

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

Initial U.S. Approval: 1991

<p>WARNING: PANCREATITIS, LACTIC ACIDOSIS and HEPATOMEGALY with STEATOSIS</p> <p><i>See full prescribing information for complete boxed warning.</i></p> <ul style="list-style-type: none"> Fatal and nonfatal pancreatitis. VIDEX EC should be suspended in patients with suspected pancreatitis and discontinued in patients with confirmed pancreatitis. (5.1) Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases. Fatal lactic acidosis has been reported in pregnant women who received the combination of didanosine and stavudine. (5.2)

RECENT MAJOR CHANGES

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

DOSAGE AND ADMINISTRATION

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

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

- Renal impairment: Dose reduction is recommended. (2.2)
- Coadministration with tenofovir: Dose reduction is recommended. Patients should be monitored closely for didanosine-associated adverse reactions. (2.3, 7.1)

DOSAGE FORMS AND STRENGTHS

Capsules: 125 mg, 200 mg, 250 mg, 400 mg (3)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 01/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: PANCREATITIS, LACTIC ACIDOSIS AND HEPATOMEGALY WITH STEATOSIS

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dosage (Adult and Pediatric Patients)
- 2.2 Renal Impairment
- 2.3 Dose Adjustment

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

- 4.1 Allopurinol
- 4.2 Ribavirin

5 WARNINGS AND PRECAUTIONS

- 5.1 Pancreatitis
- 5.2 Lactic Acidosis/Severe Hepatomegaly with Steatosis
- 5.3 Hepatic Toxicity
- 5.4 Non-cirrhotic Portal Hypertension
- 5.5 Peripheral Neuropathy
- 5.6 Retinal Changes and Optic Neuritis
- 5.7 Immune Reconstitution Syndrome
- 5.8 Fat Redistribution

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Established Drug Interactions
- 7.2 Predicted Drug Interactions

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics
- 12.4 Microbiology

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 Adult Patients
- 14.2 Pediatric Patients

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

- 17.1 Pancreatitis
- 17.2 Peripheral Neuropathy
- 17.3 Lactic Acidosis and Severe Hepatomegaly with Steatosis
- 17.4 Hepatic Toxicity
- 17.5 Non-cirrhotic Portal Hypertension
- 17.6 Retinal Changes and Optic Neuritis
- 17.7 Fat Redistribution
- 17.8 Concomitant Therapy
- 17.9 General Information

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

1 **FULL PRESCRIBING INFORMATION**

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

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

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

2 **1 INDICATIONS AND USAGE**

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

6 **2 DOSAGE AND ADMINISTRATION**

7 VIDEX EC should be administered on an empty stomach. VIDEX EC Delayed-Release Capsules
8 should be swallowed intact.

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

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

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

Table 1: Recommended Dosage (Adult and Pediatric Patients)

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

18 **2.2 Renal Impairment**

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

23 **Adult Patients**

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

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

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

^a Based on studies using a buffered formulation of didanosine.

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

27 **Pediatric Patients**

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

32 **Patients Requiring Continuous Ambulatory Peritoneal Dialysis (CAPD) or** 33 **Hemodialysis**

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

37 **2.3 Dose Adjustment**

38 **Concomitant Therapy with Tenofovir Disoproxil Fumarate**

39 In patients who are also taking tenofovir disoproxil fumarate, a dose reduction of VIDEX EC to
 40 250 mg (adults weighing at least 60 kg with creatinine clearance of at least 60 mL/min) or
 41 200 mg (adults weighing less than 60 kg with creatinine clearance of at least 60 mL/min) once
 42 daily taken together with tenofovir disoproxil fumarate and a light meal (400 kcalories or less,
 43 20% fat or less) or in the fasted state is recommended. The appropriate dose of VIDEX EC

44 coadministered with tenofovir disoproxil fumarate in patients with creatinine clearance of less
45 than 60 mL/min has not been established [see *Drug Interactions (7)* and *Clinical Pharmacology*
46 *(12.3)*].

