

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

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

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

Initial U.S. Approval: 1991

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

*See full prescribing information for complete boxed warning.*

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

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

Dosage and Administration (2)	09/2008
Contraindications	
Allopurinol (4.1)	06/2009
Ribavirin (4.2)	06/2009

-----**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)
- Patients may develop peripheral neuropathy (5.4), retinal changes and optic neuritis (5.5), immune reconstitution syndrome (5.6), and redistribution/accumulation of body fat (5.7).

-----**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](http://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 FDA-approved patient labeling**

**Revised: 06/2009**

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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 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<sup>®</sup> 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 (didanosine, USP) should be administered on an empty stomach. VIDEX EC  
8 Delayed-Release Capsules 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)**

<b>Body Weight</b>	<b>Dose</b>
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<sup>a</sup>**

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

<sup>a</sup> Based on studies using a buffered formulation of didanosine.

<sup>b</sup> Not suitable for use in patients less than 60 kg with CL<sub>CR</sub> 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 Peripheral Neuropathy**

112 Peripheral neuropathy, manifested by numbness, tingling, or pain in the hands or feet, has been  
113 reported in patients receiving didanosine therapy. Peripheral neuropathy has occurred more  
114 frequently in patients with advanced HIV disease, in patients with a history of neuropathy, or in  
115 patients being treated with neurotoxic drug therapy, including stavudine. Discontinuation of  
116 VIDEX EC should be considered in patients who develop peripheral neuropathy. [*See Adverse*  
117 *Reactions (6).*]

118 **5.5 Retinal Changes and Optic Neuritis**

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

122 **5.6 Immune Reconstitution Syndrome**

123 Immune reconstitution syndrome has been reported in patients treated with combination  
124 antiretroviral therapy, including VIDEX EC. During the initial phase of combination  
125 antiretroviral treatment, patients whose immune system responds may develop an inflammatory  
126 response to indolent or residual opportunistic infections (such as *Mycobacterium avium*

127 infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia [PCP], or tuberculosis), which  
128 may necessitate further evaluation and treatment.

## 129 **5.7 Fat Redistribution**

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

## 135 **6 ADVERSE REACTIONS**

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

- 137 • Pancreatitis [*see Boxed Warning, Warnings and Precautions (5.1)*]
- 138 • Lactic acidosis/severe hepatomegaly with steatosis [*see Boxed Warning, Warnings and*  
139 *Precautions (5.2)*]
- 140 • Hepatic toxicity [*see Warnings and Precautions (5.3)*]
- 141 • Peripheral neuropathy [*see Warnings and Precautions (5.4)*]
- 142 • Retinal changes and optic neuritis [*see Warnings and Precautions (5.5)*]

### 143 **6.1 Clinical Trials Experience**

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

#### 147 **Adults**

148 Study AI454-152 was a 48-week, randomized, open-label study comparing VIDEX EC (400 mg  
149 once daily) plus stavudine (40 mg twice daily) plus nelfinavir (750 mg three times daily) to  
150 zidovudine (300 mg) plus lamivudine (150 mg) combination tablets twice daily plus nelfinavir  
151 (750 mg three times daily) in 511 treatment-naive patients. Selected clinical adverse reactions  
152 that occurred in combination with other antiretroviral agents are provided in Table 3.

**Table 3: Selected Clinical Adverse Reactions, Study AI454-152<sup>a</sup>**

Adverse Reactions	Percent of Patients <sup>b,c</sup>	
	VIDEX EC + stavudine + nelfinavir n=258	zidovudine/ lamivudine <sup>d</sup> + 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	*

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

<sup>b</sup> Percentages based on treated patients.

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

<sup>d</sup> Zidovudine/lamivudine combination tablet.

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

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

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

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

**Table 4: Selected Laboratory Abnormalities, Study AI454-152<sup>a</sup>**

Parameter	Percent of Patients <sup>b</sup>			
	VIDEX EC + stavudine + nelfinavir n=258		zidovudine/lamivudine <sup>c</sup> + nelfinavir n=253	
	Grades 3-4 <sup>d</sup>	All Grades	Grades 3-4 <sup>d</sup>	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

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

<sup>b</sup> Percentages based on treated patients.

<sup>c</sup> Zidovudine/lamivudine combination tablet.

<sup>d</sup> 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).

## 164 **Pediatric Patients**

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

168 In pediatric phase 1 studies, pancreatitis occurred in 2 of 60 (3%) patients treated at entry doses  
169 below 300 mg/m<sup>2</sup>/day and in 5 of 38 (13%) patients treated at higher doses. In study ACTG 152,  
170 pancreatitis occurred in none of the 281 pediatric patients who received didanosine 120 mg/m<sup>2</sup>  
171 every 12 hours and in less than 1% of the 274 pediatric patients who received didanosine  
172 90 mg/m<sup>2</sup> every 12 hours in combination with zidovudine [*see Clinical Studies (14)*].

