1099814

Rx only

VIDEX â (didanosine)

VIDEX® (didanosine) Chewable/Dispersible Buffered Tablets

VIDEX® (didanosine) Buffered Powder for Oral Solution

VIDEX® (didanosine) Pediatric Powder for Oral Solution

WARNING

FATAL AND NONFATAL PANCREATITIS HAS OCCURRED DURING THERAPY WITH VIDEX USED ALONE OR IN COMBINATION REGIMENS IN BOTH TREATMENT-NAIVE AND TREATMENT-EXPERIENCED PATIENTS, REGARDLESS OF DEGREE OF IMMUNOSUPPRESSION. VIDEX SHOULD BE SUSPENDED IN PATIENTS WITH SUSPECTED PANCREATITIS AND DISCONTINUED IN PATIENTS WITH CONFIRMED PANCREATITIS (SEE WARNINGS).

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 (SEE WARNINGS).

DESCRIPTION

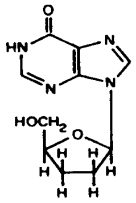
VIDEX is the brand name for didanosine (ddI), a synthetic purine nucleoside analogue active against the Human Immunodeficiency Virus (HIV). VIDEX Chewable/Dispersible Buffered Tablets are available for oral administration in strengths of 25, 50, 100, 150, and 200 mg of didanosine. Each tablet is buffered with calcium carbonate and magnesium hydroxide. VIDEX tablets also contain aspartame, sorbitol, microcrystalline cellulose, polyplasdone, mandarin-orange flavor and magnesium stearate.

VIDEX Buffered Powder for Oral Solution is supplied for oral administration in single-dose packets containing 100, 167, or 250 mg of didanosine. Packets of each

product strength also contain a citrate-phosphate buffer (composed of dibasic sodium phosphate, sodium citrate, and citric acid) and sucrose.

VIDEX Pediatric Powder for Oral Solution is supplied for oral administration in 4- or 8-ounce glass bottles containing 2 or 4 grams of didanosine, respectively.

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



Didanosine is a 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 < 3 and 37°C, 10% of didanosine decomposes to hypoxanthine in less than 2 minutes.

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.

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. The concentration of drug necessary to inhibit viral replication by 50% (IC_{50}) 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 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 mutation 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 vitro* compared to baseline isolates. Clinical isolates that exhibited a decrease in didanosine susceptibility harbored one or more didanosine-associated mutations. The clinical relevance of genotypic and phenotypic changes associated with didanosine therapy has not been established.

Cross-resistance

HIV-1 isolates from 2 of 39 patients receiving combination therapy for up to 2 years with zidovudine and didanosine exhibited decreased susceptibility to zidovudine, didanosine, zalcitabine, stavudine, and lamivudine *in vitro.* These isolates harbored five mutations (A62V, V75I, F77L, F116Y, and Q151M) in the reverse transcriptase gene. The clinical relevance of these observations has not been established.

CLINICAL PHARMACOLOGY

Animal Toxicology

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 VIDEX (didanosine) to cause myopathy in humans is unclear. However, human myopathy has been associated with administration of VIDEX and other nucleoside analogues.

Pharmacokinetics

The pharmacokinetic parameters of didanosine are summarized in Table 1. Didanosine is rapidly absorbed, with peak plasma concentrations generally observed from 0.25 to 1.50 hours following oral dosing. Increases in plasma didanosine concentrations were dose proportional over the range of 50-400 mg. 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 (<5%). Based on data from *in vitro* and animal studies, it is presumed that the metabolism of didanosine in man occurs by the same pathways responsible for the elimination of endogenous purines.

Table 1
Mean ± SD Pharmacokinetic Parameters for Didanosine in Adult and Pediatric Patients

Parameter	Adult Patients	n	Pediatric Patients	n
Oral bioavailability	42 ± 12%	6	25 ± 20%	46
Apparent volume of distribution[a]	1.08 ± 0.22 L/kg	6	28 ± 15 L/m^2	49
CSF-plasma ratio[b]	21 ± 0.03%[c]	5	46% (range 12-85%)	7
Systemic clearance[a]	13.0 ± 1.6 mL/min/kg	6	516 ± 184 mL/min/m^2	49
Renal clearance[d]	5.5 ± 2.1 mL/min/kg	6	240 ± 90 mL/min/m^2	15
Elimination half-life[d]	1.5 ± 0.4 hr	6	0.8 ± 0.3 hr	60
Urinary recovery of didanosine[d]	18 ± 8%	6	18 ± 10%	15

CSF = cerebrospinal fluid
[a] following IV administration
[b] following IV administration in adults and IV or oral administration in pediatric patients
[c] mean ± SE
[d] following oral administration

Effect of Food on Absorption of Didanosine: Didanosine peak plasma concentrations (C_{MAX}) and area under the plasma concentration time curve (AUC) were decreased by approximately 55% when VIDEX tablets were administered up to 2 hours after a meal. Administration of VIDEX tablets up to 30 minutes before a meal did not result in any significant changes in bioavailability. VIDEX should be taken on an empty

stomach, at least 30 minutes before or 2 hours after eating. (See **DOSAGE AND ADMINISTRATION.**)

