

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use didanosine delayed-released capsules safely and effectively. See full prescribing information for Didanosine Delayed-Release Capsules. **Didanosine Delayed-Release Capsules (Enteric-Coated Beadlets)**
Initial U.S. Approval: 1991

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

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

RECENT MAJOR CHANGES

Contraindications

Allopurinol (4.1) 6/2009

Ribavirin (4.2) 6/2009

Warnings and Precautions

Non-cirrhotic Portal Hypertension (5.4) 1/2010

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

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

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

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Mylan Pharmaceuticals at 1-877-446-3679 (1-877-4-INFO-RX), or FDA at 1-800-FDA-1088 or go to www.fda.gov/medwatch

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DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION and the FDA-approved Medication Guide

Revised: 01/2010

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MEDICATION GUIDE

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FULL PRESCRIBING INFORMATION

WARNING: PANCREATITIS, LACTIC ACIDOSIS AND HEPATOMEGALY WITH STEATOSIS

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

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

1 INDICATIONS AND USAGE

Didanosine, also known as ddI, in combination with other antiretroviral agents is indicated for the treatment of human immunodeficiency virus (HIV)-1 infection [see *Clinical Studies (14)*].

2 DOSAGE AND ADMINISTRATION

Didanosine delayed-release capsules should be administered on an empty stomach. Didanosine delayed-release capsules should be swallowed intact.

2.1 Recommended Dosage (Adult and Pediatric Patients)

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

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 1).

Table 1: Recommended Dosage (Adult and Pediatric Patients)

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

2.2 Renal Impairment

Dosing recommendations for didanosine delayed-release capsules and didanosine pediatric powder for oral solution are different for patients with renal impairment. Please consult the complete prescribing information on administration of didanosine pediatric powder for oral solution to patients with renal impairment.

Adult Patients

In adult patients with impaired renal function, the dose of didanosine delayed-release capsules should be adjusted to compensate for the slower rate of elimination. The recommended doses and dosing intervals of didanosine delayed-release capsules in adult patients with renal insufficiency are presented in Table 2.

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

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

*Based on studies using a buffered formulation of didanosine.

†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 delayed-release in this patient population, a reduction in the dose should be considered (see Table 2).

Patients Requiring Continuous Ambulatory Peritoneal Dialysis (CAPD) or Hemodialysis

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

2.3 Dose Adjustment

Concomitant Therapy with Tenofovir Disoproxil Fumarate

In patients who are also taking tenofovir disoproxil fumarate, a dose reduction of didanosine delayed-release 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 delayed-release coadministered with tenofovir disoproxil fumarate in patients with creatinine clearance of less than 60 mL/min has not been established [*see Drug Interactions (7) and Clinical Pharmacology (12.3)*].

Hepatic Impairment

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

3 DOSAGE FORMS AND STRENGTHS

Didanosine Delayed-Release Capsules are available containing 125 mg, 200 mg, 250 mg or 400 mg of didanosine, USP as enteric-coated beadlets.

- 125 mg capsule printed with **M159** on both the white opaque cap and white opaque body
- 200 mg capsule printed with **M160** on both the yellow opaque cap and white opaque body
- 250 mg capsule printed with **M161** on both the yellow opaque cap and yellow opaque body
- 400 mg capsule printed with **M162** on both the white opaque cap and yellow opaque body

4 CONTRAINDICATIONS

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

4.1 Allopurinol

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

4.2 Ribavirin

Coadministration 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.

5 WARNINGS AND PRECAUTIONS

5.1 Pancreatitis

Fatal and nonfatal 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. Didanosine delayed-release should be suspended in patients with signs or symptoms of pancreatitis and discontinued in patients with confirmed pancreatitis. Patients treated with didanosine delayed-release in combination with stavudine may be at increased risk for pancreatitis.

When treatment with life-sustaining drugs known to cause pancreatic toxicity is required, suspension of didanosine delayed-release therapy is recommended. In patients with risk factors for pancreatitis, didanosine delayed-release 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 Adverse Reactions (6)*].

5.2 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 antiretrovirals. 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 Use in Specific Populations (8.1)*]. Particular caution should be exercised when administering didanosine delayed-release 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 didanosine delayed-release 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).

5.3 Hepatic Toxicity

The safety and efficacy of didanosine delayed-release have not been established in HIV-infected patients with significant underlying liver disease. 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, interruption or discontinuation of treatment must be considered.

Hepatotoxicity and hepatic failure resulting in death were reported during post-marketing 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 Adverse Reactions (6)*].

5.4 Non-cirrhotic Portal Hypertension

Post-marketing 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 didanosine delayed-release should be monitored for early signs of portal hypertension (e.g., thrombocytopenia and splenomegaly) during routine medical visits. Appropriate laboratory testing including liver enzymes, serum bilirubin, albumin, complete blood count and international normalized ration (INR) and ultrasonography should be considered. Didanosine delayed-release should be discontinued in patients with evidence of non-cirrhotic portal hypertension.

