AGENERASE®
(amprenavir)
Oral Solution

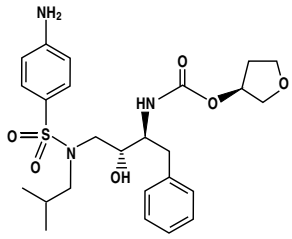
PATIENT INFORMATION INCLUDED

Because of the potential risk of toxicity from the large amount of the excipient, propylene glycol, AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole (see CONTRAINDICATIONS AND WARNINGS).

AGENERASE Oral Solution should be used only when AGENERASE Capsules or other protease inhibitor formulations are not therapeutic options.

DESCRIPTION

AGENERASE (amprenavir) is an inhibitor of the human immunodeficiency virus (HIV) protease. The chemical name of amprenavir is (3*S*)-tetrahydro-3-furyl *N*-[(1*S*,2*R*)-3-(4-amino-*N*-isobutylbenzenesulfonamido)-1-benzyl-2-hydroxypropyl]carbamate. Amprenavir is a single stereoisomer with the (3*S*)(1*S*,2*R*) configuration. It has a molecular formula of $C_{25}H_{35}N_3O_6S$ and a molecular weight of 505.64. It has the following structural formula:



Amprenavir is a white to cream-colored solid with a solubility of approximately 0.04 mg/mL in water at 25°C.

AGENERASE Oral Solution is for oral administration. One milliliter (1 mL) of AGENERASE Oral Solution contains 15 mg of amprenavir in solution and the inactive ingredients acesulfame potassium, artificial grape bubblegum flavor, citric acid (anhydrous), d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS), menthol, natural peppermint flavor, polyethylene glycol 400 (PEG 400) (170 mg), propylene glycol (550 mg), saccharin sodium, sodium chloride, and sodium citrate (dihydrate). Solutions of sodium hydroxide and/or diluted hydrochloric acid may have been added to adjust pH. Each mL of AGENERASE Oral Solution contains 46 IU vitamin E in the form of TPGS. Propylene glycol is in the formulation to achieve adequate solubility of amprenavir. The recommended daily dose of AGENERASE Oral Solution of 22.5 mg/kg twice daily corresponds to a propylene glycol intake of 1,650 mg/kg/day. Acceptable intake of propylene glycol for pharmaceuticals has not been established.

MICROBIOLOGY

Mechanism of Action: Amprenavir is an inhibitor of HIV-1 protease. Amprenavir binds to the active site of HIV-1 protease and thereby prevents the processing of viral gag and gag-pol polyprotein precursors, resulting in the formation of immature non-infectious viral particles.

Antiviral Activity in Vitro: The in vitro antiviral activity of amprenavir was evaluated against HIV-1 IIIB in both acutely and chronically infected lymphoblastic cell lines (MT-4, CEM-CCRF, H9) and in peripheral blood lymphocytes. The 50% inhibitory concentration (IC_{50}) of amprenavir ranged from 0.012 to 0.08 μM in acutely infected cells and was 0.41 μM in chronically infected cells (1 μM = 0.50 mcg/mL). Amprenavir exhibited synergistic anti–HIV-1 activity in combination with abacavir, zidovudine, didanosine, or saquinavir, and additive anti–HIV-1 activity in combination with indinavir, nelfinavir, and ritonavir in vitro. These drug combinations have not been adequately studied in humans. The relationship between in vitro anti–HIV-1 activity of amprenavir and the inhibition of HIV-1 replication in humans has not been defined.

Resistance: HIV-1 isolates with a decreased susceptibility to amprenavir have been selected in vitro and obtained from patients treated with amprenavir. Genotypic analysis of isolates from amprenavir-treated patients showed mutations in the HIV-1 protease gene resulting in amino acid substitutions primarily at positions V32I, M46I/L, I47V, I50V, I54L/M, and I84V as well as mutations in the p7/p1 and p1/p6 gag cleavage sites. Phenotypic analysis of HIV-1 isolates from 21 nucleoside reverse transcriptase inhibitor–(NRTI-) experienced, protease inhibitor-naive patients treated with amprenavir in combination with NRTIs for 16 to 48 weeks identified isolates from 15 patients who exhibited a 4- to 17-fold decrease in susceptibility to amprenavir in vitro compared to wild-type virus. Clinical isolates that exhibited a decrease in amprenavir susceptibility harbored one or more amprenavir-associated mutations. The clinical relevance of the genotypic and phenotypic changes associated with amprenavir therapy is under evaluation.

Cross-Resistance: Varying degrees of HIV-1 cross-resistance among protease inhibitors have been observed. Five of 15 amprenavir-resistant isolates exhibited 4- to 8-fold decrease in susceptibility to ritonavir. However, amprenavir-resistant isolates were susceptible to either indinavir or saquinavir.

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults: The pharmacokinetic properties of amprenavir have been studied in asymptomatic, HIV-infected adult patients after administration of single oral doses of 150 to 1,200 mg and multiple oral doses of 300 to 1,200 mg twice daily.

Absorption and Bioavailability: Amprenavir was rapidly absorbed after oral administration in HIV-1-infected patients with a time to peak concentration (T_{max}) typically between 1 and 2 hours after a single oral dose. The absolute oral bioavailability of amprenavir in humans has not been established.

Increases in the area under the plasma concentration versus time curve (AUC) after single oral doses between 150 and 1,200 mg were slightly greater than dose proportional. Increases in AUC were dose proportional after 3 weeks of dosing with doses from 300 to 1,200 mg twice daily. The pharmacokinetic parameters after administration of amprenavir 1,200 mg twice daily for 3 weeks to HIV-infected subjects are shown in Table 1.

Table 1. Average (%CV) Pharmacokinetic Parameters After 1,200 mg Twice Daily of Amprenavir Capsules (n = 54)

C_{max} (mcg/mL)	T_{max} (hours)	$AUC_{0\text{-}12}$ (mcg•hr/mL)	C_{avg} (mcg/mL)	C_{min} (mcg/mL)	CL/F (mL/min/kg)
7.66 (54%)	1.0 (42%)	17.7 (47%)	1.48 (47%)	0.32 (77%)	19.5 (46%)

The relative bioavailability of AGENERASE Capsules and Oral Solution was assessed in healthy adults. AGENERASE Oral Solution was 14% less bioavailable compared to the capsules.

Effects of Food on Oral Absorption: The relative bioavailability of AGENERASE Capsules was assessed in the fasting and fed states in healthy volunteers (standardized high-fat meal: 967 kcal, 67 grams fat, 33 grams protein, 58 grams carbohydrate). Administration of a single 1,200-mg dose of amprenavir in the fed state compared to the fasted state was associated with changes in C_{max} (fed: 6.18 ± 2.92 mcg/mL, fasted: 9.72 ± 2.75 mcg/mL), T_{max} (fed: 1.51 ± 0.68, fasted: 1.05 ± 0.63), and $AUC_{0\text{-}\infty}$ (fed: 22.06 ± 11.6 mcg•hr/mL, fasted: 28.05 ± 10.1 mcg•hr/mL). AGENERASE may be taken with or without food, but should not be taken with a high-fat meal (see DOSAGE AND ADMINISTRATION).

Distribution: The apparent volume of distribution (V_z/F) is approximately 430 L in healthy adult subjects. In vitro binding is approximately 90% to plasma proteins. The high affinity binding protein for amprenavir is alpha1-acid glycoprotein (AAG). The partitioning of amprenavir into erythrocytes is low, but increases as amprenavir concentrations increase, reflecting the higher amount of unbound drug at higher concentrations.

Metabolism: Amprenavir is metabolized in the liver by the cytochrome P450 3A4 (CYP3A4) enzyme system. The 2 major metabolites result from oxidation of the tetrahydrofuran and aniline moieties. Glucuronide conjugates of oxidized metabolites have been identified as minor metabolites in urine and feces.

AGENERASE Oral Solution contains a large amount of propylene glycol, which is hepatically metabolized by the alcohol and aldehyde dehydrogenase enzyme pathway. Alcohol dehydrogenase (ADH) is present in the human fetal liver at 2 months of gestational age, but at only 3% of adult activity. Although the data are limited, it appears that by 12 to 30 months of postnatal age, ADH activity is equal to or greater than that observed in adults. Additionally, certain patient groups (females, Asians, Eskimos, Native Americans) may be at increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol (see CLINICAL PHARMACOLOGY: Special Populations: Gender and Race).

Elimination: Excretion of unchanged amprenavir in urine and feces is minimal. Approximately 14% and 75% of an administered single dose of ^{14}C-amprenavir can be accounted for as radiocarbon in urine and feces, respectively. Two metabolites accounted for >90% of the radiocarbon in fecal samples. The plasma elimination half-life of amprenavir ranged from 7.1 to 10.6 hours.

Special Populations: ***Hepatic Insufficiency:*** AGENERASE Oral Solution is contraindicated in patients with hepatic failure.

Patients with hepatic impairment are at increased risk of propylene glycol-associated adverse events (see WARNINGS). AGENERASE Oral Solution should be used with caution in patients with hepatic impairment. AGENERASE Capsules have been studied in adult patients with impaired hepatic function using a single 600-mg oral dose. The $AUC_{0\text{-}\infty}$ was significantly greater in patients with moderate cirrhosis (25.76 ± 14.68 mcg•hr/mL) compared with healthy volunteers (12.00 ± 4.38 mcg•hr/mL). The $AUC_{0\text{-}\infty}$ and C_{max} were significantly greater in patients with severe cirrhosis ($AUC_{0\text{-}\infty}$: 38.66 ± 16.08 mcg•hr/mL; C_{max}: 9.43 ± 2.61 mcg/mL) compared with healthy volunteers ($AUC_{0\text{-}\infty}$: 12.00 ± 4.38 mcg•hr/mL; C_{max}: 4.90 ± 1.39 mcg/mL). Patients with impaired hepatic function require dosage adjustment (see DOSAGE AND ADMINISTRATION).

Renal Insufficiency: AGENERASE Oral Solution is contraindicated in patients with renal failure.

Patients with renal impairment are at increased risk of propylene glycol-associated adverse events. Additionally, because metabolites of the excipient, propylene glycol, in AGENERASE Oral Solution may alter acid-base balance, patients with renal impairment should be monitored for potential adverse events (see WARNINGS). AGENERASE Oral Solution should be used with caution in patients with renal impairment. The impact of renal impairment on amprenavir elimination has not been studied. The renal elimination of unchanged amprenavir represents <3% of the administered dose.

Pediatric Patients: AGENERASE Oral Solution is contraindicated in infants and children below 4 years of age (see CONTRAINDICATIONS and WARNINGS).

The pharmacokinetics of amprenavir have been studied after either single or repeat doses of AGENERASE Capsules or Oral Solution in 84 pediatric patients. Twenty HIV-1-infected children ranging in age from 4 to 12 years received single doses from 5 mg/kg to 20 mg/kg using 25-mg or 150-mg capsules. The C_{max} of amprenavir increased less than proportionally with dose. The $AUC_{0\text{-}\infty}$ increased proportionally at doses between 5 and 20 mg/kg. Amprenavir is 14% less bioavailable from the liquid formulation than from the capsules; therefore **AGENERASE Capsules and AGENERASE Oral Solution are not interchangeable on a milligram-per-milligram basis.**

Table 2. Average (%CV) Pharmacokinetic Parameters in Children Ages 4 to 12 Years Receiving 20 mg/kg Twice Daily or 15 mg/kg Three Times Daily of AGENERASE Oral Solution

Dose	n	C_{max} (mcg/mL)	T_{max} (hours)	AUC_{ss}* (mcg•hr/mL)	C_{avg} (mcg/mL)	C_{min} (mcg/mL)	CL/F (mL/min/kg)
20 mg/kg b.i.d.	20	6.77 (51%)	1.1 (21%)	15.46 (59%)	1.29 (59%)	0.24 (98%)	29 (58%)
15 mg/kg t.i.d.	17	3.99 (37%)	1.4 (90%)	8.73 (36%)	1.09 (36%)	0.27 (95%)	32 (34%)

*AUC is 0 to 12 hours for b.i.d. and 0 to 8 hours for t.i.d., therefore the C_{avg} is a better comparison of the exposures.

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

Gender: The pharmacokinetics of amprenavir do not differ between males and females. Females may have a lower amount of alcohol dehydrogenase compared with males and may be at increased risk of propylene glycol-associated adverse events; no data are available on propylene glycol metabolism in females.

Race: The pharmacokinetics of amprenavir do not differ between blacks and non-blacks. Certain ethnic populations (Asians, Eskimos, and Native Americans) may be at increased risk of propylene glycol-associated adverse events because of alcohol dehydrogenase polymorphisms; no data are available on propylene glycol metabolism in these groups.

Drug Interactions: See also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Drug Interactions.

Amprenavir is metabolized in the liver by the cytochrome P450 enzyme system. Amprenavir inhibits CYP3A4. Caution should be used when coadministering medications that are substrates, inhibitors, or inducers of CYP3A4, or potentially toxic medications that are metabolized by CYP3A4. Amprenavir does not inhibit CYP2D6, CYP1A2, CYP2C9, CYP2C19, CYP2E1, or uridine glucuronosyltransferase (UDPGT).

Drug interaction studies were performed with amprenavir capsules and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interactions. The effects of coadministration of amprenavir on the AUC, C_{max}, and C_{min} are summarized in Table 3 (effect of other drugs on amprenavir) and Table 4 (effect of amprenavir on other drugs). For information regarding clinical recommendations, see PRECAUTIONS.

Table 3. Drug Interactions: Pharmacokinetic Parameters for Amprenavir in the Presence of the Coadministered Drug

Co-administered Drug	Dose of Coadministered Drug	Dose of AGENERASE	n	% Change in **Amprenavir** Pharmacokinetic Parameters* (90% CI)		
				C_{max}	AUC	C_{min}
Abacavir	300 mg b.i.d. for 3 weeks	900 mg b.i.d. for 3 weeks	4	↑ 47 (↓ 15 to ↑ 154)	↑ 29 (↓ 18 to ↑ 103)	↑ 27 (↓ 46 to ↑ 197)
Clarithromycin	500 mg b.i.d. for 4 days	1,200 mg b.i.d. for 4 days	12	↑ 15 (↑ 1 to ↑ 31)	↑ 18 (↑ 8 to ↑ 29)	↑ 39 (↑ 31 to ↑ 47)
Delavirdine	600 mg b.i.d. for 10 days	600 mg b.i.d. for 10 days	9	↑ 40‡	↑ 130‡	↑ 125‡
Ethinyl estradiol/ Norethindrone	0.035 mg/1 mg for 1 cycle	1,200 mg b.i.d. for 28 days	10	↔ (↓ 20 to ↑ 3)	↓ 22 (↓ 35 to ↓ 8)	↓ 20 (↓ 41 to ↑ 8)
Indinavir	800 mg t.i.d. for 2 weeks (fasted)	750 or 800 mg t.i.d. for 2 weeks (fasted)	9	↑ 18 (↓ 13 to ↑ 58)	↑ 33 (↑ 2 to ↑ 73)	↑ 25 (↓ 27 to ↑ 116)
Ketoconazole	400 mg single dose	1,200 mg single dose	12	↓ 16 (↓ 25 to ↓ 6)	↑ 31 (↑ 20 to ↑ 42)	NA
Lamivudine	150 mg single dose	600 mg single dose	11	↔ (↓ 17 to ↑ 9)	↔ (↓ 15 to ↑ 14)	NA
Nelfinavir	750 mg t.i.d. for 2 weeks (fed)	750 or 800 mg t.i.d. for 2 weeks (fed)	6	↓ 14 (↓ 38 to ↑ 20)	↔ (↓ 19 to ↑ 47)	↑ 189 (↑ 52 to ↑ 448)
Rifabutin	300 mg q.d. for 10 days	1,200 mg b.i.d. for 10 days	5	↔ (↓ 21 to ↑ 10)	↓ 15 (↓ 28 to 0)	↓ 15 (↓ 38 to ↑ 17)
Rifampin	300 mg q.d. for 4 days	1,200 mg b.i.d. for 4 days	11	↓ 70 (↓ 76 to ↓ 62)	↓ 82 (↓ 84 to ↓ 78)	↓ 92 (↓ 95 to ↓ 89)
Ritonavir	100 mg b.i.d. for 2 to 4 weeks	600 mg b.i.d.	18	↓ 30† (↓ 44 to ↓ 14)	↑ 64† (↑ 37 to ↑ 97)	508† (↑ 394 to ↑ 649)
Ritonavir	200 mg q.d. for 2 to 4 weeks	1,200 mg q.d.	12	↔† (↓ 17 to ↑ 30)	↑ 62† (↑ 35 to ↑ 94)	↑ 319† (↑ 190 to ↑ 508)
Saquinavir	800 mg t.i.d. for 2 weeks (fed)	750 or 800 mg t.i.d. for 2 weeks (fed)	7	↓ 37 (↓ 54 to ↓ 14)	↓ 32 (↓ 49 to ↓ 9)	↓ 14 (↓ 52 to ↑ 54)
Zidovudine	300 mg single dose	600 mg single dose	12	↔ (↓ 5 to ↑ 24)	↑ 13 (↓ 2 to ↑ 31)	NA

* Based on total-drug concentrations.
† Compared to amprenavir capsules 1,200 mg b.i.d. in the same patients.
‡ Median percent change; confidence interval not reported.
↑ = Increase; ↓ = Decrease; ↔ = No change (↑ or ↓ <10%); NA = C_{min} not calculated for single-dose study.

Table 4. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the Presence of Amprenavir

Co-administered Drug	Dose of Coadministered Drug	Dose of AGENERASE	n	% Change in Pharmacokinetic Parameters of **Coadministered Drug** (90% CI)		
				C_{max}	AUC	C_{min}
Clarithromycin	500 mg b.i.d. for 4 days	1,200 mg b.i.d. for 4 days	12	↓ 10 (↓ 24 to ↑ 7)	↔ (↓ 17 to ↑ 11)	↔ (↓ 13 to ↑ 20)
Delavirdine	600 mg b.i.d. for 10 days	600 mg b.i.d. for 10 days	9	↓ 47*	↓ 61*	↓ 88*
Ethinyl estradiol	0.035 mg for 1 cycle	1,200 mg b.i.d. for 28 days	10	↔ (↓ 25 to ·15)	↔ (↓ 14 to ↑ 38)	↑ 32 (↓ 3 to ↑ 79)
Norethindrone	1.0 mg for 1 cycle	1,200 mg b.i.d. for 28 days	10	↔ (↓ 20 to ↑ 18)	↑ 18 (↑ 1 to ·38)	↑ 45 (↑ 13 to ↑ 88)
Ketoconazole	400 mg single dose	1,200 mg single dose	12	↑ 19 (↑ 8 to ↑ 33)	↑ 44 (↑ 31 to ↑ 59)	NA
Lamivudine	150 mg single dose	600 mg single dose	11	↔ (↓ 17 to ↑ 3)	↔ (↓ 11 to 0)	NA
Methadone	44 to 100 mg q.d. for >30 days	1,200 mg b.i.d. for 10 days	16	R-Methadone (active)		
				↓ 25 (↓ 32 to ↓ 18)	↓ 13 (↓ 21 to ↓ 5)	↓ 21 (↓ 32 to ↓ 9)
				S-Methadone (inactive)		
				↓ 48 (↓ 55 to ↓ 40)	↓ 40 (↓ 46 to ↓ 32)	↓ 53 (↓ 60 to ↓ 43)
Rifabutin	300 mg q.d. for 10 days	1,200 mg b.i.d. for 10 days	5	↑ 119 (↑ 82 to ↑ 164)	↑ 193 (↑ 156 to ↑ 235)	↑ 271 (↑ 171 to ↑ 409)
Rifampin	300 mg q.d. for 4 days	1,200 mg b.i.d. for 4 days	11	↔ (↓ 13 to ↑ 12)	↔ (↓ 10 to ↑ 13)	ND
Zidovudine	300 mg single dose	600 mg single dose	12	↑ 40 (↑ 14 to ↑ 71)	↑ 31 (↑ 19 to ↑ 45)	NA

*Median percent change; confidence interval not reported.
↑ = Increase; ↓ = Decrease; ↔ = No change (↑ or ↓ <10%); NA = C_{min} not calculated for single-dose study; ND = Interaction cannot be determined as C_{min} was below the lower limit of quantitation.

Nucleoside Reverse Transcriptase Inhibitors (NRTIs): There was no effect of amprenavir on abacavir in subjects receiving both agents based on historical data.

HIV Protease Inhibitors: Concurrent use of AGENERASE Oral Solution and NORVIR® (ritonavir) Oral Solution is not recommended because the large amount of propylene glycol in AGENERASE Oral Solution and ethanol in NORVIR Oral Solution may compete for the same metabolic pathway for elimination. This combination has not been studied in pediatric patients.

The effect of amprenavir on total drug concentrations of other HIV protease inhibitors in subjects receiving both agents was evaluated using comparisons to historical data. Indinavir steady-state C_{max}, AUC, and C_{min} were decreased by 22%, 38%, and 27%, respectively, by concomitant amprenavir. Similar decreases in C_{max} and AUC were seen after the first dose. Saquinavir steady-state C_{max}, AUC, and C_{min} were increased 21%, decreased 19%, and decreased 48%, respectively, by concomitant amprenavir. Nelfinavir steady-state C_{max}, AUC, and C_{min} were increased by 12%, 15%, and 14%, respectively, by concomitant amprenavir.

Methadone: Coadministration of amprenavir and methadone can decrease plasma levels of methadone.

Coadministration of amprenavir and methadone as compared to a non-matched historical control group resulted in a 30%, 27%, and 25% decrease in serum amprenavir AUC, C_{max}, and C_{min}, respectively.

For information regarding clinical recommendations, see PRECAUTIONS: Drug Interactions.

INDICATIONS AND USAGE

AGENERASE (amprenavir) is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

The following points should be considered when initiating therapy with AGENERASE:

In a study of NRTI-experienced, protease inhibitor-naive patients, AGENERASE was found to be significantly less effective than indinavir (see Description of Clinical Studies).

Mild to moderate gastrointestinal adverse events led to discontinuation of AGENERASE primarily during the first 12 weeks of therapy (see ADVERSE REACTIONS).

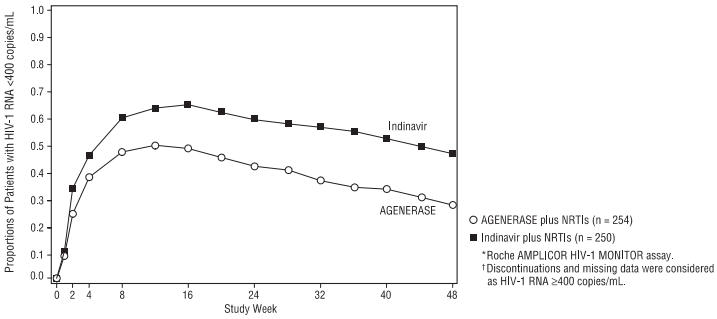
There are no data on response to therapy with AGENERASE in protease inhibitor-experienced patients.

AGENERASE Oral Solution should be used only when AGENERASE Capsules or other protease inhibitor formulations are not therapeutic options.

Description of Clinical Studies: ***Therapy-Naive Adults:*** PROAB3001, a randomized, double-blind, placebo-controlled, multicenter study, compared treatment with AGENERASE Capsules (1,200 mg twice daily) plus lamivudine (150 mg twice daily) plus zidovudine (300 mg twice daily) versus lamivudine (150 mg twice daily) plus zidovudine (300 mg twice daily) in 232 patients. Through 24 weeks of therapy, 53% of patients assigned to AGENERASE/zidovudine/lamivudine achieved HIV-1 RNA <400 copies/mL. Through Week 48, the antiviral response was 41%. Through 24 weeks of therapy, 11% of patients assigned to zidovudine/lamivudine achieved HIV-1 RNA <400 copies/mL. Antiviral response beyond Week 24 is not interpretable because the majority of patients discontinued or changed their antiretroviral therapy.

NRTI-Experienced Adults: PROAB3006, a randomized, open-label multicenter study, compared treatment with AGENERASE Capsules (1,200 mg twice daily) plus NRTIs versus indinavir (800 mg every 8 hours) plus NRTIs in 504 NRTI-experienced, protease inhibitor-naive patients, median age 37 years (range 20 to 71 years), 72% Caucasian, 80% male, with a median CD4 cell count of 404 cells/mm^3 (range 9 to 1,706 cells/mm^3) and a median plasma HIV-1 RNA level of 3.93 $\log_{10}$ copies/mL (range 2.60 to 7.01 $\log_{10}$ copies/mL) at baseline. Through 48 weeks of therapy, the median CD4 cell count increase from baseline in the amprenavir group was significantly lower than in the indinavir group, 97 cells/mm^3 versus 144 cells/mm^3, respectively. There was also a significant difference in the proportions of patients with plasma HIV-1 RNA levels <400 copies/mL through 48 weeks (see Figure 1 and Table 5).

Figure 1. Virologic Response Through Week 48, PROAB3006*,†



HIV-1 RNA status and reasons for discontinuation of randomized treatment at 48 weeks are summarized (Table 5).

Table 5. Outcomes of Randomized Treatment Through Week 48 (PROAB3006)

Outcome	AGENERASE (n = 254)	Indinavir (n = 250)
HIV-1 RNA <400 copies/mL*	30%	49%
HIV-1 RNA ≥400 copies/mL†,‡	38%	26%
Discontinued due to adverse events*,‡	16%	12%
Discontinued due to other reasons‡,§	16%	13%

* Corresponds to rates at Week 48 in Figure 1.
† Virological failures at or before Week 48.
‡ Considered to be treatment failure in the analysis.
§ Includes discontinuations due to consent withdrawn, loss to follow-up, protocol violations, non-compliance, pregnancy, never treated, and other reasons.

CONTRAINDICATIONS

Because of the potential risk of toxicity from the large amount of the excipient, propylene glycol, AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole (see WARNINGS and PRECAUTIONS).

Coadministration of AGENERASE is contraindicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs are listed in Table 6.

Table 6. Drugs That Are Contraindicated With AGENERASE Oral Solution

Drug Class	Drugs Within Class That Are CONTRAINDICATED with AGENERASE
Alcohol-dependence treatment	Disulfiram
Antibiotic	Metronidazole
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agent	Cisapride
Neuroleptic	Pimozide
Sedatives/hypnotics	Midazolam, triazolam

If AGENERASE Capsules are coadministered with ritonavir capsules, the antiarrhythmic agents flecainide and propafenone are also contraindicated.

