

PRODUCT MONOGRAPH

VIDEX* EC

(Didanosine [ddI])

Enteric Coated Beadlets Capsules, 125, 200, 250 and 400 mg

Antiretroviral Agent

Bristol-Myers Squibb Canada
Montreal, Canada

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THERAPEUTIC CLASSIFICATION

Antiretroviral Agent

ACTION AND CLINICAL PHARMACOLOGY

VIDEX EC (didanosine) capsules contain enteric-coated didanosine beadlets. Didanosine is a synthetic, purine nucleoside analogue of deoxyadenosine, active against the Human Immunodeficiency Virus (HIV).

Didanosine inhibits the *in vitro* replication of HIV in human primary cells cultures and in established cell lines. The active antiviral metabolite, dideoxyadenosine-triphosphate (ddATP), is formed in several steps by phosphorylation of didanosine by cellular enzymes. Inhibition of HIV reverse transcriptase by ddATP is through competition with endogenous deoxyadenosine triphosphate (dATP) for binding to the active site of the enzyme. In addition, ddATP is a substrate for reverse transcriptase and is incorporated into the growing DNA chain. The resulting nucleoside, dideoxyadenosine (ddA) lacks a 3'-hydroxyl group, which normally is the acceptor for covalent attachment of subsequent nucleoside 5'-monophosphates in DNA chain extension. Thus, ddA incorporated in the DNA prevents further chain extension and aborts proviral DNA synthesis. (See CLINICAL PHARMACOLOGY).

Pharmacokinetics

In VIDEX 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.

Effect of Food on Absorption of Didanosine

VIDEX EC should be taken on an empty stomach, at least 1.5 hours before or 2 hours after a meal. Compared to the fasting condition, the administration of VIDEX EC capsules with a high-fat meal significantly decreased the didanosine C_{max} (46%) and AUC (19%). Co-administering VIDEX EC capsules with a light meal, 1.5 hours before a light meal, or 2 hours after a light meal resulted in significant decrease in both C_{max} (22%, 15%, and 15% respectively) and AUC of didanosine (27%, 24%, and 10% respectively) compared to the fasting condition. Administration of VIDEX EC capsules 1.5, 2 or 3 hours before a light meal resulted in equivalent C_{max} and AUC values compared to those obtained under fasting conditions. Compared to the intact capsule administered in the fasting condition, co-administration of VIDEX EC beadlets with yogurt or

apple sauce resulted in a significant decrease in C_{max} (30% and 24% respectively) and AUC of didanosine (20% and 18% respectively).

INDICATIONS AND CLINICAL USE

VIDEX EC (didanosine) in combination with other antiretroviral agents, is indicated for the treatment of HIV-1 infection in adults (see Clinical Use subsection of CLINICAL PHARMACOLOGY).

The duration of clinical benefit from antiretroviral therapy may be limited. Alteration in antiretroviral therapy should be considered if disease progression occurs while receiving VIDEX EC.

CONTRAINDICATIONS

VIDEX EC (didanosine) is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the formulations.

WARNINGS

THE MAJOR CLINICAL TOXICITY OF DIDANOSINE IS PANCREATITIS. (See ADVERSE REACTIONS).

1. Pancreatitis

FATAL AND NONFATAL PANCREATITIS HAVE 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 SIGNS OR SYMPTOMS OF PANCREATITIS AND DISCONTINUED IN PATIENTS WITH CONFIRMED PANCREATITIS. SUSPENSION OF TREATMENT SHOULD ALSO BE CONSIDERED WHEN BIOCHEMICAL MARKERS OF PANCREATITIS HAVE INCREASED TO CLINICALLY SIGNIFICANT LEVELS, EVEN IN THE ABSENCE OF SYMPTOMS. PATIENTS TREATED WITH VIDEX EC IN COMBINATION WITH STAVUDINE, WITH OR WITHOUT HYDROXYUREA, MAY BE AT INCREASED RISK FOR PANCREATITIS.

Positive relationships have been found between the risk of pancreatitis and daily dose. Pancreatitis is also a complication of HIV infection alone.

Signs or symptoms of pancreatitis include abdominal pain and nausea, vomiting, or elevated biochemical markers for pancreatitis.

When treatment with other drugs known to cause pancreatic toxicity is required (for example, IV pentamidine), or known to increase exposure or activity of didanosine (e.g., hydroxyurea or allopurinol), suspension of didanosine therapy is recommended. Allopurinol was observed to increase exposure to didanosine in renally impaired patients and healthy volunteers and

may increase the risk of dose-related toxicities such as pancreatitis. It is recommended that these two drugs not be administered together (see PRECAUTIONS, Drug Interactions).

VIDEX EC should be used with caution in patients with risk factors for pancreatitis. For example, the following patients may be at increased risk for developing pancreatitis and should be followed closely for signs and symptoms of pancreatitis: patients with advanced HIV infection, patients with a history of pancreatitis, elevated triglycerides, or alcohol consumption; elderly patients and patients with renal impairment if treated with unadjusted doses.; and patients treated with didanosine in combination with stavudine, with or without hydroxyurea.

2. Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including didanosine and other antiretroviral agents. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Fatal lactic acidosis has been reported in pregnant 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 PRECAUTIONS: Pregnancy). Particular caution should be exercised when administering VIDEX EC to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with VIDEX EC should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

3. Liver Disease

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

The safety and efficacy of VIDEX EC have not been established in patients with significant underlying liver disorders. During combination antiretroviral therapy, patients with preexisting liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities, including severe and potentially fatal hepatic adverse events, and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, discontinuation of treatment must be considered. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION.)

4. Liver Failure

Liver failure, of unknown etiology, has occurred in patients receiving didanosine and may be fatal. Patients should be observed for liver enzyme elevations and didanosine should be suspended if enzymes rise to a clinically significant level. Rechallenge should be considered only if the potential benefits clearly outweigh the potential risks.

5. Non-cirrhotic Portal Hypertension

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

Patients receiving VIDEX 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. VIDEX EC should be discontinued in patients with evidence of non-cirrhotic portal hypertension.

6. Peripheral Neuropathy

PERIPHERAL NEUROPATHY OCCURS IN PATIENTS TREATED WITH DIDANOSINE AND THE FREQUENCY APPEARS TO BE RELATED TO DOSE AND/OR STAGE OF DISEASE. Lower rates were seen in patients with less advanced disease. Patients should be monitored for the development of a neuropathy that is usually characterized by bilateral symmetrical distal numbness, tingling, and pain in feet and, less frequently, hands. In controlled clinical trials, neuropathy has occurred more frequently in patients with a history of neuropathy or neurotoxic drug therapy, including stavudine, and these patients may be at increased risk of neuropathy during didanosine therapy.

Peripheral neuropathy, which was severe in some cases, has been reported in HIV-infected patients receiving hydroxyurea in combination with antiretroviral agents, including didanosine, with or without stavudine.

Neuropathy has been reported rarely in children treated with didanosine. However, because signs and symptoms of neuropathy are difficult to assess in children, physicians should be alerted to the possibility of this event.

7. Retinal depigmentation and Vision

There have been rare (< 1%) reports of retinal depigmentation and optic neuritis in adult patients (See ADVERSE REACTIONS). Periodic retinal examinations should be considered

for patients receiving didanosine. Consideration should be given to modifying treatment based on the physician's assessment of benefit to risk.

