346 *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<sub>max</sub> Values**

Drug	Didanosine Dosage	n	% Change of Didanosine Pharmacokinetic Parameters <sup>a</sup>	
			AUC of Didanosine (95% CI)	C <sub>max</sub> of Didanosine (95% CI)
<b>allopurinol</b> , 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 <sup>b</sup>	↓ 16%	↓ 28%
<b>ganciclovir</b> , 1000 mg every 8 hours, 2 hours after didanosine	200 mg every 12 hours	12	↑ 111%	NA
indinavir, 800 mg single dose, simultaneous	200 mg single dose	16	↔	↔
1 hour before didanosine	200 mg single dose	16	↓ 17%	↓ 13%

**Table 12: Results of Drug Interaction Studies with VIDEX: Effects of Coadministered Drug on Didanosine Plasma AUC and C<sub>max</sub> Values**

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

↑ Indicates increase.

↓ Indicates decrease.

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

<sup>a</sup> The 95% confidence intervals for the percent change in the pharmacokinetic parameter are displayed.

<sup>b</sup> HIV-infected patients.

<sup>c</sup> 90% CI.

<sup>d</sup> Comparisons are made to a parallel control group not receiving methadone (n=10).

**Table 12: Results of Drug Interaction Studies with VIDEX: Effects of Coadministered Drug on Didanosine Plasma AUC and C<sub>max</sub> Values**

Drug	Didanosine Dosage	n	% Change of Didanosine Pharmacokinetic Parameters <sup>a</sup>	
			AUC of Didanosine (95% CI)	C <sub>max</sub> of Didanosine (95% CI)

<sup>e</sup> 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<sub>max</sub> is 15 and 16, respectively.

<sup>f</sup> 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.

<sup>g</sup> Tenofovir disoproxil fumarate.

<sup>h</sup> 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.

<sup>i</sup> Patients less than 60 kg with creatinine clearance of at least 60 mL/min.

NA = Not available.

347

**Table 13: Results of Drug Interaction Studies with VIDEX: Effects of Didanosine on Coadministered Drug Plasma AUC and C<sub>max</sub> Values**

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

**Table 13: Results of Drug Interaction Studies with VIDEX: Effects of Didanosine on Coadministered Drug Plasma AUC and C<sub>max</sub> Values**

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

↑ Indicates increase.

↓ Indicates decrease.

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

<sup>a</sup> The 95% confidence intervals for the percent change in the pharmacokinetic parameter are displayed.

<sup>b</sup> HIV-infected patients.

<sup>c</sup> Tenofovir disoproxil fumarate.

<sup>d</sup> Patients less than 60 kg with creatinine clearance of at least 60 mL/min.

NA = Not available.

## 348 **12.4 Microbiology**

### 349 **Mechanism of Action**

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

### 356 **Antiviral Activity in Cell Culture**

357 The anti-HIV-1 activity of didanosine was evaluated in a variety of HIV-1 infected  
358 lymphoblastic cell lines and monocyte/macrophage cell cultures. The concentration of drug  
359 necessary to inhibit viral replication by 50% (EC<sub>50</sub>) ranged from 2.5 to 10 μM (1 μM =  
360 0.24 μg/mL) in lymphoblastic cell lines and 0.01 to 0.1 μM in monocyte/macrophage cell  
361 cultures.

### 362 **Resistance**

363 HIV-1 isolates with reduced sensitivity to didanosine have been selected in cell culture and were  
364 also obtained from patients treated with didanosine. Genetic analysis of isolates from didanosine-  
365 treated patients showed mutations in the reverse transcriptase gene that resulted in the amino acid  
366 substitutions K65R, L74V, and M184V. The L74V substitution was most frequently observed in  
367 clinical isolates. Phenotypic analysis of HIV-1 isolates from 60 patients (some with prior  
368 zidovudine treatment) receiving 6 to 24 months of didanosine monotherapy showed that isolates  
369 from 10 of 60 patients exhibited an average of a 10-fold decrease in susceptibility to didanosine  
370 in cell culture compared to baseline isolates. Clinical isolates that exhibited a decrease in  
371 didanosine susceptibility harbored one or more didanosine resistance-associated substitutions.