AGENERASE is contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of this product.

WARNINGS

ALERT: Find out about medicines that should not be taken with AGENERASE.

Because of the potential risk of toxicity from the large amount of the excipient, propylene glycol, AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole (see CLINICAL PHARMACOLOGY, CONTRAINDICATIONS, and PRECAUTIONS).

Because of the possible toxicity associated with the large amount of propylene glycol and the lack of information on chronic exposure to large amounts of propylene glycol, AGENERASE Oral Solution should be used only when AGENERASE Capsules or other protease inhibitor formulations are not therapeutic options. Certain ethnic populations (Asians, Eskimos, Native Americans) and women may be at increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol; no data are available on propylene glycol metabolism in these groups (see CLINICAL PHARMACOLOGY: Special Populations: Gender and Race).

If patients require treatment with AGENERASE Oral Solution, they should be monitored closely for propylene glycol-associated adverse events, including seizures, stupor, tachycardia, hyperosmolality, lactic acidosis, renal toxicity, and hemolysis. Patients should be switched from AGENERASE Oral Solution to AGENERASE Capsules as soon as they are able to take the capsule formulation.

Concurrent use of AGENERASE Oral Solution and NORVIR (ritonavir) Oral Solution is not recommended because the large amount of propylene glycol in AGENERASE Oral Solution and ethanol in NORVIR Oral Solution may compete for the same metabolic pathway for elimination.

Use of alcoholic beverages is not recommended in patients treated with AGENERASE Oral Solution.

Serious and/or life-threatening drug interactions could occur between amprenavir and amiodarone, lidocaine (systemic), tricyclic antidepressants, and quinidine. Concentration monitoring of these agents is recommended if these agents are used concomitantly with AGENERASE (see CONTRAINDICATIONS).

Rifampin should not be used in combination with amprenavir because it reduces plasma concentrations and AUC of amprenavir by about 90%.

A drug interaction study in healthy subjects has shown that ritonavir significantly increases plasma fluticasone propionate exposures, resulting in significantly decreased serum cortisol concentrations. Concomitant use of AGENERASE with ritonavir and fluticasone propionate is expected to produce the same effects. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported during postmarketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. Therefore, coadministration of fluticasone propionate and AGENERASE/ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects (see PRECAUTIONS: Drug Interactions).

Concomitant use of AGENERASE and St. John's wort (hypericum perforatum) or products containing St. John's wort is not recommended. Coadministration of protease inhibitors, including AGENERASE, with St. John's wort is expected to substantially decrease protease inhibitor concentrations and may result in suboptimal levels of amprenavir and lead to loss of virologic response and possible resistance to AGENERASE or to the class of protease inhibitors.

Concomitant use of AGENERASE with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including AGENERASE, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (e.g., atorvastatin). The risk of myopathy, including rhabdomyolysis, may be increased when HIV protease inhibitors, including amprenavir, are used in combination with these drugs.

Particular caution should be used when prescribing sildenafil in patients receiving amprenavir. Coadministration of AGENERASE with sildenafil is expected to substantially increase sildenafil concentrations and may result in an increase in sildenafil-associated adverse events, including hypotension, visual changes, and priapism (see PRECAUTIONS: Drug Interactions and Information for Patients, and the complete prescribing information for sildenafil).

Severe and life-threatening skin reactions, including Stevens-Johnson syndrome, have occurred in patients treated with AGENERASE (see ADVERSE REACTIONS).

Acute hemolytic anemia has been reported in a patient treated with AGENERASE.

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and causal relationships between protease inhibitor therapy and these events have not been established.

PRECAUTIONS

General: AGENERASE Capsules and AGENERASE Oral Solution are not interchangeable on a milligram-per-milligram basis (see CLINICAL PHARMACOLOGY: Pediatric Patients and CONTRAINDICATIONS).

Amprenavir is a sulfonamide. The potential for cross-sensitivity between drugs in the sulfonamide class and amprenavir is unknown. AGENERASE should be used with caution in patients with a known sulfonamide allergy.

AGENERASE is principally metabolized by the liver. AGENERASE, when used alone and in combination with low-dose ritonavir, has been associated with elevations of SGOT (AST) and SGPT (ALT) in some patients. Caution should be exercised when administering AGENERASE to patients with hepatic impairment (see DOSAGE AND ADMINISTRATION). Appropriate laboratory testing should be conducted prior to initiating therapy with AGENERASE and at periodic intervals during treatment.

Formulations of AGENERASE provide high daily doses of vitamin E (see Information for Patients, DESCRIPTION, and DOSAGE AND ADMINISTRATION). The effects of long-term, high-dose vitamin E administration in humans is not well characterized and has not been specifically studied in HIV-infected individuals. High vitamin E doses may exacerbate the blood coagulation defect of vitamin K deficiency caused by anticoagulant therapy or malabsorption.

Patients with Hemophilia: There have been reports of spontaneous bleeding in patients with hemophilia A and B treated with protease inhibitors. In some patients, additional factor VIII was required. In many of the reported cases, treatment with protease inhibitors was continued or restarted. A causal relationship between protease inhibitor therapy and these episodes has not been established.

Immune Reconstitution Syndrome: Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including AGENERASE. 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.

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.

Lipid Elevations: Treatment with AGENERASE alone or in combination with ritonavir capsules has resulted in increases in the concentration of total cholesterol and triglycerides. Triglyceride and cholesterol testing should be performed prior to initiation of therapy with AGENERASE and at periodic intervals during treatment. Lipid disorders should be managed as clinically appropriate. See PRECAUTIONS Table 8: Established and Other Potentially Significant Drug Interactions for additional information on potential drug interactions with AGENERASE and HMG-CoA reductase inhibitors.

Resistance/Cross-Resistance: Because the potential for HIV cross-resistance among protease inhibitors has not been fully explored, it is unknown what effect amprenavir therapy will have on the activity of subsequently administered protease inhibitors. It is also unknown what effect previous treatment with other protease inhibitors will have on the activity of amprenavir (see MICROBIOLOGY).

Information for Patients: A statement to patients and healthcare providers is included on the product's bottle label: **ALERT: Find out about medicines that should NOT be taken with AGENERASE.** A Patient Package Insert (PPI) for AGENERASE Oral Solution is available for patient information.

AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole. AGENERASE Oral Solution should be used only when AGENERASE Capsules or other protease inhibitor formulations are not therapeutic options.

Patients treated with AGENERASE Capsules should be cautioned against switching to AGENERASE Oral Solution because of the increased risk of adverse events from the large amount of propylene glycol in AGENERASE Oral Solution.

Women, Asians, Eskimos, or Native Americans, as well as patients who have hepatic or renal insufficiency, should be informed that they may be at increased risk of adverse events from the large amount of propylene glycol in AGENERASE Oral Solution.

Patients should be informed that AGENERASE is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of AGENERASE (amprenavir) are unknown at this time. Patients should be told that there are currently no data demonstrating that therapy with AGENERASE can reduce the risk of transmitting HIV to others through sexual contact.

Patients should remain under the care of a physician while using AGENERASE. Patients should be advised to take AGENERASE every day as prescribed. AGENERASE must always be used in combination with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting their physician. If a dose is missed, patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped, the patient should not double the next dose.

Patients should inform their doctor if they have a sulfa allergy. The potential for cross-sensitivity between drugs in the sulfonamide class and amprenavir is unknown.

AGENERASE may interact with many drugs; therefore, patients should be advised to report to their doctor the use of any other prescription or nonprescription medication or herbal products, particularly St. John's wort.

Patients taking antacids (or the buffered formulation of didanosine) should take AGENERASE at least 1 hour before or after antacid (or the buffered formulation of didanosine) use.

Patients should be advised that drinking alcoholic beverages is not recommended while taking AGENERASE Oral Solution.

Patients receiving sildenafil should be advised that they may be at an increased risk of sildenafil-associated adverse events including hypotension, visual changes, and priapism, and should promptly report any symptoms to their doctor.

Patients taking AGENERASE should be instructed **not** to use hormonal contraceptives because some birth control pills (those containing ethinyl estradiol/norethindrone) have been found to decrease the concentration of amprenavir. Therefore, patients receiving hormonal contraceptives should be instructed to use alternate contraceptive measures during therapy with AGENERASE.

High-fat meals may decrease the absorption of AGENERASE and should be avoided. AGENERASE may be taken with meals of normal fat content.

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.

Adult and pediatric patients should be advised not to take supplemental vitamin E since the vitamin E content of AGENERASE exceeds the Reference Daily Intake (adults 30 IU, pediatrics approximately 10 IU).

Laboratory Tests: The combination of AGENERASE and low-dose ritonavir has been associated with elevations of cholesterol and triglycerides, SGOT (AST), and SGPT (ALT) in some patients. Appropriate laboratory testing should be considered prior to initiating combination therapy with AGENERASE and ritonavir capsules and at periodic intervals or if any clinical signs or symptoms of hyperlipidemia or elevated liver function tests occur during therapy. For comprehensive information concerning laboratory test alterations associated with ritonavir, physicians should refer to the complete prescribing information for NORVIR (ritonavir).

Drug Interactions: See also CONTRAINDICATIONS, WARNINGS, and CLINICAL PHARMACOLOGY: Drug Interactions.

AGENERASE is an inhibitor of cytochrome P450 3A4 metabolism and therefore should not be administered concurrently with medications with narrow therapeutic windows that are substrates of CYP3A4. There are other agents that may result in serious and/or life-threatening drug interactions (see CONTRAINDICATIONS and WARNINGS).

Use of alcoholic beverages is not recommended in patients treated with AGENERASE Oral Solution.

Table 7. Drugs That Should Not Be Coadministered With AGENERASE Oral Solution

Drug Class/Drug Name	Clinical Comment
Alcohol-dependence treatment: Disulfiram	**CONTRAINDICATED** due to potential risk of toxicity from the large amount of the excipient, propylene glycol, in AGENERASE Oral Solution.
Antibiotic: Metronidazole	**CONTRAINDICATED** due to potential risk of toxicity from the large amount of the excipient, propylene glycol, in AGENERASE Oral Solution.
Antimycobacterials: Rifampin*	May lead to loss of virologic response and possible resistance to AGENERASE or to the class of protease inhibitors.
Ergot derivatives: Dihydroergotamine, ergonovine, ergotamine, methylergonovine	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI motility agents: Cisapride	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal products: St. John's wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to AGENERASE or to the class of protease inhibitors.
HIV protease inhibitor: Ritonavir oral solution	Concurrent use of AGENERASE Oral Solution and NORVIR (ritonavir) Oral Solution is not recommended because the large amount of propylene glycol in AGENERASE Oral Solution and ethanol in NORVIR Oral Solution may compete for the same metabolic pathway for elimination.
HMG co-reductase inhibitors: Lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic: Pimozide	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Non-nucleoside reverse transcriptase inhibitor: Delavirdine*	May lead to loss of virologic response and possible resistance to delavirdine.
Oral contraceptives: Ethinyl estradiol/norethindrone	May lead to loss of virologic response and possible resistance to AGENERASE. Alternative methods of non-hormonal contraception are recommended.
Sedative/hypnotics: Midazolam, triazolam	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

*See CLINICAL PHARMACOLOGY for magnitude of interaction, Tables 3 and 4.

Table 8. Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of Amprenavir or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents		
Non-nucleoside reverse transcriptase inhibitors: Efavirenz, nevirapine	↓ Amprenavir	Appropriate doses of the combinations with respect to safety and efficacy have not been established.
Nucleoside reverse transcriptase inhibitor: Didanosine (buffered formulation only)	↓ Amprenavir	Take AGENERASE at least 1 hour before or after the buffered formulation of didanosine.
HIV protease inhibitors: Indinavir*, lopinavir/ritonavir, nelfinavir*	↑ Amprenavir Amprenavir's effect on other protease inhibitors is not well established.	Appropriate doses of the combinations with respect to safety and efficacy have not been established.
HIV protease inhibitor: Ritonavir Capsules*	↑ Amprenavir	The dose of amprenavir should be reduced when used in combination with ritonavir capsules (see Dosage and Administration). Also, see the full prescribing information for NORVIR for additional drug interaction information. Concurrent use of AGENERASE Oral Solution and NORVIR (ritonavir) Oral Solution is not recommended because the large amount of propylene glycol in AGENERASE Oral Solution and ethanol in NORVIR Oral Solution may compete for the same metabolic pathway for elimination.
HIV protease inhibitor: Saquinavir*	↓ Amprenavir Amprenavir's effect on saquinavir is not well established.	Appropriate doses of the combination with respect to safety and efficacy have not been established.
Other Agents		
Antacids	↓ Amprenavir	Take AGENERASE at least 1 hour before or after antacids.
Antiarrhythmics: Amiodarone, lidocaine (systemic), and quinidine	Antiarrhythmics	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when coadministered with AGENERASE, if available.
Antiarrhythmic: Bepridil	↑ Bepridil	Use with caution. Increased bepridil exposure may be associated with life-threatening reactions such as cardiac arrhythmias.
Anticoagulant: Warfarin		Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.
Anticonvulsants: Carbamazepine, phenobarbital, phenytoin	↓ Amprenavir	Use with caution. AGENERASE may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly.
Antidepressant: Trazodone	↑ Trazodone	Concomitant use of trazodone and AGENERASE with or without ritonavir may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension, and syncope have been observed following coadministration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as AGENERASE, the combination should be used with caution and a lower dose of trazodone should be considered.
Antifungals: Ketoconazole, itraconazole	↑ Ketoconazole ↑ Itraconazole	Increase monitoring for adverse events due to ketoconazole or itraconazole. Dose reduction of ketoconazole or itraconazole may be needed for patients receiving more than 400 mg ketoconazole or itraconazole per day.
Antimycobacterial: Rifabutin*	↑ Rifabutin and rifabutin metabolite	A dosage reduction of rifabutin to at least half the recommended dose is required when AGENERASE and rifabutin are coadministered.* A complete blood count should be performed weekly and as clinically indicated in order to monitor for neutropenia in patients receiving amprenavir and rifabutin.
Benzodiazepines: Alprazolam, clorazepate, diazepam, flurazepam	↑ Benzodiazepines	Clinical significance is unknown; however, a decrease in benzodiazepine dose may be needed.
Calcium channel blockers: Diltiazem, felodipine, nifedipine, nicardipine, nimodipine, verapamil, amlodipine, nisoldipine, isradipine	↑ Calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: Dexamethasone	↓ Amprenavir	Use with caution. AGENERASE may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly.
Erectile dysfunction agent: Sildenafil	↑ Sildenafil	Use with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events.
HMG-CoA reductase inhibitors: Atorvastatin	↑ Atorvastatin	Use lowest possible dose of atorvastatin with careful monitoring or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with AGENERASE.

Table 8. Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May be Recommended Based on Drug Interaction Studies or Predicted Interaction (Cont.)

Concomitant Drug Class: Drug Name	Effect on Concentration of Amprenavir or Concomitant Drug	Clinical Comment
Other Agents		
Immunosuppressants: Cyclosporine, tacrolimus, rapamycin	↑ Immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with AGENERASE.
Inhaled/nasal steroid: Fluticasone	**AGENERASE** ↑ Fluticasone	Concomitant use of fluticasone propionate and AGENERASE (without ritonavir) may increase plasma concentrations of fluticasone propionate. Use with caution. Consider alternatives to fluticasone propionate, particularly for long-term use.
	AGENERASE/ ritonavir ↑ Fluticasone	Concomitant use of fluticasone propionate and AGENERASE/ritonavir may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Coadministration of fluticasone propionate and AGENERASE/ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects (see WARNINGS).
Narcotic analgesics: Methadone*	↓ Amprenavir	AGENERASE may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly. Alternative antiretroviral therapy should be considered.
	↓ Methadone	Dosage of methadone may need to be increased when coadministered with AGENERASE.
Tricyclic antidepressants: Amitriptyline, imipramine	↑ Tricyclics	Therapeutic concentration monitoring is recommended for tricyclic antidepressants when coadministered with AGENERASE.

*See CLINICAL PHARMACOLOGY for magnitude of interaction, Tables 3 and 4.

Carcinogenesis and Mutagenesis: Amprenavir was evaluated for carcinogenic potential by oral gavage administration to mice and rats for up to 104 weeks. Daily doses of 50, 275 to 300, and 500 to 600 mg/kg/day were administered to mice and doses of 50, 190, and 750 mg/kg/day were administered to rats. Results showed an increase in the incidence of benign hepatocellular adenomas and an increase in the combined incidence of hepatocellular adenomas plus carcinoma in males of both species at the highest doses tested. Female mice and rats were not affected. These observations were made at systemic exposures equivalent to approximately 2 times (mice) and 4 times (rats) the human exposure (based on $AUC_{0\text{-}24\ hr}$ measurement) at the recommended dose of 1,200 mg twice daily. Administration of amprenavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. It is not known how predictive the results of rodent carcinogenicity studies may be for humans. However, amprenavir was not mutagenic or genotoxic in a battery of in vitro and in vivo assays including bacterial reverse mutation (Ames), mouse lymphoma, rat micronucleus, and chromosome aberrations in human lymphocytes.

Fertility: The effects of amprenavir on fertility and general reproductive performance were investigated in male rats (treated for 28 days before mating at doses producing up to twice the expected clinical exposure based on AUC comparisons) and female rats (treated for 15 days before mating through day 17 of gestation at doses producing up to 2 times the expected clinical exposure). Amprenavir did not impair mating or fertility of male or female rats and did not affect the development and maturation of sperm from treated rats. The reproductive performance of the F1 generation born to female rats given amprenavir was not different from control animals.

Pregnancy and Reproduction: AGENERASE Oral Solution is contraindicated during pregnancy due to the potential risk of toxicity to the fetus from the high propylene glycol content. Therefore, if AGENERASE is used in pregnant women, the AGENERASE Capsules formulation should be used (see complete prescribing information for AGENERASE Capsules).

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

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Although it is not known if amprenavir is excreted in human milk, amprenavir is secreted into the milk of lactating rats. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving AGENERASE**.

Pediatric Use: AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years due to the potential risk of toxicity from the excipient, propylene glycol (see CONTRAINDICATIONS and WARNINGS). Alcohol dehydrogenase (ADH), which metabolizes propylene glycol, is present in the human fetal liver at 2 months of gestational age, but at only 3% of adult activity. Although the data are limited, it appears that by 12 to 30 months of postnatal age, ADH activity is equal to or greater than that observed in adults.

Two hundred fifty-one patients aged 4 and above have received amprenavir as single or multiple doses in studies. An adverse event profile similar to that seen in adults was seen in pediatric patients.

Concurrent use of AGENERASE Oral Solution and NORVIR (ritonavir) Oral Solution is not recommended because the large amount of propylene glycol in AGENERASE Oral Solution and ethanol in NORVIR Oral Solution may compete for the same metabolic pathway for elimination. This combination has not been studied in pediatric patients.

Geriatric Use: Clinical studies of AGENERASE did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger adults. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

In clinical studies, adverse events leading to amprenavir discontinuation occurred primarily during the first 12 weeks of therapy, and were mostly due to gastrointestinal events (nausea, vomiting, diarrhea, and abdominal pain/discomfort), which were mild to moderate in severity.

Skin rash occurred in 22% of patients treated with amprenavir in studies PROAB3001 and PROAB3006. Rashes were usually maculopapular and of mild or moderate intensity, some with pruritus. Rashes had a median onset of 11 days after amprenavir initiation and a median duration of 10 days. Skin rashes led to amprenavir discontinuation in approximately 3% of patients. In some patients with mild or moderate rash, amprenavir dosing was often continued without interruption; if interrupted, reintroduction of amprenavir generally did not result in rash recurrence.

Severe or life-threatening rash (Grade 3 or 4), including cases of Stevens-Johnson syndrome, occurred in approximately 1% of recipients of AGENERASE (see WARNINGS). Amprenavir therapy should be discontinued for severe or life-threatening rashes and for moderate rashes accompanied by systemic symptoms.

Table 9. Selected Clinical Adverse Events of All Grades Reported in >5% of Adult Patients

	PROAB3001 Therapy-Naive Patients		PROAB3006 NRTI-Experienced Patients	
Adverse Event	AGENERASE*/ Lamivudine/ Zidovudine (n = 113)	Lamivudine/ Zidovudine (n = 109)	AGENERASE*/ NRTI (n = 245)	Indinavir/ NRTI (n = 241)
Digestive				
Nausea	74%	50%	43%	35%
Vomiting	34%	17%	24%	20%
Diarrhea or loose stools	39%	35%	60%	41%
Taste disorders	10%	6%	2%	8%
Skin				
Rash	27%	6%	20%	15%
Nervous				
Paresthesia, oral/perioral	26%	6%	31%	2%
Paresthesia, peripheral	10%	4%	14%	10%
Psychiatric				
Depressive or mood disorders	16%	4%	9%	13%

*AGENERASE Capsules.

Among amprenavir-treated patients in Phase 3 studies, 2 patients developed de novo diabetes mellitus, 1 patient developed a dorsocervical fat enlargement (buffalo hump), and 9 patients developed fat redistribution.

In studies PROAB3001 and PROAB3006, no increased frequency of Grade 3 or 4 AST, ALT, amylase, or bilirubin elevations was seen compared to controls.

Pediatric Patients: An adverse event profile similar to that seen in adults was seen in pediatric patients.

Concomitant Therapy With Ritonavir: Tables 10 and 11 present adverse clinical events and laboratory abnormalities observed in subjects who received AGENERASE plus ritonavir. Since the trials were small, open-label, of varying duration, and often included different patient populations, direct comparisons to the frequency of events with AGENERASE Capsules alone (see Table 9) cannot be made.

Table 10. Selected Clinical Adverse Events of All Grades Reported in Adult Patients in Open-Label Clinical Trials of AGENERASE Capsules in Combination With Ritonavir Capsules

Adverse Event	AGENERASE 1,200 mg plus Ritonavir 200 mg q.d.* (n = 101)	AGENERASE 600 mg plus Ritonavir 100 mg b.i.d.† (n = 239)
Nausea	31%	23%
Diarrhea/loose stools	30%	28%
Headache	16%	12%
Abdominal symptoms	14%	14%
Vomiting	11%	9%
Rash	10%	9%
Paresthesias	9%	11%
Fatigue	7%	14%
Depressive & mood disorders	4%	9%

* Data from 2 open-label studies in treatment-naive patients also receiving abacavir/lamivudine.
† Data from 3 open-label studies in treatment-naive and treatment-experienced patients receiving combination antiretroviral therapy.

Table 11. Grade 3/4 Laboratory Abnormalities Reported in ≥2% of Adult Patients in Open-Label Clinical Trials of AGENERASE Capsules in Combination With Ritonavir

Laboratory Abnormality (non-fasting specimens)	AGENERASE 1,200 mg plus Ritonavir 200 mg q.d.* (n = 101)	AGENERASE 600 mg plus Ritonavir 100 mg b.i.d.† (n = 239)
Hypertriglyceridemia (>750 mg/dL)	8%	13%
Hyperglycemia (>251 mg/dL)	2%	3%
AST (>5 x ULN)	3%	5%
ALT (>5 x ULN)	4%	4%
Amylase (>2 x ULN)	4%	3%

* Data from 2 open-label studies in treatment-naive patients also receiving abacavir/lamivudine.
† Data from 3 open-label studies in treatment-naive and treatment-experienced patients receiving combination antiretroviral therapy.

OVERDOSAGE

There is no known antidote for AGENERASE. It is not known whether amprenavir can be removed by peritoneal dialysis or hemodialysis. If overdosage occurs, the patient should be monitored for evidence of toxicity and standard supportive treatment applied as necessary.

AGENERASE Oral Solution contains large amounts of propylene glycol. In the event of overdosage, monitoring and management of acid-base abnormalities is recommended. Propylene glycol can be removed by hemodialysis.

DOSAGE AND ADMINISTRATION

AGENERASE may be taken with or without food; however, a high-fat meal decreases the absorption of amprenavir and should be avoided (see CLINICAL PHARMACOLOGY: Effects of Food on Oral Absorption). **Adult and pediatric patients should be advised not to take supplemental vitamin E since the vitamin E content of AGENERASE Oral Solution exceeds the Reference Daily Intake (adults 30 IU, pediatrics approximately 10 IU) (see DESCRIPTION).**

The recommended dose of AGENERASE Oral Solution based on body weight and age is shown in Table 12. **Consideration should be given to switching patients from AGENERASE Oral Solution to AGENERASE Capsules as soon as they are able to take the capsule formulation (see WARNINGS).**

Table 12. Recommended Dosages of AGENERASE Oral Solution

Age/Weight Criteria	Dose	
	b.i.d.	t.i.d.
4 - 12 years or 13 - 16 years and <50 kg	22.5 mg/kg (1.5 mL/kg) (maximum dose 2,800 mg per day)	17 mg/kg (1.1 mL/kg) (maximum dose 2,800 mg per day)
13 - 16 years and ≥50 kg or >16 years	1,400 mg	NA

Concomitant Therapy: Concurrent use of AGENERASE Oral Solution and NORVIR (ritonavir) Oral Solution is not recommended because the large amount of propylene glycol in AGENERASE Oral Solution and ethanol in NORVIR Oral Solution may compete for the same metabolic pathway for elimination.

Patients with Hepatic Impairment: AGENERASE Oral Solution is contraindicated in patients with hepatic failure (see CONTRAINDICATIONS).

Patients with hepatic impairment are at increased risk of propylene glycol-associated adverse events (see WARNINGS). AGENERASE Oral Solution should be used with caution in patients with hepatic impairment. Based on a study with AGENERASE Capsules, adult patients with a Child-Pugh score ranging from 5 to 8 should receive a reduced dose of AGENERASE Oral Solution of 513 mg (34 mL) twice daily, and adult patients with a Child-Pugh score ranging from 9 to 12 should receive a reduced dose of AGENERASE Oral Solution of 342 mg (23 mL) twice daily (see CLINICAL PHARMACOLOGY: Hepatic Insufficiency).

AGENERASE Oral Solution has not been studied in children with hepatic impairment.

Renal Insufficiency: AGENERASE Oral Solution is contraindicated in patients with renal failure (see CONTRAINDICATIONS).

Patients with renal impairment are at increased risk of propylene glycol-associated adverse events. AGENERASE Oral Solution should be used with caution in patients with renal impairment (see WARNINGS).