8. Opportunistic Infections and Other Complications of HIV Infection

Patients receiving VIDEX EC or any antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with HIV-associated diseases

PRECAUTIONS

Frequency of Dosing

VIDEX EC should only be administered once daily. There are no data on the use of VIDEX EC dosed more frequently than once daily.

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.

Immune Reconstitution

During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as MAC, CMV, PCP, and TB), which may necessitate evaluation and treatment.

Food Interaction

Ingestion of VIDEX EC with food significantly reduces the amount of didanosine absorbed (see CLINICAL PHARMACOLOGY). VIDEX EC should be administered at least 1.5 hours before or 2 hours after eating (see DOSAGE AND ADMINISTRATION).

Use in Children

VIDEX EC capsules have not been studied in pediatric patients.

Use in Pregnancy

There are no adequate and well-controlled studies of didanosine in pregnant women. VIDEX EC 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 not known if pregnancy augments the risk of lactic acidosis/hepatic steatosis syndrome reported in nonpregnant individuals receiving nucleoside analogues (see WARNINGS: 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. Health care providers caring for HIV-infected pregnant women receiving didanosine should be alert for early diagnosis of lactic acidosis/hepatic steatosis syndrome.

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.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Use in Nursing Mothers

HIV-Infected mothers should not breast-feed their infants to avoid risking postnatal transmission of HIV. It is not known whether VIDEX is excreted in human milk. A study in rats showed that, following oral administration, didanosine and/or its metabolites were excreted into the milk of lactating rats.

Use in Elderly

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). Clinical studies of didanosine, including those for VIDEX EC, 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: Dose Adjustment).

Patients with Special Diseases and Conditions

1. Patients on Sodium-Restricted Diets

VIDEX EC Capsules: Sodium contents are minimal, 0.53 mg for the 125-mg capsule formulation, 0.85 mg for the 200-mg capsules formulation, 1.06 mg for the 250-mg capsule formulation, and 1.70 mg for the 400-mg formulation.

2. Patients with Renal Impairment

Patients with renal impairment (serum creatinine > 1.5 mg/dL or creatinine clearance < 60 mL/min) may be at greater risk for toxicity from VIDEX EC due to decreased drug clearance. The risk of pancreatitis (see WARNINGS), may be increased if allopurinol and didanosine are administered together in this patient population; it is recommended that these 2 drugs not be administered together (see DRUG INTERACTIONS).

The elimination half-life of didanosine is increased in anuric patients requiring hemodialysis (see Pharmacokinetics subsection of CLINICAL PHARMACOLOGY). Because of the potential for drug removal, VIDEX EC should be administered after dialysis. Dose reductions should be considered in patients with renal impairment (see WARNINGS and DOSAGE AND ADMINISTRATION).

3. Patients with Hepatic Impairment

Patients with hepatic impairment may be at greater risk for toxicity related to VIDEX EC treatment due to altered metabolism (see WARNINGS and DOSAGE AND ADMINISTRATION).

4. Hyperuricemia

Didanosine has been associated with asymptomatic hyperuricemia; treatment suspension may be necessary if clinical measures aimed at reducing uric acid levels fail.

5. Diabetes Mellitus

The VIDEX EC capsule formulation does not contain sucrose.

DRUG INTERACTIONS

Coadministration of VIDEX EC with drugs that are known to cause peripheral neuropathy or pancreatitis may increase the risk of these toxicities (See WARNINGS, Pancreatitis, Peripheral Neuropathy) and should be done only with extreme caution.

Methadone: When VIDEX tablets¹ were administered to opiate-dependent patients (n = 16) chronically treated with methadone, didanosine exposure, as measured by AUC, was decreased by 57% compared to untreated controls (n = 10). There was no clinically significant impact on methadone exposure. No studies have been conducted with VIDEX EC.

Tenofovir disoproxil fumarate: Exposure to VIDEX EC is increased when coadministered with tenofovir. When VIDEX EC was administered (in the fasting state) 2 hours before tenofovir disoproxil fumarate with a light meal, the AUC of didanosine increased by 48% relative to VIDEX EC alone in the fasted state. When VIDEX EC was administered together with tenofovir disoproxil fumarate and a light meal, the AUC of didanosine increased by 60% relative to VIDEX EC alone in the fasted state. Administration of reduced doses of VIDEX EC with tenofovir and a light meal resulted in didanosine exposures (AUC) similar to the recommended doses of VIDEX EC given alone in the fasted state. Therefore, a dose reduction of VIDEX EC is recommended when coadministered with tenofovir (see DOSAGE AND ADMINISTRATION: (Concomitant Therapy). Caution should be used when coadministering reduced-dose didanosine, tenofovir, and an NNRTI in treatment-naïve patients with high viral loads at baseline since such use has been associated with reports of a high rate of virologic failure and emergence of resistance at an early stage. Increased exposure may cause or worsen didanosine-related clinical toxicities including pancreatitis, symptomatic hyperlactatemia/lactic acidosis, and peripheral neuropathy. All patients receiving tenofovir disoproxil fumarate and didanosine concomitantly should be closely monitored for didanosine-related adverse events and clinical response (See WARNINGS).

Allopurinol: The AUC of didanosine was increased about 4-fold when allopurinol at 300 mg/day was coadministered with a single 200-mg dose of didanosine to two patients with renal impairment ($CL_{cr} = 15$ and 18 mL/min). In 14 healthy volunteers, the mean AUC of didanosine increased approximately 2-fold when a 300-mg dose of allopurinol (daily for 7 days) was given with a single 400 mg dose of VIDEX¹. Thus, the risk of dose-related toxicities, such as pancreatitis (see WARNINGS), may be increased if allopurinol and didanosine are administered together. It is recommended that these two drugs not be administered together.

Quinolone Antibiotics: VIDEX EC capsules do not contain an antacid component and therefore can be coadministered with tetracycline or quinolone anti-infective agents.

Ganciclovir: Administration of VIDEX (tablets¹ or the powder¹) two hours prior to, or concurrent with, ganciclovir was associated with a mean increase of 111% in the steady state AUC of didanosine. A minor decrease (21%) in the steady state AUC of ganciclovir was seen when VIDEX (tablets or the powder) was administered 2 hours prior to ganciclovir, but not when both drugs were given simultaneously. It is not known if these changes are clinically significant.

¹ Videx tablets and powder are no longer marketed in Canada

There were no changes in the renal clearance of either drug. There is no evidence that VIDEX EC potentiates the myelosuppressive effects of ganciclovir.

Ribavirin: Based on *in vitro* data, ribavirin increases the intracellular triphosphate levels of didanosine. Fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in patients receiving didanosine and ribavirin with or without stavudine. The administration of didanosine and ribavirin should be avoided unless the potential benefit outweighs the risk. Patients should be monitored for didanosine-related toxicities.

Interactions with Other Antiretroviral Drugs: There is no drug-drug interaction between VIDEX EC capsules and indinavir, therefore, these two products can be given together.

Drugs whose absorption can be affected by the level of acidity in the stomach (e.g., ketoconazole, dapsons, itraconazole): VIDEX EC capsules can be coadministered with these drugs, due to the absence of the antacid component in the VIDEX EC capsule formulation.

