

DINEX EC

Didanosine Delayed Release Capsules

WARNING: PANCREATITIS, LACTIC ACIDOSIS and HEPATOMEGALY with STEATOSIS

FATAL AND NON-FATAL PANCREATITIS HAS OCCURRED DURING THERAPY WITH DIDANOSINE USED ALONE OR IN COMBINATION REGIMENS IN BOTH TREATMENT-NAÏVE AND TREATMENT-EXPERIENCED PATIENTS, REGARDLESS OF THE DEGREE OF IMMUNOSUPPRESSION. DINEX EC CAPSULES SHOULD BE SUSPENDED IN PATIENTS WITH SUSPECTED PANCREATITIS AND DISCONTINUED IN PATIENTS WITH CONFIRMED PANCREATITIS (SEE WARNINGS AND PRECAUTIONS).

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).

COMPOSITION

DINEX EC 250mg Capsules

Each capsule contains:

Didanosine (as enteric-coated beadlets) 250 mg

DINEX EC 400mg Capsules

Each capsule contains:

Didanosine (as enteric-coated beadlets) 400 mg

DOSAGE FORM

Oral capsule

PHARMACOLOGY

Pharmacodynamics

Didanosine is a synthetic nucleoside analog of the naturally occurring nucleoside, deoxyadenosine, in which the 3'-hydroxyl group is replaced by hydrogen. Intracellularly, didanosine is converted by cellular enzymes to the active metabolite, dideoxyadenosine 5'-triphosphate. Dideoxyadenosine 5'-triphosphate inhibits the activity of HIV-1 reverse transcriptase, both by competing with the natural substrate, deoxyadenosine 5'-

triphosphate, and by its incorporation into viral DNA causing termination of viral DNA chain elongation.

Pharmacokinetics

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

Table 1: Pharmacokinetic Parameters for Didanosine in HIV-infected Patients

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

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

Comparison of Didanosine Formulations

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

In healthy volunteers, as well as subjects infected with HIV-1, the AUC is equivalent for didanosine administered as the **DINEX-EC** formulation relative to a buffered tablet

formulation. The peak plasma concentration (C_{max}) of didanosine, administered as **DINEX-EC**, is reduced approximately 40% relative to didanosine buffered tablets. The time to the peak concentration (T_{max}) increases from approximately 0.67 hours for didanosine buffered tablets to 2.0 hours for **DINEX-EC**.

Effect of Food on Oral Absorption

In the presence of food, the C_{max} and AUC for didanosine enteric-coated (didanosine EC) were reduced by approximately 46% and 19%, respectively, compared to the fasting state.(see **DOSAGE AND ADMINISTRATION**).

DINEX EC Capsules should be taken on an empty stomach.

Special Populations

Renal Insufficiency: Data from two studies using a buffered formulation of didanosine indicated that the apparent oral clearance of didanosine decreased and the terminal elimination half-life increased as creatinine clearance decreased (see Table 2). Following oral administration, didanosine was not detectable in peritoneal dialysate fluid (n = 6); recovery in hemodialysate (n = 5) ranged from 0.6% to 7.4% of the dose over a 3–4 hour dialysis period. The absolute bioavailability of didanosine was not affected in patients requiring dialysis. (see **DOSAGE AND ADMINISTRATION**).

Table 2: Mean ± SD Pharmacokinetic Parameters for Didanosine following a single oral dose of a buffered formulation

Parameter	At least 90 n = 12	Creatinine Clearance (mL/min)		10–29 n = 3	Dialysis Patients n = 11
		60–90 n=6	30–59 n = 6		
CLcr (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
CLR (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

CLcr = Creatinine clearance

CL/F = Apparent oral clearance

CLR = Renal clearance

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

hepatic impairment compared to matched healthy subjects. No dose adjustment is needed, because a similar range and distribution of AUC and C_{max} values was observed for subjects with hepatic impairment and matched healthy controls. (see **DOSAGE AND ADMINISTRATION**).

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

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

Geriatric Patients: Didanosine pharmacokinetics has not been studied in patients over 65 years of age.

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

INDICATIONS

DINEX EC Capsules in combination with other antiretroviral agents are indicated for the treatment of human immunodeficiency virus (HIV) -1 infection.