AGENERASE Capsules and AGENERASE Oral Solution are not interchangeable on a milligram-per-milligram basis (see CLINICAL PHARMACOLOGY).

HOW SUPPLIED

AGENERASE Oral Solution, a clear, pale yellow to yellow, grape-bubblegum-peppermint-flavored liquid, contains 15 mg of amprenavir in each 1 mL.

Bottles of 240 mL with child-resistant closures (NDC 0173-0687-00). This product does not require reconstitution.

Store at controlled room temperature of 25°C (77°F) (see USP).

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PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT INFORMATION

AGENERASE® (amprenavir) Oral Solution

ALERT: Find out about medicines that should not be taken with AGENERASE Oral Solution. Read the section: "What important information should I know about taking AGENERASE Oral Solution with other medicines?"

Read this information carefully before you start taking AGENERASE (ah-GEN-er-ase) Oral Solution. Read the information each time you get more medicine. There may be new information. This information does not take the place of talks with your healthcare provider when you start this medicine and at checkups.

What is the most important information I should know about AGENERASE?

AGENERASE can cause serious and life-threatening side effects if you take it with certain other medicines. For information about these medicines, see the section "What important information should I know about taking AGENERASE with other medicines?"

What is AGENERASE Oral Solution?

AGENERASE Oral Solution is a medicine you take by mouth to treat HIV infection. HIV is the virus that causes AIDS (acquired immune deficiency syndrome). AGENERASE belongs to a class of anti-HIV medicines called protease inhibitors.

AGENERASE is used only in combination with other anti-HIV medicines. When used in combination therapy, AGENERASE may help lower the amount of HIV found in your blood, raise CD4 (T) cell counts, and keep your immune system as healthy as possible, so it can help fight infection. However, AGENERASE does not have these effects in all patients.

AGENERASE does not cure HIV infection or AIDS. We do not know if AGENERASE will help you live longer or have fewer of the medical problems (opportunistic infections) that people get with HIV or AIDS. Therefore, be sure to see your healthcare provider regularly. The long-term effects of AGENERASE are not known.

AGENERASE has not been shown to reduce the risk of passing HIV to others through sexual contact or blood. Continue to practice safe sex and do not use or share dirty needles.

Children from 4 to 12 years of age can take AGENERASE. Your healthcare provider will tell you if the oral solution (liquid) or capsule is best for your child. Your child's healthcare provider will decide the right dose based on your child's weight and age.

AGENERASE has not been studied in people who have taken anti-HIV medicine combinations before that included a protease inhibitor.

Who should not take AGENERASE Oral Solution?

AGENERASE Oral Solution contains a large amount of propylene glycol, a liquid needed to dissolve amprenavir. Because of the possible side effects of the large amount of propylene glycol, AGENERASE Oral Solution should be used only when AGENERASE Capsules or other protease inhibitor formulations are not options.

If you are a woman or an Asian, Eskimo, or Native American, or if you have liver or kidney disease, you may be at increased risk of side effects from the large amount of propylene glycol in AGENERASE Oral Solution.

Do not take AGENERASE Oral Solution if

- you are taking certain medicines. Read the section entitled **"What important information should I know about taking AGENERASE Oral Solution with other medicines?"**
- you are pregnant.
- you have had an allergic reaction to AGENERASE or any of its ingredients.

Children younger than age 4 should not take AGENERASE Capsules or AGENERASE Oral Solution.

Tell your healthcare provider if

- you are pregnant. Do not use AGENERASE Oral Solution if you are pregnant.
- you are breastfeeding. Your baby can get HIV from your milk. Also, AGENERASE can pass through your milk and harm the baby.

Tell your healthcare provider about all your medical conditions. AGENERASE Oral Solution may not be right for you, or you may need a dosage change in AGENERASE. Be sure to tell your healthcare provider if you

- have liver or kidney problems.
- have hemophilia.
- are allergic to sulfa medicines. AGENERASE may cause problems for you.

What important information should I know about taking AGENERASE Oral Solution with other medicines?

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and supplements. **Some of them may cause dangerous and life-threatening side effects** if you take them during treatment with AGENERASE. For other medicines, you may need to change your dose to avoid problems.

Drinking alcoholic beverages is not recommended while taking AGENERASE Oral Solution because it may increase side effects related to propylene glycol content.

Taking AGENERASE Oral Solution and NORVIR® (ritonavir) oral solution together is not recommended because this may increase side effects related to propylene glycol and ethanol content.

If you are on methadone therapy, talk to your doctor about possible interactions.

Do NOT take the following medicines* with AGENERASE Oral Solution. You could develop serious or life-threatening problems.

- FLAGYL® (metronidazole, used to treat certain infections)
- ANTABUSE® (disulfiram, used to treat alcohol dependence)
- HALCION® (triazolam; used for insomnia)
- CAFERGOT® and other ergot medicines (used for migraine headaches)
- PROPULSID® (cisapride, used for certain stomach problems)
- VERSED® (midazolam; used for sedation)
- ORAP® (pimozide; used for Tourette's disorder)

You will need to be monitored with regular blood tests if you take the following medicines* with AGENERASE.

- CORDARONE® (amiodarone; used for certain abnormal heart rhythms)
- Quinidine (used for certain abnormal heart rhythms)
- COUMADIN® (warfarin; used for blood thinning)
- Lidocaine (used for certain abnormal heart rhythms)
- ELAVIL® (amitriptyline), TOFRANIL® (imipramine) (tricyclic antidepressants)
- SANDIMMUNE® or NEORAL® (cyclosporine), PROGRAF® (tacrolimus), RAPAMUNE® (rapamycin or sirolimus) (immunosuppressants)

You will need to have your dose adjusted if you take the following medicines* with AGENERASE.

- MYCOBUTIN® (rifabutin; used to prevent *Mycobacterium avium* complex [MAC])
- NORVIR® Capsules (ritonavir capsules; used to treat HIV infection)
- VIAGRA® (sildenafil; used for impotence). You may get increased side effects such as low blood pressure, changes in vision, or erections that last more than 4 hours. If an erection lasts more than 4 hours, get medical help right away.

The following medicines* may cause serious problems if you take them with AGENERASE. Tell your healthcare provider if you are taking any of these medicines.

- RESCRIPTOR® (delavirdine; used for HIV) and certain other anti-HIV medicines
- St. John's wort (hypericum perforatum) or products containing St. John's wort
- VASCOR® (bepridil; used for chronic stable angina)
- RIFADIN®, RIFAMATE®, RIFATER®, or RIMACTANE® (rifampin, used for tuberculosis)
- MEVACOR® (lovastatin), ZOCOR® (simvastatin), and LIPITOR® (atorvastatin) (cholesterol-lowering medicines)
- Phenobarbital (used for seizures)
- TEGRETOL®, CARBATROL® (carbamazepine; used for seizures and trigeminal neuralgia)
- DILANTIN® (phenytoin; used for seizures)
- DECADRON® (dexamethasone, used to reduce inflammation)
- Hormonal contraceptives (e.g., birth control pills) because the effectiveness of one or both drugs may be decreased. Talk to your doctor about choosing a different type of contraceptive.
- Vitamin E. AGENERASE contains high daily doses of vitamin E that could interfere with medicines that help you stop bleeding.

This list is not complete. Be sure to tell your healthcare provider about all the medicines you take.

How should I take AGENERASE Oral Solution?

- Take AGENERASE Oral Solution every day exactly as your healthcare provider has prescribed it, **so it will be as effective as possible**. Your healthcare provider will decide the right dose for you.
- If you miss a dose by more than 4 hours, wait and take the next dose at the regular time. However, if you miss a dose by fewer than 4 hours, take your missed dose right away. Then take your next dose at the regular time.
- **Do not take more or less than your prescribed dose of AGENERASE Oral Solution at any one time.** Do not change your dose or stop taking AGENERASE without talking with your healthcare provider.
- You can take AGENERASE Oral Solution with or without food. **However, do not take AGENERASE with a high-fat meal. This could reduce the effectiveness of the medicine**.
- If you take AGENERASE with the **buffered form of VIDEX® (didanosine, ddI), take them at least 1 hour apart.**
- If you take AGENERASE Oral Solution with antacids, **take them at least 1 hour apart**.
- When your supply of AGENERASE or other anti-HIV medicine starts to run low, **arrange to get more from your healthcare provider or pharmacy. The amount of virus in your blood may increase if one or more of the drugs are stopped, even for a short time.**
- Stay under the care of a healthcare provider while using AGENERASE.

What should I avoid while taking AGENERASE?

Do not

- take vitamin E while taking AGENERASE. It contains large amounts of vitamin E.
- take AGENERASE with a high-fat meal. It could reduce the effectiveness of the medicine.

What are the possible side effects of AGENERASE?

AGENERASE can cause a severe or life-threatening rash. Call your healthcare provider right away if you have a rash. Your healthcare provider will advise you whether your symptoms can be managed on therapy or whether AGENERASE should be stopped.

Common side effects of AGENERASE are nausea, vomiting, diarrhea, rash, and a tingling feeling, especially around the mouth, and change in taste. These are usually mild to moderate. Depression and mood problems have also been reported in patients taking AGENERASE.

Possible side effects from the large amount of propylene glycol in AGENERASE Oral Solution include seizures, drowsiness, fast heart rate, and kidney and blood abnormalities.

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

Other side effects include high blood sugar or diabetes, diabetes complications, high cholesterol, or high triglycerides.

This list of side effects is not complete. Your healthcare provider or pharmacist can give you a more complete list of possible side effects. Talk with your healthcare provider about any concerns about the way you are feeling while you are taking AGENERASE.

How should I store AGENERASE Oral Solution?

AGENERASE Oral Solution should be stored at room temperature and should not be refrigerated.

General advice about prescription medicines

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use AGENERASE for a condition for which it was not prescribed. Do not give AGENERASE to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about AGENERASE. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about AGENERASE that is written for health professionals.

GlaxoSmithKline
Research Triangle Park, NC 27709

Licensed from
VERTEX™
Vertex Pharmaceuticals Incorporated
Cambridge, MA 02139

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COMBIVIR®
(lamivudine/zidovudine) Tablets

WARNING

ZIDOVUDINE, ONE OF THE TWO ACTIVE INGREDIENTS IN COMBIVIR, HAS BEEN ASSOCIATED WITH HEMATOLOGIC TOXICITY INCLUDING NEUTROPENIA AND SEVERE ANEMIA, PARTICULARLY IN PATIENTS WITH ADVANCED HUMAN IMMUNODEFICIENCY VIRUS (HIV) DISEASE (SEE WARNINGS). PROLONGED USE OF ZIDOVUDINE HAS BEEN ASSOCIATED WITH SYMPTOMATIC MYOPATHY.

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING LAMIVUDINE, ZIDOVUDINE, AND OTHER ANTIRETROVIRALS (SEE WARNINGS).

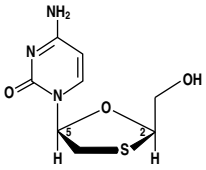
SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED WITH HEPATITIS B VIRUS (HBV) AND HIV AND HAVE DISCONTINUED LAMIVUDINE, WHICH IS ONE COMPONENT OF COMBIVIR. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE COMBIVIR AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS).

DESCRIPTION

COMBIVIR: COMBIVIR Tablets are combination tablets containing lamivudine and zidovudine. Lamivudine (EPIVIR®, 3TC®) and zidovudine (RETROVIR®, azidothymidine, AZT, or ZDV) are synthetic nucleoside analogues with activity against HIV.

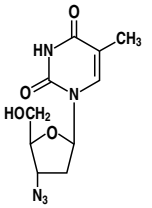
COMBIVIR Tablets are for oral administration. Each film-coated tablet contains 150 mg of lamivudine, 300 mg of zidovudine, and the inactive ingredients colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

Lamivudine: The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2´,3´-dideoxy, 3´-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.3. It has the following structural formula:



Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg/mL in water at 20°C.

Zidovudine: The chemical name of zidovudine is 3´-azido-3´-deoxythymidine. It has a molecular formula of $C_{10}H_{13}N_5O_4$ and a molecular weight of 267.24. It has the following structural formula:



Zidovudine is a white to beige, odorless, crystalline solid with a solubility of 20.1 mg/mL in water at 25°C.

MICROBIOLOGY

Mechanism of Action: ***Lamivudine:*** Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5´-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue. 3TC-TP is a weak inhibitor of cellular DNA polymerases α, β, and γ.

Zidovudine: Zidovudine is a synthetic nucleoside analogue. Intracellularly, zidovudine is phosphorylated to its active 5´-triphosphate metabolite, zidovudine triphosphate (ZDV-TP). The principal mode of action of ZDV-TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue. ZDV-TP is a weak inhibitor of the cellular DNA polymerases α and γ and has been reported to be incorporated into the DNA of cells in culture.

Antiviral Activity: ***Lamivudine Plus Zidovudine:*** In HIV-1–infected MT-4 cells, lamivudine in combination with zidovudine at various ratios exhibited synergistic antiretroviral activity.

Lamivudine: The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. EC_{50} values (50% effective concentrations) were in the range of 0.003 to 15 μM (1 μM = 0.23 mcg/mL). HIV from therapy-naive subjects with no mutations associated with resistance gave median EC_{50} values of 0.426 μM (range: 0.200 to 2.007 μM) from Virco (n = 93 baseline samples from COLA40263) and 2.35 μM (1.44 to 4.08 μM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC_{50} values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120 μM, and against HIV-2 isolates from 0.003 to 0.120 μM in peripheral blood mononuclear cells. Ribavirin (50 μM) decreased the anti-HIV-1 activity of lamivudine by 3.5 fold in MT-4 cells.

Zidovudine: The antiviral activity of zidovudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes). The EC_{50} and EC_{90} values for zidovudine were 0.01 to 0.49 μM (1 μM = 0.27 mcg/mL) and 0.1 to 9 μM, respectively. HIV from therapy-naive subjects with no mutations associated with resistance gave median EC_{50} values of 0.011 μM (range: 0.005 to 0.110 μM) from Virco (n = 93 baseline samples from COLA40263) and 0.02 μM (0.01 to 0.03 μM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC_{50} values of zidovudine against different HIV-1 clades (A-G) ranged from 0.00018 to 0.02 μM, and against HIV-2 isolates from 0.00049 to 0.004 μM. In cell culture drug combination studies, zidovudine demonstrates synergistic activity with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir, didanosine, lamivudine, and zalcitabine; the non-nucleoside reverse transcriptase inhibitors (NNRTIs) delavirdine and nevirapine; and the protease inhibitors (PIs) indinavir, nelfinavir, ritonavir, and saquinavir; and additive activity with interferon alfa. Ribavirin has been found to inhibit the phosphorylation of zidovudine in cell culture.

Resistance: ***Lamivudine Plus Zidovudine Administered As Separate Formulations:*** In patients receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most patients became phenotypically and genotypically resistant to lamivudine within 12 weeks. In some patients harboring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients after prolonged lamivudine/zidovudine therapy. Dual resistance required the presence of multiple mutations, the most essential of which may be at codon G333E. The incidence of dual resistance and the duration of combination therapy required before dual resistance occurs are unknown.

Lamivudine: Lamivudine-resistant isolates of HIV-1 have been selected in cell culture and have also been recovered from patients treated with lamivudine or lamivudine plus zidovudine. Genotypic analysis of isolates selected in cell culture and recovered from lamivudine-treated patients showed that the resistance was due to a specific amino acid substitution in the HIV-1 reverse transcriptase at codon 184 changing the methionine to either isoleucine or valine (M184V/I).

Zidovudine: HIV isolates with reduced susceptibility to zidovudine have been selected in cell culture and were also recovered from patients treated with zidovudine. Genotypic analyses of the isolates selected in cell culture and recovered from zidovudine-treated patients showed mutations in the HIV-1 RT gene resulting in 6 amino acid substitutions (M41L, D67N, K70R, L210W, T215Y or F, and K219Q) that confer zidovudine resistance. In general, higher levels of resistance were associated with greater number of mutations.

Cross-Resistance: Cross-resistance has been observed among NRTIs.

Lamivudine Plus Zidovudine: Cross-resistance between lamivudine and zidovudine has not been reported. In some patients treated with lamivudine alone or in combination with zidovudine, isolates have emerged with a mutation at codon 184, which confers resistance to lamivudine. Cross-resistance to abacavir, didanosine, tenofovir, and zalcitabine has been observed in some patients harboring lamivudine-resistant HIV-1 isolates. In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple drugs, including lamivudine, have emerged (see under Zidovudine below).

Lamivudine: See Lamivudine Plus Zidovudine (above).

Zidovudine: In a study of 167 HIV-infected patients, isolates (n = 2) with multi-drug resistance to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine were recovered from patients treated for ≥1 year with zidovudine plus didanosine or zidovudine plus zalcitabine. The pattern of resistance-associated mutations with such combination therapies was different (A62V, V75I, F77L, F116Y, Q151M) from the pattern with zidovudine monotherapy, with the Q151M mutation being most commonly associated with multi-drug resistance. The mutation at codon 151 in combination with mutations at 62, 75, 77, and 116 results in a virus with reduced susceptibility to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine. Thymidine analogue mutations (TAMs) are selected by zidovudine and confer cross-resistance to abacavir, didanosine, stavudine, tenofovir, and zalcitabine.

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults: ***COMBIVIR:*** One COMBIVIR Tablet was bioequivalent to 1 EPIVIR Tablet (150 mg) plus 1 RETROVIR Tablet (300 mg) following single-dose administration to fasting healthy subjects (n = 24).

Lamivudine: The pharmacokinetic properties of lamivudine in fasting patients are summarized in Table 1. Following oral administration, lamivudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low. Approximately 70% of an intravenous dose of lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours).

Zidovudine: The pharmacokinetic properties of zidovudine in fasting patients are summarized in Table 1. Following oral administration, zidovudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low. Zidovudine is eliminated primarily by hepatic metabolism. The major metabolite of zidovudine is 3´-azido-3´-deoxy-5´-*O*-β-*D*-glucopyranuronosylthymidine (GZDV). GZDV area under the curve (AUC) is about 3-fold greater than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 14% and 74% of the dose following oral administration, respectively. A second metabolite, 3´-amino-3´-deoxythymidine (AMT), has been identified in plasma. The AMT AUC was one fifth of the zidovudine AUC.

Table 1. Pharmacokinetic Parameters* for Lamivudine and Zidovudine in Adults

Parameter	Lamivudine		Zidovudine	
Oral bioavailability (%)	86 ± 16	n = 12	64 ± 10	n = 5
Apparent volume of distribution (L/kg)	1.3 ± 0.4	n = 20	1.6 ± 0.6	n = 8
Plasma protein binding (%)	<36		<38	
CSF:plasma ratio†	0.12 [0.04 to 0.47]	n = 38‡	0.60 [0.04 to 2.62]	n = 39§
Systemic clearance (L/hr/kg)	0.33 ± 0.06	n = 20	1.6 ± 0.6	n = 6
Renal clearance (L/hr/kg)	0.22 ± 0.06	n = 20	0.34 ± 0.05	n = 9
Elimination half-life (hr)‖	5 to 7		0.5 to 3	

* Data presented as mean ± standard deviation except where noted.
† Median [range].
‡ Children.
§ Adults.
‖ Approximate range.

Effect of Food on Absorption of COMBIVIR: COMBIVIR may be administered with or without food. The extent of lamivudine and zidovudine absorption (AUC) following administration of COMBIVIR with food was similar when compared to fasting healthy subjects (n = 24).

Special Populations: ***Impaired Renal Function: COMBIVIR:*** Because lamivudine and zidovudine require dose adjustment in the presence of renal insufficiency, COMBIVIR is not recommended for patients with impaired renal function (creatinine clearance <50 mL/min) (see PRECAUTIONS).

Impaired Hepatic Function: COMBIVIR: A reduction in the daily dose of zidovudine may be necessary in patients with mild to moderate impaired hepatic function or liver cirrhosis. Because COMBIVIR is a fixed-dose combination that cannot be adjusted for this patient population, COMBIVIR is not recommended for patients with impaired hepatic function.

Pregnancy: See PRECAUTIONS: Pregnancy.

COMBIVIR: No data are available.

Zidovudine: Zidovudine pharmacokinetics has been studied in a Phase 1 study of 8 women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation. The pharmacokinetics of zidovudine was similar to that of nonpregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery. Although data are limited, methadone maintenance therapy in 5 pregnant women did not appear to alter zidovudine pharmacokinetics. In a nonpregnant adult population, a potential for interaction has been identified (see CLINICAL PHARMACOLOGY: Drug Interactions).

Nursing Mothers: See PRECAUTIONS: Nursing Mothers.

COMBIVIR: No data are available.

Lamivudine: Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

Zidovudine: After administration of a single dose of 200 mg zidovudine to 13 HIV-infected women, the mean concentration of zidovudine was similar in human milk and serum.

Pediatric Patients: COMBIVIR: COMBIVIR should not be administered to pediatric patients less than 12 years of age because it is a fixed-dose combination that cannot be adjusted for this patient population.

Geriatric Patients: The pharmacokinetics of lamivudine and zidovudine have not been studied in patients over 65 years of age.

Gender: COMBIVIR: A pharmacokinetic study in healthy male (n = 12) and female (n = 12) subjects showed no gender differences in zidovudine exposure (AUC∞) or lamivudine AUC∞ normalized for body weight.

Race: Lamivudine: There are no significant racial differences in lamivudine pharmacokinetics.

Zidovudine: The pharmacokinetics of zidovudine with respect to race have not been determined.

Drug Interactions: See PRECAUTIONS: Drug Interactions.

COMBIVIR: No drug interaction studies have been conducted using COMBIVIR Tablets.

Lamivudine Plus Zidovudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q 12 hr).

Table 2. Effect of Coadministered Drugs on Lamivudine and Zidovudine AUC*

Note: ROUTINE DOSE MODIFICATION OF LAMIVUDINE AND ZIDOVUDINE IS NOT WARRANTED WITH COADMINISTRATION OF THE FOLLOWING DRUGS.

Drugs That May Alter Lamivudine Blood Concentrations					
Coadministered Drug and Dose	**Lamivudine Dose**	**n**	**Lamivudine Concentrations**		**Concentration of Coadministered Drug**
			AUC	**Variability**	
Nelfinavir 750 mg q 8 hr x 7 to 10 days	single 150 mg	11	↑AUC 10%	95% CI: 1% to 20%	↔
Trimethoprim 160 mg/ Sulfamethoxazole 800 mg daily x 5 days	single 300 mg	14	↑AUC 43%	90% CI: 32% to 55%	↔
Drugs That May Alter Zidovudine Blood Concentrations					
Coadministered Drug and Dose	**Zidovudine Dose**	**n**	**Zidovudine Concentrations**		**Concentration of Coadministered Drug**
			AUC	**Variability**	
Atovaquone 750 mg q 12 hr with food	200 mg q 8 hr	14	↑AUC 31%	Range 23% to 78%†	↔
Fluconazole 400 mg daily	200 mg q 8 hr	12	↑AUC 74%	95% CI: 54% to 98%	Not Reported
Methadone 30 to 90 mg daily	200 mg q 4 hr	9	↑AUC 43%	Range 16% to 64%†	↔
Nelfinavir 750 mg q 8 hr x 7 to 10 days	single 200 mg	11	↓AUC 35%	Range 28% to 41%	↔
Probenecid 500 mg q 6 hr x 2 days	2 mg/kg q 8 hr x 3 days	3	↑AUC 106%	Range 100% to 170%†	Not Assessed
Ritonavir 300 mg q 6 hr x 4 days	200 mg q 8 hr x 4 days	9	↓AUC 25%	95% CI: 15% to 34%	↔
Valproic acid 250 mg or 500 mg q 8 hr x 4 days	100 mg q 8 hr x 4 days	6	↑AUC 80%	Range 64% to 130%†	Not Assessed

↑ = Increase; ↓= Decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; CI = confidence interval.
* This table is not all inclusive.
† Estimated range of percent difference.

Ribavirin: In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV/HCV co-infected patients (see WARNINGS).

INDICATIONS AND USAGE

COMBIVIR is indicated in combination with other antiretrovirals for the treatment of HIV-1 infection.

Description of Clinical Studies: *COMBIVIR:* There have been no clinical trials conducted with COMBIVIR. See CLINICAL PHARMACOLOGY for information about bioequivalence. One COMBIVIR Tablet given twice daily is an alternative regimen to EPIVIR Tablets 150 mg twice daily plus RETROVIR 600 mg per day in divided doses.

Lamivudine Plus Zidovudine: The NUCB3007 (CAESAR) study was conducted using EPIVIR 150-mg Tablets (150 mg twice daily) and RETROVIR 100-mg Capsules (2 x 100 mg 3 times daily). CAESAR was a multi-center, double-blind, placebo-controlled study comparing continued current therapy [zidovudine alone (62% of patients) or zidovudine with didanosine or zalcitabine (38% of patients)] to the addition of EPIVIR or EPIVIR plus an investigational non-nucleoside reverse transcriptase inhibitor, randomized 1:2:1. A total of 1,816 HIV-infected adults with 25 to 250 (median 122) CD4 cells/mm^3 at baseline were enrolled: median age was 36 years, 87% were male, 84% were nucleoside-experienced, and 16% were therapy-naive. The median duration on study was 12 months. Results are summarized in Table 3.

Table 3. Number of Patients (%) With At Least 1 HIV Disease-Progression Event or Death

Endpoint	Current Therapy (n = 460)	EPIVIR plus Current Therapy (n = 896)	EPIVIR plus a NNRTI* plus Current Therapy (n = 460)
HIV progression or death	90 (19.6%)	86 (9.6%)	41 (8.9%)
Death	27 (5.9%)	23 (2.6%)	14 (3.0%)

* An investigational non-nucleoside reverse transcriptase inhibitor not approved in the United States.

CONTRAINDICATIONS

COMBIVIR Tablets are contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the product.

WARNINGS

COMBIVIR is a fixed-dose combination of lamivudine and zidovudine. Ordinarily, COMBIVIR should not be administered concomitantly with lamivudine, zidovudine, EPZICOM™, a fixed-dose combination of abacavir and lamivudine, or TRIZIVIR®, a fixed-dose combination of abacavir, lamivudine, and zidovudine.

The complete prescribing information for all agents being considered for use with COMBIVIR should be consulted before combination therapy with COMBIVIR is initiated.