INFORMATION FOR PATIENTS

VIDEX EC is not a cure for HIV infection, and patients may continue to develop HIV-associated illnesses including opportunistic infections. Therefore, patients should be informed to remain under the care of a physician when using VIDEX EC.

The major toxicity of VIDEX EC is pancreatitis, which has been fatal in some patients. Symptoms of pancreatitis include abdominal pain, and nausea and vomiting. Peripheral neuropathy occurs in patients treated with VIDEX EC. Symptoms of peripheral neuropathy include tingling, burning, pain or numbness in the hands or feet. Patients should be advised to report these symptoms to their physician. The above toxicities of VIDEX EC occur with the greatest frequency in patients with a history of these events and dose modification and/or discontinuation of VIDEX EC may be required if toxicity develops. There are other medications including alcohol which may exacerbate VIDEX EC toxicity. Patients should be advised to consult their physician about such medications.

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

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

Patients should also be informed that the long-term effects of VIDEX EC are unknown at this time. VIDEX EC therapy has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

ADVERSE REACTIONS

A SERIOUS TOXICITY OF DIDANOSINE IS PANCREATITIS, WHICH MAY BE FATAL (see WARNINGS). OTHER IMPORTANT TOXICITIES INCLUDE LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS; RETINAL CHANGES AND OPTIC NEURITIS; AND PERIPHERAL NEUROPATHY (see WARNINGS and PRECAUTIONS).

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 VIDEX EC in combination with stavudine, with or without hydroxyurea, may be at increased risk for pancreatitis, which may be fatal, and hepatotoxicity (see WARNINGS). Patients treated with VIDEX EC in combination with stavudine may also be at increased risk for peripheral neuropathy (see PRECAUTIONS).

Selected clinical adverse events that occurred in a study of VIDEX EC in combination with other antiretroviral agents are provided in Table 1.

**Table 1
Selected Clinical Adverse Events, Study AI454-152^a**

Adverse Events	Percent of Patients ^b	
	VIDEX EC + stavudine + nelfinavir n = 258	Zidovudine/ lamivudine ^c + 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)	<1	*

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

^b Percentages based on treated patients.

^c 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 VIDEX

EC plus stavudine plus hydroxyurea plus ritonavir plus indinavir plus efavirenz (see WARNINGS).

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 VIDEX EC in combination with other antiretroviral agents are shown in Table 2.

Table 2
Selected Laboratory Abnormalities, AI454-152^a

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

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

^b Percentages based on treated patients.

^c Zidovudine / lamivudine combination tablet.

^d >5 x ULN for SGOT and SGPT, ≥ 2.1 x ULN for lipase, and ≥ 2.6 x ULN for bilirubin (ULN = upper limit of normal).

Adverse Events observed during Clinical Practice

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

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

Digestive Disorders: anorexia, dyspepsia, and flatulence.

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

Hematologic Disorders: anemia, leukopenia, granulocytopenia and thrombocytopenia.

Liver: lactic acidosis and hepatic steatosis (see WARNINGS and PRECAUTIONS); non-cirrhotic portal hypertension (see WARNINGS, Non-cirrhotic Portal Hypertension); 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).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Although no data with didanosine are available, activated charcoal should be administered to aid in the removal of unabsorbed drug, as recommended in American College of Emergency Physicians guidelines. General supportive measures are also recommended.

There is no known antidote for didanosine overdose. Experience in the Phase I studies in which didanosine was initially administered at doses ten times the currently recommended doses indicates that the complications of chronic overdose would include pancreatitis, peripheral neuropathy, diarrhea, hyperuricemia and, hepatic dysfunction. Didanosine is not dialyzable by peritoneal dialysis, although there is some clearance by hemodialysis (see Pharmacokinetics subsection of CLINICAL PHARMACOLOGY). The fractional removal of didanosine during an average hemodialysis session of 3 to 4 hours is approximately 20-35% of the amount present in the body at the start of dialysis.

DOSAGE AND ADMINISTRATION

Adults

VIDEX EC (didanosine) should be administered once daily on an empty stomach at least 1.5 hours before or 2 hours after eating (see PRECAUTIONS, CLINICAL PHARMACOLOGY).

VIDEX EC Capsules should be swallowed intact. The recommended daily dose is dependent on body weight and is usually administered as one capsule given on a once-daily schedule as outlined in Table 3.

**Table 3
Adult Dosing**

Patient Weight	Videx EC Capsules
≥ 60 kg	400 mg once daily
< 60 kg	250 mg once daily

Children

The safety and efficacy of VIDEX EC in pediatric patients have not been established.

DOSE ADJUSTMENT

Clinical and laboratory signs suggestive of pancreatitis should prompt dose suspension and careful evaluation of the possibility of pancreatitis. VIDEX EC use should be discontinued in patients with confirmed pancreatitis (see WARNINGS).

Patients who have presented with symptoms of neuropathy may tolerate a reduced dose of VIDEX EC after resolution of these symptoms upon drug discontinuation.

In adult patients with impaired renal function, the dose of VIDEX EC should be adjusted to compensate for the slower rate of elimination (Table 4) (see CLINICAL PHARMACOLOGY).

Table 4

Creatinine Clearance (mL/min/1.73 m ²)	EC Capsules
Patient Weight ≥ 60 kg	
≥ 60 (normal dose)	400 mg QD
30 - 59	200 mg QD
10 - 29	125 mg QD
< 10	125 mg QD
Patient Weight < 60 kg	
≥ 60 (normal dose)	250 mg QD
30 - 59	125 mg QD
10 - 29	125 mg QD
< 10	*

* EC capsules are not suitable for use in patients < 60 kg with creatinine clearance < 10 mL/min.

For patients undergoing dialysis, the daily dose of VIDEX EC should be administered after dialysis. It is not necessary to administer a supplemental dose of VIDEX EC following hemodialysis.

Geriatric Patients

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 adjustment should be made accordingly.

Hepatic Impairment

There were no substantial alterations in didanosine pharmacokinetics in patients with moderate or severe (Child-Pugh class B or C) hepatic impairment compared with healthy subjects (see PHARMACOLOGY, Pharmacokinetics, Hepatic Impairment). No dose adjustment of VIDEX EC is necessary for patients with moderate (Child-Pugh class B) hepatic impairment. There is insufficient data to recommend a specific dose of adjustment in patients with severe (Child-Pugh class C) hepatic impairment.

During treatment with VIDEX EC, patients should be observed for liver enzyme elevations and VIDEX EC suspended if enzymes rise to a clinically significant level (see WARNINGS and PRECAUTIONS).

Concomitant Therapy

Tenofovir disoproxil fumarate: A dose reduction of VIDEX EC is recommended when coadministered with tenofovir (see DRUG INTERACTIONS).

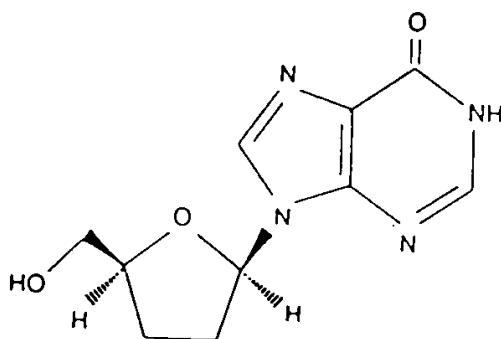
VIDEX EC: 250 mg (adults weighing ≥ 60 kg with creatinine clearance ≥ 60 mL/min) or 200 mg (adults weighing < 60 kg with creatinine clearance ≥ 60 mL/min) once daily together with tenofovir and a light meal (≤ 400 kcalories, $\leq 20\%$ fat).