Special Populations

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

Table 2
Mean ± SD Pharmacokinetic Parameters for Didanosine Following a Single Oral Dose

	Creatinine Clearance (mL/min)				
Parameter	≥ 90 (n=12)	60-90 (n=6)	30-59 (n=6)	10-29 (n=3)	Dailysis Patients (n=11)
CL_{cr} (mL/min)	112 " 22	68 " 8	46 " 8	13 " 5	ND[a]
CL/F (mL/min)	2164 " 638	1566 " 833	1023 " 378	628 " 104	543 " 174
CL_R (mL/min)	458 " 164	247 " 153	100 " 44	20 " 8	<10
$T_{½}$ (hr)	1.42 " 0.33	1.59 " 0.13	1.75 " 0.43	2.0 " 0.3	4.1 " 1.2

[a] ND = not determined due to anuria
CL_{cr} = creatinine clearance
CL/F = apparent oral clearance
CL_R = renal clearance

Pediatric Patients: The pharmacokinetics of didanosine have been evaluated in HIV-infected pediatric patients from 0.7 to 18.9 years of age (see Table 1). Overall, the pharmacokinetics of didanosine in pediatric patients greater than 0.7 years of age are similar to those of didanosine in adults. Didanosine plasma concentrations increased in proportion to oral doses ranging from 80 to 180 mg/m^2. For information on controlled

clinical studies in pediatric patients, see **PRECAUTIONS, Pediatric Use** and **Clinical Studies**.

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

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

Drug Interactions: Drug interaction studies have demonstrated that there are no clinically significant pharmacokinetic interactions between VIDEX and the following: dapsone, loperamide, metoclopramide, nevirapine, ranitidine, rifabutin, ritonavir, stavudine (see **WARNINGS**)**,** sulfamethoxazole, trimethoprim, and zidovudine. Studies with dapsone, nevirapine, rifabutin, ritonavir, stavudine, and zidovudine were multiple-dose studies. Studies with loperamide, metoclopramide, ranitidine, sulfamethoxazole, and trimethoprim were single-dose studies, and effects on pharmacokinetics at steady-state are not known. (See also **PRECAUTIONS: Drug Interactions**.)

INDICATIONS AND USAGE

VIDEX in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection (see **Clinical Studies)**.

Clinical Studies

Combination Therapy

Study AI454-148 is an ongoing, 48-week, randomized, open-label study comparing VIDEX (400 mg QD)/stavudine/nelfinavir to zidovudine/lamivudine/nelfinavir in 756 treatment-naive patients. Data from 387 patients showed that both regimens resulted in a similar proportion of patients with HIV RNA levels <400 copies/mL and increases in CD4 cell counts through 24 weeks.

START 2 was a multicenter, randomized, open-label study comparing VIDEX (200 mg BID)/stavudine/indinavir to zidovudine/lamivudine/indinavir in 205 treatment-naive patients. Both regimens resulted in a similar magnitude of suppression of HIV RNA levels and increases in CD4 cell counts through 48 weeks.

Monotherapy

The efficacy of VIDEX was demonstrated in two randomized, double-blind studies comparing VIDEX, given on a BID schedule, to zidovudine, given TID, in 617 (ACTG

116A, conducted 1989-1992) and 913 (ACTG116B/117, conducted 1989-1991) patients with symptomatic HIV infection or AIDS who were treated for more than one year. In treatment-naive patients (ACTG 116A), the rate of HIV disease progression or death was similar between the treatment groups; mortality rates were 26% for patients receiving VIDEX and 21% for patients receiving zidovudine. Of the patients who had received previous zidovudine treatment (ACTG 116B/117), those treated with VIDEX had a lower rate of HIV disease progression or death (32%) compared to those treated with zidovudine (41%); however, survival rates were similar between the treatment groups.

Efficacy in pediatric patients was demonstrated in a randomized, double-blind, controlled study (ACTG 152, conducted 1991-1995) involving 831 patients treated for more than 1.5 years with zidovudine (180 mg/m^2 q6h), VIDEX (120 mg/m^2 q12h), or zidovudine (120 mg/m^2 q6h) plus VIDEX (90 mg/m^2 q12h). Patients treated with VIDEX or VIDEX plus zidovudine had lower rates of HIV disease progression or death compared with those treated with zidovudine alone.

CONTRAINDICATION

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

WARNINGS

1. Pancreatitis

FATAL AND NONFATAL PANCREATITIS HAS OCCURRED DURING THERAPY WITH VIDEX USED ALONE OR IN COMBINATION REGIMENS IN BOTH TREATMENT-NAIVE AND TREATMENT-EXPERIENCED PATIENTS, REGARDLESS OF DEGREE OF IMMUNOSUPPRESSION. VIDEX SHOULD BE SUSPENDED IN PATIENTS WITH SIGNS OR SYMPTOMS OF PANCREATITIS AND DISCONTINUED IN PATIENTS WITH CONFIRMED PANCREATITIS. PATIENTS TREATED WITH VIDEX IN COMBINATION WITH STAVUDINE, WITH OR WITHOUT HYDROXYUREA, MAY BE AT INCREASED RISK FOR PANCREATITIS.