Bone Marrow Suppression: COMBIVIR should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count <1,000 cells/mm^3 or hemoglobin <9.5 g/dL (see ADVERSE REACTIONS).

Frequent blood counts are strongly recommended in patients with advanced HIV disease who are treated with COMBIVIR. For HIV-infected individuals and patients with asymptomatic or early HIV disease, periodic blood counts are recommended.

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 lamivudine, zidovudine, 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 COMBIVIR 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 COMBIVIR 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).

Myopathy: Myopathy and myositis, with pathological changes similar to that produced by HIV disease, have been associated with prolonged use of zidovudine, and therefore may occur with therapy with COMBIVIR.

Posttreatment Exacerbations of Hepatitis: In clinical trials in non-HIV-infected patients treated with lamivudine for chronic HBV, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence of hepatitis B viral DNA (HBV DNA). Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from post-marketing experience after changes from lamivudine-containing HIV treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters the course of posttreatment exacerbations of hepatitis.

Use With Interferon- and Ribavirin-Based Regimens: In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine and zidovudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine or zidovudine in HIV/HCV co-infected patients (see CLINICAL PHARMACOLOGY: Drug Interactions), **hepatic decompensation (some fatal) has occurred in HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon alfa with or without ribavirin.** Patients receiving interferon alfa with or without ribavirin and COMBIVIR should be closely monitored for treatment-associated toxicities, especially hepatic decompensation, neutropenia, and anemia. Discontinuation of COMBIVIR should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Childs Pugh >6) (see the complete prescribing information for interferon and ribavirin).

PRECAUTIONS

Patients With HIV and Hepatitis B Virus Co-infection: Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients dually infected with HIV and HBV. In non-HIV-infected patients treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected and has been associated with diminished treatment response (see EPIVIR-HBV package insert for additional information). Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus. Posttreatment exacerbations of hepatitis have also been reported (see WARNINGS).

Patients With Impaired Renal Function: Reduction of the dosages of lamivudine and zidovudine is recommended for patients with impaired renal function. Patients with creatinine clearance <50 mL/min should not receive COMBIVIR.

Patients With Impaired Hepatic Function: A reduction in the daily dose of zidovudine may be necessary in patients with mild to moderate impaired hepatic function or liver cirrhosis. COMBIVIR is not recommended for patients with impaired hepatic function.

Immune Reconstitution Syndrome: Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including COMBIVIR. 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.

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.

Information for Patients: COMBIVIR is not a cure for HIV infection and patients may continue to experience illnesses associated with HIV infection, including opportunistic infections. Patients should be advised that the use of COMBIVIR has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination. Patients should be advised of the importance of taking COMBIVIR exactly as it is prescribed.

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.

Lamivudine: Patients co-infected with HIV and HBV should be informed that deterioration of liver disease has occurred in some cases when treatment with lamivudine was discontinued. Patients should be advised to discuss any changes in regimen with their physician.

Zidovudine: Patients should be informed that the important toxicities associated with zidovudine are neutropenia and/or anemia. They should be told of the extreme importance of having their blood counts followed closely while on therapy, especially for patients with advanced HIV disease.

Drug Interactions: *Lamivudine:* Trimethoprim (TMP) 160 mg/sulfamethoxazole (SMX) 800 mg once daily has been shown to increase lamivudine exposure (AUC). The effect of higher doses of TMP/SMX on lamivudine pharmacokinetics has not been investigated (see CLINICAL PHARMACOLOGY). No data are available regarding the potential for interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of COMBIVIR in combination with zalcitabine is not recommended.

Zidovudine: Coadministration of ganciclovir, interferon alfa, and other bone marrow suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine.

Concomitant use of COMBIVIR with stavudine should be avoided since an antagonistic relationship with zidovudine has been demonstrated in vitro. In addition, concomitant use of COMBIVIR with doxorubicin or ribavirin should be avoided because an antagonistic relationship with zidovudine has been demonstrated in vitro.

See CLINICAL PHARMACOLOGY for additional drug interactions.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: *Carcinogenicity:*

Lamivudine: Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at the recommended therapeutic dose for HIV infection.

Zidovudine: Zidovudine was administered orally at 3 dosage levels to separate groups of mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60, and 120 mg/kg/day in mice and 80, 220, and 600 mg/kg/day in rats. The doses in mice were reduced to 20, 30, and 40 mg/kg/day after day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg/kg/day on day 91 and then to 300 mg/kg/day on day 279.

In mice, 7 late-appearing (after 19 months) vaginal neoplasms (5 nonmetastasizing squamous cell carcinomas, 1 squamous cell papilloma, and 1 squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of a middle-dose animal. No vaginal tumors were found at the lowest dose.

In rats, 2 late-appearing (after 20 months), nonmetastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle dose in rats. No other drug-related tumors were observed in either sex of either species.

At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 3 times (mouse) and 24 times (rat) the estimated human exposure at the recommended therapeutic dose of 100 mg every 4 hours.

Two transplacental carcinogenicity studies were conducted in mice. One study administered zidovudine at doses of 20 mg/kg/day or 40 mg/kg/day from gestation day 10 through parturition and lactation with dosing continuing in offspring for 24 months postnatally. The doses of zidovudine employed in this study produced zidovudine exposures approximately 3 times the estimated human exposure at recommended doses. After 24 months at the highest dose, an increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in either gender. These findings are consistent with results of the standard oral carcinogenicity study in mice, as described earlier. A second study administered zidovudine at maximum tolerated doses of 12.5 mg/day or 25 mg/day (~1,000 mg/kg nonpregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from days 12 through 18 of gestation. There was an increase in the number of tumors in the lung, liver, and female reproductive tracts in the offspring of mice receiving the higher dose level of zidovudine.

It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Mutagenicity: Lamivudine: Lamivudine was mutagenic in an L5178Y/TK$^{+/-}$ mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was negative in a microbial mutagenicity assay, in an in vitro cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver.

Zidovudine: Zidovudine was mutagenic in an L5178Y/TK$^{+/-}$ mouse lymphoma assay, positive in an in vitro cell transformation assay, clastogenic in a cytogenetic assay using cultured human lymphocytes, and positive in mouse and rat micronucleus tests after repeated doses. It was negative in a cytogenetic study in rats given a single dose.

Impairment of Fertility: Lamivudine: In a study of reproductive performance, lamivudine, administered to male and female rats at doses up to 130 times the usual adult dose based on body surface area considerations, revealed no evidence of impaired fertility (judged by conception rates) and no effect on the survival, growth, and development to weaning of the offspring.

Zidovudine: Zidovudine, administered to male and female rats at doses up to 7 times the usual adult dose based on body surface area considerations, had no effect on fertility judged by conception rates.

Pregnancy: Pregnancy Category C.

COMBIVIR: There are no adequate and well-controlled studies of COMBIVIR in pregnant women. Reproduction studies with lamivudine and zidovudine have been performed in animals (see Lamivudine and Zidovudine sections below). COMBIVIR should be used during pregnancy only if the potential benefits outweigh the risks.

Lamivudine: Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta. Reproduction studies with orally administered lamivudine have been performed in rats and rabbits at doses up to 4,000 mg/kg/day and 1,000 mg/kg/day, respectively, producing plasma levels up to approximately 35 times that for the adult HIV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryolethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 35 times those in humans.

Zidovudine: Reproduction studies with orally administered zidovudine in the rat and in the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal toxicity as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one half of the daily dose) in rats 66 to 226 times, and in rabbits 12 to 87 times, mean steady-state peak human plasma concentrations (after one sixth of the daily dose) achieved with the recommended daily dose (100 mg every 4 hours). In an additional teratology study in rats, a dose of 3,000 mg/kg/day (very near the oral median lethal dose in rats of 3,683 mg/kg) caused marked maternal toxicity and an increase in the incidence of fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations. No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg/day or less. Two rodent carcinogenicity studies were conducted (see Carcinogenesis, Mutagenesis, Impairment of Fertility).

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

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV infection. No specific studies of lamivudine and zidovudine excretion in breast milk after dosing with COMBIVIR have been performed. Lamivudine and zidovudine are excreted in human breast milk (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Nursing Mothers). A study in lactating rats administered 45 mg/kg of lamivudine showed that lamivudine concentrations in milk were slightly greater than those in plasma.

Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving COMBIVIR.**

Pediatric Use: COMBIVIR should not be administered to pediatric patients less than 12 years of age because it is a fixed-dose combination that cannot be adjusted for this patient population.

Geriatric Use: Clinical studies of COMBIVIR did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. COMBIVIR is not recommended for patients with impaired renal function (i.e., creatinine clearance <50 mL/min; see PRECAUTIONS: Patients with Impaired Renal Function and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Lamivudine Plus Zidovudine Administered As Separate Formulations: In 4 randomized, controlled trials of EPIVIR 300 mg per day plus RETROVIR 600 mg per day, the following selected clinical and laboratory adverse events were observed (see Tables 4 and 5).

Table 4. Selected Clinical Adverse Events (≥5% Frequency) in 4 Controlled Clinical Trials With EPIVIR 300 mg/day and RETROVIR 600 mg/day

Adverse Event	EPIVIR plus RETROVIR (n = 251)
Body as a whole	
Headache	35%
Malaise & fatigue	27%
Fever or chills	10%
Digestive	
Nausea	33%
Diarrhea	18%
Nausea & vomiting	13%
Anorexia and/or decreased appetite	10%
Abdominal pain	9%
Abdominal cramps	6%
Dyspepsia	5%
Nervous system	
Neuropathy	12%
Insomnia & other sleep disorders	11%
Dizziness	10%
Depressive disorders	9%
Respiratory	
Nasal signs & symptoms	20%
Cough	18%
Skin	
Skin rashes	9%
Musculoskeletal	
Musculoskeletal pain	12%
Myalgia	8%
Arthralgia	5%

Pancreatitis was observed in 3 of the 656 adult patients (<0.5%) who received EPIVIR in controlled clinical trials.

Selected laboratory abnormalities observed during therapy are listed in Table 5.

Table 5. Frequencies of Selected Laboratory Abnormalities Among Adults in 4 Controlled Clinical Trials of EPIVIR 300 mg/day plus RETROVIR 600 mg/day*

Test (Abnormal Level)	EPIVIR plus RETROVIR % (n)
Neutropenia (ANC<750/mm^3)	7.2% (237)
Anemia (Hgb<8.0 g/dL)	2.9% (241)
Thrombocytopenia (platelets<50,000/mm^3)	0.4% (240)
ALT (>5.0 x ULN)	3.7% (241)
AST (>5.0 x ULN)	1.7% (241)
Bilirubin (>2.5 x ULN)	0.8% (241)
Amylase (>2.0 x ULN)	4.2% (72)

ULN = Upper limit of normal.
ANC = Absolute neutrophil count.
n = Number of patients assessed.
* Frequencies of these laboratory abnormalities were higher in patients with mild laboratory abnormalities at baseline.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of EPIVIR, RETROVIR, and/or COMBIVIR. 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 a combination of their seriousness, frequency of reporting, or potential causal connection to EPIVIR, RETROVIR, and/or COMBIVIR.

Body as a Whole: Redistribution/accumulation of body fat (see PRECAUTIONS: Fat Redistribution).

Cardiovascular: Cardiomyopathy.

Endocrine and Metabolic: Gynecomastia, hyperglycemia.

Gastrointestinal: Oral mucosal pigmentation, stomatitis.

General: Vasculitis, weakness.

Hemic and Lymphatic: Anemia, (including pure red cell aplasia and severe anemias progressing on therapy), lymphadenopathy, splenomegaly.

Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis, pancreatitis, posttreatment exacerbation of hepatitis B (see WARNINGS).

Hypersensitivity: Sensitization reactions (including anaphylaxis), urticaria.

Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.

Nervous: Paresthesia, peripheral neuropathy, seizures.

Respiratory: Abnormal breath sounds/wheezing.

Skin: Alopecia, erythema multiforme, Stevens-Johnson syndrome.

OVERDOSAGE

COMBIVIR: There is no known antidote for COMBIVIR.

Lamivudine: One case of an adult ingesting 6 grams of lamivudine was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event.

Zidovudine: Acute overdoses of zidovudine have been reported in pediatric patients and adults. These involved exposures up to 50 grams. The only consistent findings were nausea and vomiting. Other reported occurrences included headache, dizziness, drowsiness, lethargy, confusion, and 1 report of a grand mal seizure. Hematologic changes were transient. All patients recovered. Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine, while elimination of its primary metabolite, GZDV, is enhanced.

DOSAGE AND ADMINISTRATION

The recommended oral dose of COMBIVIR for adults and adolescents (at least 12 years of age) is 1 tablet (containing 150 mg of lamivudine and 300 mg of zidovudine) twice daily.

Dose Adjustment: Because it is a fixed-dose combination, COMBIVIR should not be prescribed for patients requiring dosage adjustment such as those with reduced renal function (creatinine clearance <50 mL/min), patients with hepatic impairment, or patients experiencing dose-limiting adverse events.

HOW SUPPLIED

COMBIVIR Tablets, containing 150 mg lamivudine and 300 mg zidovudine, are white, film-coated, modified-capsule-shaped tablets engraved with "GXFC3" on one side. They are available as follows:

60 Tablets/Bottle (NDC 0173-0595-00)

Store between 2° and 30°C (36° and 86°F).

Unit Dose Pack of 120 (NDC 0173-0595-02)

Store between 2° and 30°C (36° and 86°F).

GlaxoSmithKline
Research Triangle Park, NC 27709

Lamivudine is manufactured under agreement from
Shire Pharmaceuticals Group plc
Basingstoke, UK

October 2006 RL-2315

EPIVIR® Tablets
(lamivudine tablets)

EPIVIR® Oral Solution
(lamivudine oral solution)

WARNING

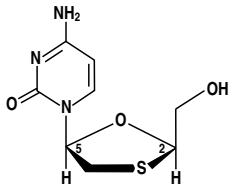
LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING LAMIVUDINE AND OTHER ANTIRETROVIRALS (SEE WARNINGS).

EPIVIR TABLETS AND ORAL SOLUTION (USED TO TREAT HUMAN IMMUNODEFICIENCY VIRUS [HIV] INFECTION) CONTAIN A HIGHER DOSE OF THE ACTIVE INGREDIENT (LAMIVUDINE) THAN EPIVIR-HBV® TABLETS AND ORAL SOLUTION (USED TO TREAT CHRONIC HEPATITIS B). PATIENTS WITH HIV INFECTION SHOULD RECEIVE ONLY DOSING FORMS APPROPRIATE FOR TREATMENT OF HIV (SEE WARNINGS AND PRECAUTIONS).

SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED WITH HEPATITIS B VIRUS (HBV) AND HIV AND HAVE DISCONTINUED EPIVIR. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE EPIVIR AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS).

DESCRIPTION

EPIVIR (also known as 3TC) is a brand name for lamivudine, a synthetic nucleoside analogue with activity against HIV-1 and HBV. The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2′,3′-dideoxy, 3′-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.3. It has the following structural formula:



Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg/mL in water at 20°C.

EPIVIR Tablets are for oral administration. Each 150-mg film-coated tablet contains 150 mg of lamivudine and the inactive ingredients hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

Each 300-mg film-coated tablet contains 300 mg of lamivudine and the inactive ingredients black iron oxide, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

EPIVIR Oral Solution is for oral administration. One milliliter (1 mL) of EPIVIR Oral Solution contains 10 mg of lamivudine (10 mg/mL) in an aqueous solution and the inactive ingredients artificial strawberry and banana flavors, citric acid (anhydrous), methylparaben, propylene glycol, propylparaben, sodium citrate (dihydrate), and sucrose (200 mg).

MICROBIOLOGY

Mechanism of Action: Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5′-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is the inhibition of HIV-1 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue into viral DNA. 3TC-TP is a weak inhibitor of mammalian DNA polymerases α, β, and γ.

Antiviral Activity: The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. EC_{50} values (50% effective concentrations) were in the range of 0.003 to 15 µM (1 µM = 0.23 mcg/mL). HIV from therapy-naive subjects with no mutations associated with resistance gave median EC_{50} values of 0.426 µM (range: 0.200 to 2.007 µM) from Virco (n = 93 baseline samples from COLA40263) and 2.35 µM (1.44 to 4.08 µM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC_{50} values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120 µM, and against HIV-2 isolates from 0.003 to 0.120 µM in peripheral blood mononuclear cells. Ribavirin (50 µM) decreased the anti-HIV-1 activity of lamivudine by 3.5 fold in MT-4 cells. In HIV–1-infected MT-4 cells, lamivudine in combination with zidovudine at various ratios exhibited synergistic antiretroviral activity. Please see the EPIVIR-HBV package insert for information regarding the inhibitory activity of lamivudine against HBV.

Resistance: Lamivudine-resistant variants of HIV-1 have been selected in cell culture. Genotypic analysis showed that the resistance was due to a specific amino acid substitution in the HIV-1 reverse transcriptase at codon 184 changing the methionine to either isoleucine or valine (M184V/I).

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients. Susceptibility of clinical isolates to lamivudine and zidovudine was monitored in controlled clinical trials. In patients receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most patients became phenotypically and genotypically resistant to lamivudine within 12 weeks. In some patients harboring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

Mutations in the HBV polymerase YMDD motif have been associated with reduced susceptibility of HBV to lamivudine in cell culture. In studies of non–HIV-infected patients with chronic hepatitis B, HBV isolates with YMDD mutations were detected in some patients who received lamivudine daily for 6 months or more, and were associated with evidence of diminished treatment response; similar HBV mutants have been reported in HIV-infected patients who received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus (see PRECAUTIONS and EPIVIR-HBV package insert).

Cross-Resistance: Lamivudine-resistant HIV-1 mutants were cross-resistant to didanosine (ddI) and zalcitabine (ddC). In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

Genotypic and Phenotypic Analysis of On-Therapy HIV-1 Isolates From Patients With Virologic Failure (see INDICATIONS AND USAGE: Description of Clinical Studies): The clinical relevance of genotypic and phenotypic changes associated with lamivudine therapy has not been fully established.

Study EPV20001: Fifty-three of 554 (10%) patients enrolled in EPV20001 were identified as virological failures (plasma HIV-1 RNA level ≥400 copies/mL) by Week 48. Twenty-eight patients were randomized to the lamivudine once-daily treatment group and 25 to the lamivudine twice-daily treatment group. The median baseline plasma HIV-1 RNA levels of patients in the lamivudine once-daily group and lamivudine twice-daily group were 4.9 $\log_{10}$ copies/mL and 4.6 $\log_{10}$ copies/mL, respectively.

Genotypic analysis of on-therapy isolates from 22 patients identified as virologic failures in the lamivudine once-daily group showed that isolates from 0/22 patients contained treatment-emergent mutations associated with zidovudine resistance (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E), isolates from 10/22 patients contained treatment-emergent mutations associated with efavirenz resistance (L100I, K101E, K103N, V108I, or Y181C), and isolates from 8/22 patients contained a treatment-emergent lamivudine resistance-associated mutation (M184I or M184V).

Genotypic analysis of on-therapy isolates from patients (n = 22) in the lamivudine twice-daily treatment group showed that isolates from 1/22 patients contained treatment-emergent zidovudine resistance mutations, isolates from 7/22 contained treatment-emergent efavirenz resistance mutations, and isolates from 5/22 contained treatment-emergent lamivudine resistance mutations.

Phenotypic analysis of baseline-matched on-therapy HIV-1 isolates from patients (n = 13) receiving lamivudine once daily showed that isolates from 12/13 patients were susceptible to zidovudine; isolates from 8/13 patients exhibited a 25- to 295-fold decrease in susceptibility to efavirenz, and isolates from 7/13 patients showed an 85- to 299-fold decrease in susceptibility to lamivudine.

Phenotypic analysis of baseline-matched on-therapy HIV-1 isolates from patients (n = 13) receiving lamivudine twice daily showed that isolates from all 13 patients were susceptible to zidovudine; isolates from 3/13 patients exhibited a 21- to 342-fold decrease in susceptibility to efavirenz, and isolates from 4/13 patients exhibited a 29- to 159-fold decrease in susceptibility to lamivudine.

Study EPV40001: Fifty patients received zidovudine 300 mg twice daily plus abacavir 300 mg twice daily plus lamivudine 300 mg once daily and 50 patients received zidovudine 300 mg plus abacavir 300 mg plus lamivudine 150 mg all twice daily. The median baseline plasma HIV-1 RNA levels for patients in the 2 groups were 4.79 $\log_{10}$ copies/mL and 4.83 $\log_{10}$ copies/mL, respectively. Fourteen of 50 patients in the lamivudine once-daily treatment group and 9 of 50 patients in the lamivudine twice-daily group were identified as virologic failures.

Genotypic analysis of on-therapy HIV-1 isolates from patients (n = 9) in the lamivudine once-daily treatment group showed that isolates from 6 patients had abacavir and/or lamivudine resistance-associated mutation M184V alone. On-therapy isolates from patients (n = 6) receiving lamivudine twice daily showed that isolates from 2 patients had M184V alone, and isolates from 2 patients harbored the M184V mutation in combination with zidovudine resistance-associated mutations.

Phenotypic analysis of on-therapy isolates from patients (n = 6) receiving lamivudine once daily showed that HIV-1 isolates from 4 patients exhibited a 32- to 53-fold decrease in susceptibility to lamivudine. HIV-1 isolates from these 6 patients were susceptible to zidovudine.

Phenotypic analysis of on-therapy isolates from patients (n = 4) receiving lamivudine twice daily showed that HIV-1 isolates from 1 patient exhibited a 45-fold decrease in susceptibility to lamivudine and a 4.5-fold decrease in susceptibility to zidovudine.

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults: The steady-state pharmacokinetic properties of the EPIVIR 300-mg tablet once daily for 7 days compared to the EPIVIR 150-mg tablet twice daily for 7 days were assessed in a crossover study in 60 healthy volunteers. EPIVIR 300 mg once daily resulted in lamivudine exposures that were similar to EPIVIR 150 mg twice daily with respect to plasma $AUC_{24,ss}$; however, $C_{max,ss}$ was 66% higher and the trough value was 53% lower compared to the 150-mg twice-daily regimen. Intracellular lamivudine triphosphate exposures in peripheral blood mononuclear cells were also similar with respect to $AUC_{24,ss}$ and $C_{max24,ss}$; however, trough values were lower compared to the 150-mg twice-daily regimen. Inter-subject variability was greater for intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough concentrations. The clinical significance of observed differences for both plasma lamivudine concentrations and intracellular lamivudine triphosphate concentrations is not known.

The pharmacokinetic properties of lamivudine have been studied in asymptomatic, HIV-infected adult patients after administration of single intravenous (IV) doses ranging from 0.25 to 8 mg/kg, as well as single and multiple (twice-daily regimen) oral doses ranging from 0.25 to 10 mg/kg.

The pharmacokinetic properties of lamivudine have also been studied as single and multiple oral doses ranging from 5 mg to 600 mg/day administered to HBV-infected patients.

Absorption and Bioavailability: Lamivudine was rapidly absorbed after oral administration in HIV-infected patients. Absolute bioavailability in 12 adult patients was 86% ± 16% (mean ± SD) for the 150-mg tablet and 87% ± 13% for the oral solution. After oral administration of 2 mg/kg twice a day to 9 adults with HIV, the peak serum lamivudine concentration (C_{max}) was 1.5 ± 0.5 mcg/mL (mean ± SD). The area under the plasma concentration versus time curve (AUC) and C_{max} increased in proportion to oral dose over the range from 0.25 to 10 mg/kg.

An investigational 25-mg dosage form of lamivudine was administered orally to 12 asymptomatic, HIV-infected patients on 2 occasions, once in the fasted state and once with food (1,099 kcal; 75 grams fat, 34 grams protein, 72 grams carbohydrate). Absorption of lamivudine was slower in the fed state (T_{max}: 3.2 ± 1.3 hours) compared with the fasted state (T_{max}: 0.9 ± 0.3 hours); C_{max} in the fed state was 40% ± 23% (mean ± SD) lower than in the fasted state. There was no significant difference in systemic exposure (AUC_∞) in the fed and fasted states; therefore, EPIVIR Tablets and Oral Solution may be administered with or without food.

The accumulation ratio of lamivudine in HIV-positive asymptomatic adults with normal renal function was 1.50 following 15 days of oral administration of 2 mg/kg twice daily.

Distribution: The apparent volume of distribution after IV administration of lamivudine to 20 patients was 1.3 ± 0.4 L/kg, suggesting that lamivudine distributes into extravascular spaces. Volume of distribution was independent of dose and did not correlate with body weight.

Binding of lamivudine to human plasma proteins is low (<36%). In vitro studies showed that, over the concentration range of 0.1 to 100 mcg/mL, the amount of lamivudine associated with erythrocytes ranged from 53% to 57% and was independent of concentration.

Metabolism: Metabolism of lamivudine is a minor route of elimination. In man, the only known metabolite of lamivudine is the trans-sulfoxide metabolite. Within 12 hours after a single oral dose of lamivudine in 6 HIV-infected adults, 5.2% ± 1.4% (mean ± SD) of the dose was excreted as the trans-sulfoxide metabolite in the urine. Serum concentrations of this metabolite have not been determined.

Elimination: The majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion. In 9 healthy subjects given a single 300-mg oral dose of lamivudine, renal clearance was 199.7 ± 56.9 mL/min (mean ± SD). In 20 HIV-infected patients given a single IV dose, renal clearance was 280.4 ± 75.2 mL/min (mean ± SD), representing 71% ± 16% (mean ± SD) of total clearance of lamivudine.

In most single-dose studies in HIV-infected patients, HBV-infected patients, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{1/2}$) ranged from 5 to 7 hours. In HIV-infected patients, total clearance was 398.5 ± 69.1 mL/min (mean ± SD). Oral clearance and elimination half-life were independent of dose and body weight over an oral dosing range from 0.25 to 10 mg/kg.

Special Populations: ***Adults With Impaired Renal Function:*** The pharmacokinetic properties of lamivudine have been determined in a small group of HIV-infected adults with impaired renal function (Table 1).