The appropriate dose of VIDEX EC coadministered with tenofovir in patients with creatinine clearance < 60 mL/min has not been established.

PHARMACEUTICAL INFORMATION

I. Drug Substance

Trade Name:	VIDEX EC
Proper Name:	didanosine [ddI]
Chemical Name:	2',3'-dideoxyinosine
Empirical Formula:	C ₁₀ H ₁₂ N ₄ O ₃
Structural Formula:	



Molecular weight:	236.2
Description:	Didanosine is a white, crystalline powder with the molecular formula C ₁₀ H ₁₂ N ₄ O ₃ and a molecular weight of 236.2 daltons. The aqueous solubility of didanosine at 25°C and pH of approximately 6 is 27.3 mg/mL. Didanosine is unstable in acidic solutions. For example, at pH<3 and 37°C, 10% of didanosine decomposes to hypoxanthine in less than 2 minutes.

II. Composition

VIDEX (didanosine) EC capsules are available for oral administration in strengths of 400, 250, 200 and 125 mg of didanosine. Inactive ingredients in the beadlets include: sodium starch glycolate, carboxymethylcellulose sodium, methacrylic acid copolymer, diethyl phthalate, talc, and sodium hydroxide. Inactive ingredients in the capsule shell include: gelatin, titanium dioxide, and sodium lauryl sulfate. Capsules are imprinted with edible ink.

III. Storage

VIDEX EC Capsules should be stored in tightly closed bottles at room temperature (15 - 30° C).

DOSAGE FORMS AND AVAILABILITY

VIDEX EC (didanosine) 400 mg capsules are white, opaque capsules with red markings. Bottles of 30 capsules.

VIDEX EC 250 mg capsules are white, opaque capsules with blue markings. Bottles of 30 capsules.

VIDEX EC 200 mg capsules are white, opaque capsules with green markings. Bottles of 30 capsules.

VIDEX EC 125 mg capsules are white, opaque capsules with tan markings. Bottles of 30 capsules.

INFORMATION FOR THE CONSUMER

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

VIDEX (pronounced VYE-dex) EC is used to treat adults who are infected with HIV (the human immunodeficiency virus, the virus that causes AIDS).

- Take VIDEX EC on an empty stomach at least 1.5 hours before or 2 hours after eating or exactly as instructed by your doctor or other healthcare professional.
- Serious side effects have occurred in some patients taking VIDEX EC. **Consult your doctor immediately if the following occur:**
 - **pancreatitis**, a dangerous inflammation of the pancreas, which has been fatal in some patients. Tell your doctor immediately if you experience stomach pain, nausea, or vomiting;
 - **peripheral neuropathy** (nerve disorder); Symptoms include tingling, burning, pain or numbness in the hands or feet. These symptoms should be reported to your physician;
 - **lactic acidosis** (severe elevation of lactic acid in the blood), **hepatitis** (inflammation of the liver), liver damage and/or **liver failure** especially in patients at high risk for liver problems. Your doctor should check your liver function periodically while you are taking VIDEX EC;
 - **portal hypertension** (high blood pressure in the large vein of the liver). Severe liver problems can lead to liver transplantation or death in some people taking VIDEX EC. Your doctor may conduct various tests, including blood counts and other tests, for this condition;
 - **vision changes**. Have regular eye examinations, and report any changes in vision immediately to your doctor.
- Inform your doctor if you think you may be allergic to any medicine.
- Other medicines, including those you can buy without a prescription, may interfere with the actions of VIDEX EC. Do not take any medicine, vitamin, or health store preparation without first checking with your doctor.

What is VIDEX EC?

VIDEX EC is a prescription medicine used to treat adults who are infected with HIV (the human immunodeficiency virus, the virus that causes AIDS). VIDEX EC belongs to a class of drugs called nucleoside analogues. It prevents HIV from copying itself once the virus has entered cells of your immune system (called CD4 cells). In this manner, VIDEX EC helps your body maintain its supply of CD4 cells, which are important for fighting HIV and other infections.

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

Will VIDEX EC cure my infection?

No. At present there is no cure for HIV infection. Even while taking VIDEX EC, you may continue to have HIV-related illnesses, including infections with other disease-producing organisms. Continue to see your doctor regularly and report any medical problems that occur.

Will VIDEX EC prevent my giving HIV to others?

No. VIDEX EC does not prevent a patient infected with HIV from passing the virus to other people. To protect others, the patient infected with HIV must continue to practice safe sex and take precautions to prevent others from coming in contact with their blood and other body fluids.

How do I take VIDEX EC? How do I store it?

VIDEX EC should only be taken once daily.

Your doctor will determine the strength of your dose based on your body weight, kidney and liver function, and any side effects that you may have had with other medications. Take VIDEX EC exactly as instructed. **VIDEX EC should be taken on an empty stomach, at least 1.5 hours before or 2 hours after eating, and should NOT be taken with food.** Try not to miss a dose, but if you do, take it as soon as possible. If it is almost time for the next dose, skip the missed dose and resume your regular dosing schedule.

VIDEX EC capsules should be swallowed intact and not chewed and should be stored in tightly closed bottles at room temperature (15-30°C).

Who should not take VIDEX EC?

Do not take VIDEX EC if you are allergic to **any** of its ingredients. Besides the active ingredient didanosine, VIDEX EC preparations contain the following inactive ingredients in the beadlets: sodium starch glycolate, carboxymethylcellulose sodium, methacrylic acid copolymer, diethyl phthalate, talc, and sodium hydroxide. Inactive ingredients in the capsule shell include: gelatin, titanium dioxide, and sodium lauryl sulfate. Capsules are imprinted with edible ink.

Tell your doctor if you think you have had an allergic reaction to any of these ingredients.

VIDEX EC is not recommended for use in children.

What are the possible side effects of VIDEX EC?

Like any medicine, VIDEX EC may cause unwanted effects, although it is not always possible to tell whether such effects are caused by VIDEX EC, another medication you may be taking, or the HIV infection. Most side effects of VIDEX EC cause only discomfort and are not considered serious.

The most serious side effect of VIDEX EC is **pancreatitis**. Pancreatitis is a dangerous inflammation of the pancreas which may be fatal. *Tell your doctor immediately if you experience stomach pain, nausea, or vomiting.* Let your doctor know if you have had pancreatitis before taking VIDEX EC because this condition occurs more often in patients who have experienced it previously. It is also more likely in people with advanced HIV disease, but can occur at any disease stage. If you experience pancreatitis, your doctor will tell you to stop taking VIDEX EC.

Other serious side effects that have occurred in some patients taking VIDEX EC included:

- **Peripheral neuropathy** (nerve disorder); symptoms include tingling, burning, pain or numbness in the hands or feet. These symptoms should be reported to your physician. This toxicity occurs more often in patients who have experienced it previously. There are other medications including alcohol which may exacerbate this toxicity.
- **Lactic acidosis** (severe elevation of lactic acid in the blood), **hepatitis** (inflammation of the liver), **liver damage**, and **liver failure**. These side effects were rare and usually occurred in adults with advanced HIV disease or who were taking more than one drug for their HIV infection. Your doctor should check your liver function periodically while you are taking VIDEX EC, especially if you have a history of heavy alcohol use or a liver problem.
- **Portal hypertension** (high blood pressure in the large vein of the liver). Your doctor may conduct various tests, including blood counts and other tests, for this condition.
- **Vision changes**. Because of possible effects from VIDEX EC on the nerves in the eye, have regular eye examinations and report any changes in vision **immediately** to your doctor.
- Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck (“buffalo hump”), breasts, and around the trunk. Loss of fat from the legs, arms and face may also happen. The cause and long term health effects of these conditions are not known at this time.