47 **Hepatic Impairment**

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

50 **3 DOSAGE FORMS AND STRENGTHS**

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

- 53 • 125 mg capsule imprinted with BMS 125 mg 6671 in Tan
- 54 • 200 mg capsule imprinted with BMS 200 mg 6672 in Green
- 55 • 250 mg capsule imprinted with BMS 250 mg 6673 in Blue
- 56 • 400 mg capsule imprinted with BMS 400 mg 6674 in Red

57 **4 CONTRAINDICATIONS**

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

60 **4.1 Allopurinol**

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

64 **4.2 Ribavirin**

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

69 **5 WARNINGS AND PRECAUTIONS**

70 **5.1 Pancreatitis**

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

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

84 **5.2 Lactic Acidosis/Severe Hepatomegaly with Steatosis**

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

99 **5.3 Hepatic Toxicity**

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

106 Hepatotoxicity and hepatic failure resulting in death were reported during postmarketing
107 surveillance in HIV-infected patients treated with hydroxyurea and other antiretroviral agents.
108 Fatal hepatic events were reported most often in patients treated with the combination of
109 hydroxyurea, didanosine, and stavudine. This combination should be avoided. [*See Adverse*
110 *Reactions (6).*]

111 **5.4 Non-cirrhotic Portal Hypertension**

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

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

123 **5.5 Peripheral Neuropathy**

124 Peripheral neuropathy, manifested by numbness, tingling, or pain in the hands or feet, has been
125 reported in patients receiving didanosine therapy. Peripheral neuropathy has occurred more
126 frequently in patients with advanced HIV disease, in patients with a history of neuropathy, or in
127 patients being treated with neurotoxic drug therapy, including stavudine. Discontinuation of

128 VIDEX EC should be considered in patients who develop peripheral neuropathy. [*See Adverse*
129 *Reactions (6).*]

130 **5.6 Retinal Changes and Optic Neuritis**

131 Retinal changes and optic neuritis have been reported in patients taking didanosine. Periodic
132 retinal examinations should be considered for patients receiving VIDEX EC [*see Adverse*
133 *Reactions (6)*].

134 **5.7 Immune Reconstitution Syndrome**

135 Immune reconstitution syndrome has been reported in patients treated with combination
136 antiretroviral therapy, including VIDEX EC. During the initial phase of combination
137 antiretroviral treatment, patients whose immune system responds may develop an inflammatory
138 response to indolent or residual opportunistic infections (such as *Mycobacterium avium*
139 infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia [PCP], or tuberculosis), which
140 may necessitate further evaluation and treatment.

141 **5.8 Fat Redistribution**

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

147 **6 ADVERSE REACTIONS**

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

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

156 **6.1 Clinical Trials Experience**

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

160 **Adults**

161 Study AI454-152 was a 48-week, randomized, open-label study comparing VIDEX EC (400 mg
 162 once daily) plus stavudine (40 mg twice daily) plus nelfinavir (750 mg three times daily) to
 163 zidovudine (300 mg) plus lamivudine (150 mg) combination tablets twice daily plus nelfinavir
 164 (750 mg three times daily) in 511 treatment-naive patients. Selected clinical adverse reactions
 165 that occurred in combination with other antiretroviral agents are provided in Table 3.

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

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

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

^b Percentages based on treated patients.

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

^d Zidovudine/lamivudine combination tablet.

* This event was not observed in this study arm.

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

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

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

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

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

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

^b Percentages based on treated patients.

^c Zidovudine/lamivudine combination tablet.

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

177 **Pediatric Patients**

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

181 In pediatric phase 1 studies, pancreatitis occurred in 2 of 60 (3%) patients treated at entry doses
182 below 300 mg/m²/day and in 5 of 38 (13%) patients treated at higher doses. In study ACTG 152,
183 pancreatitis occurred in none of the 281 pediatric patients who received didanosine 120 mg/m²
184 every 12 hours and in less than 1% of the 274 pediatric patients who received didanosine
185 90 mg/m² every 12 hours in combination with zidovudine [*see Clinical Studies (14)*].

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

187 **6.2 Postmarketing Experience**

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

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

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

196 *Digestive Disorders* - anorexia, dyspepsia, and flatulence.