5.5 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 didanosine delayed-release should be considered in patients who develop peripheral neuropathy [see *Adverse Reactions (6)*].

5.6 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 didanosine delayed-release [see *Adverse Reactions (6)*].

5.7 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including didanosine delayed-release. 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 jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

5.8 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.

6 ADVERSE REACTIONS

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

- Pancreatitis [see *Boxed Warning, Warnings and Precautions (5.1)*]
- Lactic acidosis/severe hepatomegaly with steatosis [see *Boxed Warning, Warnings and Precautions (5.2)*]
- Hepatic toxicity [see *Warnings and Precautions (5.3)*]
- Non-cirrhotic portal Hypertension [see *Warnings and Precautions (5.4)*]
- Peripheral neuropathy [see *Warnings and Precautions (5.5)*]
- Retinal changes and optic neuritis [see *Warnings and Precautions (5.6)*]

6.1 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 AI454-152 was a 48-week, randomized, open-label study comparing didanosine delayed-release (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-naive patients. Selected clinical adverse reactions that occurred in combination with other antiretroviral agents are provided in Table 3.

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

Adverse Events	Percent of Patients ^{†,‡}	
	didanosine delayed-release + stavudine + nelfinavir n = 258	zidovudine/ lamivudine [§] + 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	¶

*Median duration of treatment was 62 weeks in the didanosine delayed-release + stavudine + nelfinavir group and 61 weeks in the zidovudine/lamivudine + nelfinavir group.

†Percentages based on treated patients.

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

§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 delayed-release plus stavudine plus hydroxyurea plus ritonavir plus indinavir plus efavirenz [see *Warnings and Precautions* (5)].

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 delayed-release in combination with other antiretroviral agents are shown in Table 4.

Table 4: Selected Laboratory Abnormalities, Study AI454-152*

Parameter	Percent of Patients [†]			
	didanosine delayed-release + stavudine + nelfinavir n = 258		zidovudine/lamivudine [‡] + nelfinavir n = 253	
	Grades 3 to 4 [§]	All Grades	Grades 3 to 4 [§]	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

*Median duration of treatment was 62 weeks in the didanosine delayed-release + stavudine + nelfinavir group and 61 weeks in the zidovudine/lamivudine + nelfinavir group.

†Percentages based on treated patients.

‡Zidovudine/lamivudine combination tablet.

§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, 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 hours and in less than 1% of the 274 pediatric patients who received didanosine 90 mg/m² every 12 hours in combination with zidovudine [see *Clinical Studies* (14)].

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

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval 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* (5.8)].

Digestive Disorders - anorexia, dyspepsia, and flatulence.

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

Hepatobiliary Disorders - symptomatic hyperlactatemia/lactic acidosis and hepatic steatosis [see *Warnings and Precautions* (5.2)]; non-cirrhotic portal hypertension [see *Warnings and Precautions* (5.4)]; 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* (5.6)].

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 didanosine delayed-release 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* (5)]. The combination of didanosine delayed-release and hydroxyurea, with or without stavudine, should be avoided.

7 DRUG INTERACTIONS

7.1 Established Drug Interactions

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

Table 5: Established Drug Interactions Based on Studies with Didanosine Delayed-Release or Studies with Buffered Formulations of Didanosine and Expected to Occur with Didanosine Delayed-Release

Drug	Effect	Clinical Comment
ganciclovir	↑ didanosine concentration	If there is no suitable alternative to ganciclovir, then use in combination with didanosine delayed-release with caution. Monitor for didanosine-associated toxicity.
methadone	↓ didanosine concentration	If coadministration of methadone and didanosine is necessary, the recommended formulation of didanosine is didanosine delayed-release. Patients should be closely monitored for adequate clinical response when didanosine delayed-release is coadministered with methadone, including monitoring for changes in HIV RNA viral load. Do not coadminister methadone with didanosine pediatric powder due to significant decreases in didanosine concentrations.
nelfinavir	No interaction one hour after didanosine	Administer nelfinavir one hour after didanosine delayed-release.
tenofovir disoproxil fumarate	↑ didanosine concentration	A dose reduction of didanosine delayed-release capsules to the following dosage once daily taken together with tenofovir disoproxil fumarate and a light meal (400 kcalories or less and 20% fat or less) or in the fasted state is recommended.*

		<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) Patients should be monitored for didanosine-associated toxicities and clinical response.
↑ indicates increase ↓ indicates decrease		

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

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

7.2 Predicted Drug Interactions

Predicted drug interactions with didanosine delayed-release are listed in Table 6.

Table 6: Predicted Drug Interactions with Didanosine Delayed-Release

Drug or Drug Class	Effect	Clinical Comment
Drugs that may cause pancreatic toxicity	↑ risk of pancreatitis	Use only with extreme caution.*
Neurotoxic drugs	↑ risk of neuropathy	Use with caution.†
↑ Indicates increase		

*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 didanosine delayed-release is recommended [*see Warnings and Precautions (5.1)*].