The most frequent side effects observed in studies of adults taking the recommended dose of VIDEX EC were diarrhea, peripheral neuropathy, nausea, headache, rash, and vomiting. It was not always possible to determine which side effects were related to VIDEX EC and which were related to HIV infection or other condition.

What should I avoid while taking VIDEX EC?

Avoid drinking alcoholic beverages while taking VIDEX EC since alcohol may increase your risk of pancreatitis or liver damage. Other medicines, including those you can buy without a prescription, may interfere with the actions of VIDEX EC. Do not take any medicine, vitamin, or other health preparation without **first** checking with your doctor.

Some medicines should not be taken at the same time of day that you take VIDEX EC as they may interfere with the action of VIDEX EC or may increase the possibility of experiencing side effects. Check with your doctor. These medicines include: methadone, tenofovir, and ganciclovir.

Other medicines for example allopurinol and, ribavirin should not be taken with VIDEX EC.

However, because VIDEX EC capsules do not contain an antacid component, they can be taken with tetracycline or quinolone anti-infective agents. There is also no drug-drug interaction between VIDEX EC capsules and indinavir, therefore, these two products can be taken together.

Can I take VIDEX EC if I am pregnant or nursing a baby?

Experts advise against breast-feeding if you are HIV-positive. Because studies have shown VIDEX EC to be present in the breast milk of animals receiving the drug, it is may be present in human breast milk. Therefore, you should **not** breast-feed if infected with HIV, to avoid passing HIV to your baby.

It is not known if VIDEX EC can harm a human fetus, so VIDEX EC should be used during pregnancy only after discussion with your doctor. *Tell your doctor if you become pregnant or plan to become pregnant while taking VIDEX EC.*

Because studies have shown VIDEX EC to be present in the breast milk of animals receiving the drug, it is probably present in human breast milk. Therefore, nursing a baby while taking VIDEX EC is NOT recommended.

What else should I know about VIDEX EC?

If you are required to limit sodium (salt) intake: The sodium content in VIDEX EC is minimal, 0.53 mg for the 125-mg capsule formulation, 0.85 mg for the 200-mg capsules formulation, 1.06 mg for the 250-mg capsule formulation, and 1.70 mg for the 400-mg formulation.

If you have kidney disease: If your kidneys are not working properly, your doctor may need to monitor your kidney function while you take VIDEX EC. Also, your dosage of VIDEX EC may be lowered.

What should I do in case of an overdose?

In case of drug overdose, contact a healthcare practitioner (e.g. doctor) hospital emergency department or regional poison control centre, even if there are no symptoms.

This medicine was prescribed for your particular condition. Do not use VIDEX EC for another condition or give it to others. Keep VIDEX EC and all medicines out of the reach of children. Discard VIDEX EC when it is outdated or no longer needed by returning the unused medication to your pharmacist for proper disposal.

This summary does not include everything there is to know about VIDEX EC. If you have questions or concerns, or want more information about VIDEX EC, your physician and pharmacist have the complete prescribing information upon which this guide is based. You may want to read it and discuss it with your doctor. Remember, no written summary can replace careful discussion with your doctor.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701C
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reactions reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

Note: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

PHARMACOLOGY

CLINICAL PHARMACOLOGY

Clinical Use

The effect of didanosine, alone or in combination with ZDV (zidovudine), was evaluated in several major randomized, controlled clinical trials (ACTG 116A, ACTG 116B/117, ACTG 175, ACTG 152, DELTA, CPCRA 007). These trials confirmed the reduced risk of HIV disease progression or death with didanosine therapy, alone or in combination with ZDV, as compared with ZDV monotherapy in HIV-infected individuals, including symptomatic and asymptomatic adults with CD4 counts < 500 cells/mm³ and children with evidence of immunosuppression. The clinical benefits of initial didanosine therapy were demonstrated in adults with CD4 counts 200 - 500 cells/mm³, as well as in children. The ACTG 175 trial showed that eight weeks of treatment with ZDV, didanosine, or didanosine plus ZDV decreased mean plasma HIV RNA by 0.26, 0.65 and 0.93 log₁₀ copies /mL, respectively.

Once-Daily Dosing

BMS study AI454-152 was a 48-week randomized open-label comparison of VIDEX EC administered once daily in combination with stavudine (d4T) and nelfinavir (NLF) versus the fixed combination of zidovudine (AZT)/lamivudine (3TC) and nelfinavir (NLF) in 511 treatment naïve HIV-1 infected adult patients. The results of the 48-week final protocol-specified analysis showed no overall difference in virologic response between the VIDEX EC once-daily/d4T/NLF and the AZT/3TC/NLF regimens in the proportion of patients with HIV RNA <400 c/mL, 56% and 53%, respectively. In a protocol-specified analysis of patients with HIV RNA <50 c/mL at 48-weeks, 37% of VIDEX EC once-daily/d4T/NLF-treated patients were below the limit of detection compared to 35% of the AZT/3TC/NLF-treated patients. Similar conclusions of comparability of the regimens were obtained with a modified efficacy analysis which included additional criteria for treatment failure. Increases in CD4 cell counts above baseline at 48-weeks were 120.5 and 162 cells/mm³, in the VIDEX EC once-daily/d4T/NLF and AZT/3TC/NLF-treated patients, respectively.

BMS study AI454-148 was a 48-week randomized open-label comparison of VIDEX¹ administered once-daily in combination with stavudine (d4T) and nelfinavir (NLF) versus zidovudine (AZT)/lamivudine (3TC)/nelfinavir (NLF) in 756 treatment naïve HIV-1 infected adult patients. The results of the 48-week final analysis of all randomized patients on their initial therapy demonstrated no significant difference in virologic response between the VIDEX once daily/d4T/NLF and the AZT/3TC/NLF regimens in the proportion of patients with HIV RNA <400 c/mL, 52% and 57%, respectively. In a similar analysis of patients with HIV RNA <50 c/mL at 48-weeks, 40% of VIDEX once daily/d4T/NLF-treated patients were below the limit of detection compared to 47% of the AZT/3TC/NLF-treated patients. Results of an additional analysis of treatment response, combining measures of treatment failure as well as the proportion below the limit of detection, demonstrated response rates which favored the AZT/3TC/NLF regimen: for HIV RNA <400 c/mL response rates were 50% and 59%, and for HIV RNA <50

¹ Videx tablets are no longer marketed in Canada

c/mL were 34% and 47% for the VIDEX once daily/d4T/NLF and AZT/3TC/NLF regimens, respectively. Immunologic response, as measured by CD4 cell counts, was comparable between the treatment arms.

Pharmacokinetics

The didanosine contained within the beadlets of VIDEX EC capsules is protected against gastric acid by an enteric coating, which dissolves when the beadlets empty into the higher pH of the small intestine, the site of drug absorption. The time to reach C_{max} (T_{max}) is 2 hours following administration of the EC capsule.