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

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

202 *Metabolic Disorders* - diabetes mellitus, elevated serum alkaline phosphatase level,
203 elevated serum amylase level, elevated serum gamma-glutamyltransferase level, elevated
204 serum uric acid level, hypoglycemia, and hyperglycemia.

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

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

209 **Use with Stavudine- and Hydroxyurea-Based Regimens**

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

216 **7 DRUG INTERACTIONS**

217 **7.1 Established Drug Interactions**

218 Clinical recommendations based on the results of drug interaction studies are listed in Table 5.
219 Pharmacokinetic results of drug interaction studies are shown in Tables 9-12 [*see*
220 *Contraindications (4.1 and 4.2), Clinical Pharmacology (12.3)*].

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

Drug	Effect	Clinical Comment
ganciclovir	↑ didanosine concentration	If there is no suitable alternative to ganciclovir, then use in combination with VIDEX EC with caution. Monitor for didanosine-associated toxicity.
methadone	↓ didanosine concentration	If coadministration of methadone and didanosine is necessary, the recommended formulation of didanosine is VIDEX EC. Patients should be closely monitored for adequate clinical response when VIDEX EC is coadministered with methadone, including monitoring for changes in HIV RNA viral load. Do not coadminister methadone with VIDEX pediatric powder due to significant decreases in didanosine concentrations.
nelfinavir	No interaction 1 hour after didanosine	Administer nelfinavir 1 hour after VIDEX EC.

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

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

↑ Indicates increase.

↓ Indicates decrease.

^a Coadministration of didanosine with food decreases didanosine concentrations. Thus, although not studied, it is possible that coadministration with heavier meals could reduce didanosine concentrations further.

221 Exposure to didanosine is increased when coadministered with tenofovir disoproxil fumarate
 222 [Table 5 and *see Clinical Pharmacokinetics (12.3, Tables 9 and 10)*]. Increased exposure may
 223 cause or worsen didanosine-related clinical toxicities, including pancreatitis, symptomatic
 224 hyperlactatemia/lactic acidosis, and peripheral neuropathy. Coadministration of tenofovir
 225 disoproxil fumarate with VIDEX EC should be undertaken with caution, and patients should be
 226 monitored closely for didanosine-related toxicities and clinical response. VIDEX EC should be
 227 suspended if signs or symptoms of pancreatitis, symptomatic hyperlactatemia, or lactic acidosis
 228 develop [*see Dosage and Administration (2.3), Warnings and Precautions (5)*]. Suppression of
 229 CD4 cell counts has been observed in patients receiving tenofovir disoproxil fumarate with
 230 didanosine at a dose of 400 mg daily.

231 7.2 Predicted Drug Interactions

232 Predicted drug interactions with VIDEX EC are listed in Table 6.

Table 6: Predicted Drug Interactions with VIDEX EC

Drug or Drug Class	Effect	Clinical Comment
Drugs that may cause pancreatic toxicity	↑ risk of pancreatitis	Use only with extreme caution. ^a

Table 6: Predicted Drug Interactions with VIDEX EC

Drug or Drug Class	Effect	Clinical Comment
Neurotoxic drugs	↑ risk of neuropathy	Use with caution. ^b

↑ Indicates increase.

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

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

233 **8 USE IN SPECIFIC POPULATIONS**

234 **8.1 Pregnancy**

235 **Pregnancy Category B**

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

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

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

255 **Antiretroviral Pregnancy Registry**

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

259 **8.3 Nursing Mothers**

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

266 **8.4 Pediatric Use**

267 Use of didanosine in pediatric patients from 2 weeks of age through adolescence is supported by
268 evidence from adequate and well-controlled studies of didanosine in adult and pediatric patients
269 [*see Dosage and Administration (2), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and*
270 *Clinical Studies (14)*]. Additional pharmacokinetic studies in pediatric patients support use of
271 VIDEX EC in pediatric patients who weigh at least 20 kg.