When treatment with life-sustaining drugs known to cause pancreatic toxicity is required, suspension of VIDEX (didanosine) therapy is recommended. In patients with risk factors for pancreatitis, VIDEX should be used with extreme caution and only if

clearly indicated. Patients with advanced HIV infection 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. In phase 3 studies, incidence ranged from 1% to 10% with doses higher than are currently recommended and 1% to 7% with recommended dose.

In pediatric studies, pancreatitis occurred in 3% (2/60) of patients treated at entry doses below 300 mg/m^2/day and in 13% (5/38) of patients treated at higher doses. VIDEX use should be suspended in pediatric patients with signs or symptoms of pancreatitis and discontinued in pediatric patients with confirmed pancreatitis.

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. Particular caution should be exercised when administering VIDEX 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 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. Retinal Changes and Optic Neuritis

Retinal changes and optic neuritis have been reported in adult and pediatric patients. Periodic retinal examinations should be considered for patients receiving VIDEX. (See **ADVERSE REACTIONS**.)

PRECAUTIONS

Peripheral Neuropathy

Peripheral neuropathy, manifested by numbness, tingling, or pain in the hands or feet, has been reported in patients receiving VIDEX 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 (see **ADVERSE REACTIONS**).

General

VIDEX should be taken on an empty stomach, at least 30 minutes before or 2 hours after eating.

Patients with Phenylketonuria: VIDEX Chewable/Dispersible Buffered Tablets contain the following quantities of phenylalanine:

Table 3

	All Strengths
Phenylalanine per 2-tablet dose	73 mg
Phenylalanine per tablet	36.5 mg

Patients on Sodium-Restricted Diets: VIDEX Buffered Powder for Oral Solution: Each single-dose packet of VIDEX Buffered Powder for Oral Solution contains 1380 mg sodium.

Patients with Renal Impairment: Patients with renal impairment (creatinine clearance <60 mL/min) may be at greater risk of toxicity from VIDEX due to decreased drug clearance (see **CLINICAL PHARMACOLOGY** section). A dose reduction is recommended in these patients (see **DOSAGE AND ADMINISTRATION** section). The magnesium content of each buffered tablet of VIDEX is 8.6 mEq. This may present an excessive load of magnesium to patients with significant renal impairment, particularly after prolonged dosing.

Patients with Hepatic Impairment: It is unknown if hepatic impairment significantly affects didanosine pharmacokinetics. Therefore, these patients should be monitored closely for evidence of didanosine toxicity.

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

Information for Patients (See **Patient Information Leaflet)**

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

Patients should also be aware that peripheral neuropathy, manifested by numbness, tingling, or pain in hands or feet, may develop during therapy with VIDEX. Patients should be counseled that peripheral neuropathy occurs with greatest frequency in patients with advanced HIV disease or a history of peripheral neuropathy, and that dose modification and/or discontinuation of VIDEX may be required if toxicity develops.

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

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

Patients should be advised that to ensure proper acid neutralization in the stomach they must take at least two of the appropriate strength VIDEX tablets at each dose. To reduce the risk of gastrointestinal side effects from excess antacid, patients should take no more than four VIDEX tablets at each dose.

VIDEX (didanosine) is not a cure for HIV 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 VIDEX. Patients should be advised that VIDEX 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 VIDEX are unknown at this time.

Drug Interactions (see also CLINICAL PHARMACOLOGY, Drug Interactions)

Coadministration of VIDEX with drugs that are known to cause pancreatitis may increase the risk of this toxicity (see WARNINGS) and should be done with extreme caution, only if other alternatives are not available, and only if clearly indicated. 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 VIDEX therapy (see **ADVERSE REACTIONS**).

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 VIDEX to two patients with renal impairment (CL_{cr}=15 and 18 mL/min). The effects of allopurinol on didanosine pharmacokinetics in subjects with normal renal function are not known.

Antacids: Concomitant administration of antacids containing magnesium or aluminum with VIDEX Chewable/Dispersible Buffered Tablets or Pediatric Powder for Oral Solution may potentiate adverse events associated with the antacid components.

Drugs Whose Absorption Can Be Affected by the Level of Acidity in the Stomach: Drugs such as ketoconazole and itraconazole should be administered at least 2 hours prior to dosing with VIDEX.

Ganciclovir: Administration of VIDEX 2 hours prior to or concurrent with oral ganciclovir was associated with a 111 ("114)% increase in the steady-state AUC of didanosine (n = 12). A 21 ("17)% decrease in the steady-state AUC of ganciclovir was observed when VIDEX was administered 2 hours prior to ganciclovir, but not when the two drugs were administered simultaneously (n = 12).