Table 1. Pharmacokinetic Parameters (Mean ± SD) After a Single 300-mg Oral Dose of Lamivudine in 3 Groups of Adults With Varying Degrees of Renal Function

	Creatinine Clearance Criterion (Number of Subjects)		
Parameter	>60 mL/min (n = 6)	10-30 mL/min (n = 4)	<10 mL/min (n = 6)
Creatinine clearance (mL/min)	111 ± 14	28 ± 8	6 ± 2
C_{max} (mcg/mL)	2.6 ± 0.5	3.6 ± 0.8	5.8 ± 1.2
AUC_∞ (mcg•hr/mL)	11.0 ± 1.7	48.0 ± 19	157 ± 74
Cl/F (mL/min)	464 ± 76	114 ± 34	36 ± 11

Exposure (AUC_∞), C_{max}, and half-life increased with diminishing renal function (as expressed by creatinine clearance). Apparent total oral clearance (Cl/F) of lamivudine decreased as creatinine clearance decreased. T_{max} was not significantly affected by renal function. Based on these observations, it is recommended that the dosage of lamivudine be modified in patients with renal impairment (see DOSAGE AND ADMINISTRATION).

Based on a study in otherwise healthy subjects with impaired renal function, hemodialysis increased lamivudine clearance from a mean of 64 to 88 mL/min; however, the length of time of hemodialysis (4 hours) was insufficient to significantly alter mean lamivudine exposure after a single-dose administration. Continuous ambulatory peritoneal dialysis and automated peritoneal dialysis have negligible effects on lamivudine clearance. Therefore, it is recommended, following correction of dose for creatinine clearance, that no additional dose modification be made after routine hemodialysis or peritoneal dialysis.

It is not known whether lamivudine can be removed by continuous (24-hour) hemodialysis.

The effects of renal impairment on lamivudine pharmacokinetics in pediatric patients are not known.

Adults With Impaired Hepatic Function: The pharmacokinetic properties of lamivudine have been determined in adults with impaired hepatic function. Pharmacokinetic parameters were not altered by diminishing hepatic function; therefore, no dose adjustment for lamivudine is required for patients with impaired hepatic function. Safety and efficacy of lamivudine have not been established in the presence of decompensated liver disease.

Pediatric Patients: For pharmacokinetic properties of lamivudine in pediatric patients, see PRECAUTIONS: Pediatric Use.

Continued

Gender: There are no significant gender differences in lamivudine pharmacokinetics.

Race: There are no significant racial differences in lamivudine pharmacokinetics.

Drug Interactions: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q 12 hr).

Lamivudine and trimethoprim/sulfamethoxazole (TMP/SMX) were coadministered to 14 HIV-positive patients in a single-center, open-label, randomized, crossover study. Each patient received treatment with a single 300-mg dose of lamivudine and TMP 160 mg/SMX 800 mg once a day for 5 days with concomitant administration of lamivudine 300 mg with the fifth dose in a crossover design. Coadministration of TMP/SMX with lamivudine resulted in an increase of 43% ± 23% (mean ± SD) in lamivudine AUC_{∞}, a decrease of 29% ± 13% in lamivudine oral clearance, and a decrease of 30% ± 36% in lamivudine renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by coadministration with lamivudine.

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of lamivudine in combination with zalcitabine is not recommended.

There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in a study of 19 healthy male subjects.

Ribavirin: In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multidrug regimen to HIV/HCV co-infected patients (see WARNINGS).

INDICATIONS AND USAGE

EPIVIR in combination with other antiretroviral agents is indicated for the treatment of HIV infection (see Description of Clinical Studies).

Description of Clinical Studies: The use of EPIVIR is based on the results of clinical studies in HIV-infected patients in combination regimens with other antiretroviral agents. Information from trials with clinical endpoints or a combination of CD4+ cell counts and HIV-1 RNA measurements is included below as documentation of the contribution of lamivudine to a combination regimen in controlled trials.

Clinical Endpoint Study in Adults: B3007 (CAESAR) was a multi-center, double-blind, placebo-controlled study comparing continued current therapy (zidovudine alone [62% of patients] or zidovudine with didanosine or zalcitabine [38% of patients]) to the addition of EPIVIR or EPIVIR plus an investigational non-nucleoside reverse transcriptase inhibitor (NNRTI), randomized 1:2:1. A total of 1,816 HIV-infected adults with 25 to 250 CD4+ cells/mm^3 (median = 122 cells/mm^3) at baseline were enrolled: median age was 36 years, 87% were male, 84% were nucleoside-experienced, and 16% were therapy-naive. The median duration on study was 12 months. Results are summarized in Table 2.

Table 2. Number of Patients (%) With at Least One HIV Disease Progression Event or Death

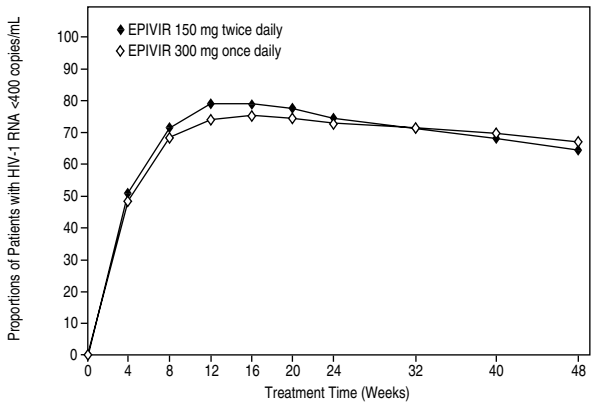
Endpoint	Current Therapy (n = 460)	EPIVIR plus Current Therapy (n = 896)	EPIVIR plus an NNRTI* plus Current Therapy (n = 460)
HIV progression or death	90 (19.6%)	86 (9.6%)	41 (8.9%)
Death	27 (5.9%)	23 (2.6%)	14 (3.0%)

* An investigational non-nucleoside reverse transcriptase inhibitor not approved in the United States.

Surrogate Endpoint Studies in Adults: Dual Nucleoside Analogue Studies: Principal clinical trials in the initial development of lamivudine compared lamivudine/zidovudine combinations against zidovudine monotherapy or against zidovudine plus zalcitabine. These studies demonstrated the antiviral effect of lamivudine in a 2-drug combination. More recent uses of lamivudine in treatment of HIV infection incorporate it into multiple-drug regimens containing at least 3 antiretroviral drugs for enhanced viral suppression.

Dose Regimen Comparison Surrogate Endpoint Studies in Therapy-Naive Adults: EPV20001 was a multicenter, double-blind, controlled study in which patients were randomized 1:1 to receive EPIVIR 300 mg once daily or EPIVIR 150 mg twice daily, in combination with zidovudine 300 mg twice daily and efavirenz 600 mg once daily. A total of 554 antiretroviral treatment-naive HIV-infected adults enrolled: male (79%), Caucasian (50%), median age of 35 years, baseline CD4+ cell counts of 69 to 1,089 cells/mm^3 (median = 362 cells/mm^3), and median baseline plasma HIV-1 RNA of 4.66 $\log_{10}$ copies/mL. Outcomes of treatment through 48 weeks are summarized in Figure 1 and Table 3.

Figure 1. Virologic Response Through Week 48, EPV20001*† (Intent-to-Treat)



* Roche AMPLICOR HIV-1 MONITOR.

† Responders at each visit are patients who had achieved and maintained HIV-1 RNA <400 copies/mL without discontinuation by that visit.

Table 3. Outcomes of Randomized Treatment Through 48 Weeks (Intent-to-Treat)

Outcome	EPIVIR 300 mg Once Daily plus RETROVIR® plus Efavirenz (n = 278)	EPIVIR 150 mg Twice Daily plus RETROVIR plus Efavirenz (n = 276)
Responder*	67%	65%
Virologic failure†	8%	8%
Discontinued due to clinical progression	<1%	0%
Discontinued due to adverse events	6%	12%
Discontinued due to other reasons‡	18%	14%

* Achieved confirmed plasma HIV-1 RNA <400 copies/mL and maintained through 48 weeks.

† Achieved suppression but rebounded by Week 48, discontinued due to virologic failure, insufficient viral response according to the investigator, or never suppressed through Week 48.

‡ Includes consent withdrawn, lost to followup, protocol violation, data outside the study-defined schedule, and randomized but never initiated treatment.

The proportions of patients with HIV-1 RNA <50 copies/mL (via Roche Ultrasensitive assay) through Week 48 were 61% for patients receiving EPIVIR 300 mg once daily and 63% for patients receiving EPIVIR 150 mg twice daily. Median increases in CD4+ cell counts were 144 cells/mm^3 at Week 48 in patients receiving EPIVIR 300 mg once daily and 146 cells/mm^3 for patients receiving EPIVIR 150 mg twice daily.

A small, randomized, open-label pilot study, EPV40001, was conducted in Thailand. A total of 159 treatment-naive adult patients (male 32%, Asian 100%, median age 30 years, baseline median CD4+ cell count 380 cells/mm^3, median plasma HIV-1 RNA 4.8 $\log_{10}$ copies/mL) were enrolled. Two of the treatment arms in this study provided a comparison between lamivudine 300 mg once daily (n = 54) and lamivudine 150 mg twice daily (n = 52), each in combination with zidovudine 300 mg twice daily and abacavir 300 mg twice daily. In intent-to-treat analyses of 48-week data, the proportions of patients with HIV-1 RNA below 400 copies/mL were 61% (33/54) in the group randomized to once-daily lamivudine and 75% (39/52) in the group randomized to receive all 3 drugs twice daily; the proportions with HIV-1 RNA below 50 copies/mL were 54% (29/54) in the once-daily lamivudine group and 67% (35/52) in the all-twice-daily group; and the median increases in CD4+ cell counts were 166 cells/mm^3 in the once-daily lamivudine group and 216 cells/mm^3 in the all-twice-daily group.

Clinical Endpoint Study in Pediatric Patients: ACTG300 was a multi-center, randomized, double-blind study that provided for comparison of EPIVIR plus RETROVIR (zidovudine) to didanosine monotherapy. A total of 471 symptomatic, HIV-infected therapy-naive (≤56 days of antiretroviral therapy) pediatric patients were enrolled in these 2 treatment arms. The median age was 2.7 years (range 6 weeks to 14 years), 58% were female, and 86% were non-Caucasian. The mean baseline CD4+ cell count was 868 cells/mm^3 (mean: 1,060 cells/mm^3 and range: 0 to 4,650 cells/mm^3 for patients ≤5 years of age; mean 419 cells/mm^3 and range: 0 to 1,555 cells/mm^3 for patients >5 years of age) and the mean baseline plasma HIV-1 RNA was 5.0 $\log_{10}$ copies/mL. The median duration on study was 10.1 months for the patients receiving EPIVIR plus RETROVIR and 9.2 months for patients receiving didanosine monotherapy. Results are summarized in Table 4.

Table 4. Number of Patients (%) Reaching a Primary Clinical Endpoint (Disease Progression or Death)

Endpoint	EPIVIR plus RETROVIR (n = 236)	Didanosine (n = 235)
HIV disease progression or death (total)	15 (6.4%)	37 (15.7%)
Physical growth failure	7 (3.0%)	6 (2.6%)
Central nervous system deterioration	4 (1.7%)	12 (5.1%)
CDC Clinical Category C	2 (0.8%)	8 (3.4%)
Death	2 (0.8%)	11 (4.7%)

CONTRAINDICATIONS

EPIVIR Tablets and Oral Solution are contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the products.

WARNINGS

In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, EPIVIR should be used with caution. Treatment with EPIVIR should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur (see ADVERSE REACTIONS).

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 lamivudine 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 EPIVIR 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 EPIVIR 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).

Important Differences Among Lamivudine-Containing Products: EPIVIR Tablets and Oral Solution contain a higher dose of the same active ingredient (lamivudine) than in EPIVIR-HBV Tablets and Oral Solution. EPIVIR-HBV was developed for patients with chronic hepatitis B. The formulation and dosage of lamivudine in EPIVIR-HBV are not appropriate for patients dually infected with HIV and HBV. Lamivudine has not been adequately studied for treatment of chronic hepatitis B in patients dually infected with HIV and HBV. If treatment with EPIVIR-HBV is prescribed for chronic hepatitis B for a patient with unrecognized or untreated HIV infection, rapid emergence of HIV resistance is likely to result because of the subtherapeutic dose and the inappropriateness of monotherapy HIV treatment. If a decision is made to administer lamivudine to patients dually infected with HIV and HBV, EPIVIR Tablets, EPIVIR Oral Solution, COMBIVIR® (lamivudine/zidovudine) Tablets, or EPZICOM™ (abacavir sulfate and lamivudine) Tablets should be used as part of an appropriate combination regimen. COMBIVIR (a fixed-dose combination tablet of lamivudine and zidovudine) should not be administered concomitantly with EPIVIR, EPIVIR-HBV, EPZICOM, RETROVIR, or TRIZIVIR®.

Posttreatment Exacerbations of Hepatitis: In clinical trials in non-HIV-infected patients treated with lamivudine for chronic hepatitis B, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to reemergence of HBV DNA. Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from postmarketing experience after changes from lamivudine-containing HIV treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory followup for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters the course of posttreatment exacerbations of hepatitis.

Use With Interferon- and Ribavirin-Based Regimens: In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV/HCV co-infected patients (see CLINICAL PHARMACOLOGY: Drug Interactions), **hepatic decompensation (some fatal) has occurred in HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon alfa with or without ribavirin.** Patients receiving interferon alfa with or without ribavirin and EPIVIR should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of EPIVIR should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Childs Pugh >6) (see the complete prescribing information for interferon and ribavirin).

PRECAUTIONS

Patients With Impaired Renal Function: Reduction of the dosage of EPIVIR is recommended for patients with impaired renal function (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Patients With HIV and Hepatitis B Virus Co-infection: Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients dually infected with HIV and HBV. In non–HIV-infected patients treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected and has been associated with diminished treatment response (see EPIVIR-HBV package insert for additional information). Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus. Posttreatment exacerbations of hepatitis have also been reported (see WARNINGS).

Immune Reconstitution Syndrome: Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including EPIVIR. 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.

Differences Between Dosing Regimens: Trough levels of lamivudine in plasma and of intracellular lamivudine triphosphate were lower with once-daily dosing than with twice-daily dosing (see CLINICAL PHARMACOLOGY). The clinical significance of this observation is not known.

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.

Information for Patients: EPIVIR is not a cure for HIV infection and patients may continue to experience illnesses associated with HIV infection, including opportunistic infections. Patients should remain under the care of a physician when using EPIVIR. Patients should be advised that the use of EPIVIR has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Continued

Patients should be advised that EPIVIR Tablets and Oral Solution contain a higher dose of the same active ingredient (lamivudine) as EPIVIR-HBV Tablets and Oral Solution. If a decision is made to include lamivudine in the HIV treatment regimen of a patient dually infected with HIV and HBV, the formulation and dosage of lamivudine in EPIVIR (not EPIVIR-HBV) should be used.

Patients co-infected with HIV and HBV should be informed that deterioration of liver disease has occurred in some cases when treatment with lamivudine was discontinued. Patients should be advised to discuss any changes in regimen with their physician.

Patients should be advised that the long-term effects of EPIVIR are unknown at this time.

EPIVIR Tablets and Oral Solution are for oral ingestion only.

Patients should be advised of the importance of taking EPIVIR with combination therapy on a regular dosing schedule and to avoid missing doses.

Parents or guardians should be advised to monitor pediatric patients for signs and symptoms of pancreatitis.

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.

Diabetic patients should be advised that each 15-mL dose of EPIVIR Oral Solution contains 3 grams of sucrose.

Drug Interactions: Lamivudine is predominantly eliminated in the urine by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system (e.g., trimethoprim).

TMP 160 mg/SMX 800 mg once daily has been shown to increase lamivudine exposure (AUC) by 43% (see CLINICAL PHARMACOLOGY). No change in dose of either drug is recommended. There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used to treat PCP. No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of lamivudine in combination with zalcitabine is not recommended.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at the recommended therapeutic dose for HIV infection. Lamivudine was not active in a microbial mutagenicity screen or an in vitro cell transformation assay, but showed weak in vitro mutagenic activity in a cytogenetic assay using cultured human lymphocytes and in the mouse lymphoma assay. However, lamivudine showed no evidence of in vivo genotoxic activity in the rat at oral doses of up to 2,000 mg/kg, producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV infection. In a study of reproductive performance, lamivudine administered to rats at doses up to 4,000 mg/kg/day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

Pregnancy: Pregnancy Category C. Reproduction studies have been performed in rats and rabbits at orally administered doses up to 4,000 mg/kg/day and 1,000 mg/kg/day, respectively, producing plasma levels up to approximately 35 times that for the adult HIV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryolethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 35 times those in humans. Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta.

In 2 clinical studies conducted in South Africa, pharmacokinetic measurements were performed on samples from pregnant women who received lamivudine beginning at Week 38 of gestation (10 women who received 150 mg twice daily in combination with zidovudine and 10 who received lamivudine 300 mg twice daily without other antiretrovirals) or beginning at Week 36 of gestation (16 women who received lamivudine 150 mg twice daily in combination with zidovudine). These studies were not designed or powered to provide efficacy information. Lamivudine pharmacokinetics in the pregnant women were similar to those obtained following birth and in non-pregnant adults. Lamivudine concentrations were generally similar in maternal, neonatal, and cord serum samples. In a subset of subjects from whom amniotic fluid specimens were obtained following natural rupture of membranes, amniotic fluid concentrations of lamivudine ranged from 1.2 to 2.5 mcg/mL (150 mg twice daily) and 2.1 to 5.2 mcg/mL (300 mg twice daily) and were typically greater than 2 times the maternal serum levels. See the ADVERSE REACTIONS section for the limited late-pregnancy safety information available from these studies. Lamivudine should be used during pregnancy only if the potential benefits outweigh the risks.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to lamivudine, a Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV infection.

A study in lactating rats administered 45 mg/kg of lamivudine showed that lamivudine concentrations in milk were slightly greater than those in plasma. Lamivudine is also excreted in human milk. Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving lamivudine.**

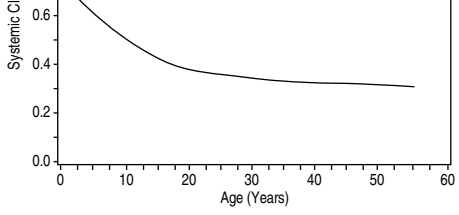
Pediatric Use: ***HIV:*** Limited, uncontrolled pharmacokinetic and safety data are available from administration of lamivudine (and zidovudine) to 36 infants up to 1 week of age in 2 studies in South Africa. In these studies, lamivudine clearance was substantially reduced in 1-week-old neonates relative to pediatric patients (>3 months of age) studied previously. There is insufficient information to establish the time course of changes in clearance between the immediate neonatal period and the age-ranges >3 months old. See the ADVERSE REACTIONS section for the limited safety information available from these studies.

The safety and effectiveness of twice-daily EPIVIR in combination with other antiretroviral agents have been established in pediatric patients 3 months of age and older.

In Study A2002, pharmacokinetic properties of lamivudine were assessed in a subset of 57 HIV-infected pediatric patients (age range: 4.8 months to 16 years, weight range: 5 to 66 kg) after oral and IV administration of 1, 2, 4, 8, 12, and 20 mg/kg/day. In the 9 infants and children (range: 5 months to 12 years of age) receiving oral solution 4 mg/kg twice daily (the usual recommended pediatric dose), absolute bioavailability was 66% ± 26% (mean ± SD), which was less than the 86% ± 16% (mean ± SD) observed in adults. The mechanism for the diminished absolute bioavailability of lamivudine in infants and children is unknown.

Systemic clearance decreased with increasing age in pediatric patients, as shown in Figure 2.

Figure 2. Systemic Clearance (L/hr•kg) of Lamivudine in Relation to Age



After oral administration of lamivudine 4 mg/kg twice daily to 11 pediatric patients ranging from 4 months to 14 years of age, C_{max} was 1.1 ± 0.6 mcg/mL and half-life was 2.0 ± 0.6 hours. (In adults with similar blood sampling, the half-life was 3.7 ± 1 hours.) Total exposure to lamivudine, as reflected by mean AUC values, was comparable between pediatric patients receiving an 8-mg/kg/day dose and adults receiving a 4-mg/kg/day dose.

Distribution of lamivudine into cerebrospinal fluid (CSF) was assessed in 38 pediatric patients after multiple oral dosing with lamivudine. CSF samples were collected between 2 and 4 hours postdose. At the dose of 8 mg/kg/day, CSF lamivudine concentrations in 8 patients ranged from 5.6% to 30.9% (mean ± SD of 14.2% ± 7.9%) of the concentration in a simultaneous serum sample, with CSF lamivudine concentrations ranging from 0.04 to 0.3 mcg/mL.

The effect of renal impairment on lamivudine pharmacokinetics in pediatric patients is not known.

The safety and pharmacokinetic properties of EPIVIR in combination with antiretroviral agents other than zidovudine have not been established in pediatric patients.

See INDICATIONS AND USAGE: Description of Clinical Studies, CLINICAL PHARMACOLOGY, WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION.

HBV: See the complete prescribing information for EPIVIR-HBV Tablets and Oral Solution for additional information on the pharmacokinetics of lamivudine in HBV-infected children.

Geriatric Use: Clinical studies of EPIVIR did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. In particular, because lamivudine is substantially excreted by the kidney and elderly patients are more likely to have decreased renal function, renal function should be monitored and dosage adjustments should be made accordingly (see PRECAUTIONS: Patients with Impaired Renal Function and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Clinical Trials in HIV: ***Adults:*** Selected clinical adverse events with a ≥5% frequency during therapy with EPIVIR 150 mg twice daily plus RETROVIR 200 mg 3 times daily compared with zidovudine are listed in Table 5.

Table 5. Selected Clinical Adverse Events (≥5% Frequency) in Four Controlled Clinical Trials (A3001, A3002, B3001, B3002)

Adverse Event	EPIVIR 150 mg Twice Daily plus RETROVIR (n = 251)	RETROVIR* (n = 230)
Body as a Whole		
Headache	35%	27%
Malaise & fatigue	27%	23%
Fever or chills	10%	12%
Digestive		
Nausea	33%	29%
Diarrhea	18%	22%
Nausea & vomiting	13%	12%
Anorexia and/or decreased appetite	10%	7%
Abdominal pain	9%	11%
Abdominal cramps	6%	3%
Dyspepsia	5%	5%
Nervous System		
Neuropathy	12%	10%
Insomnia & other sleep disorders	11%	7%
Dizziness	10%	4%
Depressive disorders	9%	4%
Respiratory		
Nasal signs & symptoms	20%	11%
Cough	18%	13%
Skin		
Skin rashes	9%	6%
Musculoskeletal		
Musculoskeletal pain	12%	10%
Myalgia	8%	6%
Arthralgia	5%	5%

* Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

The types and frequencies of clinical adverse events reported in patients receiving EPIVIR 300 mg once daily or EPIVIR 150 mg twice daily (in 3-drug combination regimens in EPV20001 and EPV40001) were similar. The most common adverse events in both treatment groups were nausea, dizziness, fatigue and/or malaise, headache, dreams, insomnia and other sleep disorders, and skin rash.

Pancreatitis was observed in 9 of the 2,613 adult patients (0.3%) who received EPIVIR in the controlled clinical trials EPV20001, NUCA3001, NUCB3001, NUCA3002, NUCB3002, and B3007.

Selected laboratory abnormalities observed during therapy are summarized in Table 6.

Table 6. Frequencies of Selected Laboratory Abnormalities in Adults in Four 24-Week Surrogate Endpoint Studies (A3001, A3002, B3001, B3002) and a Clinical Endpoint Study (B3007)

Test (Threshold Level)	24-Week Surrogate Endpoint Studies*		Clinical Endpoint Study*	
	EPIVIR plus RETROVIR	RETROVIR†	EPIVIR plus Current Therapy	Placebo plus Current Therapy‡
Absolute neutrophil count (<750/mm^3)	7.2%	5.4%	15%	13%
Hemoglobin (<8.0 g/dL)	2.9%	1.8%	2.2%	3.4%
Platelets (<50,000/mm^3)	0.4%	1.3%	2.8%	3.8%
ALT (>5.0 x ULN)	3.7%	3.6%	3.8%	1.9%
AST (>5.0 x ULN)	1.7%	1.8%	4.0%	2.1%
Bilirubin (>2.5 x ULN)	0.8%	0.4%	ND	ND
Amylase (>2.0 x ULN)	4.2%	1.5%	2.2%	1.1%

* The median duration on study was 12 months.
† Either zidovudine monotherapy or zidovudine in combination with zalcitabine.
‡ Current therapy was either zidovudine, zidovudine plus didanosine, or zidovudine plus zalcitabine.
ULN = Upper limit of normal.
ND = Not done.

In small, uncontrolled studies in which pregnant women were given lamivudine alone or in combination with zidovudine beginning in the last few weeks of pregnancy (see PRECAUTIONS: Pregnancy), reported adverse events included anemia, urinary tract infections, and complications of labor and delivery. In postmarketing experience, liver function abnormalities and pancreatitis have been reported in women who received lamivudine in combination with other antiretroviral drugs during pregnancy. It is not known whether risks of adverse events associated with lamivudine are altered in pregnant women compared to other HIV-infected patients.

The frequencies of selected laboratory abnormalities reported in patients receiving EPIVIR 300 mg once daily or EPIVIR 150 mg twice daily (in 3-drug combination regimens in EPV20001 and EPV40001) were similar.

Pediatric Patients: Selected clinical adverse events and physical findings with a ≥5% frequency during therapy with EPIVIR 4 mg/kg twice daily plus RETROVIR 160 mg/m^2 3 times daily compared with didanosine in therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in Table 7.

Table 7. Selected Clinical Adverse Events and Physical Findings (≥5% Frequency) in Pediatric Patients in Study ACTG300

Adverse Event	EPIVIR plus RETROVIR (n = 236)	Didanosine (n = 235)
Body as a Whole		
Fever	25%	32%
Digestive		
Hepatomegaly	11%	11%
Nausea & vomiting	8%	7%
Diarrhea	8%	6%
Stomatitis	6%	12%
Splenomegaly	5%	8%

Continued

Table 7. Selected Clinical Adverse Events and Physical Findings (≥5% Frequency) in Pediatric Patients in Study ACTG300 (cont'd)

Adverse Event	EPIVIR plus RETROVIR (n = 236)	Didanosine (n = 235)
Respiratory		
Cough	15%	18%
Abnormal breath sounds/wheezing	7%	9%
Ear, Nose, and Throat		
Signs or symptoms of ears*	7%	6%
Nasal discharge or congestion	8%	11%
Other		
Skin rashes	12%	14%
Lymphadenopathy	9%	11%

* Includes pain, discharge, erythema, or swelling of an ear.