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

## 174 **6.2 Postmarketing Experience**

175 The following adverse reactions have been identified during postapproval use of didanosine.  
176 Because they are reported voluntarily from a population of unknown size, estimates of frequency

177 cannot be made. These reactions have been chosen for inclusion due to their seriousness,  
178 frequency of reporting, causal connection to didanosine, or a combination of these factors.

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

180 *Body as a Whole* - abdominal pain, alopecia, anaphylactoid reaction, asthenia,  
181 chills/fever, pain, and redistribution/accumulation of body fat [*see Warnings and*  
182 *Precautions (5.7)*].

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

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

186 *Hepatobiliary Disorders* - symptomatic hyperlactatemia/lactic acidosis and hepatic  
187 steatosis [*see Warnings and Precautions (5.2)*]; hepatitis and liver failure.

188 *Metabolic Disorders* - diabetes mellitus, elevated serum alkaline phosphatase level,  
189 elevated serum amylase level, elevated serum gamma-glutamyltransferase level, elevated  
190 serum uric acid level, hypoglycemia, and hyperglycemia.

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

193 *Ophthalmologic Disorders* - retinal depigmentation and optic neuritis [*see Warnings and*  
194 *Precautions (5.5)*].

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

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

202 **7 DRUG INTERACTIONS**

203 **7.1 Established Drug Interactions**

204 Clinical recommendations based on the results of drug interaction studies are listed in Table 5.  
205 Pharmacokinetic results of drug interaction studies are shown in Tables 9-12 [*see*  
206 *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.
tenofovir disoproxil fumarate	↑ didanosine concentration	A dose reduction of VIDEX EC to the following dosage once daily taken together with tenofovir disoproxil fumarate and a light meal (400 kcalories or less and 20% fat or less) or in the fasted state is recommended. <sup>a</sup> <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> Patients should be monitored for didanosine-associated toxicities and clinical response.

↑ Indicates increase.

↓ Indicates decrease.

<sup>a</sup> 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.

207 Exposure to didanosine is increased when coadministered with tenofovir disoproxil fumarate  
208 [Table 5 and *see Clinical Pharmacokinetics (12.3, Tables 9 and 11)*]. Increased exposure may  
209 cause or worsen didanosine-related clinical toxicities, including pancreatitis, symptomatic

210 hyperlactatemia/lactic acidosis, and peripheral neuropathy. Coadministration of tenofovir  
211 disoproxil fumarate with VIDEX EC should be undertaken with caution, and patients should be  
212 monitored closely for didanosine-related toxicities and clinical response. VIDEX EC should be  
213 suspended if signs or symptoms of pancreatitis, symptomatic hyperlactatemia, or lactic acidosis  
214 develop [see *Dosage and Administration (2.3)*, *Warnings and Precautions (5)*]. Suppression of  
215 CD4 cell counts has been observed in patients receiving tenofovir disoproxil fumarate with  
216 didanosine at a dose of 400 mg daily.

## 217 **7.2 Predicted Drug Interactions**

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

**Table 6: Predicted Drug Interactions with VIDEX EC**

<b>Drug or Drug Class</b>	<b>Effect</b>	<b>Clinical Comment</b>
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>

↑ Indicates increase.

<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 EC is recommended [see *Warnings and Precautions (5.1)*].

<sup>b</sup> [See *Warnings and Precautions (5.5)*.]

## 219 **8 USE IN SPECIFIC POPULATIONS**

### 220 **8.1 Pregnancy**

#### 221 **Pregnancy Category B**

222 Reproduction studies have been performed in rats and rabbits at doses up to 12 and 14.2 times  
223 the estimated human exposure (based upon plasma levels), respectively, and have revealed no  
224 evidence of impaired fertility or harm to the fetus due to didanosine. At approximately 12 times  
225 the estimated human exposure, didanosine was slightly toxic to female rats and their pups during  
226 mid and late lactation. These rats showed reduced food intake and body weight gains but the  
227 physical and functional development of the offspring was not impaired and there were no major  
228 changes in the F2 generation. A study in rats showed that didanosine and/or its metabolites are

229 transferred to the fetus through the placenta. Animal reproduction studies are not always  
230 predictive of human response.