272 **8.5 Geriatric Use**

273 In an Expanded Access Program using a buffered formulation of didanosine for the treatment of
274 advanced HIV infection, patients aged 65 years and older had a higher frequency of pancreatitis
275 (10%) than younger patients (5%) [*see Warnings and Precautions (5.1)*]. Clinical studies of
276 didanosine, including those for VIDEX EC, did not include sufficient numbers of subjects aged
277 65 years and over to determine whether they respond differently than younger subjects.
278 Didanosine is known to be substantially excreted by the kidney, and the risk of toxic reactions to
279 this drug may be greater in patients with impaired renal function. Because elderly patients are
280 more likely to have decreased renal function, care should be taken in dose selection. In addition,
281 renal function should be monitored and dosage adjustments should be made accordingly [*see*
282 *Dosage and Administration (2.2)*].

283 **8.6 Renal Impairment**

284 Patients with renal impairment (creatinine clearance of less than 60 mL/min) may be at greater
285 risk of toxicity from didanosine due to decreased drug clearance [*see Clinical Pharmacology*
286 (12.3)]. A dose reduction is recommended for these patients [*see Dosage and*
287 *Administration (2)*].

288 **10 OVERDOSAGE**

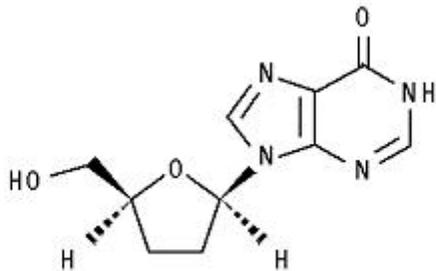
289 There is no known antidote for didanosine overdosage. In phase 1 studies, in which buffered
290 formulations of didanosine were initially administered at doses ten times the currently
291 recommended dose, toxicities included: pancreatitis, peripheral neuropathy, diarrhea,
292 hyperuricemia, and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

294 **11 DESCRIPTION**

295 VIDEX[®] EC is the brand name for an enteric-coated formulation of didanosine, USP, a synthetic
296 purine nucleoside analogue active against HIV-1. VIDEX EC Delayed-Release Capsules,
297 containing enteric-coated beadlets, are available for oral administration in strengths of 125, 200,
298 250, and 400 mg of didanosine. The inactive ingredients in the beadlets include
299 carboxymethylcellulose sodium 12, diethyl phthalate, methacrylic acid copolymer, sodium
300 hydroxide, sodium starch glycolate, and talc. The capsule shells contain gelatin and titanium
301 dioxide. The capsules are imprinted with edible inks.

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

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



305 Didanosine is a white crystalline powder with the molecular formula $C_{10}H_{12}N_4O_3$ and a
306 molecular weight of 236.2. The aqueous solubility of didanosine at 25° C and pH of
307 approximately 6 is 27.3 mg/mL. Didanosine is unstable in acidic solutions. For example, at pH
308 less than 3 and 37° C, 10% of didanosine decomposes to hypoxanthine in less than 2 minutes. In
309 VIDEX EC, an enteric coating is used to protect didanosine from degradation by stomach acid.

310 **12 CLINICAL PHARMACOLOGY**

311 **12.1 Mechanism of Action**

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

313 **12.3 Pharmacokinetics**

314 The pharmacokinetic parameters of didanosine in HIV-infected adult and pediatric patients are
315 summarized in Table 7, by weight ranges that correspond to recommended doses (Table 1).
316 Didanosine is rapidly absorbed, with peak plasma concentrations generally observed from
317 0.25 to 1.50 hours following oral dosing with a buffered formulation. Increases in plasma
318 didanosine concentrations were dose proportional over the range of 50 to 400 mg. In adults, the
319 mean (\pm standard deviation) oral bioavailability following single oral dosing with a buffered
320 formulation is 42 (\pm 12)%. After oral administration, the urinary recovery of didanosine is
321 approximately 18 (\pm 8)% of the dose. The CSF-plasma ratio following IV administration is
322 21 (\pm 0.03)%. Steady-state pharmacokinetic parameters did not differ significantly from values
323 obtained after a single dose. Binding of didanosine to plasma proteins *in vitro* was low (less than
324 5%). Based on data from *in vitro* and animal studies, it is presumed that the metabolism of
325 didanosine in man occurs by the same pathways responsible for the elimination of endogenous
326 purines.