†[*See Warnings and Precautions (5.6)*]

8 USE IN SPECIFIC POPULATIONS

8.1 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 nonpregnant individuals receiving nucleoside analogues [*see Warnings and Precautions (5.2)*]. **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 early diagnosis of lactic acidosis/hepatic steatosis syndrome.

Antiretroviral Pregnancy Registry

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

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed 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 in 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 breast-feed if they are receiving didanosine.**

8.4 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* (2), *Adverse Reactions* (6.1), *Clinical Pharmacology* (12.3), and *Clinical Studies* (14)]. Additional pharmacokinetic studies in pediatric patients support use of didanosine delayed-release in pediatric patients who weigh at least 20 kg.

8.5 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* (5.1)]. Clinical studies of didanosine, including those for didanosine delayed-release, 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* (2.2)].

8.6 Renal Impairment

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

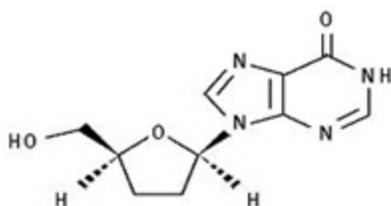
10 OVERDOSAGE

There is no known antidote for didanosine overdosage. In phase 1 studies, in which buffered formulations of didanosine were initially administered at doses 10 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 *Clinical Pharmacology* (12.3)].

11 DESCRIPTION

Didanosine delayed-release capsules are the brand name for an enteric-coated formulation of didanosine, USP, a synthetic purine nucleoside analogue active against HIV-1. Didanosine delayed-release capsules, containing enteric-coated beadlets, are available for oral administration in strengths of 125 mg, 200 mg, 250 mg, or 400 mg of didanosine, USP. The inactive ingredients in the beadlets include carboxymethylcellulose sodium, colloidal silicon dioxide, diethyl phthalate, hypromellose, methacrylic acid copolymer, sodium citrate hydrous, sodium lauryl sulfate, sodium starch glycolate and talc. The capsule shells contain gelatin, red iron oxide, sodium lauryl sulfate, titanium dioxide and yellow iron oxide. The capsules are imprinted with edible inks which contain black iron oxide, potassium hydroxide, propylene glycol and shellac.

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



Didanosine, USP is a white to off-white crystalline powder with the molecular formula $C_{10}H_{12}N_4O_3$ and a molecular weight of 236.2. 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 less than 3 and 37°C, 10% of didanosine decomposes to hypoxanthine in less than 2 minutes. In didanosine delayed-release capsules, an enteric coating is used to protect didanosine from degradation by stomach acid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

The pharmacokinetic parameters of didanosine in HIV-infected adult and pediatric patients are summarized in Table 7, 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 mg 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 7: Pharmacokinetic Parameters for Didanosine in HIV-infected Patients

Parameter *	Pediatrics		Adults	
	20 kg to less than 25 kg (n = 10)	25 kg to less than 60 kg (n = 17)	At least 60 kg (n = 7)	At least 60 kg (n = 44)
Apparent clearance (L/h)	89.5 \pm 21.6	116.2 \pm 38.6	196 \pm 55.8	174.5 \pm 69.7
Apparent volume of distribution (L)	98.1 \pm 30.2	154.7 \pm 55	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 0.7	2.25 \pm 0.89	2.65 \pm 1.07

*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 didanosine delayed-release capsules, 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 didanosine delayed-release formulation relative to a buffered tablet formulation.

The peak plasma concentration (C_{max}) of didanosine, administered as didanosine delayed-release, 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 hours for didanosine delayed-release capsules.

Effect of Food

In the presence of food, the C_{max} and AUC for didanosine delayed-release were reduced by approximately 46% and 19%, respectively, compared to the fasting state [see *Dosage and Administration* (2)]. Didanosine delayed-release 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 8). 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 to 4 hour dialysis period. The absolute bioavailability of didanosine was not affected in patients requiring dialysis [see *Dosage and Administration* (2.2)].

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

Creatinine Clearance (mL/min)

Parameter	at least 90 n = 12	60 to 90 n = 6	30 to 59 n = 6	10 to 29 n = 3	Dialysis Patients n = 11
CL _{cr} (mL/min)	112 ± 22	68 ± 8	46 ± 8	13 ± 5	ND
CL/F (mL/min)	2,164 ± 638	1,566 ± 833	1,023 ± 378	628 ± 104	543 ± 174
CL _R (mL/min)	458 ± 164	247 ± 153	100 ± 44	20 ± 8	less than 10
T _{1/2} (h)	1.42 ± 0.33	1.59 ± 0.13	1.75 ± 0.43	2 ± 0.3	4.1 ± 1.2

ND = not determined due to anuria

CL_{cr} = creatinine clearance

CL/F = apparent oral clearance

CL_R = 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 (2.3)*].

Pediatric Patients: The pharmacokinetics of didanosine have 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 nine clinical trials in 106 pediatric (neonate to 18 years of age) and 45 adult patients (greater 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 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 (2)*].