Quinolone Antibiotics: VIDEX should be administered at least 2 hours after or 6 hours before dosing with ciprofloxacin because plasma concentrations of ciprofloxacin are decreased when administered with antacids containing magnesium, calcium, or aluminum. In eight HIV-infected patients, the steady-state AUC of ciprofloxacin was decreased an average of 26% (95% CI = 14%, 37%) when ciprofloxacin was administered 2 hours prior to a marketed chewable/dispersible tablet formulation of VIDEX. The AUC of ciprofloxacin was decreased an average of 15-fold in 12 healthy subjects given ciprofloxacin and didanosine-placebo tablets concurrently. In a single subject given one dose of ciprofloxacin 2 hours after a dose of didanosine-placebo tablets, a greater than 50% reduction in the AUC of ciprofloxacin was observed.

Plasma concentrations of quinolone antibiotics are decreased when administered with antacids containing magnesium, calcium, or aluminum. The optimal dosing interval for coadministration with VIDEX should be determined by consulting the appropriate quinolone package insert.

Interactions with Other Antiretroviral Drugs: Significant decreases in the AUC of delavirdine (20%) and indinavir (84%) occurred following simultaneous administration of these agents with VIDEX. To avoid this interaction, delavirdine or indinavir should be given 1 hour prior to dosing with VIDEX. The pharmacokinetics of nelfinavir are not altered to a clinically significant degree when it is administered with a light meal 1 hour after VIDEX.

Carcinogenesis and Mutagenesis

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.

Pregnancy, Reproduction and Fertility

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. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies

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

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 (800) 258-4263.

Nursing Mothers

The US Public Health Service Centers for Disease Control advises HIV-infected women not to breastfeed to avoid postnatal transmission of HIV to a child who may not yet be infected. 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.

Pediatric Use

Use of VIDEX in pediatric patients is supported by evidence from adequate and well-controlled studies of VIDEX in adults and pediatric patients (see **Clinical Studies, CLINICAL PHARMACOLOGY, ADVERSE REACTIONS,** and **DOSAGE AND ADMINISTRATION).**

ADVERSE REACTIONS

A SERIOUS TOXICITY OF VIDEX (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 VIDEX is used in combination with other agents with similar toxicities, the incidence of these toxicities may be higher than when VIDEX is used alone. Thus, patients treated with VIDEX in combination with stavudine, with or without hydroxyurea, may be at increased risk for pancreatitis and liver function abnormalities (see **WARNINGS). Patients treated with VIDEX in combination with stavudine may also be at increased risk for peripheral neuropathy (**see **PRECAUTIONS).**

Adults: Selected clinical adverse events that occurred in adult patients in clinical studies with VIDEX are provided in Table 4 and Table 5.

Table 4
Selected Clinical Adverse Events from Monotherapy Studies

	Percent of Patients			
	ACTG 116A		ACTG 116B/117	
Adverse Events	VIDEX n=197	zidovudine n=212	VIDEX n=298	zidovudine n=304
Diarrhea	19	15	28	21
Peripheral Neurologic Symptoms/Neuropathy	17	14	20	12
Rash/Pruritus	7	8	9	5
Abdominal Pain	13	8	7	8
Pancreatitis	7	3	6	2

Table 5
Selected Clinical Adverse Events from Combination Studies

	Percent of Patients			
	AI454-148[a]		**START 2[b]**	
Adverse Events	VIDEX + stavudine + nelfinavir n=478	zidovudine + lamivudine + nelfinavir n=247	VIDEX + stavudine + indinavir n=102	zidovudine + lamivudine + indinavir n=103
Diarrhea	69	60	45	39
Nausea	24	38	53	67
Headache	20	30	46	37
Peripheral Neurologic Symptoms/Neuropathy	22	7	21	10
Rash	11	13	30	18
Vomiting	8	12	30	35
Pancreatitis (see below)	<1		<1	

[a] Data through a median of 32 weeks of treatment.
[b] Data through 48 weeks of treatment.

Pancreatitis resulting in death was observed in one patient who received VIDEX plus stavudine plus nelfinavir in Study AI454-148 and in one patient who

received VIDEX plus stavudine plus indinavir in the START 2 study. In addition, pancreatitis resulting in death was observed in 2 of 68 patients who received VIDEX plus stavudine plus indinavir plus hydroxyurea in an ACTG clinical trial (see WARNINGS).

Selected laboratory abnormalities in clinical studies with VIDEX are shown in Table 6, Table 7, and Table 8.

Table 6
Selected Laboratory Abnormalities from Monotherapy Studies

	Percent of Patients			
	ACTG 116A		ACTG 116B/117	
Parameter	VIDEX n=197	zidovudine n=212	VIDEX n=298	zidovudine n=304
SGOT (AST) (>5 x ULN)	9	4	7	6
SGPT (ALT) (>5 x ULN)	9	6	6	6
Alkaline phosphatase (>5 x ULN)	4	1	1	1
Amylase (≥1.4 x ULN)	17	12	15	5
Uric Acid (>12 mg/dL)	3	1	2	1

ULN = upper limit of normal.