### 372 **Cross-resistance**

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

376 In data from clinical

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

## 379 **13 NONCLINICAL TOXICOLOGY**

### 380 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

381 Lifetime carcinogenicity studies were conducted in mice and rats for 22 and 24 months,  
382 respectively. In the mouse study, initial doses of 120, 800, and 1200 mg/kg/day for each sex  
383 were lowered after 8 months to 120, 210, and 210 mg/kg/day for females and 120, 300, and  
384 600 mg/kg/day for males. The two higher doses exceeded the maximally tolerated dose in  
385 females and the high dose exceeded the maximally tolerated dose in males. The low dose in  
386 females represented 0.68-fold maximum human exposure and the intermediate dose in males  
387 represented 1.7-fold maximum human exposure based on relative AUC comparisons. In the rat  
388 study, initial doses were 100, 250, and 1000 mg/kg/day, and the high dose was lowered to  
389 500 mg/kg/day after 18 months. The upper dose in male and female rats represented 3-fold  
390 maximum human exposure.

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

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

### 400 **13.2 Animal Toxicology and/or Pharmacology**

401 Evidence of a dose-limiting skeletal muscle toxicity has been observed in mice and rats (but not  
402 in dogs) following long-term (greater than 90 days) dosing with didanosine at doses that were  
403 approximately 1.2 to 12 times the estimated human exposure. The relationship of this finding to  
404 the potential of VIDEX (didanosine) to cause myopathy in humans is unclear. However, human  
405 myopathy has been associated with administration of VIDEX and other nucleoside analogues.

406 **14 CLINICAL STUDIES**

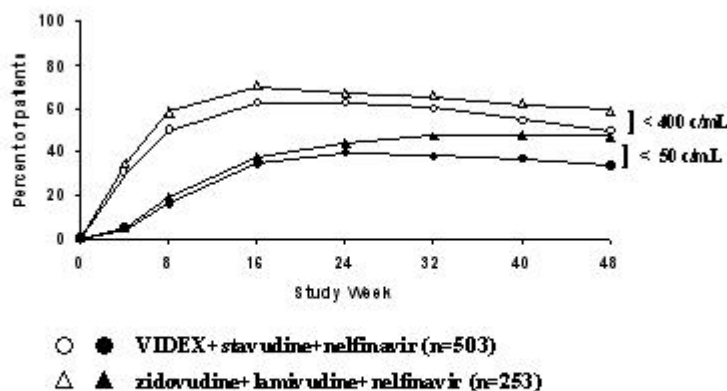
407 **14.1 Adult Patients**

408 **Combination Therapy**

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

413 Study AI454-148 was a randomized, open-label, multicenter study comparing treatment with  
414 VIDEX (400 mg once daily) plus stavudine (40 mg twice daily) and nelfinavir (750 mg three  
415 times daily) versus zidovudine (300 mg twice daily) plus lamivudine (150 mg twice daily) and  
416 nelfinavir (750 mg three times daily) in 756 treatment-naive patients, with a median CD4 cell  
417 count of 340 cells/mm<sup>3</sup> (range 80 to 1568 cells/mm<sup>3</sup>) and a median plasma HIV-1 RNA of  
418 4.69 log<sub>10</sub> copies/mL (range 2.6 to 5.9 log<sub>10</sub> copies/mL) at baseline. Median CD4 cell count  
419 increases at 48 weeks were 188 cells/mm<sup>3</sup> in both treatment groups. Treatment response and  
420 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.

421

**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 <sup>a</sup>	50* (34*)	59 (47)
Virologic failure <sup>b</sup>	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 <sup>c</sup>	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.

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

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

<sup>c</sup> Includes lost to follow-up, noncompliance, withdrawal, and pregnancy.