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

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

Drug Interactions

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

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

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

	with tenofovir and a light meal		(-13, 5%) [#]	(-32, -7%) [#]
	325 mg single dose with tenofovir and a light meal	33	↑ 13% (3, 24%) [#]	↓ 11% (-24, 4%) [#]
methadone , chronic maintenance dose	400 mg single dose	15, 16 ^P	↓17% (-29, -2%)	↓16% (-33, 4%)

↑ Indicates increase.

↓ Indicates decrease.

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

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

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

‡Tenofovir disoproxil fumarate

§373 kcalories, 8.2 grams fat

¶Compared with didanosine delayed-release capsule 250 mg administered alone under fasting conditions.

#Compared with didanosine delayed-release capsule 400 mg administered alone under fasting conditions.

^PComparisons 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 10: Results of Drug Interaction Studies with Didanosine Delayed-Release: Effects of Didanosine on Coadministered Drug Plasma AUC and C_{max} Values

Drug	Didanosine Dosage	n	% Change of Coadministered Drug Pharmacokinetic Parameters ^{*†}	
			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, [‡] 300 mg once daily with a light meal [§]	400 mg single dose fasting 2 hours before tenofovir	25	↔	↔
tenofovir, [‡] 300 mg once daily with a light meal [§]	400 mg single dose with tenofovir and a light meal	25	↔	↔

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

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

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

‡Tenofovir disoproxil fumarate

§373 kcalories, 8.2 grams fat

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

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

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

sulfamethoxazole, 1000 mg single dose	200 mg single dose	8 [†]	↔	↔
trimethoprim, 200 mg single dose	200 mg single dose	8 [†]	↔	↑ 17% (-23, 77%)
zidovudine, 200 mg every 8 hours for 3 days	200 mg every 12 hours for 3 days	6 [†]	↔	↔

↑ Indicates increase.
↓ Indicates decrease.
↔ Indicates no change, or mean increase or decrease of less than 10%.
NA = Not available

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

[†]HIV-infected patients

[‡]90% CI

Table 12: Results of Drug Interaction Studies with Buffered Formulations of Didanosine: Effects of Didanosine on Coadministered Drug Plasma AUC and C_{max} Values

Drug	Didanosine Dosage	n	% Change of Coadministered Drug Pharmacokinetic Parameters*	
			AUC of Coadministered Drug (95% CI)	C _{max} of Coadministered Drug (95% CI)
dapsone, 100 mg single dose	200 mg every 12 hours for 14 days	6 [†]	↔	↔
ganciclovir, 1000 mg every 8 hours, 2 hours after didanosine	200 mg every 12 hours	12 [†]	↓ 21%	NA
nelfinavir , 750 mg single dose, 1 hour after didanosine	200 mg single dose	10 [†]	↑ 12%	↔
ranitidine, 150 mg single dose, 2 hours before didanosine	375 mg single dose	12 [†]	↓ 16%	↔
ritonavir, 600 mg every 12 hours for 4 days	200 mg every 12 hours for 4 days	12	↔	↔
stavudine, 40 mg every 12 hours for 4 days	100 mg every 12 hours for 4 days	10 [†]	↔	↑ 17%
sulfamethoxazole, 1000 mg single dose	200 mg single dose	8 [†]	↓ 11% (-17, -4%)	↓ 12% (-28, 8%)
trimethoprim, 200 mg single dose	200 mg single dose	8 [†]	↑ 10% (-9, 34%)	↓ 22% (-59, 49%)
zidovudine, 200 mg every 8 hours for 3 days	200 mg every 12 hours for 3 days	6 [†]	↓ 10% (-27, 11%)	↓ 16.5% (-53, 47%)

↑ Indicates increase.
↓ Indicates decrease.
↔ Indicates no change, or mean increase or decrease of less than 10%.
NA = Not available.

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

[†]HIV-infected patients.

12.4 Microbiology

Mechanism of Action

Didanosine is a synthetic nucleoside analogue 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.

Antiviral Activity in Cell Culture

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

Resistance

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

Cross-resistance

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

13.2 Animal Toxicology and/or Pharmacology

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 to 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 didanosine and other nucleoside analogues.