Table 7
Selected Laboratory Abnormalities from Combination Studies (Grades 3-4)

	Percent of Patients			
	AI454-148[a]		**START 2[b]**	
Parameter	VIDEX + stavudine + nelfinavir n=478	zidovudine + lamivudine + nelfinavir n=247	videx + stavudine + indinavir n=102	zidovudine + lamivudine + indinavir n=103
Bilirubin (>2.6 x ULN)	1	<1	16	8
SGOT (AST) (>5 x ULN)	2	2	7	7
SGPT (ALT) (>5 x ULN)	3	4	8	5
GGT (>5 x ULN)	NC	NC	5	2
Lipase (>2 x ULN)	3	1	5	5
Amylase (>2 x ULN)	NC	NC	8	2

ULN = upper limit of normal.
NC=Not Collected
[a] Data through a median of 32 weeks of treatment.
[b] Data through 48 weeks of treatment.

Table 8
Selected Laboratory Abnormalities from Combination Studies (All Grades)

	Percent of Patients			
	AI454-148[a]		**START 2[b]**	
Parameter	VIDEX + stavudine + nelfinavir n=478	zidovudine + lamivudine + nelfinavir n=247	VIDEX + Stavudine + Indinavir n=102	Zidovudine + Lamivudine + Indinavir n=103
Bilirubin	6	4	68	55
SGOT (AST)	38	20	53	20
SGPT (ALT)	34	22	50	18
GGT	NC	NC	28	12
Lipase	11	11	26	19
Amylase	NC	NC	31	17

NC=Not Collected

[a] Data through a median of 32 weeks of treatment.

[b] Data through 48 weeks of treatment.

Observed during Clinical Practice: The following events have been identified during post approval use of VIDEX. 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 VIDEX, or a combination of these factors.

Body as a Whole - alopecia, anaphylactoid reaction, asthenia, chills/fever, and pain.

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, and thrombocytopenia.

Liver - lactic acidosis and hepatic steatosis (see **WARNINGS**); hepatitis and liver failure.

Metabolic Disorders - diabetes mellitus, hypoglycemia, and hyperglycemia.

Musculoskeletal Disorders - myalgia (with or without increases in creatinine phosphokinase), rhabdomyolysis including acute renal failure and hemodialysis, arthralgia, and myopathy.

Ophthalmologic Disorders - Retinal depigmentation and optic neuritis (see **WARNINGS**).

Pediatric Patients: Adverse events and laboratory abnormalities reported to occur in the pediatric patients in ACTG 152 were generally similar to adverse events and laboratory abnormalities reported in adult patients.

In pediatric phase 1 studies, pancreatitis occurred in 2 of 60 (3%) patients treated at entry doses below 300 mg/m^2/day and in 5 of 38 (13%) patients treated at higher doses.

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

OVERDOSAGE

There is no known antidote for VIDEX (didanosine) overdosage. In phase 1 studies, in which VIDEX was initially administered at doses ten times the currently recommended dose, toxicities included: pancreatitis, peripheral neuropathy, diarrhea, hyperuricemia and hepatic dysfunction. Didanosine is not dialyzable by peritoneal dialysis, although there is some clearance by hemodialysis (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**).

DOSAGE AND ADMINISTRATION

Dosage:

All VIDEX formulations should be administered on an empty stomach, at least 30 minutes before or 2 hours after eating. For either a once-daily or twice-daily regimen, patients must take at least two of the appropriate strength tablets at each dose to provide adequate buffering and prevent gastric acid degradation of didanosine. Because of the need for adequate buffering, the 200 mg strength tablet should only be used as a component of the 400 mg once-daily regimen. To reduce the risk of gastrointestinal side effects, patients should take no more than four tablets at each dose.

Adults: The recommended daily dose in adult patients is dependent on weight and may be administered on a once-daily (QD) or twice-daily (BID) schedule as outlined in Table 9.

Table 9
Adult Dosing

Patient Weight	VIDEX Tablets	VIDEX Buffered Powder[a]
$ 60 kg	400 mg QD or 200 mg BID[b]	250 mg BID
< 60 kg	250 mg QD or 125 mg BID	167 mg BID

[a] Not suitable for QD dosing except for patients with renal impairment. See Table 10

[b] The 200 mg strength tablet should only be used as a component of the 400 mg once-daily regimen.

Pediatric Patients: The recommended dose of VIDEX (didanosine) in pediatric patients is 120 mg/m^2 BID. There are no data on once-daily dosing of VIDEX in pediatric patients.

Dose Adjustment:

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

Patients with symptoms of peripheral neuropathy may tolerate a reduced dose of VIDEX after resolution of the symptoms of peripheral neuropathy upon drug discontinuation. If neuropathy recurs after resumption of VIDEX, permanent discontinuation of VIDEX should be considered.