Table 7: Pharmacokinetic Parameters for Didanosine in HIV-infected Patients

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

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

327 **Comparison of Didanosine Formulations**

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

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

339 **Effect of Food**

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

343 **Special Populations**

344 *Renal Insufficiency:* Data from two studies using a buffered formulation of didanosine indicated
 345 that the apparent oral clearance of didanosine decreased and the terminal elimination half-life
 346 increased as creatinine clearance decreased (see Table 8). Following oral administration,
 347 didanosine was not detectable in peritoneal dialysate fluid (n=6); recovery in hemodialysate
 348 (n=5) ranged from 0.6% to 7.4% of the dose over a 3-4 hour dialysis period. The absolute
 349 bioavailability of didanosine was not affected in patients requiring dialysis. [See *Dosage and*
 350 *Administration (2.2).*]

Table 8: Mean ± SD Pharmacokinetic Parameters for Didanosine Following a Single Oral Dose of a Buffered Formulation

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 ± 22	68 ± 8	46 ± 8	13 ± 5	ND
CL/F (mL/min)	2164 ± 638	1566 ± 833	1023 ± 378	628 ± 104	543 ± 174
CL _R (mL/min)	458 ± 164	247 ± 153	100 ± 44	20 ± 8	less than 10
T _{1/2} (h)	1.42 ± 0.33	1.59 ± 0.13	1.75 ± 0.43	2.0 ± 0.3	4.1 ± 1.2

ND = not determined due to anuria.

CL_{CR} = creatinine clearance.

CL/F = apparent oral clearance.

CL_R = renal clearance.

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

358 *Pediatric Patients:* The pharmacokinetics of didanosine have been evaluated in HIV-exposed
 359 and HIV-infected pediatric patients from birth to adulthood.

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

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

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

371 Drug Interactions

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

Table 9: Results of Drug Interaction Studies with VIDEX EC: Effects of Coadministered Drug on Didanosine Plasma AUC and C_{max} Values

Drug	Didanosine Dosage	n	% Change of Didanosine Pharmacokinetic Parameters ^a	
			AUC of Didanosine (90% CI)	C _{max} of Didanosine (90% CI)
tenofovir , ^{b,c} 300 mg once daily with a light meal ^d	400 mg single dose fasting 2 hours before tenofovir	26	↑ 48% (31, 67%)	↑ 48% (25, 76%)
tenofovir , ^{b,c} 300 mg once daily with a light meal ^d	400 mg single dose with tenofovir and a light meal	25	↑ 60% (44, 79%)	↑ 64% (41, 89%)
tenofovir , ^{b,c} 300 mg once daily with a light meal ^d	200 mg single dose with tenofovir and a light meal	33	↑ 16% (6, 27%) ^e	↓ 12% (-25, 3%) ^e
	250 mg single dose with tenofovir and a light meal	33	↔ (-13, 5%) ^f	↓ 20% (-32, -7%) ^f

Table 9: Results of Drug Interaction Studies with VIDEX EC: Effects of Coadministered Drug on Didanosine Plasma AUC and C_{max} Values

Drug	Didanosine Dosage	n	% Change of Didanosine Pharmacokinetic Parameters ^a	
			AUC of Didanosine (90% CI)	C _{max} of Didanosine (90% CI)
	325 mg single dose with tenofovir and a light meal	33	↑ 13% (3, 24%) ^f	↓ 11% (-24, 4%) ^f
methadone, chronic maintenance dose	400 mg single dose	15, 16 ^g	↓ 17% (-29, -2%)	↓ 16% (-33, 4%)

↑ Indicates increase.

↓ Indicates decrease.

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

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

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

^c Tenofovir disoproxil fumarate.

^d 373 kcalories, 8.2 grams fat.

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

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

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

376

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

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

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

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

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

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

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

^c Tenofovir disoproxil fumarate.

^d 373 kcalories, 8.2 grams fat.