Hepatic Impairment: The pharmacokinetics of didanosine has been studied in 12 non-HIV infected patients with moderate (n=8) and severe (n=4) hepatic impairment (Child-Pugh class B or C, respectively). The mean C_{max} and AUC values following a single 400 mg dose of didanosine were approximately 11% lower and 7% higher, respectively, in subjects with Child-Pugh class B hepatic impairment compared to matched healthy controls. Insufficient data are available from patients with Child-Pugh class C hepatic impairment. As a whole, the C_{max} and AUC values in these patients with hepatic impairment were similar to those observed in healthy subjects from other studies and are within the pharmacokinetic variability of didanosine.

Effect of Food on Oral Absorption: **VIDEX EC should be administered on an empty stomach.**

In study AI454-153, the C_{MAX} and AUC of didanosine following administration of VIDEX EC capsules were reduced by approximately 46% and 19%, respectively, in the presence of food compared to the fasting state.

The intracellular half-life of ddATP, the metabolite presumed to be responsible for the antiretroviral activity of didanosine, is reported to be 8 to 24 hours *in vitro*. The half-life of intracellular ddATP *in vivo* has not been measured.

There are currently incomplete data concerning the effect of impaired hepatic function on the pharmacokinetics of didanosine. (See PRECAUTIONS).

Because *in vitro* human plasma protein binding is less than 5% with didanosine, drug interactions involving binding site displacement are not anticipated.

Tenofovir disoproxil fumarate: In pharmacokinetic studies in healthy subjects, the exposure (AUC) from a 250-mg dose of VIDEX EC capsules given with tenofovir and a light meal was equivalent to the exposure from a 400-mg dose of VIDEX EC alone in the fasted state (5% decrease in didanosine AUC). The same 250-mg dose given with tenofovir in the fasted state resulted in a 14% increase in didanosine AUC. A 325-mg dose of VIDEX EC capsules given with tenofovir and a light meal resulted in a 13% increase in the AUC of didanosine compared with 400 mg alone in the fasted state. A 200-mg dose of VIDEX EC capsules given with tenofovir and a light meal resulted in a 16% increase in the AUC of didanosine compared with didanosine 250 mg alone in the fasted state.

Results of Drug Interaction Studies with VIDEX EC: Effects of Coadministered Drug on Didanosine Plasma AUC and C_{MAX} Values^a				
Drug	Didanosine Dosage	n	AUC of Didanosine (90% CI)	C_{MAX} of Didanosine (90% CI)
tenofovir , ^b 300 mg once daily with a light meal ^c	400 mg single dose fasting 2 h before tenofovir	26	↑ 48% (31, 67%)	↑ 48% (25, 76%)
tenofovir , ^b 300 mg once daily with a light meal ^c	400 mg single dose with tenofovir and a light meal	25	↑ 60% (44, 79%)	↑ 64% (41, 89%)
tenofovir , ^b 300 mg once daily with a light meal ^c	200 mg single dose with tenofovir and a light meal	33	↑ 16% (6, 27%) ^d	↓ 12% (-25, 3%) ^d
	250 mg single dose with tenofovir and a light meal	33	« (-13, 5%) ^e	↓ 20% (-32, -7%) ^e
	325 mg single dose with tenofovir and a light meal	33	↑ 13% (3, 24%) ^e	↓ 11% (-24, 4%) ^e
↑ indicates increase. ↓ indicates decrease. ↔ indicates no change, or mean increase or decrease of <10%. ^a All studies conducted in healthy volunteers ≥ 60 kg. ^b tenofovir disoproxil fumarate. ^c 373 kcalories, 8.2 grams fat. ^d Compared with VIDEX EC 250 mg administered alone under fasting conditions. ^e Compared with VIDEX EC 400 mg administered alone under fasting conditions.				

VIROLOGY

***In Vitro* HIV Susceptibility**

The *in vitro* anti-HIV-1 activity of didanosine was evaluated in a variety of HIV-1 infected lymphoblastic cell lines and monocyte/macrophage cell cultures. Didanosine has shown antiviral activity against laboratory and clinical isolates of HIV-1. The concentration of drug necessary to inhibit viral replication by 50 percent (IC₅₀) ranged from 2.5 to 10 μM (1 μM = 0.24 μg/mL) in lymphoblastic cell lines and 0.01 to 0.1 μM in monocyte/macrophage cell cultures. The relationship between *in vitro* susceptibility of HIV to didanosine and the inhibition of HIV replication in humans has not been established.

Drug Resistance

HIV-1 isolates with reduced sensitivity to didanosine have been selected *in vitro* and were also obtained from patients treated with didanosine. Genetic analysis of these isolates showed a predominant mutation at Leu 74 (Leu 74 Val) and another mutation at Met 184 (Met 184 Val) in the Pol gene that encodes for the reverse transcriptase.

Cross-resistance

The potential for cross-resistance between reverse transcriptase inhibitors and protease inhibitors is low because of the different enzyme targets involved. Mutations in the reverse transcriptase gene at both codons 74 and 184 are associated with cross-resistance to zalcitabine. Lamivudine-resistant isolates containing only the Met 184 Val mutation have been recovered and these isolates showed a 4- to 8-fold decrease in didanosine sensitivity. HIV-1 isolates with multidrug resistance mutations to zidovudine, didanosine, zalcitabine, stavudine and lamivudine have been reported (2/39 patients) following combination therapy with zidovudine and didanosine for 2 years. Multidrug resistance was dependent on five mutations (Ala 62 Val, Val 75 Ile, Phe 77 Leu, Phe 116 Tyr and Gln 151 Met) in the reverse transcriptase gene. Of these, the mutation at codon position 151 (Q151M) played a significant role in the development of viable virus with a multidrug resistance phenotype.

TOXICOLOGY

Acute Toxicity

Species	Sex	Route	Approximate Minimal Lethal Dose (mg/kg)	Pharmacotoxic Signs
Mouse	M & F	Oral gavage with buffer	> 2000	No signs during 14-day observation period.
Rat	M & F	Oral gavage with buffer	> 2000	No signs during 14-day observation period.
Dog	M & F	Oral gavage with buffer	> 2000	Emesis in both didanosine-treated dogs 40-75 min after dosing. Otherwise no signs during 14-day observation period.

The minimal lethal oral single dose of didanosine was determined to be greater than 2000 mg/kg in male and female mice, rats and dogs.

All animals appeared clinically normal throughout the 14-day observation period except for emesis in the treated dogs at 40-75 minutes after didanosine administration.