In adult patients with impaired renal function, the dose of VIDEX should be adjusted to compensate for the slower rate of elimination. The recommended doses and dosing intervals of VIDEX in adult patients with renal insufficiency are presented in Table 10.

Table 10
Recommended Dosage of VIDEX in Renal Impairment

	≥ 60 kg		< 60 kg	
Creatinine Clearance (mL/min)	Tablet[a] (mg)	Buffered Powder[b] (mg)	Tablet[a] (mg)	Buffered Powder[b] (mg)
≥60	400 QD or 200 BID	250 BID	250 QD or 125 BID	167 BID
30-59	200 QD or 100 BID	100 BID	150 QD or 75 BID	100 BID
10-29	150 QD	167 QD	100 QD	100 QD
<10	100 QD	100 QD	75 QD	100 QD

[a] VIDEX Chewable/Dispersible Buffered Tablet. Two VIDEX tablets must be taken with each dose; different strengths of tablets may be combined to yield the recommended dose.
[b] VIDEX Buffered Powder for Oral Solution

Urinary excretion is also a major route of elimination of didanosine in pediatric patients; therefore, the clearance of didanosine may be altered in children with renal impairment. Although there are insufficient data to recommend a specific dose adjustment of VIDEX in this patient population, a reduction in the dose and/or an increase in the interval between doses should be considered.

Patients Requiring Continuous Ambulatory Peritoneal Dialysis (CAPD) or Hemodialysis: It is recommended that one fourth of the total daily dose of VIDEX be administered once a day (see Table 10, recommended dosage for patients with CL_{cr}<10 mL/min). It is not necessary to administer a supplemental dose of VIDEX following hemodialysis.

Hepatic Impairment: See **WARNINGS** and **PRECAUTIONS.**

Method of Preparation:

VIDEX Chewable/Dispersible Buffered Tablets

Adult Dosing: To provide adequate buffering, at least two of the appropriate strength tablets, but no more than four tablets, should be thoroughly chewed or

dispersed in at least 1 ounce of water prior to consumption (see **PRECAUTIONS: Information for Patients**). To disperse tablets, add 2 tablets to at least 1 ounce of drinking water. Stir until a uniform dispersion forms, and drink the entire dispersion immediately. If additional flavoring is desired, the dispersion may be diluted with one ounce of clear apple juice. Stir the further diluted dispersion just prior to consumption. The dispersion with clear apple juice is stable at room temperature, 62Eto 73EF (17-23EC), for up to one hour.

VIDEX Buffered Powder for Oral Solution

1. Open packet carefully and pour contents into a container with approximately 4 ounces of drinking water. Do not mix with fruit juice or other acid-containing liquid.
2. Stir until the powder completely dissolves (approximately 2 to 3 minutes).
3. Drink the entire solution immediately.

VIDEX Pediatric Powder for Oral Solution

Prior to dispensing, the pharmacist must constitute dry powder with Purified Water, USP, to an initial concentration of 20 mg/mL and immediately mix the resulting solution with antacid to a final concentration of 10 mg/mL as follows:

20 mg/mL Initial Solution: Constitute the product to 20 mg/mL by adding 100 mL or 200 mL of Purified Water, USP, to the 2 g or 4 g of VIDEX powder, respectively, in the product bottle.

10 mg/mL Final Admixture: 1. Immediately mix one part of the 20 mg/mL initial solution with one part of either Mylanta® Double Strength Liquid (Mylanta® is a registered trademark of Stuart Pharmaceuticals, a business unit of Zeneca, Inc., Mylanta® Double Strength, formerly Mylanta® ll, is distributed by Johnson & Johnson/Merck, Consumer Pharmaceuticals Company, Fort Washington, PA 19034 [USA]), Extra Strength Maalox® Plus Suspension, or Maalox® TC Suspension (Maalox® is a registered trademark of William H. Rorer Inc., Unit of Rhone-Poulenc) for a final dispensing concentration of 10 mg VIDEX per mL. For patient home use, the admixture should be dispensed in appropriately sized, flint-glass or plastic (HDPE, PET, or PETG) bottles with child-resistant closures. This admixture is stable for 30 days under refrigeration, 36° to 46° F (2° to 8° C).

2. Instruct the patient to shake the admixture thoroughly prior to use and to store the tightly closed container in the refrigerator, 36° to 46° F (2° to 8° C), up to 30 days.

HOW SUPPLIED

VIDEX® (didanosine) Chewable/Dispersible Buffered Tablets are round, off white to light orange/yellow with a mottled appearance, orange-flavored, tablets embossed with "VIDEX" on one side and the product strength on the other. The tablets are available in the following strengths of VIDEX: 25, 50, 100, 150, and 200 mg. Sixty tablets are packaged in bottles with child-resistant closures.

The tablets should be stored in tightly closed bottles at 59° to 86° F (15° to 30° C). If dispersed in water, the dose may be held for up to 1 hour at ambient temperature.

VIDEX (didanosine) Buffered Powder for Oral Solution is supplied in single-dose, child-resistant foil packets in the following strengths of VIDEX: 100, 167, or 250 mg. Each product strength provides a sweetened, buffered solution of VIDEX.