377 *Didanosine Buffered Formulations:* Tables 11 and 12 summarize the effects on AUC and C_{max},
378 with a 90% or 95% CI when available, following coadministration of buffered formulations of
379 didanosine with a variety of drugs. The results of these studies may be expected to apply to
380 VIDEX EC. For most of the listed drugs, no clinically significant pharmacokinetic interactions
381 were noted. For clinical recommendations based on drug interaction studies for drugs in bold
382 font, see *Dosage and Administration (2.3 for Concomitant Therapy with Tenofovir Disoproxil*
383 *Fumarate)*, *Contraindications (4.1)*, and *Drug Interactions (7.1)*.

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

Drug	Didanosine Dosage	n	% Change of Didanosine Pharmacokinetic Parameters ^a	
			AUC of Didanosine (95% CI)	C _{max} of Didanosine (95% CI)
allopurinol, renally impaired, 300 mg/day	200 mg single dose	2	↑ 312%	↑ 232%
healthy volunteer, 300 mg/day for 7 days	400 mg single dose	14	↑ 113%	↑ 69%
ganciclovir, 1000 mg every 8 hours, 2 hours after didanosine	200 mg every 12 hours	12	↑ 111%	NA
ciprofloxacin, 750 mg every 12 hours for 3 days, 2 hours before didanosine	200 mg every 12 hours for 3 days	8 ^c	↓ 16%	↓ 28%
indinavir, 800 mg single dose simultaneous	200 mg single dose	16	↔	↔
1 hour before didanosine	200 mg single dose	16	↓ 17% (-27, -7%) ^b	↓ 13% (-28, 5%) ^b
ketoconazole, 200 mg/day for 4 days, 2 hours before didanosine	375 mg every 12 hours for 4 days	12 ^c	↔	↓ 12%
loperamide, 4 mg every 6 hours for 1 day	300 mg single dose	12 ^c	↔	↓ 23%
metoclopramide, 10 mg single dose	300 mg single dose	12 ^c	↔	↑ 13%
ranitidine, 150 mg single dose, 2 hours before didanosine	375 mg single dose	12 ^c	↑ 14%	↑ 13%
rifabutin, 300 mg or 600 mg/day for 12 days	167 mg or 250 mg every 12 hours for 12 days	11	↑ 13% (-1, 27%)	↑ 17% (-4, 38%)
ritonavir, 600 mg every 12 hours for 4 days	200 mg every 12 hours for 4 days	12	↓ 13% (0, 23%)	↓ 16% (5, 26%)
stavudine, 40 mg every 12 hours for 4 days	100 mg every 12 hours for 4 days	10	↔	↔
sulfamethoxazole, 1000 mg single dose	200 mg single dose	8 ^c	↔	↔
trimethoprim, 200 mg single dose	200 mg single dose	8 ^c	↔	↑ 17% (-23, 77%)
zidovudine, 200 mg every 8 hours for 3 days	200 mg every 12 hours for 3 days	6 ^c	↔	↔

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

Drug	Didanosine Dosage	n	% Change of Didanosine Pharmacokinetic Parameters ^a	
			AUC of Didanosine (95% CI)	C _{max} of Didanosine (95% CI)

↑ Indicates increase.

↓ Indicates decrease.

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

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

^b 90% CI.

^c HIV-infected patients.

NA = Not available.

384

Table 12: Results of Drug Interaction Studies with Buffered Formulations of Didanosine : 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)
dapsone, 100 mg single dose	200 mg every 12 hours for 14 days	6 ^b	↔	↔
ganciclovir, 1000 mg every 8 hours, 2 hours after didanosine	200 mg every 12 hours	12 ^b	↓ 21%	NA
nelfinavir , 750 mg single dose, 1 hour after didanosine	200 mg single dose	10 ^b	↑ 12%	↔
ranitidine, 150 mg single dose, 2 hours before didanosine	375 mg single dose	12 ^b	↓ 16%	↔
ritonavir, 600 mg every 12 hours for 4 days	200 mg every 12 hours for 4 days	12	↔	↔

Table 12: Results of Drug Interaction Studies with Buffered Formulations of Didanosine : 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)
stavudine, 40 mg every 12 hours for 4 days	100 mg every 12 hours for 4 days	10 ^b	↔	↑ 17%
sulfamethoxazole, 1000 mg single dose	200 mg single dose	8 ^b	↓ 11% (-17, -4%)	↓ 12% (-28, 8%)
trimethoprim, 200 mg single dose	200 mg single dose	8 ^b	↑ 10% (-9, 34%)	↓ 22% (-59, 49%)
zidovudine, 200 mg every 8 hours for 3 days	200 mg every 12 hours for 3 days	6 ^b	↓ 10% (-27, 11%)	↓ 16.5% (-53, 47%)

↑ Indicates increase.