Subacute Toxicity

Species/ Strain	N/Dose Sex	Route	Dosage Regimen (mg/kg/day)	Time	NOEL (No observed effect level)	Treatment Related Findings
Mouse/CD-1	10 M	Oral gavage in CMC	0, 100, 250, 500 or 1000	1 month	1000	Lower average body weight gain in mice at 1000, 500 and 250 mg/kg. A mild anemia was seen at 500 and 1000 mg/kg. Leukopenia with lymphopenia and thrombocytopenia was noted at 1000 mg/kg. Nephrotoxicity which consisted of minimal to mild focal tubular degeneration was seen in 2/10 mice at 1000 mg/kg. Minimal to mild lymphoid depletion was seen in the spleen and thymus of a few mice at 500 and 1000 mg/kg.
Mouse/CD-1	10 M	Oral gavage in CMC	0, 100, 250, 500 or 1000	1 month	-	Low incidence of leukopenia and absolute lymphopenia on Day 24. Low incidence of thymic and splenic depletion at high dose.
Mouse/CD-1	10 M 10 F	Oral in diet	0, 50, 100, 250, 500 or 1000	3 months	500	Lower terminal body weight in males and lower average food intake in males and females at 1000 mg/kg. Slight but significant reduction in distal compound sensory amplitude which is an early indicator of distal axonopathy. Elevated serum phosphorus in male mice at high dose. Mild tubular degeneration in kidneys, increased pigment in Kupffer cells in liver and lymphoid depletion in spleen and thymus.
Rat/ Sprague- Dawley	10 or 15 M 10 or 15 F	Oral gavage with buffer	0, 100, 300 or 1000	1 month	1000	No pharmacotoxic clinical signs. Increased WBC counts were observed in 1000 mg/kg male rats. Small differences (12-17% higher) in mean absolute kidney (male and female) and liver (male) weights were present between the control and 1000 mg/kg/day male and female rats.

Subacute Toxicity

Species/ Strain	N/Dose Sex	Route	Dosage Regimen (mg/kg/day)	Time	NOEL (No observed effect level)	Treatment Related Findings
Rat/ Sprague- Dawley	10 M 10 F	Oral gavage with buffer	0, 100, 300 or 1000	3 months	300	Statistically lower gain and percent gain in body weight in high dose female rats. Total white blood cell count and absolute lymphocyte values of the high dose females were slightly decreased compared to controls. Liver sections of 4/10 high dose female rats had histologic evidence of slight chronic passive congestion, a finding indicative of slight, treatment-related, cardiovascular dysfunction at the high dose.
Rat/ Sprague- Dawley	10 M 10 F	Oral in diet	0, 50, 100, 250, 500 or 1000	3 months	50	Drug-related decreased body weight, weight gain and food intake at 1000 mg/kg. Decreased WBC values at 100 mg/kg/day or more. Decreased ALT values and increased serum cholesterol and LDH values at 500 or 1000 mg/kg/day. Microscopic changes involving hepatic blood vasculature included arterial lesions (medial necrosis and hemorrhage, adventitial reactive changes, endothelial hypertrophy) at 250 mg/kg or more and changes indicative of reduced blood flow (pigment-laden Kupffer cells accompanied by centrilobular hepatocyte degeneration) at 1000 mg/kg/day.
Dog/Beagle	2 or 3 M 2 or 3 F	Oral gavage with buffer	0, 80, 250 or 500 (divided b.i.d.)	1 month	250	No pharmacotoxic clinical signs. Minimal anemia and decreased platelet counts in high-dose dogs on Day 12. Increased uric acid and mildly increased fasting blood sugar in high-dose dogs on Day 29. No gross or histopathologic findings.

Subacute Toxicity (cont'd)

Species/ Strain	N/Dose Sex	Route	Dosage Regimen (mg/kg/day)	Time	NOEL (No observed effect level)	Treatment Related Findings
Dog/Beagle	3 M 3 F	Oral capsule	0, 80, 250 or 500 (divided b.i.d.)	3 months	80	Soft stool, liquid and mucoid stools, body weight loss and decreased food intake. 3 (2 M and 1 F) high dose dogs died or were sacrificed showing clinical signs of decreased activity, hypothermia, dehydration, thin body condition, decreased body weight and food intake, tremors and pale color. No ECG evidence of a drug effect on the heart. Clinicopathologic changes seen at 500 or 250 mg/kg but not at 80 mg/kg were elevated liver enzymes, bilirubin, uric acid, urea nitrogen, creatinine, creatine kinase, total protein, phosphorus, amylase and lipase in serum; thrombocytopenia; borderline anemia; hemoconcentration; reticulocytosis, neutropenia; lymphopenia; hyperfibrinogenemia; elevated clotting times; bilirubinuria. Several of these changes were seen only in moribund dogs and some were reversible during continuous dosing at 250 mg/kg. Histopathologic changes were seen at 500 and 250 mg/kg, but not at 80 mg/kg. The most significant organ-specific changes were found in the liver, heart, kidney, lymph tissue, bone marrow and testes. In addition, hemorrhage, congestion and edema occurred in some of the above organs, as well as a number of others.
Dog/Beagle	1 M 1 F	IV infusion	93.9 mg/kg/h	48 h	-	Drug-related emesis, diarrhea and increased heart rate were observed. No clinical or anatomical pathological changes were reported.
Dog/Beagle	1 M 1 F	IV infusion	9.39 mg/kg/h	120 h	-	Emesis, diarrhea, increased heart rate and body weight losses. Leukopenia and increased BUN. Gross lesions in the gastrointestinal tract. Microscopic lesions consisted of thymic lymphoid depletion or necrosis and bone marrow atrophy and hemorrhage. Recovery was almost complete by Day 34.

Subacute Toxicity (cont'd)

Species/ Strain	N/Dose Sex	Route	Dosage Regimen (mg/kg/day)	Time	NOEL (No observed effect level)	Treatment Related Findings
Dog/Beagle	2 M 1 or 2 F	IV infusion	Control 93.9 mg/kg/h 31.3 mg/kg/h	200 h 240 h	-	Emesis diarrhea (bloody), increased heart rate, body weight loss and moribund condition. Leukopenia, increased glucose, decreased potassium and changes in kidney parameters, especially BUN. Gross lesions consisted of mucosal necrosis and congestion in small and large intestine, thymic lymphoid depletion or necrosis and bone marrow atrophy and hemorrhage at 93.9 mg/kg/hour. Moderate thymic lymphoid depletion and mild mucosal congestion was seen in the 31.3 mg/kg/hour dogs. These dogs showed complete recovery by Day 38.

Chronic Toxicity

Species/ Strain	N/Dose Sex	Route	Dosage Regimen (mg/kg/day)	Time	NOEL (No observed effect level)	Treatment Related Findings
Dog/Beagle	5 M 5 F	Oral Capsule	0, 30, 80, 180 (divided bid)	12 months	30	<p>Drug-related clinical signs included emesis, body weight loss and decreased food intake. Additional clinical signs seen prior to sacrifice of 2 moribund dogs consisted of hypothermia, emaciation, decreased activity and dehydration. No drug-related clinicopathologic or histopathologic changes were observed in low-dose dogs at any sampling time. Drug-related changes in blood chemistries observed in high-dose dogs (and as indicated in intermediate-dose dogs[1]) during the treatment period included elevations of ALT (1), AST(1), bilirubin, blood ammonia, BSP retention, GGT, uric acid, sodium, lipase, and BUN and decreases in fasting glucose and creatinine. Drug-related changes observed only in 2 moribund high-dose males immediately prior to euthanasia included alterations in K, Ca, alkaline phosphatase, cholesterol, total protein, albumin, and amylase. Drug-related changes in hematologic and urinalytical parameters were anemia, reticulocytopenia, thrombocytopenia, leukopenia, lymphopenia (1), hemoconcentration, increased urine volume (1), decreased urine specific gravity (1), and increase in number of casts in urine sediment (1). Only the increase in urine volume and decrease in urine specific gravity (1) were observed after a 3-month recovery period.</p> <p>After 12 months of treatment or in moribund dogs, drug-related histopathologic changes at the high-dose (and, as indicated [1], in the intermediate-dose) level were observed in A) liver (hepatocellular degeneration (1), cytoplasmic inclusion bodies (1), glycogen depletion, pigment-laden Kupffer cells, intrahepatocellular pigmentation, hepatocellular atrophy, bile stasis, fatty change, centrolobular fibrosis (1), extramedullary hematopoiesis, and hepatocellular necrosis), B) kidney (tubular degeneration (1), tubular necrosis, cytoplasmic inclusion bodies, tubular dilatation, fibrosis, tubular hypertrophy, subacute inflammation, and pyelitis), C) lymphoid tissue (lymphoid depletion (1)), splenic subcapsular fibrosis, splenic and lymph node hemosiderosis, and erythrophagocytosis in lymph nodes), D) bone marrow (hypocellularity), E) testes (atrophy and an increase in giant cells), F) epididymis (atrophy and</p>