Selected laboratory abnormalities experienced by therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in Table 8.

Table 8. Frequencies of Selected Laboratory Abnormalities in Pediatric Patients in Study ACTG300

Test (Threshold Level)	EPIVIR plus RETROVIR	Didanosine
Absolute neutrophil count (<400/mm^3)	8%	3%
Hemoglobin (<7.0 g/dL)	4%	2%
Platelets (<50,000/mm^3)	1%	3%
ALT (>10 x ULN)	1%	3%
AST (>10 x ULN)	2%	4%
Lipase (>2.5 x ULN)	3%	3%
Total Amylase (>2.5 x ULN)	3%	3%

ULN = Upper limit of normal.

Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced pediatric patients receiving EPIVIR alone or in combination with other antiretroviral agents. In an open-label dose-escalation study (A2002), 14 patients (14%) developed pancreatitis while receiving monotherapy with EPIVIR. Three of these patients died of complications of pancreatitis. In a second open-label study (A2005), 12 patients (18%) developed pancreatitis. In Study ACTG300, pancreatitis was not observed in 236 patients randomized to EPIVIR plus RETROVIR. Pancreatitis was observed in 1 patient in this study who received open-label EPIVIR in combination with RETROVIR and ritonavir following discontinuation of didanosine monotherapy.

Paresthesias and peripheral neuropathies were reported in 15 patients (15%) in Study A2002, 6 patients (9%) in Study A2005, and 2 patients (<1%) in Study ACTG300.

Limited short-term safety information is available from 2 small, uncontrolled studies in South Africa in neonates receiving lamivudine with or without zidovudine for the first week of life following maternal treatment starting at Week 38 or 36 of gestation (see PRECAUTIONS: Pediatric Use). Adverse events reported in these neonates included increased liver function tests, anemia, diarrhea, electrolyte disturbances, hypoglycemia, jaundice and hepatomegaly, rash, respiratory infections, sepsis, and syphilis; 3 neonates died (1 from gastroenteritis with acidosis and convulsions, 1 from traumatic injury, and 1 from unknown causes). Two other nonfatal gastroenteritis or diarrhea cases were reported, including 1 with convulsions; 1 infant had transient renal insufficiency associated with dehydration. The absence of control groups further limits assessments of causality, but it should be assumed that perinatally-exposed infants may be at risk for adverse events comparable to those reported in pediatric and adult HIV-infected patients treated with lamivudine-containing combination regimens. Long-term effects of in utero and infant lamivudine exposure are not known.

Lamivudine in Patients With Chronic Hepatitis B: Clinical trials in chronic hepatitis B used a lower dose of lamivudine (100 mg daily) than the dose used to treat HIV. The most frequent adverse events with lamivudine versus placebo were ear, nose, and throat infections (25% versus 21%); malaise and fatigue (24% versus 28%); and headache (21% versus 21%), respectively. The most frequent laboratory abnormalities reported with lamivudine were elevated ALT, elevated serum lipase, elevated CPK, and posttreatment elevations of liver function tests. Emergence of HBV viral mutants during lamivudine treatment, associated with reduced drug susceptibility and diminished treatment response, was also reported (also see WARNINGS and PRECAUTIONS). Please see the complete prescribing information for EPIVIR-HBV Tablets and Oral Solution for more information.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of lamivudine. 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 a combination of their seriousness, frequency of reporting, or potential causal connection to lamivudine.

Body as a Whole: Redistribution/accumulation of body fat (see PRECAUTIONS: Fat Redistribution).

Digestive: Stomatitis.

Endocrine and Metabolic: Hyperglycemia.

General: Weakness.

Hemic and Lymphatic: Anemia (including pure red cell aplasia and severe anemias progressing on therapy), lymphadenopathy, splenomegaly.

Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis, pancreatitis, posttreatment exacerbation of hepatitis B (see WARNINGS and PRECAUTIONS).

Hypersensitivity: Anaphylaxis, urticaria.

Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.

Nervous: Paresthesia, peripheral neuropathy.

Respiratory: Abnormal breath sounds/wheezing.

Skin: Alopecia, rash, pruritus.

OVERDOSAGE

There is no known antidote for EPIVIR. One case of an adult ingesting 6 g of EPIVIR was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. Two cases of pediatric overdose were reported in ACTG300. One case was a single dose of 7 mg/kg of EPIVIR; the second case involved use of 5 mg/kg of EPIVIR twice daily for 30 days. There were no clinical signs or symptoms noted in either case. Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event. If overdose occurs, the patient should be monitored, and standard supportive treatment applied as required.

DOSAGE AND ADMINISTRATION

Adults: The recommended oral dose of EPIVIR for adults is 300 mg daily, administered as either 150 mg twice daily or 300 mg once daily, in combination with other antiretroviral agents (see DESCRIPTION OF CLINICAL STUDIES, PRECAUTIONS, MICROBIOLOGY, and CLINICAL PHARMACOLOGY). If lamivudine is administered to a patient dually infected with HIV and HBV, the dosage indicated for HIV therapy should be used as part of an appropriate combination regimen (see WARNINGS).

Pediatric Patients: ***Infants/Children/Adolescents:*** The recommended oral dose of EPIVIR for HIV-infected pediatric patients 3 months up to 16 years of age is 4 mg/kg twice daily (up to a maximum of 150 mg twice a day), administered in combination with other antiretroviral agents.

Dose Adjustment: It is recommended that doses of EPIVIR be adjusted in accordance with renal function (see Table 9) (see CLINICAL PHARMACOLOGY).

Table 9. Adjustment of Dosage of EPIVIR in Adults and Adolescents in Accordance With Creatinine Clearance

Creatinine Clearance (mL/min)	Recommended Dosage of EPIVIR
≥50	150 mg twice daily or 300 mg once daily
30-49	150 mg once daily
15-29	150 mg first dose, then 100 mg once daily
5-14	150 mg first dose, then 50 mg once daily
<5	50 mg first dose, then 25 mg once daily

No additional dosing of EPIVIR is required after routine (4-hour) hemodialysis or peritoneal dialysis.

Although there are insufficient data to recommend a specific dose adjustment of EPIVIR in pediatric patients with renal impairment, a reduction in the dose and/or an increase in the dosing interval should be considered.

HOW SUPPLIED

EPIVIR Tablets, 150 mg, are white, modified diamond-shaped, film-coated tablets engraved with "GX CJ7" on one side and plain on the reverse side.

Bottle of 60 tablets (NDC 0173-0470-01) with child-resistant closure.

EPIVIR Tablets, 300 mg, are gray, modified diamond-shaped, film-coated tablets engraved with "GX EJ7" on one side and plain on the reverse side.

Bottle of 30 tablets (NDC 0173-0714-00) with child-resistant closure.

Store at 25ºC (77ºF); excursions permitted to 15º to 30ºC (59º to 86ºF) [see USP Controlled Room Temperature].

EPIVIR Oral Solution, a clear, colorless to pale yellow, strawberry-banana flavored liquid, contains 10 mg of lamivudine in each 1 mL.

Plastic bottle of 240 mL (NDC 0173-0471-00) with child-resistant closures. This product does not require reconstitution.

Store in tightly closed bottles at 25ºC (77ºF) [see USP Controlled Room Temperature].

GlaxoSmithKline
Research Triangle Park, NC 27709

Manufactured under agreement from
Shire Pharmaceuticals Group plc
Basingstoke, UK

October 2006 RL-2317

EPZICOM™
(abacavir sulfate and lamivudine)
Tablets

WARNINGS

EPZICOM contains 2 nucleoside analogues (abacavir sulfate and lamivudine) and is intended only for patients whose regimen would otherwise include these 2 components.

Hypersensitivity Reactions: Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate, a component of EPZICOM. Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups: (1) fever, (2) rash, (3) gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain), (4) constitutional (including generalized malaise, fatigue, or achiness), and (5) respiratory (including dyspnea, cough, or pharyngitis). Discontinue EPZICOM as soon as a hypersensitivity reaction is suspected. Permanently discontinue EPZICOM if hypersensitivity cannot be ruled out, even when other diagnoses are possible.

Following a hypersensitivity reaction to abacavir, NEVER restart EPZICOM or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.

Reintroduction of EPZICOM or any other abacavir-containing product, even in patients who have no identified history or unrecognized symptoms of hypersensitivity to abacavir therapy, can result in serious or fatal hypersensitivity reactions. Such reactions can occur within hours (see WARNINGS and PRECAUTIONS: Information for Patients).

Lactic Acidosis and Severe Hepatomegaly: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir, lamivudine, and other antiretrovirals (see WARNINGS).

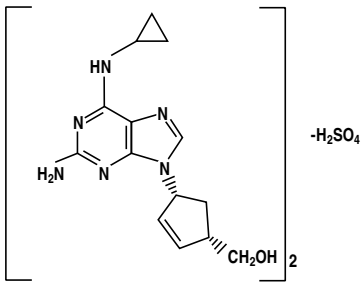
Exacerbations of Hepatitis B: Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV) and have discontinued lamivudine, which is one component of EPZICOM. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue EPZICOM and are co-infected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted (see WARNINGS).

DESCRIPTION

EPZICOM: EPZICOM Tablets contain the following 2 synthetic nucleoside analogues: abacavir sulfate (ZIAGEN®, also a component of TRIZIVIR®) and lamivudine (also known as EPIVIR® or 3TC) with inhibitory activity against HIV.

EPZICOM Tablets are for oral administration. Each orange, film-coated tablet contains the active ingredients 600 mg of abacavir as abacavir sulfate and 300 mg of lamivudine and the inactive ingredients magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablets are coated with a film (Opadry® orange YS-1-13065-A) that is made of FD&C Yellow No. 6, hypromellose, polyethylene glycol 400, polysorbate 80, and titanium dioxide.

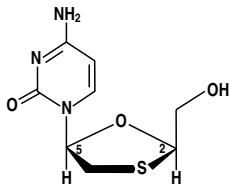
Abacavir Sulfate: The chemical name of abacavir sulfate is *(1S,cis)*-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1). Abacavir sulfate is the enantiomer with *1S, 4R* absolute configuration on the cyclopentene ring. It has a molecular formula of $(C_{14}H_{18}N_6O)_2 \bullet H_2SO_4$ and a molecular weight of 670.76 daltons. It has the following structural formula:



Abacavir sulfate is a white to off-white solid with a solubility of approximately 77 mg/mL in distilled water at 25°C.

In vivo, abacavir sulfate dissociates to its free base, abacavir. All dosages for abacavir sulfate are expressed in terms of abacavir.

Lamivudine: The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2′,3′-dideoxy, 3′-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.3 daltons. It has the following structural formula:



Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg/mL in water at 20°C.

MICROBIOLOGY

Mechanism of Action: Abacavir is a carbocyclic synthetic nucleoside analogue. Abacavir is converted by cellular enzymes to the active metabolite, carbovir triphosphate (CBV-TP), an analogue of deoxyguanosine-5′-triphosphate (dGTP). CBV-TP inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation into viral DNA. The lack of a 3′-OH group in the incorporated nucleotide analogue prevents the formation of the 5′ to 3′ phosphodiester linkage essential for DNA chain elongation, and therefore, the viral DNA growth is terminated. CBV-TP is a weak inhibitor of cellular DNA polymerases α, β, and γ.

Lamivudine is a synthetic nucleoside analogue. Intracellularly lamivudine is phosphorylated to its active 5′-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue. CBV-TP and 3TC-TP are weak inhibitors of cellular DNA polymerases α, β, and γ.

Antiviral Activity: ***Abacavir:*** The antiviral activity of abacavir against HIV-1 was evaluated against a T-cell tropic laboratory strain HIV-1_{IIIB} in lymphoblastic cell lines, a monocyte/macrophage tropic laboratory strain HIV-1_{BaL} in primary monocytes/macrophages, and clinical isolates in peripheral blood mononuclear cells. The concentration of drug necessary to effect viral replication by 50 percent (EC_{50}) ranged from 3.7 to 5.8 μM (1 μM = 0.28 mcg/mL) and 0.07 to 1.0 μM against HIV-1_{IIIB} and HIV-1_{BaL}, respectively, and was 0.26 ± 0.18 μM against 8 clinical isolates. The EC_{50} values of abacavir against different HIV-1 clades (A-G) ranged from 0.0015 to 1.05 μM, and against HIV-2 isolates, from 0.024 to 0.49 μM. Ribavirin (50 μM) had no effect on the anti–HIV-1 activity of abacavir in cell culture.

Lamivudine: The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. EC_{50} values were in the range of 0.003 to 15 μM (1 μM = 0.23 mcg/mL). HIV from therapy-naive subjects with no mutations associated with resistance gave median EC_{50} values of 0.426 μM (range: 0.200 to 2.007 μM) from Virco (n = 93 baseline samples from COLA40263) and 2.35 μM (1.44 to 4.08 μM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC_{50} values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120 μM, and against HIV-2 isolates from 0.003 to 0.120 μM in peripheral blood mononuclear cells. Ribavirin (50 μM) decreased the anti–HIV-1 activity of lamivudine by 3.5 fold in MT_4 cells.

The combination of abacavir and lamivudine has demonstrated antiviral activity in cell culture against non-subtype B isolates and HIV-2 isolates with equivalent antiviral activity as for subtype B isolates. Abacavir/lamivudine had additive to synergistic activity in cell culture in combination with the nucleoside reverse transcriptase inhibitors (NRTIs: emtricitabine, stavudine, tenofovir, zalcitabine, zidovudine), the non-nucleoside reverse transcriptase inhibitors (NNRTIs: delavirdine, efavirenz, nevirapine), the protease inhibitors (PIs: amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir), or the fusion inhibitor, enfuvirtide. Ribavirin, used in combination with interferon for the treatment of HCV infection, decreased the anti-HIV potency of abacavir/lamivudine reproducibly by 2- to 6-fold in cell culture.

Resistance: HIV-1 isolates with reduced susceptibility to the combination of abacavir and lamivudine have been selected in cell culture and have also been obtained from patients failing abacavir/lamivudine-containing regimens. Genotypic characterization of abacavir/lamivudine-resistant viruses selected in cell culture identified amino acid substitutions M184V/I, K65R, L74V, and Y115F in HIV-1 RT.

Genotypic analysis of isolates selected in cell culture and recovered from abacavir-treated patients demonstrated that amino acid substitutions K65R, L74V, Y115F, and M184V/I in HIV-1 RT contributed to abacavir resistance. Genotypic analysis of isolates selected in cell culture and recovered from lamivudine-treated patients showed that the resistance was due to a specific amino acid substitution in HIV-1 RT at codon 184 changing the methionine to either isoleucine or valine (M184V/I). In a study of therapy-naive adults receiving ZIAGEN 600 mg once daily (n = 384) or 300 mg twice daily (n = 386) in a background regimen of lamivudine 300 mg and efavirenz 600 mg once daily (Study CNA30021), the incidence of virologic failure at 48 weeks was similar between the 2 groups (11% in both arms). Genotypic (n = 38) and phenotypic analyses (n = 35) of virologic failure isolates from this study showed that the RT mutations that emerged during abacavir/lamivudine once-daily and twice-daily therapy were K65R, L74V, Y115F, and M184V/I. The abacavir- and lamivudine-associated resistance mutation M184V/I was the most commonly observed mutation in virologic failure isolates from patients receiving abacavir/lamivudine once daily (56%, 10/18) and twice daily (40%, 8/20).

Thirty-nine percent (7/18) of the isolates from patients who experienced virologic failure in the abacavir once-daily arm had a >2.5-fold decrease in abacavir susceptibility with a median-fold decrease of 1.3 (range 0.5 to 11) compared with 29% (5/17) of the failure isolates in the twice-daily arm with a median-fold decrease of 0.92 (range 0.7 to 13). Fifty-six percent (10/18) of the virologic failure isolates in the once-daily abacavir group compared to 41% (7/17) of the failure isolates in the twice-daily abacavir group had a >2.5-fold decrease in lamivudine susceptibility with median-fold changes of 81 (range 0.79 to >116) and 1.1 (range 0.68 to >116) in the once-daily and twice-daily abacavir arms, respectively.

Cross-Resistance: Cross-resistance has been observed among nucleoside reverse transcriptase inhibitors. Viruses containing abacavir and lamivudine resistance-associated mutations, namely, K65R, L74V, M184V, and Y115F, exhibit cross-resistance to didanosine, emtricitabine, lamivudine, tenofovir, and zalcitabine in cell culture and in patients. The K65R mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine; the L74V mutation can confer resistance to abacavir, didanosine, and zalcitabine; and the M184V mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, and zalcitabine.

The combination of abacavir/lamivudine has demonstrated decreased susceptibility to viruses with the mutations K65R with or without the M184V/I mutation, viruses with L74V plus the M184V/I mutation, and viruses with thymidine analog mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219 E/R/H/Q/N) plus M184V. An increasing number of TAMs is associated with a progressive reduction in abacavir susceptibility.

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults: ***EPZICOM:*** In a single-dose, 3-way crossover bioavailability study of 1 EPZICOM Tablet versus 2 ZIAGEN Tablets (2 x 300 mg) and 2 EPIVIR Tablets (2 x 150 mg) administered simultaneously in healthy subjects (n = 25), there was no difference in the extent of absorption, as measured by the area under the plasma concentration-time curve (AUC) and maximal peak concentration (C_{max}), of each component.

Abacavir: Following oral administration, abacavir is rapidly absorbed and extensively distributed. After oral administration of a single dose of 600 mg of abacavir in 20 patients, C_{max} was 4.26 ± 1.19 mcg/mL (mean ± SD) and AUC_∞ was 11.95 ± 2.51 mcg•hr/mL. Binding of abacavir to human plasma proteins is approximately 50% and was independent of concentration. Total blood and plasma drug-related radioactivity concentrations are identical, demonstrating that abacavir readily distributes into erythrocytes. The primary routes of elimination of abacavir are metabolism by alcohol dehydrogenase to form the 5′-carboxylic acid and glucuronyl transferase to form the 5′-glucuronide.

Lamivudine: Following oral administration, lamivudine is rapidly absorbed and extensively distributed. After multiple-dose oral administration of lamivudine 300 mg once daily for 7 days to 60 healthy volunteers, steady-state C_{max} ($C_{max,ss}$) was 2.04 ± 0.54 mcg/mL (mean ± SD) and the 24-hour steady-state AUC ($AUC_{24,ss}$) was 8.87 ± 1.83 mcg•hr/mL. Binding to plasma protein is low. Approximately 70% of an intravenous dose of lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours).

The steady-state pharmacokinetic properties of the EPIVIR 300-mg Tablet once daily for 7 days compared to the EPIVIR 150-mg Tablet twice daily for 7 days were assessed in a crossover study in 60 healthy volunteers. EPIVIR 300 mg once daily resulted in lamivudine exposures that were similar to EPIVIR 150 mg twice daily with respect to plasma $AUC_{24,ss}$; however, $C_{max,ss}$ was 66% higher and the trough value was 53% lower compared to the 150-mg twice-daily regimen. Intracellular lamivudine triphosphate exposures in peripheral blood mononuclear cells were also similar with respect to $AUC_{24,ss}$ and $C_{max24,ss}$; however, trough values were lower compared to the 150-mg twice-daily regimen. Inter-subject variability was greater for intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough concentrations. The clinical significance of observed differences for both plasma lamivudine concentrations and intracellular lamivudine triphosphate concentrations is not known.

In humans, abacavir and lamivudine are not significantly metabolized by cytochrome P450 enzymes.

The pharmacokinetic properties of abacavir and lamivudine in fasting patients are summarized in Table 1.

Table 1. Pharmacokinetic Parameters* for Abacavir and Lamivudine in Adults

Parameter	Abacavir		Lamivudine	
Oral bioavailability (%)	86 ± 25	n = 6	86 ± 16	n = 12
Apparent volume of distribution (L/kg)	0.86 ± 0.15	n = 6	1.3 ± 0.4	n = 20
Systemic clearance (L/hr/kg)	0.80 ± 0.24	n = 6	0.33 ± 0.06	n = 20
Renal clearance (L/hr/kg)	.007 ± .008	n = 6	0.22 ± 0.06	n = 20
Elimination half-life (hr)	1.45 ± 0.32	n = 20	5 to 7†	

*Data presented as mean ± standard deviation except where noted.
†Approximate range.

Effect of Food on Absorption of EPZICOM: EPZICOM may be administered with or without food. Administration with a high-fat meal in a single-dose bioavailability study resulted in no change in AUC_{last}, AUC_∞, and C_{max} for lamivudine. Food did not alter the extent of systemic exposure to abacavir (AUC_∞), but the rate of absorption (C_{max}) was decreased approximately 24% compared to fasted conditions (n = 25). These results are similar to those from previous studies of the effect of food on abacavir and lamivudine tablets administered separately.

Special Populations: ***Impaired Renal Function:***

EPZICOM: Because lamivudine requires dose adjustment in the presence of renal insufficiency, EPZICOM is not recommended for use in patients with creatinine clearance <50 mL/min (see PRECAUTIONS).

Impaired Hepatic Function: EPZICOM: Abacavir is contraindicated in patients with moderate to severe hepatic impairment and dose reduction is required in patients with mild hepatic impairment. Because EPZICOM is a fixed-dose combination and cannot be dose adjusted, EPZICOM is contraindicated for patients with hepatic impairment.

Pregnancy: See PRECAUTIONS: Pregnancy.

Abacavir and Lamivudine: No data are available on the pharmacokinetics of abacavir or lamivudine during pregnancy.

Nursing Mothers: See PRECAUTIONS: Nursing Mothers.

Abacavir: No data are available on the pharmacokinetics of abacavir in nursing mothers.

Lamivudine: Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

Pediatric Patients: EPZICOM: The pharmacokinetics of EPZICOM in pediatric patients are under investigation. There are insufficient data at this time to recommend a dose (see PRECAUTIONS: Pediatric Use).

Geriatric Patients: The pharmacokinetics of abacavir and lamivudine have not been studied in patients over 65 years of age.

Gender: Abacavir: A population pharmacokinetic analysis in HIV-infected male (n = 304) and female (n = 67) patients showed no gender differences in abacavir AUC normalized for lean body weight.

Lamivudine: A pharmacokinetic study in healthy male (n = 12) and female (n = 12) subjects showed no gender differences in lamivudine AUC_∞ normalized for body weight.

Race: Abacavir: There are no significant differences between blacks and Caucasians in abacavir pharmacokinetics.

Lamivudine: There are no significant racial differences in lamivudine pharmacokinetics.

Drug Interactions: See PRECAUTIONS: Drug Interactions. The drug interactions described are based on studies conducted with the individual nucleoside analogues. In humans, abacavir and lamivudine are not significantly metabolized by cytochrome P450 enzymes nor do they inhibit or induce this enzyme system; therefore, it is unlikely that clinically significant drug interactions will occur with drugs metabolized through these pathways.

Abacavir: Fifteen HIV-infected patients were enrolled in a crossover-designed drug interaction study evaluating single doses of abacavir (600 mg), lamivudine (150 mg), and zidovudine (300 mg) alone or in combination. Analysis showed no clinically relevant changes in the pharmacokinetics of abacavir with the addition of lamivudine or zidovudine or the combination of lamivudine and zidovudine. Lamivudine exposure (AUC decreased 15%) and zidovudine exposure (AUC increased 10%) did not show clinically relevant changes with concurrent abacavir.

In a study of 11 HIV-infected patients receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of ZIAGEN twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI 6% to 42%). This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients.

Lamivudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q 12 hr). Lamivudine pharmacokinetics are not significantly affected by abacavir.

Table 2. Effect of Coadministered Drugs on Abacavir and Lamivudine AUC*

Note: ROUTINE DOSE MODIFICATION OF ABACAVIR AND LAMIVUDINE IS NOT WARRANTED WITH COADMINISTRATION OF THE FOLLOWING DRUGS.

Drugs That May Alter Abacavir Blood Concentrations					
Coadministered Drug and Dose	Abacavir Dose	n	Abacavir Concentrations		Concentration of Coadministered Drug
			AUC	Variability	
Ethanol 0.7 g/kg	Single 600 mg	24	↑41%	90% CI: 35% to 48%	↔
Drugs That May Alter Lamivudine Blood Concentrations					
Coadministered Drug and Dose	Lamivudine Dose	n	Lamivudine Concentrations		Concentration of Coadministered Drug
			AUC	Variability	
Nelfinavir 750 mg q 8 hr x 7 to 10 days	Single 150 mg	11	↑10%	95% CI: 1% to 20%	↔
Trimethoprim 160 mg/ Sulfamethoxazole 800 mg daily x 5 days	Single 300 mg	14	↑43%	90% CI: 32% to 55%	↔

↑ = Increase; ↔ = no significant change; AUC = area under the concentration versus time curve; CI = confidence interval.
*See PRECAUTIONS: Drug Interactions for additional information on drug interactions.

Ribavirin: In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV/HCV co-infected patients (see WARNINGS).

INDICATIONS AND USAGE

EPZICOM Tablets, in combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection.

Additional important information on the use of EPZICOM for treatment of HIV-1 infection:

- EPZICOM is one of multiple products containing abacavir. Before starting EPZICOM, review medical history for prior exposure to any abacavir-containing product in order to avoid reintroduction in a patient with a history of hypersensitivity to abacavir.
- In one controlled study (CNA30021), more patients taking ZIAGEN 600 mg once daily had severe hypersensitivity reactions compared to patients taking ZIAGEN 300 mg twice daily.
- As part of a triple-drug regimen, EPZICOM Tablets are recommended for use with antiretroviral agents from different pharmacological classes and not with other nucleoside/nucleotide reverse transcriptase inhibitors.

See WARNINGS, ADVERSE REACTIONS, and Description of Clinical Studies.

Description of Clinical Studies: *EPZICOM:* There have been no clinical trials conducted with EPZICOM (see CLINICAL PHARMACOLOGY for information about bioequivalence of EPZICOM). One EPZICOM Tablet given once daily is an alternative regimen to EPIVIR Tablets 300 mg once daily plus ZIAGEN Tablets 2 x 300 mg once daily as a component of antiretroviral therapy.

The following study was conducted with the individual components of EPZICOM.