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

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

#### 241 **Antiretroviral Pregnancy Registry**

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

### 245 **8.3 Nursing Mothers**

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

### 252 **8.4 Pediatric Use**

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

258 **8.5 Geriatric Use**

259 In an Expanded Access Program using a buffered formulation of didanosine for the treatment of  
260 advanced HIV infection, patients aged 65 years and older had a higher frequency of pancreatitis  
261 (10%) than younger patients (5%) [*see Warnings and Precautions (5.1)*]. Clinical studies of  
262 didanosine, including those for VIDEX EC, did not include sufficient numbers of subjects aged  
263 65 years and over to determine whether they respond differently than younger subjects.  
264 Didanosine is known to be substantially excreted by the kidney, and the risk of toxic reactions to  
265 this drug may be greater in patients with impaired renal function. Because elderly patients are  
266 more likely to have decreased renal function, care should be taken in dose selection. In addition,  
267 renal function should be monitored and dosage adjustments should be made accordingly [*see*  
268 *Dosage and Administration (2.2)*].

269 **8.6 Renal Impairment**

270 Patients with renal impairment (creatinine clearance of less than 60 mL/min) may be at greater  
271 risk of toxicity from didanosine due to decreased drug clearance [*see Clinical Pharmacology*  
272 *(12.3)*]. A dose reduction is recommended for these patients [*see Dosage and*  
273 *Administration (2)*].

274 **10 OVERDOSAGE**

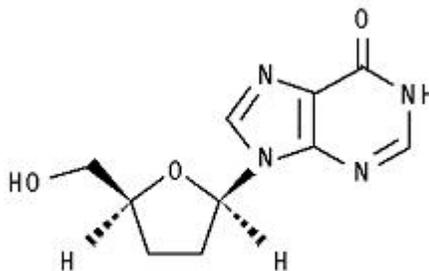
275 There is no known antidote for didanosine overdosage. In phase 1 studies, in which buffered  
276 formulations of didanosine were initially administered at doses ten times the currently  
277 recommended dose, toxicities included: pancreatitis, peripheral neuropathy, diarrhea,  
278 hyperuricemia,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

280 **11 DESCRIPTION**

281 VIDEX<sup>®</sup> EC is the brand name for an enteric-coated formulation of didanosine, USP, a synthetic  
282 purine nucleoside analogue active against HIV-1. VIDEX EC Delayed-Release Capsules,  
283 containing enteric-coated beadlets, are available for oral administration in strengths of 125, 200,  
284 250, and 400 mg of didanosine. The inactive ingredients in the beadlets include  
285 carboxymethylcellulose sodium 12, diethyl phthalate, methacrylic acid copolymer, sodium  
286 hydroxide, sodium starch glycolate, and talc. The capsule shells contain gelatin and titanium  
287 dioxide. The capsules are imprinted with edible inks.

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

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



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

## 296 **12 CLINICAL PHARMACOLOGY**

### 297 **12.1 Mechanism of Action**

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

### 299 **12.3 Pharmacokinetics**

300 The pharmacokinetic parameters of didanosine in HIV-infected adult and pediatric patients are  
301 summarized in Table 7, by weight ranges that correspond to recommended doses (Table 1).  
302 Didanosine is rapidly absorbed, with peak plasma concentrations generally observed from  
303 0.25 to 1.50 hours following oral dosing with a buffered formulation. Increases in plasma  
304 didanosine concentrations were dose proportional over the range of 50 to 400 mg. In adults, the  
305 mean ( $\pm$  standard deviation) oral bioavailability following single oral dosing with a buffered  
306 formulation is 42 ( $\pm$ 12)%. After oral administration, the urinary recovery of didanosine is  
307 approximately 18 ( $\pm$ 8)% of the dose. The CSF-plasma ratio following IV administration is  
308 21 ( $\pm$ 0.03)%. Steady-state pharmacokinetic parameters did not differ significantly from values

309 obtained after a single dose. Binding of didanosine to plasma proteins *in vitro* was low (less than  
310 5%). Based on data from *in vitro* and animal studies, it is presumed that the metabolism of  
311 didanosine in man occurs by the same pathways responsible for the elimination of endogenous  
312 purines.

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

Parameter <sup>a</sup>	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

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

### 313 Comparison of Didanosine Formulations

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

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

325 **Effect of Food**

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

329 **Special Populations**

330 *Renal Insufficiency:* Data from two studies using a buffered formulation of didanosine indicated  
331 that the apparent oral clearance of didanosine decreased and the terminal elimination half-life  
332 increased as creatinine clearance decreased (see Table 8). Following oral administration,  
333 didanosine was not detectable in peritoneal dialysate fluid (n=6); recovery in hemodialysate  
334 (n=5) ranged from 0.6% to 7.4% of the dose over a 3-4 hour dialysis period. The absolute  
335 bioavailability of didanosine was not affected in patients requiring dialysis. [*See Dosage and*  
336 *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 <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.