DOSAGE AND ADMINISTRATION

DINEX- EC Capsules (didanosine, USP) should be administered on an empty stomach.

Recommended Dosage (Adult and Pediatric Patients)

The recommended daily dose is dependent on body weight and is administered as one capsule given on a once-daily schedule in Table 3:

The recommended total daily dose to be administered once daily to pediatric patients weighing at least 20 kg who can swallow capsules is based on body weight (kg), consistent with the recommended adult dosing guidelines (see Table 3). Please consult the complete prescribing information for didanosine. Pediatric Powder for Oral Solution for dosage and administration of didanosine to pediatric patients weighing less than 20 kg or who cannot swallow capsules.

Table 3: Recommended Dosage (Adult and Pediatric Patients)

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

Renal Impairment

Dosing recommendations for the enteric-coated and didanosine pediatric powder for oral solution are different for patients with renal impairment.

Adult Patients

In adult patients with impaired renal function, the dose of the enteric-coated formulation should be adjusted to compensate for the slower rate of elimination. The recommended doses and dosing intervals of this formulation in adult patients with renal insufficiency are given in Table 4.

Table 4: Recommended dosage in patients with renal impairment by body weight^a

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

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

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

Pediatric Patients

Urinary excretion is also a major route of elimination of didanosine in pediatric patients, therefore the clearance of didanosine may be altered in pediatric patients with renal impairment. Although there are insufficient data to recommend a specific dose adjustment of didanosine in this patient population, a reduction in the dose should be considered (see Table 3).

Patients Requiring Continuous Ambulatory Peritoneal Dialysis (CAPD) or Hemodialysis:

For patients requiring CAPD or hemodialysis, follow dosing recommendations for patients with creatinine clearance less than 10 ml/min, as shown in Table 3. It is not necessary to administer a supplemental dose of didanosine following hemodialysis.

Dose Adjustment

Concomitant Therapy with Tenofovir Disoproxil Fumarate: In patients who are also taking tenofovir disoproxil fumarate, a dose reduction of didanosine to 250 mg (adults weighing at least 60 kg with creatinine clearance of at least 60 mL/min) or 200 mg (adults weighing less than 60 kg with creatinine clearance of at least 60 mL/min) once

daily taken together with tenofovir disoproxil fumarate and a light meal (400 kcalories or less, 20% fat or less) or in the fasted state is recommended. The appropriate dose of didanosine coadministered with tenofovir disoproxil fumarate in patients with creatinine clearance of less than 60 mL/min has not been established (**SEE DRUG INTERACTIONS AND PHARMACOLOGY**)

Hepatic Impairment

No dose adjustment is required in patients with hepatic impairment (see **WARNINGS AND PRECAUTIONS AND PHARMACOLOGY**).

CONTRAINDICATIONS

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

Allopurinol

Coadministration of didanosine and allopurinol is contraindicated because systemic exposures of didanosine are increased, which may increase didanosine-associated toxicity (see **PHARMACOLOGY**).

Ribavirin

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

WARNINGS AND PRECAUTIONS

Drug Interactions

Established Drug Interactions

Clinical recommendations based on the results of drug interaction studies are listed in Table 5 (see **CONTRAINDICATIONS**). Pharmacokinetic results of drug interaction studies are shown in Tables 7 & 8. (see **CONTRAINDICATIONS ,PHARMACOLOGY**).

Table 5: Established drug interactions based on studies with didanosine EC or studies with buffered formulations of didanosine and expected to occur with didanosine EC

Drug	Effect	Clinical Comment
Ganciclovir	↑ didanosine concentration	If there is no suitable alternative to ganciclovir, then use in combination with DINEX EC Capsules with caution. Monitor for didanosine-associated toxicity.