Therapy-Naive Adults: **CNA30021** was an international, multi-center, double-blind, controlled study in which 770 HIV-infected, therapy-naive adults were randomized and received either ZIAGEN 600 mg once daily or ZIAGEN 300 mg twice daily, both in combination with EPIVIR 300 mg once daily and efavirenz 600 mg once daily. The double-blind treatment duration was at least 48 weeks. Study participants had a mean age of 37 years, were: male (81%), Caucasian (54%), black (27%), and American Hispanic (15%). The median baseline CD4+ cell count was 262 cells/mm^3 (range 21 to 918 cells/mm^3) and the median baseline plasma HIV-1 RNA was 4.89 $\log_{10}$ copies/mL (range: 2.60 to 6.99 $\log_{10}$ copies/mL).

The outcomes of randomized treatment are provided in Table 3.

Table 3. Outcomes of Randomized Treatment Through Week 48 (CNA30021)

Outcome	ZIAGEN 600 mg q.d. plus EPIVIR plus Efavirenz (n = 384)	ZIAGEN 300 mg b.i.d. plus EPIVIR plus Efavirenz (n = 386)
Responder*	64% (71%)	65% (72%)
Virologic failure†	11% (5%)	11% (5%)
Discontinued due to adverse reactions	13%	11%
Discontinued due to other reasons‡	11%	13%

* Patients achieved and maintained confirmed HIV-1 RNA <50 copies/mL (<400 copies/mL) through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR® standard test version 1.0).
† Includes viral rebound, failure to achieve confirmed <50 copies/mL (<400 copies/mL) by Week 48, and insufficient viral load response.
‡ Includes consent withdrawn, lost to follow up, protocol violations, clinical progression, and other.

After 48 weeks of therapy, the median CD4+ cell count increases from baseline were 188 cells/mm^3 in the group receiving ZIAGEN 600 mg once daily and 200 cells/mm^3 in the group receiving ZIAGEN 300 mg twice daily. Through Week 48, 6 subjects (2%) in the group receiving ZIAGEN 600 mg once daily (4 CDC classification C events and 2 deaths) and 10 subjects (3%) in the group receiving ZIAGEN 300 mg twice daily (7 CDC classification C events and 3 deaths) experienced clinical disease progression. None of the deaths were attributed to study medications.

CONTRAINDICATIONS

EPZICOM Tablets are contraindicated in patients with previously demonstrated hypersensitivity to abacavir or to any other component of the product (see WARNINGS). Following a hypersensitivity reaction to abacavir, NEVER restart EPZICOM or any other abacavir-containing product. Fatal rechallenge reactions have been associated with readministration of abacavir to patients with a prior history of a hypersensitivity reaction to abacavir (see WARNINGS and PRECAUTIONS).

EPZICOM Tablets are contraindicated in patients with hepatic impairment (see CLINICAL PHARMACOLOGY).

WARNINGS

Hypersensitivity Reaction: Serious and sometimes fatal hypersensitivity reactions have been associated with EPZICOM and other abacavir-containing products. To minimize the risk of a life-threatening hypersensitivity reaction, permanently discontinue EPZICOM if hypersensitivity cannot be ruled out, even when other diagnoses are possible. Important information on signs and symptoms of hypersensitivity, as well as clinical management, is presented below.

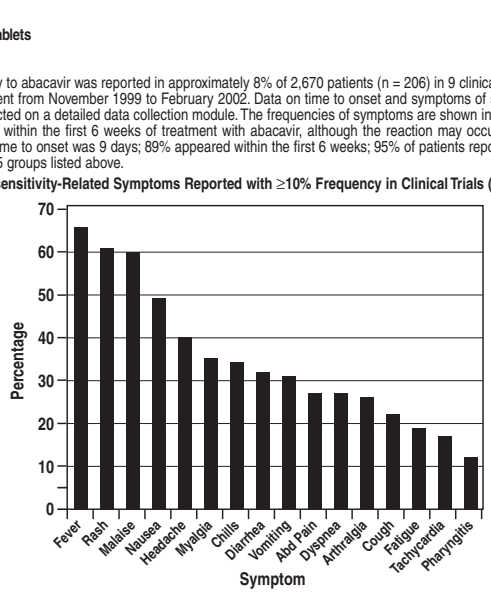
***Signs and Symptoms of Hypersensitivity*:** Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups.

Group 1: Fever
Group 2: Rash
Group 3: Gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain)
Group 4: Constitutional (including generalized malaise, fatigue, or achiness)
Group 5: Respiratory (including dyspnea, cough, or pharyngitis)

Hypersensitivity to abacavir following the presentation of a single sign or symptom has been reported infrequently.

Hypersensitivity to abacavir was reported in approximately 8% of 2,670 patients (n = 206) in 9 clinical trials (range: 2% to 9%) with enrollment from November 1999 to February 2002. Data on time to onset and symptoms of suspected hypersensitivity were collected on a detailed data collection module. The frequencies of symptoms are shown in Figure 1. Symptoms usually appeared within the first 6 weeks of treatment with abacavir, although the reaction may occur at any time during therapy. Median time to onset was 9 days; 89% appeared within the first 6 weeks; 95% of patients reported symptoms from 2 or more of the 5 groups listed above.

Figure 1: Hypersensitivity-Related Symptoms Reported with ≥10% Frequency in Clinical Trials (n = 206 Patients)



Other less common signs and symptoms of hypersensitivity include lethargy, myolysis, edema, abnormal chest x-ray findings (predominantly infiltrates, which can be localized), and paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure, and death have occurred in association with hypersensitivity reactions. In one study, 4 patients (11%) receiving ZIAGEN 600 mg once daily experienced hypotension with a hypersensitivity reaction compared with 0 patients receiving ZIAGEN 300 mg twice daily.

Physical findings associated with hypersensitivity to abacavir in some patients include lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and rash. The rash usually appears maculopapular or urticarial, but may be variable in appearance. There have been reports of erythema multiforme. Hypersensitivity reactions have occurred without rash.

Laboratory abnormalities associated with hypersensitivity to abacavir in some patients include elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, and lymphopenia.

Clinical Management of Hypersensitivity: **Discontinue EPZICOM as soon as a hypersensitivity reaction is suspected. To minimize the risk of a life-threatening hypersensitivity reaction, permanently discontinue EPZICOM if hypersensitivity cannot be ruled out, even when other diagnoses are possible (e.g., acute onset respiratory diseases such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions to other medications).**

Following a hypersensitivity reaction to abacavir, NEVER restart EPZICOM or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.

When therapy with EPZICOM has been discontinued for reasons other than symptoms of a hypersensitivity reaction, and if reinitiation of EPZICOM or any other abacavir-containing product is under consideration, carefully evaluate the reason for discontinuation of EPZICOM to ensure that the patient did not have symptoms of a hypersensitivity reaction. If hypersensitivity cannot be ruled out, DO NOT reintroduce EPZICOM or any other abacavir-containing product. If symptoms consistent with hypersensitivity are not identified, reintroduction can be undertaken with continued monitoring for symptoms of a hypersensitivity reaction. Make patients aware that a hypersensitivity reaction can occur with reintroduction of EPZICOM or any other abacavir-containing product and that reintroduction of EPZICOM or introduction of any other abacavir-containing product needs to be undertaken only if medical care can be readily accessed by the patient or others.

Abacavir Hypersensitivity Reaction Registry: To facilitate reporting of hypersensitivity reactions and collection of information on each case, an Abacavir Hypersensitivity Registry has been established. **Physicians should register patients by calling 1-800-270-0425.**

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 abacavir and lamivudine 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 EPZICOM 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 EPZICOM 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).

Posttreatment Exacerbations of Hepatitis: In clinical trials in non-HIV-infected patients treated with lamivudine for chronic HBV, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence of HBV DNA. Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from post-marketing experience after changes from lamivudine-containing HIV treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters the course of posttreatment exacerbations of hepatitis.

Use With Interferon- and Ribavirin-Based Regimens: In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine, a component of EPZICOM. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV/HCV co-infected patients (see CLINICAL PHARMACOLOGY: Drug Interactions), **hepatic decompensation (some fatal) has occurred in HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon alfa with or without ribavirin.** Patients receiving interferon alfa with or without ribavirin and EPZICOM should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of EPZICOM should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Childs Pugh >6) (see the complete prescribing information for interferon and ribavirin).

Other: EPZICOM contains fixed doses of 2 nucleoside analogues, abacavir and lamivudine, and should not be administered concomitantly with other abacavir-containing and/or lamivudine-containing products (ZIAGEN, EPIVIR, COMBIVIR®, or TRIZIVIR).

The complete prescribing information for all agents being considered for use with EPZICOM should be consulted before combination therapy with EPZICOM is initiated.

PRECAUTIONS

Therapy-Experienced Patients: *Abacavir:* In clinical trials, patients with prolonged prior NRTI exposure or who had HIV-1 isolates that contained multiple mutations conferring resistance to NRTIs had limited response to abacavir. The potential for cross-resistance between abacavir and other NRTIs should be considered when choosing new therapeutic regimens in therapy-experienced patients (see MICROBIOLOGY: Cross-Resistance).

Patients With HIV and Hepatitis B Virus Co-infection: *Lamivudine:* Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients dually infected with HIV and HBV. In non-HIV-infected patients treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected and has been associated with diminished treatment response (see EPIVIR-HBV package insert for additional information). Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

Patients With Impaired Renal Function: *EPZICOM:* Since EPZICOM is a fixed-dose tablet and the dosage of the individual components cannot be altered, patients with creatinine clearance <50 mL/min should not receive EPZICOM.

Patients With Impaired Hepatic Function: *EPZICOM*: EPZICOM is contraindicated in patients with hepatic impairment since it is a fixed-dose tablet and the dosage of the individual components cannot be altered.

Immune Reconstitution Syndrome: Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including EPZICOM. 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.

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.

Information for Patients:

Abacavir: Hypersensitivity Reaction: Inform patients:

- **that a Medication Guide and Warning Card summarizing the symptoms of the abacavir hypersensitivity reaction and other product information will be dispensed by the pharmacist with each new prescription and refill of EPZICOM, and encourage the patient to read the Medication Guide and Warning Card every time to obtain any new information that may be present about EPZICOM. (The complete text of the Medication Guide is reprinted at the end of this document.)**
- **to carry the Warning Card with them.**
- how to identify a hypersensitivity reaction (see WARNINGS and MEDICATION GUIDE).
- that if they develop symptoms consistent with a hypersensitivity reaction to discontinue treatment with EPZICOM and seek medical evaluation immediately.
- that a hypersensitivity reaction can worsen and lead to hospitalization or death if EPZICOM is not immediately discontinued.
- **to not restart EPZICOM or any other abacavir-containing product following a hypersensitivity reaction because more severe symptoms can occur within hours and may include life-threatening hypotension and death.**
- that a hypersensitivity reaction is usually reversible if it is detected promptly and EPZICOM is stopped right away.
- that if they have interrupted EPZICOM for reasons other than symptoms of hypersensitivity (for example, those who have an interruption in drug supply), a serious or fatal hypersensitivity reaction may occur with reintroduction of abacavir.
- that in one study, more severe hypersensitivity reactions were seen when ZIAGEN was dosed 600 mg once daily.
- **to not restart EPZICOM or any other abacavir-containing product without medical consultation and that restarting abacavir needs to be undertaken only if medical care can be readily accessed by the patient or others.**

Lamivudine: Patients co-infected with HIV and HBV should be informed that deterioration of liver disease has occurred in some cases when treatment with lamivudine was discontinued. Patients should be advised to discuss any changes in regimen with their physician.

EPZICOM: Inform patients that some HIV medicines, including EPZICOM, can cause a rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly).

EPZICOM is not a cure for HIV infection and patients may continue to experience illnesses associated with HIV infection, including opportunistic infections. Patients should remain under the care of a physician when using EPZICOM. Advise patients that the use of EPZICOM has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Inform patients 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.

EPZICOM Tablets are for oral ingestion only.

Patients should be advised of the importance of taking EPZICOM exactly as it is prescribed.

Drug Interactions: ***EPZICOM:*** No clinically significant changes to pharmacokinetic parameters were observed for abacavir or lamivudine when administered together.

Abacavir: Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol decreases the elimination of abacavir causing an increase in overall exposure (see CLINICAL PHARMACOLOGY: Drug Interactions).

The addition of methadone has no clinically significant effect on the pharmacokinetic properties of abacavir. In a study of 11 HIV-infected patients receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of ZIAGEN twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI 6% to 42%). This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients.

Lamivudine: Trimethoprim (TMP) 160 mg/sulfamethoxazole (SMX) 800 mg once daily has been shown to increase lamivudine exposure (AUC). No change in dose of either drug is recommended. The effect of higher doses of TMP/SMX on lamivudine pharmacokinetics has not been investigated (see CLINICAL PHARMACOLOGY).

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of EPZICOM in combination with zalcitabine is not recommended.

See CLINICAL PHARMACOLOGY for additional drug interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: ***Carcinogenicity:***

Abacavir: Abacavir was administered orally at 3 dosage levels to separate groups of mice and rats in 2-year carcinogenicity studies. Results showed an increase in the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver of female rats. In addition, non-malignant tumors also occurred in the liver and thyroid gland of female rats. These observations were made at systemic exposures in the range of 6 to 32 times the human exposure at the recommended dose.

Lamivudine: Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at the recommended therapeutic dose for HIV infection.

It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Mutagenicity: Abacavir: Abacavir induced chromosomal aberrations both in the presence and absence of metabolic activation in an in vitro cytogenetic study in human lymphocytes. Abacavir was mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence of metabolic activation in an L5178Y mouse lymphoma assay. Abacavir was clastogenic in males and not clastogenic in females in an in vivo mouse bone marrow micronucleus assay. Abacavir was not mutagenic in bacterial mutagenicity assays in the presence and absence of metabolic activation.

Lamivudine: Lamivudine was mutagenic in an L5178Y mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was not mutagenic in a microbial mutagenicity assay, in an in vitro cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver.

Impairment of Fertility: Abacavir or lamivudine induced no adverse effects on the mating performance or fertility of male and female rats at doses producing systemic exposure levels approximately 8 or 130 times, respectively, higher than those in humans at the recommended dose based on body surface area comparisons.

Pregnancy: Pregnancy Category C. There are no adequate and well-controlled studies of EPZICOM in pregnant women. Reproduction studies with abacavir and lamivudine have been performed in animals (see Abacavir and Lamivudine sections below). EPZICOM should be used during pregnancy only if the potential benefits outweigh the risks.

Abacavir: Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. Fetal malformations (increased incidences of fetal anasarca and skeletal malformations) and developmental toxicity (depressed fetal body weight and reduced crown-rump length) were observed in rats at a dose which produced 35 times the human exposure, based on AUC. Embryonic and fetal toxicities (increased resorptions, decreased fetal body weights) and toxicities to the offspring (increased incidence of stillbirth and lower body weights) occurred at half of the above-mentioned dose in separate fertility studies conducted in rats. In the rabbit, no developmental toxicity and no increases in fetal malformations occurred at doses that produced 8.5 times the human exposure at the recommended dose based on AUC.

Lamivudine: Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. Reproduction studies with orally administered lamivudine have been performed in rats and rabbits at doses producing plasma levels up to approximately 35 times that for the recommended adult HIV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryolethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 35 times those in humans.

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

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV infection.

Abacavir: Abacavir is secreted into the milk of lactating rats.

Lamivudine: Lamivudine is excreted in human breast milk and into the milk of lactating rats.

Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving EPZICOM.**

Pediatric Use: Safety and effectiveness of EPZICOM in pediatric patients have not been established.

Geriatric Use: Clinical studies of abacavir and lamivudine did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. EPZICOM is not recommended for patients with impaired renal function or impaired hepatic function (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Abacavir: ***Hypersensitivity Reaction:*** **Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate, a component of EPZICOM.**

In one study, once-daily dosing of ZIAGEN was associated with more severe hypersensitivity reactions (see WARNINGS and PRECAUTIONS: Information for Patients).

Therapy-Naive Adults: Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a ≥5% frequency during therapy with ZIAGEN 600 mg once daily or ZIAGEN 300 mg twice daily, both in combination with lamivudine 300 mg once daily and efavirenz 600 mg once daily are listed in Table 4.

Table 4. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Naive Adults (CNA30021) Through 48 Weeks of Treatment

Adverse Event	ZIAGEN 600 mg q.d. plus EPIVIR plus Efavirenz (n = 384)	ZIAGEN 300 mg b.i.d. plus EPIVIR plus Efavirenz (n = 386)
Drug hypersensitivity*†	9%	7%
Insomnia	7%	9%
Depression/Depressed mood	7%	7%
Headache/Migraine	7%	6%
Fatigue/Malaise	6%	8%
Dizziness/Vertigo	6%	6%
Nausea	5%	6%
Diarrhea*	5%	6%
Rash	5%	5%
Pyrexia	5%	3%
Abdominal pain/gastritis	4%	5%
Abnormal dreams	4%	5%
Anxiety	3%	5%

* Patients receiving ZIAGEN 600 mg once daily, experienced a significantly higher incidence of severe drug hypersensitivity reactions and severe diarrhea compared to patients who received ZIAGEN 300 mg twice daily. Five percent (5%) of patients receiving ZIAGEN 600 mg once daily had severe drug hypersensitivity reactions compared to 2% of patients receiving ZIAGEN 300 mg twice daily. Two percent (2%) of patients receiving ZIAGEN 600 mg once daily had severe diarrhea while none of the patients receiving ZIAGEN 300 mg twice daily had this event.

† Study **CNA30024** was a multi-center, double-blind, controlled study in which 649 HIV-infected, therapy-naive adults were randomized and received either ZIAGEN (300 mg twice daily), EPIVIR (150 mg twice daily), and efavirenz (600 mg once daily) or zidovudine (300 mg twice daily), EPIVIR (150 mg twice daily), and efavirenz (600 mg once daily). CNA30024 used double-blind ascertainment of suspected hypersensitivity reactions. During the blinded portion of the study, **suspected hypersensitivity to abacavir was reported by investigators in 9% of 324 patients in the abacavir group and 3% of 325 patients in the zidovudine group.**

Laboratory Abnormalities: Laboratory abnormalities observed in clinical studies of ZIAGEN were anemia, neutropenia, liver function test abnormalities, and elevations of CPK, blood glucose, and triglycerides. Additional laboratory abnormalities observed in clinical studies of EPIVIR were thrombocytopenia and elevated levels of bilirubin, amylase, and lipase.

The frequencies of treatment-emergent laboratory abnormalities were comparable between treatment groups in Study CNA30021.

Other Adverse Events: In addition to adverse reactions listed above, other adverse events observed in the expanded access program for abacavir were pancreatitis and increased GGT**.**

Observed During Clinical Practice: The following reactions have been identified during post-approval use of abacavir and lamivudine. 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 a combination of their seriousness, frequency of reporting, or potential causal connection to abacavir and/or lamivudine.

Abacavir: Suspected Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients receiving abacavir primarily in combination with medications known to be associated with SJS and TEN, respectively. Because of the overlap of clinical signs and symptoms between hypersensitivity to abacavir and SJS and TEN, and the possibility of multiple drug sensitivities in some patients, abacavir should be discontinued and not restarted in such cases.

There have also been reports of erythema multiforme with abacavir use.

Abacavir and Lamivudine:

Body as a Whole: Redistribution/accumulation of body fat (see PRECAUTIONS: Fat Redistribution).
Digestive: Stomatitis.
Endocrine and Metabolic: Hyperglycemia.
General: Weakness.
Hemic and Lymphatic: Aplastic anemia, anemia (including pure red cell aplasia and severe anemias progressing on therapy), lymphadenopathy, splenomegaly.
Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis, pancreatitis, posttreatment exacerbation of hepatitis B (see WARNINGS).
Hypersensitivity: Sensitization reactions (including anaphylaxis), urticaria.
Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.
Nervous: Paresthesia, peripheral neuropathy, seizures.
Respiratory: Abnormal breath sounds/wheezing.
Skin: Alopecia, erythema multiforme, Stevens-Johnson syndrome.

OVERDOSAGE

Abacavir: There is no known antidote for abacavir. It is not known whether abacavir can be removed by peritoneal dialysis or hemodialysis.

Lamivudine: One case of an adult ingesting 6 grams of lamivudine was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. It is not known whether lamivudine can be removed by peritoneal dialysis or hemodialysis.

DOSAGE AND ADMINISTRATION

A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill. To facilitate reporting of hypersensitivity reactions and collection of information on each case, an Abacavir Hypersensitivity Registry has been established. **Physicians should register patients by calling 1-800-270-0425.**

The recommended oral dose of EPZICOM for adults is one tablet daily, in combination with other antiretroviral agents (see INDICATIONS AND USAGE: Description of Clinical Studies, PRECAUTIONS, MICROBIOLOGY, and CLINICAL PHARMACOLOGY).

EPZICOM can be taken with or without food.

Dose Adjustment: Because it is a fixed-dose tablet, EPZICOM should not be prescribed for patients requiring dosage adjustment such as those with creatinine clearance <50 mL/min, those with hepatic impairment, or those experiencing dose-limiting adverse events. Use of EPIVIR Oral Solution and ZIAGEN Oral Solution may be considered.

HOW SUPPLIED

EPZICOM is available as tablets. Each tablet contains 600 mg of abacavir as abacavir sulfate and 300 mg of lamivudine. The tablets are orange, film-coated, modified capsule-shaped, and debossed with GS FC2 on one side with no markings on the reverse side. They are packaged as follows:

Bottles of 30 Tablets (NDC 0173-0742-00).

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature).

ANIMAL TOXICOLOGY

Myocardial degeneration was found in mice and rats following administration of abacavir for 2 years. The systemic exposures were equivalent to 7 to 24 times the expected systemic exposure in humans. The clinical relevance of this finding has not been determined.

MEDICATION GUIDE

EPZICOM™ (ep′ zih com) Tablets

Generic name: abacavir sulfate and lamivudine

Read the Medication Guide that comes with Epzicom before you start taking it and each time you get a refill because there may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment. Be sure to carry your Epzicom Warning Card with you at all times.

What is the most important information I should know about Epzicom?

- **Serious Allergic Reaction to Abacavir. Epzicom contains abacavir (also contained in Ziagen® and Trizivir®).** Patients taking Epzicom may have a serious allergic reaction (hypersensitivity reaction) that can cause death. **If you get a symptom from 2 or more of the following groups while taking Epzicom, stop taking Epzicom and call your doctor right away.**

	Symptom(s)
Group 1	**Fever**
Group 2	**Rash**
Group 3	**Nausea, vomiting, diarrhea, abdominal (stomach area) pain**
Group 4	**Generally ill feeling, extreme tiredness, or achiness**
Group 5	**Shortness of breath, cough, sore throat**

A list of these symptoms is on the Warning Card your pharmacist gives you. Carry this Warning Card with you.

If you stop Epzicom because of an allergic reaction, NEVER take Epzicom (abacavir sulfate and lamivudine) or any other abacavir-containing medicine (Ziagen and Trizivir) again. If you take Epzicom or any other abacavir-containing medicine again after you have had an allergic reaction, **WITHIN HOURS** you may get **life-threatening symptoms** that may include **very low blood pressure** or **death**.

If you stop Epzicom for any other reason, even for a few days, and you are not allergic to Epzicom, talk with your doctor before taking it again. Taking Epzicom again can cause a serious allergic or life-threatening reaction, even if you never had an allergic reaction to it before. If your doctor tells you that you can take Epzicom again, **start taking it when you are around medical help or people who can call a doctor if you need one.**

- **Lactic Acidosis. Some HIV medicines, including Epzicom, can cause a rare but serious condition called lactic acidosis with liver enlargement (hepatomegaly).** Nausea and tiredness that don't get better may be symptoms of lactic acidosis. In some cases this condition can cause death. Women, overweight people, and people who have taken HIV medicines like Epzicom for a long time have a higher chance of getting lactic acidosis and liver enlargement. Lactic acidosis is a medical emergency and must be treated in the hospital.
- **Worsening of hepatitis B virus (HBV) infection.** Patients with HBV infection, who take Epzicom and then stop it, may get "flare-ups" of their hepatitis. "Flare-up" is when the disease suddenly returns in a worse way than before. If you have HBV infection, your doctor should closely monitor your liver function for several months after stopping Epzicom. You may need to take anti-HBV medicines.
- **Use with interferon- and ribavirin-based regimens.** Worsening of liver disease (sometimes resulting in death) has occurred in patients infected with both HIV and hepatitis C virus who are taking anti-HIV medicines and are also being treated for hepatitis C with interferon with or without ribavirin. If you are taking Epzicom as well as interferon with or without ribavirin and you experience side effects, be sure to tell your doctor.

Epzicom can have other serious side effects. Be sure to read the section below entitled "What are the possible side effects of Epzicom?"

What is Epzicom?

Epzicom is a prescription medicine used to treat HIV infection. Epzicom includes 2 medicines: abacavir (Ziagen) and lamivudine or 3TC (Epivir®). See the end of this Medication Guide for a complete list of ingredients in Epzicom. Both of these medicines are called nucleoside analogue reverse transcriptase inhibitors (NRTIs). When used together, they help lower the amount of HIV in your blood. This helps to keep your immune system as healthy as possible so that it can help fight infection.

Different combinations of medicines are used to treat HIV infection. You and your doctor should discuss which combination of medicines is best for you.

- **Epzicom does not cure HIV infection or AIDS.** We do not know if Epzicom will help you live longer or have fewer of the medical problems that people get with HIV or AIDS. It is very important that you see your doctor regularly while you are taking Epzicom.
- **Epzicom does not lower the risk of passing HIV to other people through sexual contact, sharing needles, or being exposed to your blood.** For your health and the health of others, it is important to always practice safe sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood. Never use or share dirty needles.

Who should not take Epzicom?

Do not take Epzicom if you:

- **have ever had a serious allergic reaction (a hypersensitivity reaction) to Epzicom or any other medicine that has abacavir as one of its ingredients (Trizivir and Ziagen).** See the end of this Medication Guide for a complete list of ingredients in Epzicom. If you have had such a reaction, return all of your unused Epzicom to your doctor or pharmacist.
- **have a liver that does not function properly.**
- **are less than 18 years of age.**

Before starting Epzicom tell your doctor about all your medical conditions, including if you:

- **are pregnant or planning to become pregnant.** We do not know if Epzicom will harm your unborn child. You and your doctor will need to decide if Epzicom is right for you. If you use Epzicom while you are pregnant, talk to your doctor about how you can be on the Antiviral Pregnancy Registry for Epzicom.
- **are breastfeeding.** Some of the ingredients in Epzicom can be passed to your baby in your breast milk. It is not known if they could harm your baby. Also, mothers with HIV should not breastfeed because HIV can be passed to the baby in the breast milk.
- **have liver problems including hepatitis B virus infection.**
- **have kidney problems.**

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Especially tell your doctor if you take:

- **methadone**
- **Hivid® (zalcitabine, ddC)**
- **Epivir or Epivir-HBV® (lamivudine, 3TC), Ziagen (abacavir sulfate), Combivir® (lamivudine and zidovudine), or Trizivir (abacavir sulfate, lamivudine, and zidovudine).**

How should I take Epzicom?