Chronic Toxicity (cont'd)

Species/ Strain	N/Dose Sex		Route	Dosage Regimen (mg/kg/day)	Time	NOEL (No observed effect level)	Treatment Related Findings
Dog/Beagle (cont'd)							<p>degeneration), G) prostate (atrophy), H) stomach (submucosal edema), I) adrenal glands (degeneration (I)), J) pancreas (atrophy and hydropic degeneration), and K) skeletal muscle (secondary atrophy). Some of these changes were observed only in the 2 high-dose males that were euthanatized in moribund condition on Days 149 and 176: hepatocellular pigmentation, fatty change, and atrophy; bile stasis; renal cytoplasmic inclusion bodies; thymic lymphoid depletion; splenic hemosiderosis; lymph node hemosiderosis and erythrophagocytosis; and changes in testis, epididymis, prostate, pancreas, and skeletal muscle. After a 3-month recovery period, the following drug-related histopathologic changes persisted: hepatocellular degeneration, renal tubular degeneration (I), periglomerular fibrosis (I), renal tubular hypertrophy, lymphoid depletion (I), splenic subcapsular fibrosis, and adrenal degeneration.</p> <p>Of these changes only renal tubular hypertrophy did not show some degree of reversibility.</p>

Chronic Toxicity (cont'd)

Species/ Strain	N/Dose Sex	Route	Dosage Regimen (mg/kg/day)	Time	NOEL (No observed effect level)	Treatment Related Findings
Rats/Sprague Dawley	25 M 25 F	Oral Gavage with buffer	0, 100, 300, 1000	363-367 days	300	<p>Clinical signs of toxicity included a high incidence of salivation and a moderate increase in body soiling in M and F high dose group animals. Significantly reduced body weight gains were seen in the high dose group female rats beginning at 2 months and continuing until termination of treatment with improvement during recovery. The male and female high dose rats showed significantly lower average food intake values during the treatment period.</p> <p>Clinical pathology changes included increased cholesterol values for the high dose males, decreased ALT values and an increased phosphorus value for the high dose females, decreased RBC values for the intermediate and high dose males and females, and increased reticulocyte values for the intermediate and high dose males.</p> <p>At necropsy, the high dose group had a high incidence of esophageal dilatation and the intermediate and high dose male groups had slightly increased kidney weights.</p> <p>Histopathology revealed dose-related skeletal muscle alterations at several sites; dose-related alterations in the collecting veins and other evidence of chronically reduced blood flow in the liver; secondary hepatocyte changes at the high dose, including an increase incidence of eosinophilic foci of alteration; and, at the high dose, cytological alterations in the kidney tubules. The muscle and hepatic effects were infrequent and minimal at the lowest dose (100 mg/kg/day). All tissue effects showed evidence of reversibility and were less evident or absent after a 3-month recovery period.</p> <p>The myopathic effects were most evident in the wall of the esophagus and were expressed clinically by esophageal dilatation and a few deaths at the high dose.</p>

Chronic Toxicity (Cont'd)

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

Reproduction and Teratology

Species/Strain	N/dose Sex	Route	Dose Regimen (mg/kg/day)	Time	Treatment Related Findings
SEGMENT I					
Rat/CD	28 M 28 F	Oral gavage	0, 100, 300 or 1000	<u>Males</u> : 64 days before mating and during mating <u>Females</u> : 14 days before mating through time of hysterectomy or Day 21 postpartum	Didanosine was slightly toxic to females and pups in the high dose group, during mid and late lactation. The rats showed reduced food intake and body weight gains. With the exception of this transient drug effect, didanosine did not induce toxicity and did not impair the reproductive ability of the parents or the physical or functional development of the pups. There was no increase in spontaneous external malformations.
SEGMENT II					
Rat/CD	22 F	Oral gavage	0, 100, 300 or 1000	From Day 7 to Day 17 of gestation	No evidence of embryotoxic, fetotoxic or teratogenic effects.
Rabbit/NZW	24 F	Oral gavage	0, 75, 200 or 600	From Day 6 through Day 18 of gestation	No maternal toxicity, embryotoxicity or teratogenicity.
SEGMENT III					
Rat/CD	22 F	Oral gavage	0, 100, 300 or 1000	From gestation Day 17 to post-natal Day 21 or 22	No adverse effects on gestation, parturition or lactation (FO generation), or on development, behavior or reproduction (F1 generation).

Carcinogenicity and Mutagenicity

Lifetime carcinogenicity studies were conducted in mice and rats for 22 and 24 months, respectively. No drug-related neoplasms were observed in any didanosine-treated group of mice during, or at the end of, the dosing period. In rats, statistically significant increases were noted for granulosa cell tumors in high dose females, subcutaneous fibrosarcomas and histiocytic sarcomas in high dose males, and hemangiomas in intermediate and high dose males. These increases were attributed to biological variation or other factors, such as increased longevity at the high dose, that are known to influence spontaneous tumor rate variability, and were not considered toxicologically significant.

No evidence of mutagenicity (with or without metabolic activation) was observed in Ames *Salmonella* mutagenicity assays or in a mutagenicity assay conducted with *Escherichia coli* tester strain WP2 uvrA where only a slight increase in revertants was observed with didanosine. In a mammalian cell gene mutation assay conducted in L5178Y/TK+/- mouse lymphoma cells, didanosine was weakly positive both in the absence and presence of metabolic activation at concentrations of approximately 2000 µg/mL and above. In an *in vitro* cytogenic study performed in cultured human peripheral lymphocytes, high concentrations of didanosine (≥ 500 µg/mL) elevated the frequency of cells bearing chromosome aberrations. Another *in vitro* mammalian cell chromosome aberration study using Chinese Hamster Lung cells revealed that didanosine produces chromosome aberrations at ≥ 500 µg/mL after 48 hours of exposure. However, no significant elevations in the frequency of cells with chromosome aberrations were seen at didanosine concentrations up to 250 µg/mL. In a BALB/c 3T3 *in vitro* transformation assay, didanosine was considered positive only at concentrations of 3000 µg/mL and above.

No evidence of genotoxicity was observed in rat and mouse micronucleus assays. The results from the genotoxicity studies suggest that didanosine is not mutagenic at biologically and pharmacologically relevant dose levels. At significantly elevated doses *in vitro*, the genotoxic effects of didanosine are similar in magnitude to those seen with natural DNA nucleosides.

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