Methadone	↓ didanosine concentration	If co-administration of methadone and didanosine is necessary, the recommended formulation of didanosine is DINEX EC Capsules . Patients should be closely monitored for adequate clinical response when DINEX EC Capsules are co-administered with methadone, including monitoring for changes in HIV RNA viral load. Do not co-administer methadone with didanosine pediatric powder due to significant decreases in didanosine concentrations.
Nelfinavir	No interaction 1 hour after didanosine	Administer nelfinavir 1 hour after DINEX EC Capsules .
Tenofovir disoproxil fumarate	↑ didanosine concentration	A dose reduction of DINEX EC Capsules to the dosage given below once daily and 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 <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 Co-administration of didanosine with food decreases didanosine concentrations. Thus, although not studied, it is possible that co-administration with heavier meals could reduce didanosine concentrations further.

Exposure to didanosine is increased when co-administered with tenofovir disoproxil fumarate (Table 5). Increased exposure may cause or worsen didanosine-related clinical toxicities, including pancreatitis, symptomatic hyperlactatemia/lactic acidosis, and peripheral neuropathy. Co-administration of tenofovir disoproxil fumarate with **DINEX EC Capsules** should be undertaken with caution, and patients should be monitored closely for didanosine-related toxicities and clinical response. **DINEX EC Capsules** should be suspended if signs or symptoms of pancreatitis, symptomatic hyperlactatemia, or lactic acidosis develop (see **DOSAGE AND ADMINISTRATION; WARNINGS AND PRECAUTIONS**). Suppression of CD4 cell counts has been observed in patients receiving tenofovir disoproxil fumarate with didanosine at a dose of 400 mg daily.

Predicted Drug Interactions

Predicted drug interactions with **DINEX EC Capsules** are listed in Table 6.

Table 6: Predicted drug interactions with DINEX EC

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

↑ Indicates increase.

^a Only if other drugs are not available and if clearly indicated. If treatment with life-sustaining drugs that cause pancreatic toxicity is required, suspension of **DINEX EC Capsules** is recommended (see **WARNINGS AND PRECAUTIONS**).

^b (See **WARNINGS AND PRECAUTIONS**).

Tables 7 and 8 summarize the effects on AUC and C_{max}, with a 90% confidence interval (CI) when available, following coadministration of Didanosine EC with a variety of drugs. For clinical recommendations based on drug interaction studies for drugs in bold font, (see **DOSAGE AND ADMINISTRATION AND DRUG INTERACTIONS**).

Table 7: Results of Drug Interaction Studies with Didanosine 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
methadone, chronic maintenance dose	325 mg single dose with tenofovir and a light meal	33	↑ 13% (3, 24%) ^f	↓ 11% (-24, 4%) ^f
	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%.

^aThe 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.

^cTenofovir disoproxil fumarate.

^d

373 kcalories, 8.2 grams fat. ^e

^eCompared with Didanosine EC 250 mg administered alone under fasting conditions.

^f

Compared with Didanosine EC 400 mg administered alone under fasting conditions.

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

Table 8: Results of Drug Interaction Studies with Didanosine 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	↔	↔
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%.

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

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

^cTenofovir disoproxil fumarate.

^d373 kcalories, 8.2 grams fat.

Pancreatitis

Fatal and non-fatal pancreatitis has occurred during therapy with didanosine used alone or in combination regimens in both treatment-naïve and treatment-experienced patients, regardless of degree of immunosuppression. DINEX EC Capsules should be suspended in patients with signs or symptoms of pancreatitis. Patients treated with DINEX EC Capsules in combination with stavudine, with or without hydroxyurea, may be at increased risk for pancreatitis.

When treatment with life-sustaining drugs known to cause pancreatic toxicity is required, suspension of didanosine therapy is recommended. In patients with risk factors for pancreatitis, **DINEX EC Capsules** should be used with extreme caution and only if clearly indicated. Patients with advanced HIV-1 infection, especially the elderly, are at increased risk of pancreatitis and should be followed closely. Patients with renal impairment may be at greater risk for pancreatitis if treated without dose adjustment. The frequency of pancreatitis is dose-related.(see **UNDESIRABLE EFFECTS**)

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including didanosine and other antiretrovirals. A majority of these have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Fatal lactic acidosis has been reported in pregnant women who received the

combination of didanosine and stavudine with other antiretroviral agents. The combination of didanosine and stavudine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk (see **WARNINGS AND PRECAUTIONS, Pregnancy**).