The packets should be stored at 59° to 86° F (15° to 30° C). After dissolving in water, the solution may be stored at ambient room temperature for up to 4 hours.

VIDEX (didanosine) Pediatric Powder for Oral Solution is supplied in 4- and 8-ounce glass bottles containing 2 g or 4 g of VIDEX, respectively.

The bottles of powder should be stored at 59° to 86° F (15° to 30° C). The VIDEX admixture may be stored up to 30 days in a refrigerator, 36° to 46° F (2° to 8° C). Discard any unused portion after 30 days.

The NDC numbers for the previously described VIDEX products are:

Table 11

NDC NO.	Packaging Information	Product Strength
VIDEX â Chewable/Dispersible Buffered Tablets		
0087-6650-01	60 tablets/bottle	25 mg/tablet
0087-6651-01	60 tablets/bottle	50 mg/tablet
0087-6652-01	60 tablets/bottle	100 mg/tablet
0087-6653-01	60 tablets/bottle	150 mg/tablet
0087-6665-15	60 tablets/bottle	200 mg/tablet
VIDEX â Buffered Powder for Oral Solution		
0087-6614-43	One single-dose foil packet*	100 mg/packet
0087-6615-43	One single-dose foil packet*	167 mg/packet
0087-6616-43	One single-dose foil packet*	250 mg/packet
VIDEX â Pediatric Powder for Oral Solution		
0087-6632-41	One bottle per carton	2 g/bottle
0087-6633-41	One bottle per carton	4 g/bottle

*Packaged as 30 packets per carton.

US Patent Nos.: 4,861,759 and 5,616,566.

HANDLING AND DISPOSAL

Spill, Leak and Disposal Procedure

Avoid generating dust during clean-up of powdered products; use wet mop or damp sponge. Clean surface with soap and water as necessary. Containerize larger spills.

There is no single preferred method of disposal of containerized waste. Disposal options include incineration, landfill, or sewer as dictated by specific circumstances and relevant national, state, and local regulations.

Patient Information

VIDEX®

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

VIDEX® (didanosine) Chewable/Dispersible Buffered Tablets
VIDEX® (didanosine) Buffered Powder for Oral Solution
VIDEX® (didanosine) Pediatric Powder for Oral Solution

What is VIDEX?

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

VIDEX will not cure your HIV infection. At present there is no cure for HIV infection. Even while taking VIDEX, 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.

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

There is limited information on the effects of long-term use of VIDEX.

Who should not take VIDEX?

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

How should I take VIDEX? How should I store it?

Your doctor will determine your dose based on your body weight, kidney and liver function, and any side effects that you may have had with other medicines. Take VIDEX **on an empty stomach - that means at least 30 minutes before or 2 hours after eating. Do not take VIDEX 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 continue your regular dosing schedule.

Chewable/Dispersible Tablets: Each VIDEX tablet contains antacid. To be sure that enough antacid is present to prevent the breakdown of didanosine, you must take at least two VIDEX tablets at each dose. To reduce the risk of stomach problems, you should take no more than four VIDEX tablets at each dose. **DO NOT** swallow VIDEX tablets whole. Chew the tablets well or mix them in water. Many patients prefer to drop the tablets in at least one ounce of water and stir well before swallowing. If you choose to mix the tablets in water, you may add one ounce (2 tablespoons) of clear apple juice to the mixture for flavor (do not use any other kind of juice). Store tablets in a tightly closed container at room temperature away from heat and out of the reach of children and pets. Do NOT store the tablets in a damp place such as a bathroom medicine cabinet or near the kitchen sink.

Buffered Powder for Oral Solution: Pour the contents of a packet into a glass with 4 ounces (1/2 measuring cup) of water. Stir until completely dissolved. Drink the entire solution right away. Do NOT mix with fruit juice. Store packets at room temperature before use.

Pediatric Oral Solution: Your pharmacist will prepare the oral solution. Shake the solution well before each use. Store in the refrigerator. Throw away any unused portion after 30 days.

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, and your dosage of VIDEX may be lowered.

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

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

What should I avoid while taking VIDEX?

Alcohol. Avoid drinking alcohol while taking VIDEX since alcohol may increase your risk of pancreatitis (pain and inflammation of the pancreas) or liver damage.

Other medicines. Other medicines, including those you can buy without a prescription, may interfere with the actions of VIDEX. **Do not take any medicine, vitamin supplement, or other health preparation without first checking with your doctor.**

Antacids. Since VIDEX contains some of the same ingredients found in antacids, any side effects related to VIDEX's ingredients may get worse if you also take an antacid.

Medicines at the same time as VIDEX. Some medicines should not be taken at the same time of day that you take VIDEX. Check with your doctor.