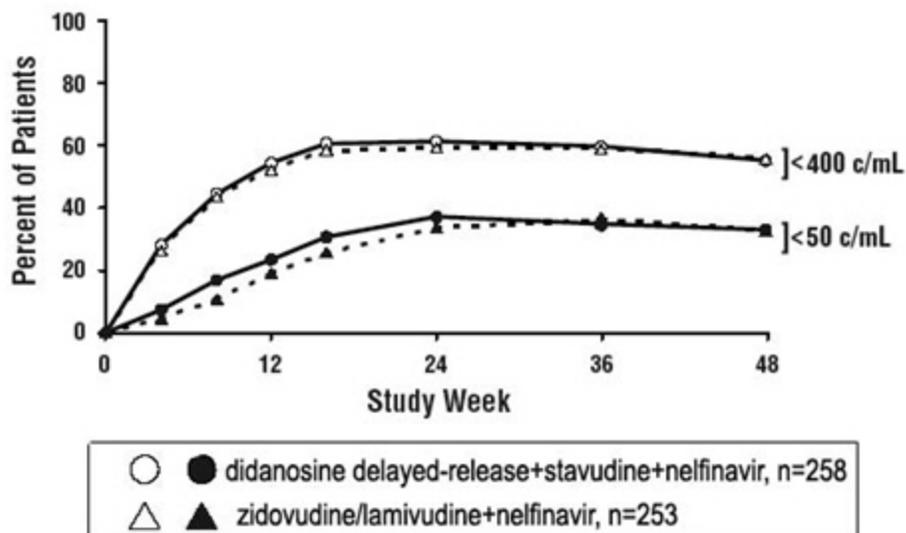
14 CLINICAL STUDIES

14.1 Adult Patients

Study AI454-152 was a 48-week, randomized, open-label study comparing didanosine delayed-release (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-naive patients, with a mean CD4 cell count of 411 cells/mm³ (range 39 to 1,105 cells/mm³) and a mean plasma HIV-1 RNA of 4.71 log₁₀ copies/mL (range 2.8 to 5.9 log₁₀ copies/mL) at baseline. Patients were primarily males (72%) and Caucasian (53%) with a mean age of 35 years (range 18 to 73 years).

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

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



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

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

Outcome	Percent of Patients with HIV-1 RNA less than 400 copies/mL (less than 50 copies/mL)	
	didanosine delayed-release + stavudine + nelfinavir n = 258	zidovudine/lamivudine* + nelfinavir n = 253
Responder ^{†‡}	55% (33%)	56% (33%)
Virologic failure [§]	22% (45%)	21% (43%)
Death or discontinued due to disease progression	1% (1%)	2% (2%)
Discontinued due to adverse event	6% (6%)	7% (7%)
Discontinued due to other reasons [¶]	16% (16%)	15% (16%)

*Zidovudine/lamivudine combination tablet

†Corresponds to rates at Week 48 in Figure 1.

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

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

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

14.2 Pediatric Patients

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Didanosine Delayed-Release Capsules are available containing 125 mg, 200 mg, 250 mg or 400 mg of didanosine, USP as enteric-coated beadlets.

The 125 mg capsule is a hard-shell gelatin capsule with a white opaque cap and white opaque body radially printed with **M159** in black ink on both the cap and body. The capsule is filled with white to off-white beads. They are available as follows

NDC 0378-8886-93

bottles of 30 capsules

NDC 0378-8886-05

bottles of 500 capsules

The 200 mg capsule is a hard-shell gelatin capsule with a yellow opaque cap and white opaque body radially printed with **M160** in black ink on both the cap and body. The capsule is filled with white to off-white beads. They are available as follows

NDC 0378-8887-93

bottles of 30 capsules

NDC 0378-8887-05

bottles of 500 capsules

The 250 mg capsule is a hard-shell gelatin capsule with a yellow opaque cap and yellow opaque body radially printed with **M161** in black ink on both the cap and body. The capsule is filled with white to off-white beads. They are available as follows

NDC 0378-8888-93

bottles of 30 capsules

NDC 0378-8888-05

bottles of 500 capsules

The 400 mg capsule is a hard-shell gelatin capsule with a white opaque cap and yellow opaque body radially printed with **M162** in black ink on both the cap and body. The capsule is filled with white to off-white beads. They are available as follows

NDC 0378-8889-93

bottles of 30 capsules

NDC 0378-8889-05

bottles of 500 capsules

Storage

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature].

Protect from moisture.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

PHARMACIST: Dispense Medication Guide with each prescription.

17 PATIENT COUNSELING INFORMATION

See Medication Guide.

17.1 Pancreatitis

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

17.2 Peripheral Neuropathy

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

17.3 Lactic Acidosis and Severe Hepatomegaly with Steatosis

Patients should be informed that 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.

17.4 Hepatic Toxicity

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

17.5 Non-cirrhotic Portal Hypertension

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

17.6 Retinal Changes and Optic Neuritis

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

17.7 Fat Redistribution

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.

17.8 Concomitant Therapy

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

Patients should be cautioned about the use of medications or other substances, including alcohol, which may exacerbate didanosine delayed-release toxicities.

17.9 General Information

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

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

Patients should be instructed to not miss a dose but if they do, patients should take didanosine delayed-release as soon as possible.

Patients should be told that if it is almost time for the next dose, they should skip the missed dose and continue with the regular dosing schedule.

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

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

MEDICATION GUIDE

Didanosine (also known as ddI)

Delayed-release Capsules (Enteric-Coated Beadlets)

125 mg, 200 mg, 250 mg and 400 mg

Read this Medication Guide before you start taking didanosine delayed-release capsules and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment. You and your healthcare provider should talk about your treatment with didanosine delayed-release capsules before you start taking it and at regular check-ups. You should stay under your healthcare provider's care when taking didanosine delayed-release capsules.

What is the most important information I should know about didanosine delayed-release capsules?