Particular caution should be exercised when administering didanosine to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with **DINEX EC Capsules** should be suspended in any patient who develops clinical signs or symptoms with or without laboratory findings consistent with symptomatic hyperlactatemia, lactic acidosis, or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Hepatic Toxicity

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

Hepatotoxicity and hepatic failure resulting in death were reported during postmarketing surveillance in HIV-infected patients treated with hydroxyurea and other antiretroviral agents. Fatal hepatic events were reported most often in patients treated with the combination of hydroxyurea, didanosine and stavudine. This combination should be avoided. (see **UNDESIRABLE EFFECTS**).

Non-cirrhotic Portal Hypertension

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

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

Peripheral Neuropathy

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

including stavudine. Discontinuation of **DINEX-EC** should be considered in patients who develop peripheral neuropathy (see **UNDESIRABLE EFFECTS**).

Retinal Changes and Optic Neuritis

Retinal changes and optic neuritis have been reported in patients taking didanosine. Periodic retinal examinations should be considered for patients receiving **DINEX EC Capsules** (see **UNDESIRABLE EFFECTS**).

Immune Reconstitution Syndrome

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

Fat Redistribution

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

Renal Impairment

Patients with renal impairment (creatinine clearance <60 mL/min) may be at greater risk of toxicity from didanosine due to decreased drug clearance. A dose reduction is recommended in these patients (see **DOSAGE AND ADMINISTRATION**).

Pregnancy

Pregnancy Category B

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

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

Fatal lactic acidosis has been reported in pregnant women who received the combination of didanosine and stavudine with other antiretroviral agents. It is unclear if

pregnancy augments the risk of lactic acidosis/hepatic steatosis syndrome reported in non-pregnant individuals receiving nucleoside analogs (see **WARNINGS AND PRECAUTIONS**, Lactic Acidosis/Severe Hepatomegaly with Steatosis). **The combination of didanosine and stavudine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk.** Healthcare providers caring for HIV-infected pregnant women receiving didanosine should be alert for an early diagnosis of lactic acidosis/hepatic steatosis syndrome.

Lactation

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

Pediatric Use

Use of didanosine in pediatric patients from 2 weeks of age through adolescence is supported by evidence from adequate and well-controlled studies of didanosine in adult and pediatric patients (see **DOSAGE AND ADMINISTRATION; UNDESIRABLE EFFECTS; PHARMACOLOGY**). Additional pharmacokinetic studies in pediatric patients support the use of didanosine in pediatric patients who weigh at least 20 kg.

Geriatric Use

In an Expanded Access Program using a buffered formulation of didanosine for the treatment of advanced HIV infection, patients aged 65 years and older had a higher frequency of pancreatitis (10%) than younger patients (5%) (see **WARNINGS AND PRECAUTIONS**). Clinical studies of didanosine, including those for **DINEX EC Capsules**, did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently than younger subjects. Didanosine is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. In addition, renal function should be monitored and dosage adjustments should be made accordingly (see **DOSAGE AND ADMINISTRATION**).

UNDESIRABLE EFFECTS

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

- Pancreatitis (see **BOXED WARNING; WARNINGS AND PRECAUTIONS**).
- Lactic acidosis/severe hepatomegaly with steatosis (see **BOXED WARNING, WARNINGS AND PRECAUTIONS**)
- Hepatic toxicity (see **WARNINGS AND PRECAUTIONS**).

- Non-cirrhotic portal hypertension (see **WARNINGS AND PRECAUTIONS**).
- Peripheral neuropathy (see **WARNINGS AND PRECAUTIONS**).
- Retinal changes and optic neuritis (see **WARNINGS AND PRECAUTIONS**).

Clinical Trials Experience

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

Adults

Study A1454-152 was a 48-week, randomized, open-label study comparing **DINEX EC Capsules** (400 mg once daily) plus stavudine (40 mg twice daily) plus nelfinavir (750 mg three times daily) to zidovudine (300 mg) plus lamivudine (150 mg) combination tablets twice daily plus nelfinavir (750 mg three times daily) in 511 treatment-naïve patients. Selected clinical adverse reactions that occurred in combination with other antiretroviral agents are provided in Table 9.