Pregnancy. It is not known if VIDEX can harm a human fetus, so VIDEX 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.**

Nursing. Because studies have shown VIDEX is in the breast milk of animals receiving the drug, it may be present in human breast milk. The Centers for Disease Control and Prevention (CDC) recommends that HIV-infected mothers **not** breast-feed to reduce the risk of passing HIV infection to their babies. Therefore, do not nurse a baby while taking VIDEX.

What are the possible side effects of VIDEX?

Serious side effects of VIDEX include:

- **Pancreatitis**, a dangerous inflammation of the pancreas.
- **Lactic acidosis,** severe increase of lactic acid in the blood, **severe liver enlargement** including inflammation (pain and swelling) of the liver, and **liver failure,** which can cause death.
- **Vision changes**.
- **Peripheral neuropathy,** a nerve disorder of the feet and/or hands.

People who take VIDEX along with other medicines that may cause similar side effects may have a higher chance of developing these side effects than if they took VIDEX alone. For example, if you use VIDEX in combination with other drugs (including stavudine with or without hydroxyurea) that may be associated with pancreatitis, peripheral neuropathy, and liver enlargement, you may be at increased risk for these side effects. Children experience side effects that are similar to those experienced by adults.

Pancreatitis. Pancreatitis is a dangerous inflammation of the pancreas. It may cause death. ***Tell your doctor right away if you or the child taking VIDEX develops stomach pain, nausea, or vomiting. These can be signs of pancreatits*.** Before starting VIDEX therapy, let your doctor know if you or a child for whom it has been prescribed has ever had pancreatitis. This condition occurs more often in patients who have had it previously. It is also more likely in people with advanced HIV disease, but can occur at any disease stage. It may be more common in patients with kidney problems. If you develop pancreatitis, your doctor will tell you to stop taking VIDEX.

Lactic acidosis, severe liver enlargement, and **liver failure.** Lactic acidosis, severe liver enlargement, and liver failure, including deaths, have been reported among patients taking VIDEX. The symptoms that may indicate a liver problem may include:

- feeling very weak, tired, or uncomfortable,

- unusual or unexpected stomach discomfort,
- feeling cold,
- feeling dizzy or lightheaded,
- suddenly developing a slow or irregular heartbeat.

If you notice any of these symptoms or if your medical condition has suddenly changed, stop taking VIDEX and **call your doctor right away. Lactic acidosis is a medical emergency that must be treated in a hospital.** Women, overweight patients, and those who have had lengthy treatment with nucleoside medicines are more likely to develop lactic acidosis. Your doctor should check your liver function periodically while you are taking VIDEX, especially if you have a history of heavy alcohol use or a liver problem.

Vision changes. Because of possible effects from VIDEX on the nerves in the eye, you should have regular eye examinations and report any changes in vision, such as seeing colors abnormally or blurred vision, to your doctor right away.

Peripheral neuropathy. This nerve disorder may be serious. ***Tell your doctor right away if you or a child taking VIDEX has continuing numbness, tingling, or pain in the feet or hands.*** A child may not recognize these symptoms or know to tell you that his or her feet or hands are numb, burning, tingling, or painful. Ask your child's doctor for instructions on how to find out if your child develops peripheral neuropathy.

Before starting VIDEX therapy, let your doctor know if you or a child for whom is has been prescribed has ever had peripheral neuropathy. This condition occurs more often in patients who have had it previously. Peripheral neuropathy is also more likely to occur in patients taking drugs that affect the nerves and in patients with advanced HIV disease, but it can occur at any disease stage. If you develop peripheral neuropathy, your doctor may tell you to stop taking VIDEX. In some cases the symptoms worsen for a short time before getting better. Once symptoms of peripheral neuropathy go away completely, VIDEX may be started again at a lower dose.

Other side effects. The most frequent side effects in studies of adults taking VIDEX were diarrhea, neuropathy (nerve disorders), chills or fever, rash, abdominal pain, weakness, headache and nausea and vomiting.

What else should I know about VIDEX?

If you should limit sodium (salt) intake: Each single-dose packet of Buffered Powder for Oral Solution contains 1380 mg of sodium. Each Chewable/Dispersible Tablet contains 264.5 mg of sodium.
If you have phenylketonuria: Each Chewable/Dispersible Tablet contains 36.5 mg of phenylalanine.

Inactive Ingredients:

Chewable/Dispersible Tablets: calcium carbonate, magnesium hydroxide, aspartame, sorbitol, mandarin orange flavor, polyplasdone, microcrystalline cellulose, and magnesium stearate.
Buffered Powder for Oral Solution: citrate-phosphate buffer (dibasic sodium phosphate, sodium citrate, and citric acid) and sucrose.
Pediatric Oral Solution: Mylanta® Double Strength Liquid, Extra Strength Maalox® Plus or Maalox® TC Suspension.

This medicine was prescribed for your particular condition. Do not use VIDEX for another condition or give it to others. Keep VIDEX and all medicines out of the reach of children. Throw away VIDEX when it is outdated or no longer needed by flushing it down the toilet or pouring it down the sink.

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

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Issue Date: xxxxxx, 1999
Based on P9691-xx (8/99)

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