337 *Hepatic Impairment:* The pharmacokinetics of didanosine have been studied in 12 non-HIV-  
338 infected subjects with moderate (n=8) to severe (n=4) hepatic impairment (Child-Pugh Class B  
339 or C). Mean AUC and  $C_{max}$  values following a single 400 mg dose of didanosine were  
340 approximately 13% and 19% higher, respectively, in patients with hepatic impairment compared

341 to matched healthy subjects. No dose adjustment is needed, because a similar range and  
342 distribution of AUC and C<sub>max</sub> values was observed for subjects with hepatic impairment and  
343 matched healthy controls. [See *Dosage and Administration* (2.3).]

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

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

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

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

### 357 **Drug Interactions**

358 Tables 9 and 10 summarize the effects on AUC and C<sub>max</sub>, with a 90% confidence interval (CI)  
359 when available, following coadministration of VIDEX EC with a variety of drugs. For clinical  
360 recommendations based on drug interaction studies for drugs in bold font, see *Dosage and*  
361 *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<sub>max</sub> Values**

Drug	Didanosine Dosage	n	% Change of Didanosine Pharmacokinetic Parameters <sup>a</sup>	
			AUC of Didanosine (90% CI)	C <sub>max</sub> of Didanosine (90% CI)
tenofovir, <sup>b,c</sup> 300 mg once daily with a light meal <sup>d</sup>	400 mg single dose fasting 2 hours before tenofovir	26	↑ 48% (31, 67%)	↑ 48% (25, 76%)

**Table 9: Results of Drug Interaction Studies with VIDEX EC: 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 (90% CI)	C <sub>max</sub> of Didanosine (90% CI)
tenofovir, <sup>b,c</sup> 300 mg once daily with a light meal <sup>d</sup>	400 mg single dose with tenofovir and a light meal	25	↑ 60% (44, 79%)	↑ 64% (41, 89%)
tenofovir, <sup>b,c</sup> 300 mg once daily with a light meal <sup>d</sup>	200 mg single dose with tenofovir and a light meal	33	↑ 16% (6, 27%) <sup>e</sup>	↓ 12% (-25, 3%) <sup>e</sup>
	250 mg single dose with tenofovir and a light meal	33	↔ (-13, 5%) <sup>f</sup>	↓ 20% (-32, -7%) <sup>f</sup>
	325 mg single dose with tenofovir and a light meal	33	↑ 13% (3, 24%) <sup>f</sup>	↓ 11% (-24, 4%) <sup>f</sup>
<b>methadone</b> , chronic maintenance dose	400 mg single dose	15, 16 <sup>g</sup>	↓ 17% (-29, -2%)	↓ 16% (-33, 4%)

↑ Indicates increase.

↓ Indicates decrease.

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

<sup>a</sup> The 90% confidence intervals for the percent change in the pharmacokinetic parameter are displayed.

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

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

<sup>d</sup> 373 kcalories, 8.2 grams fat.

<sup>e</sup> Compared with VIDEX EC 250 mg administered alone under fasting conditions.

<sup>f</sup> Compared with VIDEX EC 400 mg administered alone under fasting conditions.

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

**Table 10: Results of Drug Interaction Studies with VIDEX EC: Effects of Didanosine on Coadministered Drug Plasma AUC and C<sub>max</sub> Values**

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

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

<sup>a</sup> The 90% confidence intervals for the percent change in the pharmacokinetic parameter are displayed.

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

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

<sup>d</sup> 373 kcalories, 8.2 grams fat.

363 *Didanosine Buffered Formulations:* Tables 11 and 12 summarize the effects on AUC and C<sub>max</sub>,  
364 with a 90% or 95% CI when available, following coadministration of buffered formulations of  
365 didanosine with a variety of drugs. Except as noted in table footnotes, the results of these studies  
366 may be expected to apply to VIDEX EC. For most of the listed drugs, no clinically significant  
367 pharmacokinetic interactions were noted. For clinical recommendations based on drug  
368 interaction studies for drugs in bold font, see *Dosage and Administration (2.3 for Concomitant*  
369 *Therapy with Tenofovir Disoproxil Fumarate)* and *Drug Interactions (7.3)*.

**Table 11: Results of Drug Interaction Studies with Buffered Formulations of Didanosine: 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)
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 <sup>c</sup>	↓ 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%) <sup>b</sup>	↓ 13% (-28, 5%) <sup>b</sup>
ketoconazole, 200 mg/day for 4 days, 2 hours before didanosine	375 mg every 12 hours for 4 days	12 <sup>c</sup>	↔	↓ 12%
loperamide, 4 mg every 6 hours for 1 day	300 mg single dose	12 <sup>c</sup>	↔	↓ 23%
metoclopramide, 10 mg single dose	300 mg single dose	12 <sup>c</sup>	↔	↑ 13%
ranitidine, 150 mg single dose, 2 hours before didanosine	375 mg single dose	12 <sup>c</sup>	↑ 14%	↑ 13%
rifabutin, 300 or 600 mg/day for 12 days	167 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 <sup>c</sup>	↔	↔
trimethoprim, 200 mg single dose	200 mg single dose	8 <sup>c</sup>	↔	↑ 17% (-23, 77%)
zidovudine, 200 mg every 8 hours for 3 days	200 mg every 12 hours for 3 days	6 <sup>c</sup>	↔	↔

**Table 11: Results of Drug Interaction Studies with Buffered Formulations of Didanosine: 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)

↑ 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> 90% CI.