Table 9: Selected clinical adverse events (Study A1454-152)

Adverse Reactions	Percentage of Patients ^{b,c}	
	Didanosine 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 didanosine EC + stavudine + nelfinavir group and 61 weeks in the zidovudine/lamivudine + nelfinavir group.

^b Percentage based on treated patients.

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

^d Zidovudine/lamivudine combination tablet.

* This event was not observed in this study arm.

In clinical trials using a buffered formulation of didanosine, pancreatitis resulting in death was observed in one patient who received didanosine plus stavudine plus nelfinavir, one patient who received didanosine plus stavudine plus indinavir, and 2 of 68 patients

who received didanosine plus stavudine plus indinavir plus hydroxyurea. In an early access program, pancreatitis resulting in death was observed in one patient who received didanosine EC plus stavudine plus hydroxyurea plus ritonavir plus indinavir plus efavirenz.

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

Selected laboratory abnormalities that occurred in a study of didanosine EC in combination with other antiretroviral agents are shown in Table 10 below:

Table 10: Selected laboratory abnormalities (Study A1454-152)*

Parameter	Percent of Patients ^b			
	Didanosine EC + Stavudine + Nelfinavir n = 258		Zidovudine/Lamivudine ^c + Nelfinavir n = 253	
	Grade 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 didanosine EC + stavudine + nelfinavir group and 61 weeks in the zidovudine/lamivudine + nelfinavir group.

^b Percentages based on treated patients.

^c Zidovudine/lamivudine combination tablet.

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

Pediatric Patients

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

In pediatric phase 1 studies,² pancreatitis occurred in 2 of 60 (3%) patients treated at entry doses below 300 mg/m²/day and in 5 of 38 (13%) patients treated at higher doses. In study ACTG 152, pancreatitis occurred in none of the 281 pediatric patients who received didanosine 120 mg/m² every 12 hours² and in less than 1% of the 274 pediatric patients who received didanosine 90 mg/m² every 12 hours in combination with zidovudine.

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

Observed During Clinical Practice

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

Blood and Lymphatic System Disorders: Anemia, leukopenia, and thrombocytopenia.

Body as a Whole: abdominal pain, alopecia, anaphylactoid reaction, asthenia, chills/fever, pain, and redistribution/accumulation of body fat. (see **WARNINGS AND PRECAUTIONS**).

Digestive Disorders: anorexia, dyspepsia, and flatulence.

Exocrine Gland Disorders: pancreatitis (including fatal cases) (see **WARNINGS AND PRECAUTIONS**), sialoadenitis, parotid gland enlargement, dry mouth, and dry eyes.

Hepatobiliary Disorders: symptomatic hyperlactatemia/lactic acidosis and hepatic steatosis(see **WARNINGS AND PRECAUTIONS**),non-cirrhotic portal hypertension(see **WARNINGS AND PRECAUTIONS**), hepatitis and liver failure.

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

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

Ophthalmologic Disorders: retinal depigmentation and optic neuritis (see **WARNINGS AND PRECAUTIONS**).

Use with Stavudine- and Hydroxyurea-Based Regimens

When didanosine is used in combination with other agents with similar toxicities, the incidence of these toxicities may be higher than when didanosine is used alone. Thus, patients treated with **DINEX EC Capsules** in combination with stavudine, with or without hydroxyurea, may be at increased risk for pancreatitis and hepatotoxicity, which may be fatal, and severe peripheral neuropathy (see **WARNINGS AND PRECAUTIONS**). The combination of **DINEX EC Capsules** and hydroxyurea, with or without stavudine, should be avoided.

OVERDOSAGE

There is no known antidote for didanosine overdosage. In phase 1 studies, in which buffered formulations of didanosine were initially administered at doses ten times the currently recommended dose, toxicities included pancreatitis, peripheral neuropathy,

diarrhea, hyperuricemia, and hepatic dysfunction. Didanosine is not dialyzable by peritoneal dialysis, although there is some clearance by hemodialysis (see **PHARMACOLOGY**).

PACKAGING INFORMATION

DINEX EC 250 Delayed –Release Capsules..... Container of 30 capsules
DINEX EC 400 Delayed –Release Capsules..... Container of 30 capsules

Last updated: October 2010