Didanosine delayed-release capsules may cause serious side effects, including:

- 1. Swelling of your pancreas (pancreatitis) that may cause death. Pancreatitis can happen at any time during your treatment with didanosine delayed-release capsules.** Before you start taking didanosine delayed-release capsules, tell your healthcare provider if you:
 - have had pancreatitis
 - have advanced HIV (human immunodeficiency virus) infection
 - have kidney problems
 - drink alcoholic beverages
 - take a medicine called ZERIT[®] (stavudine)

It is important to call your healthcare provider right away if you have:

- stomach pain
- swelling of your stomach

- nausea and vomiting
- fever

2. **Build-up of acid in your blood (lactic acidosis).** Lactic acidosis must be treated in the hospital as it may cause death. Before you start taking didanosine delayed-release capsules, tell your healthcare provider if you:

- have liver problems
- are pregnant. There have been deaths reported in pregnant women who get lactic acidosis after taking didanosine delayed-release capsules and ZERIT (stavudine).
- are overweight
- have been treated for a long time with other medicines to treat HIV

It is important to call your healthcare provider right away if you:

- feel weak or tired
- have unusual (not normal) muscle pain
- have trouble breathing
- have stomach pain with nausea and vomiting
- feel cold, especially in your arms and legs
- feel dizzy or light-headed
- have a fast or irregular heartbeat

3. **Liver problems.** Serious liver problems have happened in some people (including pregnant women) who take didanosine delayed-release capsules. These problems include liver enlargement (hepatomegaly), fat in the liver (steatosis), liver failure and high blood pressure in the large vein of the liver (portal hypertension). Severe liver problems can lead to liver transplantation or death in some people taking didanosine delayed-release capsules. Your healthcare provider should check your liver function while you are taking didanosine delayed-release capsules. You should be especially careful if you have a history of heavy alcohol use or liver problems.

It is important to call your healthcare provider right away if you have:

- yellowing of your skin or the white of your eyes (jaundice)
- dark urine
- pain on the right side of your stomach
- swelling of your stomach
- easy bruising or bleeding
- loss of appetite
- nausea or vomiting
- vomiting blood or dark colored stools (bowel movements)

What are didanosine delayed-release capsules?

Didanosine delayed-release capsules are a prescription medicine used with other antiretroviral medicines to treat human immunodeficiency virus (HIV) infection in children and adults. Didanosine delayed-release capsules belong to a class of drugs called nucleoside analogues.

Didanosine delayed-release capsules will not cure your HIV infection. At present there is no cure for HIV infection. Even while taking didanosine delayed-release capsules, you may continue to have HIV-related illnesses, including infections with other disease-producing organisms. Continue to see your healthcare provider regularly and report any medical problems that occur.

Who should not take didanosine delayed-release capsules?

Do not take didanosine delayed-release capsules if you take:

- ZYLOPRIM[®], LOPURIN[®], ALOPRIM[®] (allopurinol)
- COPEGUS[®], REBETOL[®], RIBASPHERE[®], RIBAVIRIN[®], VIRAZOLE[®] (ribavirin)

What should I tell my healthcare provider before taking didanosine delayed-release capsules?

Before you take didanosine delayed-release capsules, tell your healthcare provider if you:

- have or had kidney problems
- have or had liver problems (such as hepatitis)
- have or had persistent numbness, tingling, or pain in the hands or feet (neuropathy)
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if didanosine delayed-release capsules will harm your unborn baby. Tell your healthcare provider right away if you become pregnant while taking didanosine delayed-release capsules. You and your healthcare provider will decide if you should take didanosine delayed-release capsules while you are pregnant.

Pregnancy Registry: There is a pregnancy registry for women who take antiviral medicines during pregnancy. The purpose of the registry is to collect information about the health of you and your baby. Talk to your doctor about how you can take part in this registry.

- are breast-feeding or plan to breast-feed. **Do not breast-feed while you take didanosine delayed-release capsules.** It is not known if didanosine delayed-release capsules passes into your breast milk. The Centers for Disease Control and Prevention (CDC) recommends that HIV-infected mothers **not** breast-feed to avoid the risk of passing HIV infection to your baby.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Didanosine delayed-release capsules may affect the way other medicines work, and other medicines may affect how didanosine delayed-release capsules works.

Especially tell your healthcare provider if you take:

- CYTOVENE[®], VALCYTE[®] (ganciclovir)
- DOLOPHINE[®] HYDROCHLORIDE, METHADOSE[®] (methadone)
- VIRACEPT[®] (nelfinavir)
- VIREAD[®] (tenofovir disoproxil fumarate)
- alcoholic beverages

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

Ask your healthcare provider if you are not sure if you take one of the medicines listed above.

How should I take didanosine delayed-release capsules?