↓ Indicates decrease.

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

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

^b HIV-infected patients.

NA = Not available.

385 12.4 Microbiology

386 Mechanism of Action

387 Didanosine is a synthetic nucleoside analogue of the naturally occurring nucleoside
 388 deoxyadenosine in which the 3'-hydroxyl group is replaced by hydrogen. Intracellularly,
 389 didanosine is converted by cellular enzymes to the active metabolite, dideoxyadenosine
 390 5'-triphosphate. Dideoxyadenosine 5'-triphosphate inhibits the activity of HIV-1 reverse
 391 transcriptase both by competing with the natural substrate, deoxyadenosine 5'-triphosphate, and
 392 by its incorporation into viral DNA causing termination of viral DNA chain elongation.

393 **Antiviral Activity in Cell Culture**

394 The anti-HIV-1 activity of didanosine was evaluated in a variety of HIV-1 infected
395 lymphoblastic cell lines and monocyte/macrophage cell cultures. The concentration of drug
396 necessary to inhibit viral replication by 50% (EC₅₀) ranged from 2.5 to 10 μM
397 (1 μM = 0.24 μg/mL) in lymphoblastic cell lines and 0.01 to 0.1 μM in monocyte/macrophage
398 cell cultures.

399 **Resistance**

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

409 **Cross-resistance**

410 HIV-1 isolates from 2 of 39 patients receiving combination therapy for up to 2 years with
411 didanosine and zidovudine exhibited decreased susceptibility to didanosine, lamivudine,
412 stavudine, zalcitabine, and zidovudine in cell culture. These isolates harbored five substitutions
413 (A62V, V75I, F77L, F116Y, and Q151M) in the reverse transcriptase gene. In data from clinical
414 studies, the presence of thymidine analogue mutations (M41L, D67N, L210W, T215Y, K219Q)
415 has been shown to decrease the response to didanosine.

416 **13 NONCLINICAL TOXICOLOGY**

417 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

418 Lifetime carcinogenicity studies were conducted in mice and rats for 22 and 24 months,
419 respectively. In the mouse study, initial doses of 120, 800, and 1200 mg/kg/day for each sex
420 were lowered after 8 months to 120, 210, and 210 mg/kg/day for females and 120, 300, and
421 600 mg/kg/day for males. The two higher doses exceeded the maximally tolerated dose in

422 females and the high dose exceeded the maximally tolerated dose in males. The low dose in
423 females represented 0.68-fold maximum human exposure and the intermediate dose in males
424 represented 1.7-fold maximum human exposure based on relative AUC comparisons. In the rat
425 study, initial doses were 100, 250, and 1000 mg/kg/day, and the high dose was lowered to
426 500 mg/kg/day after 18 months. The upper dose in male and female rats represented 3-fold
427 maximum human exposure.