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

NA = Not available.

370

**Table 12: Results of Drug Interaction Studies with Buffered Formulations of Didanosine : 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)
dapsone, 100 mg single dose	200 mg every 12 hours for 14 days	6 <sup>b</sup>	↔	↔
ganciclovir, 1000 mg every 8 hours, 2 hours after didanosine	200 mg every 12 hours	12 <sup>b</sup>	↓ 21%	NA
nelfinavir, 750 mg single dose, 1 hour after didanosine	200 mg single dose	10 <sup>b</sup>	↑ 12%	↔
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	↔	↔

**Table 12: Results of Drug Interaction Studies with Buffered Formulations of Didanosine : 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)
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%)
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.

NA = Not available.

## 371 12.4 Microbiology

### 372 Mechanism of Action

373 Didanosine is a synthetic nucleoside analogue of the naturally occurring nucleoside  
374 deoxyadenosine in which the 3'-hydroxyl group is replaced by hydrogen. Intracellularly,  
375 didanosine is converted by cellular enzymes to the active metabolite, dideoxyadenosine  
376 5'-triphosphate. Dideoxyadenosine 5'-triphosphate inhibits the activity of HIV-1 reverse  
377 transcriptase both by competing with the natural substrate, deoxyadenosine 5'-triphosphate, and  
378 by its incorporation into viral DNA causing termination of viral DNA chain elongation.

### 379 **Antiviral Activity in Cell Culture**

380 The anti-HIV-1 activity of didanosine was evaluated in a variety of HIV-1 infected  
381 lymphoblastic cell lines and monocyte/macrophage cell cultures. The concentration of drug  
382 necessary to inhibit viral replication by 50% (EC<sub>50</sub>) ranged from 2.5 to 10 μM  
383 (1 μM = 0.24 μg/mL) in lymphoblastic cell lines and 0.01 to 0.1 μM in monocyte/macrophage  
384 cell cultures.

### 385 **Resistance**

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

### 395 **Cross-resistance**

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

## 402 **13 NONCLINICAL TOXICOLOGY**

### 403 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

404 Lifetime carcinogenicity studies were conducted in mice and rats for 22 and 24 months,  
405 respectively. In the mouse study, initial doses of 120, 800, and 1200 mg/kg/day for each sex  
406 were lowered after 8 months to 120, 210, and 210 mg/kg/day for females and 120, 300, and  
407 600 mg/kg/day for males. The two higher doses exceeded the maximally tolerated dose in

408 females and the high dose exceeded the maximally tolerated dose in males. The low dose in  
409 females represented 0.68-fold maximum human exposure and the intermediate dose in males  
410 represented 1.7-fold maximum human exposure based on relative AUC comparisons. In the rat  
411 study, initial doses were 100, 250, and 1000 mg/kg/day, and the high dose was lowered to  
412 500 mg/kg/day after 18 months. The upper dose in male and female rats represented 3-fold  
413 maximum human exposure.