- Take didanosine delayed-release capsules exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much didanosine delayed-release capsules to take and when to take it.
- Your healthcare provider may change your dose. Do not change your dose of didanosine delayed-release capsules without talking to your healthcare provider.
- **Do not take didanosine delayed-release capsules with food.** Take didanosine delayed-release capsules on an empty stomach.
- Take didanosine delayed-release capsules whole. Do not break, crush, dissolve or chew didanosine delayed-release capsules before swallowing. If you cannot swallow didanosine delayed-release capsules whole, tell your healthcare provider. You may need a different medicine.
- 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 continue your regular dosing schedule.
- **Some medicines should not be taken at the same time of day that you take didanosine delayed-release capsules.** Check with your healthcare provider.
- If your kidneys are not working well, your healthcare provider will need to do regular blood and urine tests to check how they are working while you take didanosine delayed-release capsules. Your healthcare provider may also lower your dosage of didanosine delayed-release capsules if your kidneys are not working well.
- **If you take too much didanosine delayed-release capsules**, contact a poison control center or emergency room right away.

What should I avoid while taking didanosine delayed-release capsules?

- **Alcohol.** Do not drink alcohol while taking didanosine delayed-release capsules. Alcohol may increase your risk of getting pain and swelling of your pancreas (pancreatitis) or may damage your liver.

What are the possible side effects of didanosine delayed-release capsules?

Didanosine delayed-release capsules can cause pancreatitis, lactic acidosis and liver problems. See **“What is the most important information I should know about didanosine delayed-release capsules?”** at the beginning of this Medication Guide.

- **Vision changes.** You should have regular eye exams while taking didanosine delayed-release capsules.

- **Peripheral neuropathy. Symptoms include:** numbness, tingling or pain in your hands or feet. This condition is more likely to happen in people who have had it before, in patients taking medicines that affect the nerves and in people with advanced HIV disease. A child may not notice these symptoms. Ask the child's healthcare provider for the signs and symptoms of peripheral neuropathy in children.
- **Changes in your immune system (immune reconstitution syndrome).** Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider if you start having new or worse symptoms of infection after you start taking HIV medicine.
- **Changes in body fat (fat redistribution).** Changes in body fat have been seen in people who take antiretroviral medicines. These changes may include:
 - more fat in or around your
 - upper back and neck (buffalo hump)
 - breasts or chest
 - trunk
 - less fat in your
 - legs
 - arms
 - face

Tell your healthcare provider if you have any of the symptoms listed above.

The most common side effects of didanosine delayed-release capsules include:

- diarrhea
- stomach pain
- nausea
- vomiting
- headache
- rash

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of didanosine delayed-release capsules. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store didanosine delayed-release capsules?

- Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
- Safely throw away any unused didanosine delayed-release capsules.

Keep didanosine delayed-release capsules and all medicines out of the reach of children and pets.

General Information about the safe and effective use of didanosine delayed-release capsules.

Didanosine delayed-release capsules have not been shown to prevent a patient infected with HIV from passing the virus to other people. To protect others, you must continue to practice safer sex and take precautions to prevent others from coming in contact with your blood and other body fluids. Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use didanosine delayed-release capsules for a condition for which it was not prescribed. Do not give didanosine delayed-release capsules to other people, even if they have the same symptoms as you have. It may harm them.

Do not keep medicine that is out of date or that you no longer need. Dispose of unused medicines through community take-back disposal programs when available or place didanosine delayed-release capsules in an unrecognizable closed container in the household trash.

This Medication Guide summarizes the most important information about didanosine delayed-release capsules. If you would like more information about didanosine delayed-release capsules, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about didanosine delayed-release capsules that is written for health professionals. For more information, call Mylan Pharmaceuticals Inc. at 1-877-4-INFO-RX (1-877-446-3679).

What are the ingredients in didanosine delayed-release capsules?

Active Ingredient: didanosine

Inactive Ingredients: The inactive ingredients in the beadlets include carboxymethylcellulose sodium, colloidal silicon dioxide, diethyl phthalate, hypromellose, methacrylic acid copolymer, sodium citrate hydrous, sodium lauryl sulfate, sodium starch glycolate

and talc. The capsule shells contain gelatin, red iron oxide, sodium lauryl sulfate, titanium dioxide and yellow iron oxide. The capsules are imprinted with edible inks which contain black iron oxide, potassium hydroxide, propylene glycol and shellac.

Manufactured in India by:

Matrix Laboratories Limited

Secunderabad — 500 003, India

Code No.: MH/DRUGS/25/NKD/89

Manufactured for:

Mylan Pharmaceuticals Inc.

Morgantown, WV 26505 U.S.A.

REVISED JANUARY 2010

MX: DIDNODR:R4mt

PRINCIPAL DISPLAY PANEL - 125 mg

NDC 0378-8886-93

DIDANOSINE

DELAYED-RELEASE

CAPSULES

125 mg

(Enteric-coated beadlets)

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

30 CAPSULES (Rx only)

Each capsule contains 125 mg didanosine, USP as enteric-coated beadlets.

Usual Dosage: See accompanying prescribing information.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F).

[See USP Controlled Room Temperature.]

Protect from moisture.

Manufactured in India by:

Matrix Laboratories Limited

Secunderabad-500 003, India

Manufactured for:

Mylan Pharmaceuticals Inc.