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

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

437 **13.2 Animal Toxicology and/or Pharmacology**

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

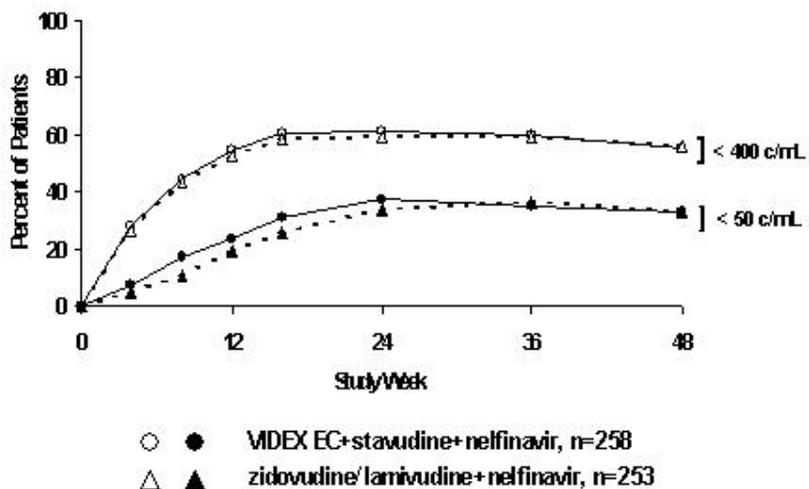
443 **14 CLINICAL STUDIES**

444 **14.1 Adult Patients**

445 Study AI454-152 was a 48-week, randomized, open-label study comparing VIDEX EC (400 mg
446 once daily) plus stavudine (40 mg twice daily) plus nelfinavir (750 mg three times daily) to
447 zidovudine (300 mg) plus lamivudine (150 mg) combination tablets twice daily plus nelfinavir
448 (750 mg three times daily) in 511 treatment-naïve patients, with a mean CD4 cell count of
449 411 cells/mm³ (range 39 to 1105 cells/mm³) and a mean plasma HIV-1 RNA of
450 4.71 log₁₀ copies/mL (range 2.8 to 5.9 log₁₀ copies/mL) at baseline. Patients were primarily
451 males (72%) and Caucasian (53%) with a mean age of 35 years (range 18 to 73 years). The

452 percentages of patients with HIV-1 RNA less than 400 and less than 50 copies/mL and outcomes
453 of patients through 48 weeks are summarized in Figure 1 and Table 13, respectively.

Figure 1
Treatment Response Through Week 48*, AI454-152



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

454

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

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

^a Zidovudine/lamivudine combination tablet.

^b Corresponds to rates at Week 48 in Figure 1.

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

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

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

455 14.2 Pediatric Patients

456 Efficacy in pediatric patients was demonstrated in a randomized, double-blind, controlled study
 457 (ACTG 152, conducted 1991-1995) involving 831 patients 3 months to 18 years of age treated
 458 for more than 1.5 years with zidovudine (180 mg/m² every 6 hours), didanosine (120 mg/m²
 459 every 12 hours), or zidovudine (120 mg/m² every 6 hours) plus didanosine (90 mg/m² every
 460 12 hours). Patients treated with didanosine or didanosine plus zidovudine had lower rates of
 461 HIV-1 disease progression or death compared with those treated with zidovudine alone.

462 16 HOW SUPPLIED/STORAGE AND HANDLING

463 VIDEX EC (didanosine, USP) Delayed-Release Capsules are white, opaque capsules that are
 464 packaged in bottles with child-resistant closures as described in Table 14.

Table 14: VIDEX EC Delayed-Release Capsules

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

465 **Storage**

466 The capsules should be stored in tightly closed containers at 25° C (77° F). Excursions between
467 15° C and 30° C (59° F and 86° F) are permitted (see USP Controlled Room Temperature).

468 **17 PATIENT COUNSELING INFORMATION**

469 *See Medication Guide.*

470 **17.1 Pancreatitis**

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

473 **17.2 Peripheral Neuropathy**

474 Patients should be informed that peripheral neuropathy, manifested by numbness, tingling, or
475 pain in hands or feet, may develop during therapy with VIDEX EC (didanosine). Patients should
476 be counseled that peripheral neuropathy occurs with greatest frequency in patients with advanced
477 HIV-1 disease or a history of peripheral neuropathy, and that discontinuation of VIDEX EC may
478 be required if toxicity develops.

479 **17.3 Lactic Acidosis and Severe Hepatomegaly with Steatosis**

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

483 **17.4 Hepatic Toxicity**

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

487 **17.5 Non-cirrhotic Portal Hypertension**

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

490 **17.6 Retinal Changes and Optic Neuritis**

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

493 **17.7 Fat Redistribution**

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

497 **17.8 Concomitant Therapy**

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

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

503 **17.9 General Information**

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

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

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

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

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

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

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