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

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

## 423 **13.2 Animal Toxicology and/or Pharmacology**

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

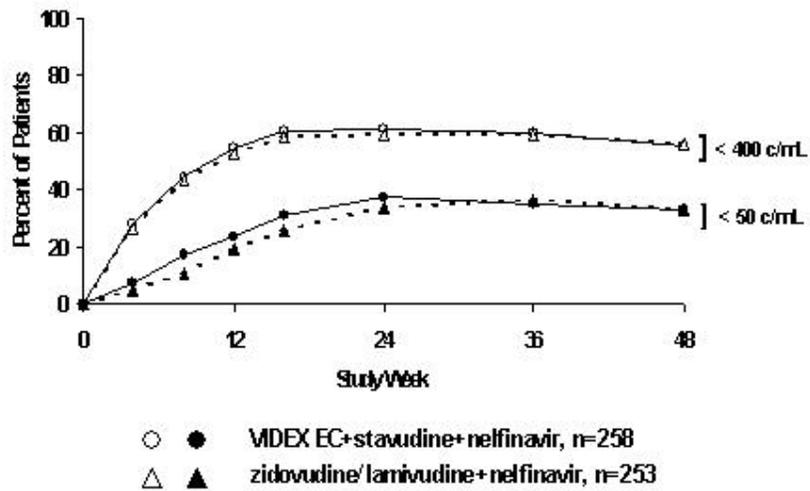
## 429 **14 CLINICAL STUDIES**

### 430 **14.1 Adult Patients**

431 Study AI454-152 was a 48-week, randomized, open-label study comparing VIDEX EC (400 mg  
432 once daily) plus stavudine (40 mg twice daily) plus nelfinavir (750 mg three times daily) to  
433 zidovudine (300 mg) plus lamivudine (150 mg) combination tablets twice daily plus nelfinavir  
434 (750 mg three times daily) in 511 treatment-naïve patients, with a mean CD4 cell count of  
435 411 cells/mm<sup>3</sup> (range 39 to 1105 cells/mm<sup>3</sup>) and a mean plasma HIV-1 RNA of  
436 4.71 log<sub>10</sub> copies/mL (range 2.8 to 5.9 log<sub>10</sub> copies/mL) at baseline. Patients were primarily  
437 males (72%) and Caucasian (53%) with a mean age of 35 years (range 18 to 73 years). The

438 percentages of patients with HIV-1 RNA less than 400 and less than 50 copies/mL and outcomes  
439 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).

440

**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 <sup>a</sup> + nelfinavir n=253
Responder <sup>b,c</sup>	55% (33%)	56% (33%)
Virologic failure <sup>d</sup>	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 <sup>e</sup>	16% (16%)	15% (16%)

<sup>a</sup> Zidovudine/lamivudine combination tablet.

<sup>b</sup> Corresponds to rates at Week 48 in Figure 1.

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

<sup>d</sup> 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.

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

## 441 14.2 Pediatric Patients

442 Efficacy in pediatric patients was demonstrated in a randomized, double-blind, controlled study  
443 (ACTG 152, conducted 1991-1995) involving 831 patients 3 months to 18 years of age treated  
444 for more than 1.5 years with zidovudine (180 mg/m<sup>2</sup> every 6 hours), didanosine (120 mg/m<sup>2</sup>  
445 every 12 hours), or zidovudine (120 mg/m<sup>2</sup> every 6 hours) plus didanosine (90 mg/m<sup>2</sup> every  
446 12 hours). Patients treated with didanosine or didanosine plus zidovudine had lower rates of  
447 HIV-1 disease progression or death compared with those treated with zidovudine alone.

## 448 16 HOW SUPPLIED/STORAGE AND HANDLING

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

**Table 14: VIDEX EC Delayed-Release Capsules**

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

451 **Storage**

452 The capsules should be stored in tightly closed containers at 25° C (77° F). Excursions between  
453 15° C and 30° C (59° F and 86° F) are permitted (see USP Controlled Room Temperature).

454 **17 PATIENT COUNSELING INFORMATION**

455 See *FDA-approved Patient Labeling (17.6)*

456 **17.1 Pancreatitis**

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

459 **17.2 Peripheral Neuropathy**

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

465 **17.3 Lactic Acidosis and Severe Hepatomegaly with Steatosis**

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

469 **17.4 Hepatic Toxicity**

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

473 **17.5 Retinal Changes and Optic Neuritis**

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

476 **17.6 Fat Redistribution**

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

480 **17.7 Concomitant Therapy**

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

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

486 **17.8 General Information**

487 VIDEX EC (didanosine) is not a cure for HIV-1 infection, and patients may continue to develop  
488 HIV-associated illnesses, including opportunistic infection. Therefore, patients should remain  
489 under the care of a physician when using VIDEX EC. Patients should be advised that VIDEX EC  
490 therapy has not been shown to reduce the risk of transmission of HIV to others through sexual  
491 contact or blood contamination. Patients should be informed that the long-term effects of  
492 VIDEX EC are unknown at this time.

493 **17.9 FDA-Approved Patient Labeling**

494 **VIDEX<sup>®</sup> EC**

495 (generic name = **didanosine** also known as **ddI**)

496 VIDEX<sup>®</sup> EC (didanosine, USP) Delayed-Release Capsules  
497 Enteric-Coated Beadlets

498 **What is VIDEX EC?**

499 VIDEX EC (pronounced *VY dex ee see*) is a prescription medicine used in combination with  
500 other drugs to treat children and adults who are infected with HIV (the human immunodeficiency  
501 virus, the virus that causes AIDS). VIDEX EC belongs to a class of drugs called nucleoside  
502 analogues. By reducing the growth of HIV, VIDEX EC helps your body maintain its supply of  
503 CD4 cells, which are important for fighting HIV and other infections.