Morgantown, WV 26505 U.S.A.

RMX8886H1

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Code No.: MH/DRUGS/25/NKD/89

Each capsule contains 125 mg didanosine, USP as enteric-coated beadlets.

Usual Dosage: See accompanying prescribing information.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Protect from moisture.

Manufactured in India by:
Matrix Laboratories Limited
Secunderabad-500 003, India

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

RMX8886H1

30 CAPSULES

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

30 CAPSULES (Rx only)

MYLAN®
DIDANOSINE
DELAYED-RELEASE
CAPSULES
125 mg
(Enteric-coated beadlets)

NDC 0378-8886-93

0378-8886-93

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Code No.: MH/DRUGS/25/NKD/89

Lot

Exp.

PRINCIPAL DISPLAY PANEL - 200 mg

NDC 0378-8887-93

DIDANOSINE

DELAYED-RELEASE

CAPSULES

200 mg

(Enteric-coated beadlets)

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

30 CAPSULES (Rx only)

Each capsule contains 200 mg didanosine, USP as enteric-coated beadlets.

Usual Dosage: See accompanying prescribing information.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F).

[See USP Controlled Room Temperature.]

Protect from moisture.

Manufactured in India by:

Matrix Laboratories Limited

Secunderabad-500 003, India

Manufactured for:

Mylan Pharmaceuticals Inc.

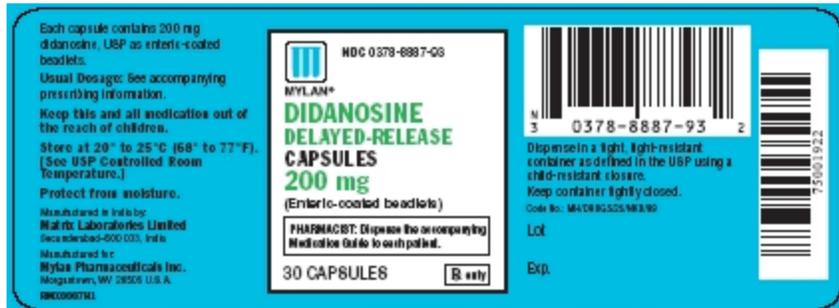
Morgantown, WV 26505 U.S.A.

RMX8887H1

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Code No.: MH/DRUGS/25/NKD/89



PRINCIPAL DISPLAY PANEL - 250 mg

NDC 0378-8888-93

DIDANOSINE

DELAYED-RELEASE

CAPSULES

250 mg

(Enteric-coated beadlets)

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

30 CAPSULES (Rx only)

Each capsule contains 250 mg didanosine, USP as enteric-coated beadlets.

Usual Dosage: See accompanying prescribing information.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F).

[See USP Controlled Room Temperature.]

Protect from moisture.

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Manufactured for:

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Morgantown, WV 26505 U.S.A.
RMX8888H1

Dispense in a tight, light-resistant
container as defined in the USP using a
child-resistant closure.
Keep container tightly closed.
Code No.: MH/DRUGS/25/NKD/89



PRINCIPAL DISPLAY PANEL - 400 mg
NDC 0378-8889-93
DIDANOSINE
DELAYED-RELEASE
CAPSULES
400 mg
(Enteric-coated beadlets)

**PHARMACIST: Dispense the accompanying
Medication Guide to each patient.**
30 CAPSULES (Rx only)

Each capsule contains 400 mg
didanosine, USP as enteric-coated
beadlets.

Usual Dosage: See accompanying
prescribing information.

**Keep this and all medication out of
the reach of children.**

Store at 20° to 25°C (68° to 77°F).
**[See USP Controlled Room
Temperature.]**

Protect from moisture.

Manufactured in India by:
Matrix Laboratories Limited
Secunderabad-500 003, India
Manufactured for:

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
RMX8889H1

Dispense in a tight, light-resistant
container as defined in the USP using a
child-resistant closure.
Keep container tightly closed.
Code No.: MH/DRUGS/25/NKD/89

Each capsule contains 400 mg didanosine, USP as enteric-coated beads.

Usual Dosage: See accompanying prescribing information.

Keep this and all medications out of the reach of children.

Store at 20° to 25° C (68° to 77° F). (See USP Controlled Room Temperature.)

Protect from moisture.

Manufactured in India by Mylan Laboratories Limited Secunderabad-500 033, India

Manufactured for Mylan Pharmaceuticals Inc., Morgantown, WV 26505 U.S.A.

IND0099961

MYLAN®
DIDANOSINE
DELAYED-RELEASE
CAPSULES
400 mg
 (Enteric-coated beads)

NDC 0378-8889-93

3 0378-8889-93 6

Dispense in a light, light-resistant container as defined in the USP using a child-resistant closure. Keep container tightly closed.

Code No.: MATR8525MS/93

Lot

Exp.

PHARMACIST: Dispense like accompanying Medication Guide to each patient.

30 CAPSULES 

15001928

Revised: 01/2010

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