422 **Monotherapy**

423 The efficacy of VIDEX was demonstrated in two randomized, double-blind studies comparing  
424 VIDEX, given on a twice-daily schedule, to zidovudine, given three times daily, in 617 (ACTG  
425 116A, conducted 1989-1992) and 913 (ACTG 116B/117, conducted 1989-1991) patients with  
426 symptomatic HIV infection or AIDS who were treated for more than one year. In treatment-  
427 naive patients (ACTG 116A), the rate of HIV disease progression or death was similar between  
428 the treatment groups; mortality rates were 26% for patients receiving VIDEX and 21% for  
429 patients receiving zidovudine. Of the patients who had received previous zidovudine treatment  
430 (ACTG 116B/117), those treated with VIDEX had a lower rate of HIV disease progression or  
431 death (32%) compared to those treated with zidovudine (41%); however, survival rates were  
432 similar between the treatment groups.

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

435 **14.2 Pediatric Patients**

436 Efficacy in pediatric patients was demonstrated in a randomized, double-blind, controlled study  
437 (ACTG 152, conducted 1991-1995) involving 831 patients 3 months to 18 years of age treated  
438 for more than 1.5 years with zidovudine (180 mg/m<sup>2</sup> every 6 hours), VIDEX (120 mg/m<sup>2</sup> every  
439 12 hours), or zidovudine (120 mg/m<sup>2</sup> every 6 hours) plus VIDEX (90 mg/m<sup>2</sup> every 12 hours).  
440 Patients treated with VIDEX or VIDEX plus zidovudine had lower rates of HIV-1 disease  
441 progression or death compared with those treated with zidovudine alone.

442 **16 HOW SUPPLIED/STORAGE AND HANDLING**

443 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

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

447 **20 mg/mL Initial Solution**

448 Reconstitute the product to 20 mg/mL by adding 100 mL or 200 mL of Purified Water, USP, to  
449 the 2 g or 4 g of VIDEX powder, respectively, in the product bottle.

450 **10 mg/mL Final Admixture**

- 451 1. Immediately mix one part of the 20 mg/mL initial solution with one part of Maximum  
452 Strength Mylanta<sup>®</sup> Liquid for a final dispensing concentration of 10 mg VIDEX per mL. For  
453 patient home use, the admixture should be dispensed in appropriately sized, flint-glass or  
454 plastic (HDPE, PET, or PETG) bottles with child-resistant closures.
- 455 2. Instruct the patient to shake the admixture thoroughly prior to use and to store the tightly  
456 closed container in the refrigerator.

457 **Storage**

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

461 \_\_\_\_\_

462 Mylanta<sup>®</sup> is a registered trademark of Johnson & Johnson-Merck Consumer Pharmaceuticals  
463 Company.

464 **17 PATIENT COUNSELING INFORMATION**

465 *See Medication Guide.*

466 **17.1 Pancreatitis**

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

469 **17.2 Peripheral Neuropathy**

470 Patients should be informed that peripheral neuropathy, manifested by numbness, tingling, or  
471 pain in hands or feet, may develop during therapy with VIDEX. Patients should be counseled  
472 that peripheral neuropathy occurs with greatest frequency in patients with advanced HIV-1  
473 disease or a history of peripheral neuropathy, and that discontinuation of VIDEX may be  
474 required if toxicity develops.

475 **17.3 Lactic Acidosis and Severe Hepatomegaly with Steatosis**

476 Patients should be informed that lactic acidosis and severe hepatomegaly with steatosis,  
477 including fatal cases, have been reported with the use of nucleoside analogues alone or in  
478 combination, including didanosine and other antiretrovirals.

479 **17.4 Hepatic Toxicity**

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

483 **17.5 Non-cirrhotic Portal Hypertension**

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

486 **17.6 Retinal Changes and Optic Neuritis**

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

489 **17.7 Fat Redistribution**

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

493 **17.8 Concomitant Therapy**

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

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

499 **17.9 General Information**

500 VIDEX (didanosine) is not a cure for HIV-1 infection, and patients may continue to develop  
501 HIV-associated illnesses, including opportunistic infection. Therefore, patients should remain  
502 under the care of a physician when using VIDEX. Patients should be advised that VIDEX  
503 therapy has not been shown to reduce the risk of transmission of HIV to others through sexual

504 contact or blood contamination. Patients should be informed that the long-term effects of VIDEX  
505 are unknown at this time.

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

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

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

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

518