504 VIDEX EC will not cure your HIV infection. At present there is no cure for HIV infection. Even  
505 while taking VIDEX EC, you may continue to have HIV-related illnesses, including infections  
506 with other disease-producing organisms. Continue to see your doctor regularly and report any  
507 medical problems that occur.

508 VIDEX EC does not prevent a patient infected with HIV from passing the virus to other people.  
509 To protect others, you must continue to practice safe sex and take precautions to prevent others  
510 from coming in contact with your blood and other body fluids.

511 There is limited information on the antiviral response of long-term use of VIDEX EC.

512 In VIDEX EC, an enteric coating is used to protect the medicine while it is in your stomach since  
513 stomach acids can break it down. The enteric coating dissolves when the medicine reaches your  
514 small intestine.

515 **Who should not take VIDEX EC?**

516 Do not take VIDEX EC if you are allergic to any of its ingredients, including its active  
517 ingredient, didanosine, and the inactive ingredients. (See *Inactive Ingredients* at the end of this  
518 leaflet.) Tell your doctor if you think you have had an allergic reaction to any of these  
519 ingredients.

520 **How should I take VIDEX EC? How should I store it?**

521 VIDEX EC should only be taken once daily. Your doctor will determine your dose based on  
522 your body weight, kidney and liver function, other medicines you are taking, and any side effects  
523 that you may have had with VIDEX EC or other medicines. Take VIDEX EC **on an empty**  
524 **stomach. Do not take VIDEX EC with food.** Swallow the capsule whole; do not open it. Try  
525 not to miss a dose, but if you do, take it as soon as possible. If it is almost time for the next dose,  
526 skip the missed dose and continue your regular dosing schedule.

527 Store capsules in a tightly closed container at room temperature away from heat and out of the  
528 reach of children and pets.

529 **If you have kidney disease:** If your kidneys are not working properly, your doctor will need to  
530 do regular tests to check how they are working while you take VIDEX EC. Your doctor may also  
531 lower your dosage of VIDEX EC.

532 **What should I do if someone takes an overdose of VIDEX EC?**

533 If someone may have taken an overdose of VIDEX EC, get medical help right away. Contact  
534 their doctor or a poison control center.

535 **What should I avoid while taking VIDEX EC?**

536 **Alcohol.** Do not drink alcohol while taking VIDEX EC since alcohol may increase your risk of  
537 pancreatitis (pain and inflammation of the pancreas) or liver damage.

538 **Allopurinol**, also known as ZYLOPRIM<sup>®</sup>, ALOPRIM<sup>®</sup>, or others. Do not take allopurinol while  
539 taking VIDEX EC because the risk of side-effects of didanosine are increased.

540 **Ribavirin**, also known as COPEGUS<sup>®</sup>, REBETOL<sup>®</sup>, or others. Do not take ribavirin while  
541 taking VIDEX EC because pancreatitis, peripheral neuropathy, lactic acidosis and fatal liver  
542 damage have been reported. (See "What are the possible side effects of VIDEX EC?")

543 **Other medicines.** Other medicines, including those you can buy without a prescription, may  
544 interfere with the actions of VIDEX EC or may increase the possibility or severity of side  
545 effects. **Do not take any medicine, vitamin supplement, or other health preparation without**  
546 **first checking with your doctor.**

547 **Pregnancy.** It is not known if VIDEX EC can harm a human fetus. Also, pregnant women have  
548 experienced serious side effects when taking didanosine (the active ingredient in VIDEX EC) in  
549 combination with ZERIT (stavudine), also known as d4T, and other HIV medicines. VIDEX EC  
550 should be used during pregnancy only after discussion with your doctor. **Tell your doctor if you**  
551 **become pregnant or plan to become pregnant while taking VIDEX EC.**

552 **Nursing.** Studies have shown didanosine (the active ingredient in VIDEX EC) is in the breast  
553 milk of animals getting the drug. It may also be in human breast milk. The Centers for Disease  
554 Control and Prevention (CDC) recommends that HIV-infected mothers **not** breast-feed. This  
555 should reduce the risk of passing HIV infection to their babies and the potential for serious  
556 adverse reactions in nursing infants. Therefore, do not nurse a baby while taking VIDEX EC.

#### 557 **What are the possible side effects of VIDEX EC?**

558 **Pancreatitis.** Pancreatitis is a dangerous inflammation of the pancreas that may cause death. ***Tell***  
559 ***your doctor right away if you or a child taking VIDEX EC develop stomach pain, nausea, or***  
560 ***vomiting. These can be signs of pancreatitis.*** Before starting VIDEX EC therapy, let your  
561 doctor know if you or a child for whom it has been prescribed have ever had pancreatitis. This  
562 condition is more likely to happen in people who have had it before. It is also more likely in  
563 people with advanced HIV disease. However, it can occur at any stage of HIV disease. It may be  
564 more common in patients with kidney problems, those who drink alcohol, and those who are also  
565 treated with stavudine. If you get pancreatitis, your doctor will tell you to stop taking  
566 VIDEX EC.

567 **Lactic acidosis, severe liver enlargement, and liver failure,** including deaths, have been  
568 reported among patients taking VIDEX EC (including pregnant women). Symptoms that may  
569 indicate a liver problem are:

- 570 • feeling very weak, tired, or uncomfortable
- 571 • unusual or unexpected stomach discomfort
- 572 • feeling cold
- 573 • feeling dizzy or lightheaded

- 574
- suddenly developing a slow or irregular heartbeat

575 **Lactic acidosis is a medical emergency that must be treated in a hospital.**

576 If you notice any of these symptoms or if your medical condition changes, stop taking  
577 VIDEX EC and **call your doctor right away**. Women, overweight patients, and those who have  
578 been treated for a long time with other medicines used to treat HIV infection are more likely to  
579 develop lactic acidosis. Your doctor should check your liver function periodically while you are  
580 taking VIDEX EC. You should be especially careful if you have a history of heavy alcohol use  
581 or a liver problem.

582 **Vision changes.** VIDEX EC may affect the nerves in your eyes. Because of this, you should  
583 have regular eye examinations. You should also report any changes in vision to your doctor right  
584 away. This includes, for example, seeing colors abnormally or blurred vision.

585 **Peripheral neuropathy.** This is a problem with the nerves in your hands or feet. The nerve  
586 problem may be serious. *Tell your doctor right away if you or a child taking VIDEX EC have*  
587 *continuing numbness, tingling, or pain in the feet or hands.* A child may not recognize these  
588 symptoms or know to tell you that his or her feet or hands are numb, burning, tingling, or  
589 painful. Ask your child's doctor how to find out if your child is developing peripheral  
590 neuropathy.

591 Before starting VIDEX EC therapy, let your doctor know if you or a child for whom it has been  
592 prescribed have ever had peripheral neuropathy. This condition is more likely to happen in  
593 people who have had it before. It is also more likely in patients taking medicines that affect the  
594 nerves and in people with advanced HIV disease. However, it can occur at any stage of HIV  
595 disease. If you get peripheral neuropathy, your doctor will tell you to stop taking VIDEX EC.  
596 After stopping VIDEX EC, the symptoms may get worse for a short time and then get better.  
597 Once symptoms of peripheral neuropathy go away completely, you and your doctor should  
598 decide if starting VIDEX EC again is right for you.

599 **Special note about other medicines.** If you take VIDEX EC along with other medicines with  
600 similar side effects, you may increase the chance of having these side effects. For example, using  
601 VIDEX EC in combination with other medicines that may cause pancreatitis, peripheral  
602 neuropathy, or liver problems (including stavudine) may increase your chance of having these  
603 side effects.

604 **Other side effects:** The most common side effects in adults taking VIDEX EC in combination  
605 with other HIV drugs included diarrhea, nausea, headache, vomiting, and rash. Children may  
606 have similar side effects as adults.

607 Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes  
608 may include an increased amount of fat in the upper back and neck (“buffalo hump”), breast, and  
609 around the trunk. Loss of fat from the legs, arms, and face may also happen. The cause and long-  
610 term health effects of these conditions are not known at this time.

611 **Inactive Ingredients:**

612 Carboxymethylcellulose sodium 12, diethyl phthalate, methacrylic acid copolymer, sodium  
613 hydroxide, sodium starch glycolate, talc, gelatin, and titanium dioxide.

614 \_\_\_\_\_

615 This medicine was prescribed for your particular condition. Do not use VIDEX EC for another  
616 condition or give it to others. Keep all medicines out of the reach of children and pets at all  
617 times. Do not keep medicine that is out of date or that you no longer need. Dispose of unused  
618 medicines through community take-back disposal programs when available or place VIDEX EC  
619 in an unrecognizable closed container in the household trash.

620 This summary does not include everything there is to know about VIDEX EC. Medicines are  
621 sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. If you  
622 have questions or concerns, or want more information about VIDEX EC, your physician and  
623 pharmacist have the complete prescribing information upon which this leaflet is based. You may  
624 want to read it and discuss it with your doctor or other healthcare professional. Remember, no  
625 written summary can replace careful discussion with your doctor.

626 VIDEX<sup>®</sup> EC and Zerit<sup>®</sup> are registered trademarks of Bristol-Myers Squibb Company. All other  
627 trademarks are the property of their respective owners.

628 Bristol-Myers Squibb Company  
629 Princeton, NJ 08543 USA

630 This Patient Information Leaflet has been approved by the U.S. Food and Drug Administration.

631 XXXXXX

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