- **Take Epzicom by mouth exactly as your doctor prescribes it.** The usual dose is 1 tablet once a day. Do not skip doses.
- **You can take Epzicom with or without food.**
- **If you miss a dose of Epzicom, take the missed dose right away. Then, take the next dose at the usual time.**
- **Do not let your Epzicom run out.**
- **Starting Epzicom again can cause a serious allergic or life-threatening reaction, even if you never had an allergic reaction to it before**. If you run out of Epzicom even for a few days, you must ask your doctor if you can start Epzicom again. If your doctor tells you that you can take Epzicom again, start taking it when you are around medical help or people who can call a doctor if you need one.
- **If you stop your anti-HIV drugs, even for a short time, the amount of virus in your blood may increase and the virus may become harder to treat.**
- **If you take too much Epzicom, call your doctor or poison control center right away.**

What should I avoid while taking Epzicom?

- Do not take Epivir **(lamivudine, 3TC)**, Combivir **(lamivudine and zidovudine)**, Ziagen **(abacavir sulfate)**, or Trizivir **(abacavir sulfate, lamivudine, and zidovudine)** while taking Epzicom. Some of these medicines are already in Epzicom.
- Do not take zalcitabine (Hivid, ddC) while taking Epzicom.

Avoid doing things that can spread HIV infection, as Epzicom does not stop you from passing the HIV infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** Epzicom can be passed to babies in breast milk and could harm the baby. Also, mothers with HIV should not breastfeed because HIV can be passed to the baby in the breast milk.

What are the possible side effects of Epzicom?

Epzicom can cause the following serious side effects:

- **Serious allergic reaction that can cause death.** (See "What is the most important information I should know about Epzicom?" at the beginning of this Medication Guide.)
- **Lactic acidosis with liver enlargement (hepatomegaly) that can cause death.** (See "What is the most important information I should know about Epzicom?" at the beginning of this Medication Guide.)
- **Worsening of HBV infection.** (See "What is the most important information I should know about Epzicom?" at the beginning of this Medication Guide.)
- **Changes in immune system.** When you start taking HIV medicines, your immune system may get stronger and could begin to fight infections that have been hidden in your body, such as pneumonia, herpes virus, or tuberculosis. If you have new symptoms after starting your HIV medicines, be sure to tell your doctor.
- **Changes in body fat.** These changes have happened in patients taking antiretroviral medicines like Epzicom. The changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the back, chest, and stomach area. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known.

The most common side effects with Epzicom are trouble sleeping, depression, headache, tiredness, dizziness, nausea, diarrhea, rash, fever, stomach pain, abnormal dreams, and anxiety. Most of these side effects did not cause people to stop taking Epzicom.

This list of side effects is not complete. Ask your doctor or pharmacist for more information.

How should I store Epzicom?

- Store Epzicom at room temperature between 59° to 86°F (15° to 30°C).
- Keep Epzicom and all medicines out of the reach of children.

General information for safe and effective use of Epzicom

Medicines are sometimes prescribed for conditions that are not mentioned in Medication Guides. Do not use Epzicom for a condition for which it was not prescribed. Do not give Epzicom to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Epzicom. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for the information that is written for healthcare professionals or call 1-888-825-5249.

What are the ingredients in Epzicom?

Active ingredients: abacavir sulfate and lamivudine

Inactive ingredients: Each film-coated Epzicom Tablet contains the inactive ingredients magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablets are coated with a film (Opadry® orange YS-1-13065-A) that is made of FD&C Yellow No. 6, hypromellose, polyethylene glycol 400, polysorbate 80, and titanium dioxide.

March 2006 MG-036

This Medication Guide has been approved by the US Food and Drug Administration.

GlaxoSmithKline
Research Triangle Park, NC 27709

Lamivudine is manufactured under agreement from
Shire Pharmaceuticals Group plc
Basingstoke, UK

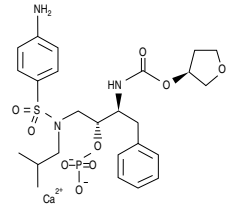
October 2006 RL-2319

LEXIVA®
(fosamprenavir calcium) Tablets

PATIENT INFORMATION INCLUDED

DESCRIPTION

LEXIVA (fosamprenavir calcium) is a prodrug of amprenavir, an inhibitor of human immunodeficiency virus (HIV) protease. The chemical name of fosamprenavir calcium is (3*S*)-tetrahydrofuran-3-yl (1*S*,2*R*)-3-[[(4-aminophenyl) sulfonyl](isobutyl) amino]-1-benzyl-2-(phosphonooxy) propylcarbamate monocalcium salt. Fosamprenavir calcium is a single stereoisomer with the (3*S*)(1*S*,2*R*) configuration. It has a molecular formula of $C_{25}H_{34}CaN_3O_9PS$ and a molecular weight of 623.7. It has the following structural formula:



Fosamprenavir calcium is a white to cream-colored solid with a solubility of approximately 0.31 mg/mL in water at 25°C.

LEXIVA Tablets are available for oral administration in a strength of 700 mg of fosamprenavir as fosamprenavir calcium (equivalent to approximately 600 mg of amprenavir). Each 700-mg tablet contains the inactive ingredients colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and povidone K30. The tablet film-coating contains the inactive ingredients hypromellose, iron oxide red, titanium dioxide, and triacetin.

MICROBIOLOGY

Mechanism of Action: Fosamprenavir is rapidly converted to amprenavir by cellular phosphatases in vivo. Amprenavir is an inhibitor of HIV-1 protease. Amprenavir binds to the active site of HIV-1 protease and thereby prevents the processing of viral Gag and Gag-Pol polyprotein precursors, resulting in the formation of immature non-infectious viral particles.

Antiviral Activity: Fosamprenavir has little or no antiviral activity in vitro. The in vitro antiviral activity of amprenavir was evaluated against HIV-1 IIIB in both acutely and chronically infected lymphoblastic cell lines (MT-4, CEM-CCRF, H9) and in peripheral blood lymphocytes. The 50% effective concentration (EC_{50}) of amprenavir ranged from 0.012 to 0.08 µM in acutely infected cells and was 0.41 µM in chronically infected cells (1 µM = 0.50 mcg/mL). The median EC_{50} value of amprenavir against HIV-1 isolates from clades A to G was 0.00095 µM in peripheral blood mononuclear cells (PBMCs). Similarly, the EC_{50} values for amprenavir against monocytes/macrophage tropic HIV-1 isolates (clade B) ranged from 0.003 to 0.075 µM in monocyte/macrophage cultures. The EC_{50} values of amprenavir against HIV-2 isolates grown in PBMCs were higher than those for HIV-1 isolates, and ranged from 0.003 to 0.11 µM. Amprenavir exhibited synergistic anti–HIV-1 activity in combination with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir, didanosine, lamivudine, stavudine, tenofovir, and zidovudine; the non-nucleoside reverse transcriptase inhibitors (NNRTIs) delavirdine and efavirenz; and the protease inhibitors (PIs) atazanavir and saquinavir. Amprenavir exhibited additive anti–HIV-1 activity in combination with the NNRTI nevirapine, the PIs indinavir, lopinavir, nelfinavir, and ritonavir; and the fusion inhibitor enfuvirtide. These drug combinations have not been adequately studied in humans.

Resistance: HIV-1 isolates with decreased susceptibility to amprenavir have been selected in vitro and obtained from patients treated with fosamprenavir. Genotypic analysis of isolates from treatment-naive patients failing amprenavir-containing regimens showed mutations in the HIV-1 protease gene resulting in amino acid substitutions primarily at positions V32I, M46I/L, I47V, I50V, I54L/M, and I84V, as well as mutations in the p7/p1 and p1/p6 Gag and Gag-Pol polyprotein precursor cleavage sites. Some of these amprenavir resistance-associated mutations have also been detected in HIV-1 isolates from antiretroviral-naive patients treated with LEXIVA. Of the 488 antiretroviral-naive patients treated with LEXIVA or LEXIVA/ritonavir in studies APV30001 and APV30002, respectively, 61 patients (29 receiving LEXIVA and 32 receiving LEXIVA/ritonavir) with virologic failure (plasma HIV-1 RNA 1,000 copies/mL on 2 occasions on or after Week 12) were genotyped. Five of the 29 antiretroviral-naive patients (17%) receiving LEXIVA without ritonavir in study APV30001 had evidence of genotypic resistance to amprenavir: I54L/M (n = 2), I54L + L33F (n = 1), V32I + I47V (n = 1), and M46I + I47V (n = 1). No amprenavir resistance-associated mutations were detected in antiretroviral-naive patients treated with LEXIVA/ritonavir for 48 weeks in study APV30002. However, the M46I and I50V mutations were detected in isolates from 1 virologic failure patient receiving LEXIVA/ritonavir once daily at Week 160 (HIV-1 RNA >500 copies/mL). Upon retrospective analysis of stored samples using an ultrasensitive assay, these resistant mutants were traced back to Week 84 (76 weeks prior to clinical virologic failure).

Cross-Resistance: Varying degrees of cross-resistance among HIV-1 protease inhibitors have been observed. An association between virologic response at 48 weeks (HIV-1 RNA level <400 copies/mL) and PI-resistance mutations detected in baseline HIV-1 isolates from PI-experienced patients receiving LEXIVA/ritonavir twice daily (n = 88), or lopinavir/ritonavir twice daily (n = 85) in study APV30003 is shown in Table 1. The majority of subjects had previously received either one (47%) or 2 PIs (36%), most commonly nelfinavir (57%) and indinavir (53%). Out of 102 subjects with baseline phenotypes receiving twice-daily LEXIVA/ritonavir, 54% (n = 55) had resistance to at least one PI, with 98% (n = 54) of those having resistance to nelfinavir. Out of 97 subjects with baseline phenotypes in the lopinavir/ritonavir arm, 60% (n = 58) had resistance to at least one PI, with 97% (n = 56) of those having resistance to nelfinavir.

Table 1. Responders at Study Week 48 by Presence of Baseline PI Resistance-Associated Mutations*

PI-mutations†	LEXIVA/Ritonavir b.i.d. (n = 88)		Lopinavir/Ritonavir b.i.d. (n = 85)	
D30N	21/22	95%	17/19	89%
N88D/S	20/22	91%	12/12	100%
L90M	16/31	52%	17/29	59%
M46I/L	11/22	50%	12/24	50%
V82A/F/T/S	2/9	22%	6/17	35%
I54V	2/11	18%	6/11	55%
I84V	1/6	17%	2/5	40%

* Results should be interpreted with caution because the subgroups were small.
† Most patients had >1 PI resistance-associated mutation at baseline.

The virologic response based upon baseline phenotype was assessed. Baseline isolates from PI-experienced patients responding to LEXIVA/ritonavir twice daily had a median shift in susceptibility to amprenavir relative to a standard wild-type reference strain of 0.7 (range: 0.1 to 5.4, n = 62), and baseline isolates from individuals failing therapy had a median shift in susceptibility of 1.9 (range: 0.2 to 14, n = 29). Because this was a select patient population, these data do not constitute definitive clinical susceptibility break points. Additional data are needed to determine clinically relevant break points for LEXIVA.

Isolates from 15 of the 20 patients receiving twice-daily LEXIVA/ritonavir up to Week 48 and experiencing virologic failure/ongoing replication were subjected to genotypic analysis. The following amprenavir resistance-associated mutations were found either alone or in combination: V32I, M46I/L, I47V, I50V, I54L/M, and I84V. Isolates from 4 of the 16 patients continuing to receive twice-daily LEXIVA/ritonavir up to Week 96 who experienced virologic failure underwent genotypic analysis. Isolates from 2 patients contained amprenavir resistance-associated mutations: V32I, M46I, and I47V in 1 isolate and I84V in the other.

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults: Fosamprenavir is a prodrug, which is rapidly hydrolyzed to amprenavir by enzymes in the gut epithelium as it is absorbed.

The pharmacokinetic properties of amprenavir after administration of LEXIVA, with or without ritonavir, have been evaluated in both healthy adult volunteers and in HIV-infected patients; no substantial differences in steady-state amprenavir concentrations were observed between the 2 populations.

Absorption and Bioavailability: After administration of a single dose of LEXIVA to HIV–1-infected patients, the time to peak amprenavir concentration (T_{max}) occurred between 1.5 and 4 hours (median 2.5 hours). The absolute oral bioavailability of amprenavir after administration of LEXIVA in humans has not been established.

The pharmacokinetic parameters of amprenavir after administration of LEXIVA (with and without concomitant ritonavir) are shown in Table 2.

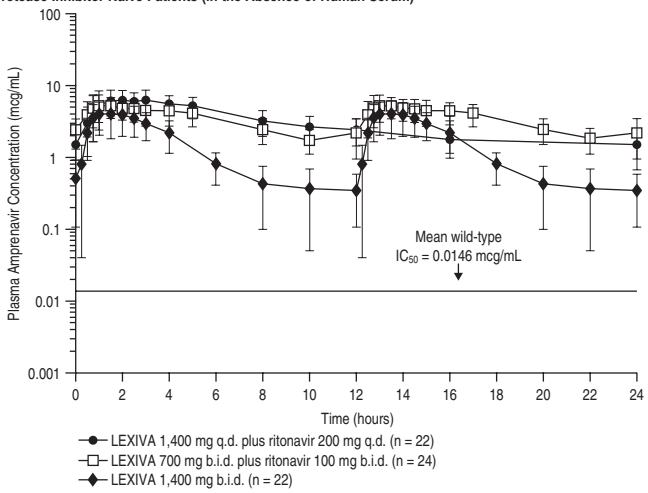
Table 2. Geometric Mean (95% CI) Steady-State Plasma Amprenavir Pharmacokinetic Parameters

Regimen	C_{max} (mcg/mL)	T_{max} (hours)*	AUC_{24} (mcg•hr/mL)	C_{min} (mcg/mL)
LEXIVA 1,400 mg b.i.d.	4.82 (4.06-5.72)	1.3 (0.8-4.0)	33.0 (27.6-39.2)	0.35 (0.27-0.46)
LEXIVA 1,400 mg q.d. plus Ritonavir 200 mg q.d.	7.24 (6.32-8.28)	2.1 (0.8-5.0)	69.4 (59.7-80.8)	1.45 (1.16-1.81)
LEXIVA 700 mg b.i.d. plus Ritonavir 100 mg b.i.d.	6.08 (5.38-6.86)	1.5 (0.75-5.0)	79.2 (69.0-90.6)	2.12 (1.77-2.54)

*Data shown are median (range).

The median plasma amprenavir concentrations of the dosing regimens over the dosing intervals are displayed in Figure 1.

Figure 1. Mean (± SD) Steady-State Plasma Amprenavir Concentrations and Mean IC_{50} Values Against HIV from Protease Inhibitor-Naive Patients (in the Absence of Human Serum)



Effects of Food on Oral Absorption: LEXIVA Tablets may be taken with or without food (see DOSAGE AND ADMINISTRATION). Administration of a single 1,400-mg dose of LEXIVA in the fed state (standardized high-fat meal: 967 kcal, 67 grams fat, 33 grams protein, 58 grams carbohydrate) compared to the fasted state was associated with no significant changes in amprenavir C_{max}, T_{max}, or $AUC_{0-\infty}$.

Distribution: In vitro, amprenavir is approximately 90% bound to plasma proteins, primarily to alpha$_1$-acid glycoprotein. In vitro, concentration-dependent binding was observed over the concentration range of 1 to 10 mcg/mL, with decreased binding at higher concentrations. The partitioning of amprenavir into erythrocytes is low, but increases as amprenavir concentrations increase, reflecting the higher amount of unbound drug at higher concentrations.

Metabolism: After oral administration, fosamprenavir is rapidly and almost completely hydrolyzed to amprenavir and inorganic phosphate prior to reaching the systemic circulation. This occurs in the gut epithelium during absorption. Amprenavir is metabolized in the liver by the cytochrome P450 3A4 (CYP3A4) enzyme system. The 2 major metabolites result from oxidation of the tetrahydrofuran and aniline moieties. Glucuronide conjugates of oxidized metabolites have been identified as minor metabolites in urine and feces.

Elimination: Excretion of unchanged amprenavir in urine and feces is minimal. Unchanged amprenavir in urine accounts for approximately 1% of the dose; unchanged amprenavir was not detectable in feces. Approximately 14% and 75% of an administered single dose of ^{14}C-amprenavir can be accounted for as metabolites in urine and feces, respectively. Two metabolites accounted for >90% of the radiocarbon in fecal samples. The plasma elimination half-life of amprenavir is approximately 7.7 hours.

Special Populations: ***Hepatic Insufficiency:*** The pharmacokinetics of amprenavir after administration of LEXIVA have not been studied in patients with hepatic insufficiency.

The pharmacokinetics of amprenavir have been studied after administration of amprenavir given as AGENERASE® Capsules to adult patients with impaired hepatic function using a single 600-mg oral dose. The $AUC_{0-\infty}$ of amprenavir was significantly greater in patients with moderate cirrhosis (25.76 ± 14.68 mcg•hr/mL) compared with healthy volunteers (12.00 ± 4.38 mcg•hr/mL). The $AUC_{0-\infty}$ and C_{max} were significantly greater in patients with severe cirrhosis ($AUC_{0-\infty}$: 38.66 ± 16.08 mcg•hr/mL; C_{max}: 9.43 ± 2.61 mcg/mL) compared with healthy volunteers ($AUC_{0-\infty}$ 12.00 ± 4.38 mcg•hr/mL; C_{max}: 4.90 ± 1.39 mcg/mL). Based on these data, patients with impaired hepatic function receiving LEXIVA without concurrent ritonavir may require dosage reduction. There are no data on the use of LEXIVA in combination with ritonavir in patients with any degree of hepatic impairment (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Insufficiency: The impact of renal impairment on amprenavir elimination in adult patients has not been studied. The renal elimination of unchanged amprenavir represents approximately 1% of the administered dose; therefore, renal impairment is not expected to significantly impact the elimination of amprenavir.

Pediatric Patients: The pharmacokinetics of amprenavir after administration of LEXIVA to pediatric patients are under investigation. There are insufficient data at this time to recommend a dose.

Geriatric Patients: The pharmacokinetics of amprenavir after administration of LEXIVA to patients over 65 years of age have not been studied.

Gender: The pharmacokinetics of amprenavir after administration of LEXIVA do not differ between males and females.

Race: The pharmacokinetics of amprenavir after administration of LEXIVA do not differ between blacks and non-blacks.

Drug Interactions: See also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Drug Interactions.

Amprenavir, the active metabolite of fosamprenavir, is metabolized in the liver by the cytochrome P450 enzyme system. Amprenavir inhibits CYP3A4. Data also suggest that amprenavir induces CYP3A4. Caution should be used when coadministering medications that are substrates, inhibitors, or inducers of CYP3A4, or potentially toxic medications that are metabolized by CYP3A4. Amprenavir does not inhibit CYP2D6, CYP1A2, CYP2C9, CYP2C19, CYP2E1, or uridine glucuronosyltransferase (UDPGT).

Drug interaction studies were performed with LEXIVA and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interactions. The effects of coadministration on AUC, C_{max}, and C_{min} values are summarized in Table 3 (effect of other drugs on amprenavir) and Table 5 (effect of LEXIVA on other drugs). In addition, since LEXIVA delivers comparable amprenavir plasma concentrations as AGENERASE, drug interaction data derived from studies with AGENERASE are provided in Tables 4 and 6. For information regarding clinical recommendations, see PRECAUTIONS: Drug Interactions.

Table 3. Drug Interactions: Pharmacokinetic Parameters for Amprenavir After Administration of LEXIVA in the Presence of the Coadministered Drug(s)

Coadministered Drug(s) and Dose(s)	Dose of **LEXIVA***	n	% Change in **Amprenavir** Pharmacokinetic Parameters (90% CI)		
			C_{max}	AUC	C_{min}
Antacid (MAALOX TC®) 30 mL single dose	1,400 mg single dose	30	↓ 35 (↓ 24 to ↓ 42)	↓ 18 (↓ 9 to ↓ 26)	↑ 14 (↓ 7 to ↑ 39)
Atazanavir 300 mg q.d. for 10 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 10 days	22	↔	↔	↔
Atorvastatin 10 mg q.d. for 4 days	1,400 mg b.i.d. for 2 weeks	16	↓ 18 (↓ 34 to ↑ 1)	↓ 27 (↓ 41 to ↓ 12)	↓ 12 (↓ 27 to ↑ 6)
Atorvastatin 10 mg q.d. for 4 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	16	↔	↔	↔
Efavirenz 600 mg q.d. for 2 weeks	1,400 mg q.d. plus ritonavir 200 mg q.d. for 2 weeks	16	↔	↓ 13 (↓30 to ↑ 7)	↓ 36 (↓8 to ↓56)
Efavirenz 600 mg q.d. plus additional ritonavir 100 mg q.d. for 2 weeks	1,400 mg q.d. plus ritonavir 200 mg q.d. for 2 weeks	16	↑ 18 (↑ 1 to ↑ 38)	↑ 11 (0 to ↑ 24)	↔
Efavirenz 600 mg q.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	16	↔	↔	↓ 17 (↓ 4 to ↓ 29)
Esomeprazole 20 mg q.d. for 2 weeks	1,400 mg b.i.d. for 2 weeks	25	↔	↔	↔
Esomeprazole 20 mg q.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	23	↔	↔	↔
Ethinyl estradiol/norethindrone 0.035 mg/0.5 mg q.d. for 21 days	700 mg b.i.d. plus ritonavir† 100 mg b.i.d. for 21 days	25	↔	↔	↔
Ketoconazole§ 200 mg q.d. for 4 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 4 days	15	↔	↔	↔
Lopinavir/ritonavir 533 mg/133 mg b.i.d.	1,400 mg b.i.d. for 2 weeks	18	See following section: **HIV Protease Inhibitors**		
Lopinavir/ritonavir 400 mg/100 mg b.i.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	18	↓ 58 (↓ 42 to ↓ 70)	↓ 63 (↓ 51 to ↓ 72)	↓ 65 (↓ 54 to ↓ 73)

Table 3. (Cont.)

Coadministered Drug(s) and Dose(s)	Dose of **LEXIVA***	n	% Change in **Amprenavir** Pharmacokinetic Parameters (90% CI) C_{max}	AUC	C_{min}
Nevirapine 200 mg b.i.d. for 2 weeks‖	1,400 mg b.i.d. for 2 weeks	17	↓ 25 (↓ 37 to ↓ 10)	↓ 33 (↓ 45 to ↓ 20)	↓ 35 (↓ 50 to ↓ 15)
Nevirapine 200 mg b.i.d. for 2 weeks‖	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	17	↔	↓ 11 (↓23 to ↑ 3)	↓ 19 (↓ 32 to ↓ 4)
Ranitidine 300 mg single dose (administered 1 hour before fosamprenavir)	1,400 mg single dose	30	↓ 51 (↓ 43 to ↓ 58)	↓ 30 (↓ 22 to ↓ 37)	↔ (↓ 19 to ↑ 21)
Rifabutin 150 mg q.o.d. for 2 weeks	700 mg b.i.d plus ritonavir 100 mg b.i.d. for 2 weeks	15	↑ 36‡ (↑ 18 to ↑ 55)	↑ 35‡ (↑ 17 to ↑ 56)	↑ 17‡ (↓1 to ↑ 39)

* Concomitant medication is also shown in this column where appropriate.
† Ritonavir C_{max}, AUC, and C_{min} increased by 63%, 45%, and 13%, respectively, compared to historical control.
‡ Compared to historical control.
§ Patients were receiving LEXIVA/ritonavir for 10 days prior to the 4-day treatment period with both ketoconazole and LEXIVA/ritonavir.
‖ Patients were receiving nevirapine for at least 12 weeks prior to study.
↑ = Increase; ↓ = Decrease; ↔ = No change (↑ or ↓ ≤10%).

Table 4. Drug Interactions: Pharmacokinetic Parameters for Amprenavir After Administration of AGENERASE in the Presence of the Coadministered Drug(s)

Coadministered Drugs and Dose(s)	Dose of **AGENERASE***	n	% Change in **Amprenavir** Pharmacokinetic Parameters (90% CI) C_{max}	AUC	C_{min}
Clarithromycin 500 mg b.i.d. for 4 days	1,200 mg b.i.d. for 4 days	12	↑ 15 (↑ 1 to ↑ 31)	↑ 18 (↑ 8 to ↑ 29)	↑ 39 (↑ 31 to ↑ 47)
Delavirdine 600 mg b.i.d. for 10 days	600 mg b.i.d. for 10 days	9	↑ 40*	↑ 130*	↑ 125*
Ethinyl estradiol/norethindrone 0.035 mg/1 mg for 1 cycle	1,200 mg b.i.d. for 28 days	10	↔	↓ 22 (↓ 35 to ↓ 8)	↓ 20 (↓ 41 to ↑ 8)
Indinavir 800 mg t.i.d. for 2 weeks (fasted)	750 or 800 mg t.i.d. for 2 weeks (fasted)	9	↑ 18 (↓ 13 to ↑ 58)	↑ 33 (↑ 2 to ↑ 73)	↑ 25 (↓ 27 to ↑ 116)
Ketoconazole 400 mg single dose	1,200 mg single dose	12	↓ 16 (↓ 25 to ↓ 6)	↑ 31 (↑ 20 to ↑ 42)	NA
Lamivudine 150 mg single dose	600 mg single dose	11	↔	↔	NA
Nelfinavir 750 mg t.i.d. for 2 weeks (fed)	750 or 800 mg t.i.d. for 2 weeks (fed)	6	↓ 14 (↓ 38 to ↑ 20)	↔	↑ 189 (↑ 52 to ↑ 448)
Rifabutin 300 mg q.d. for 10 days	1,200 mg b.i.d. for 10 days	5	↔	↓ 15 (↓ 28 to 0)	↓ 15 (↓ 38 to ↑ 17)
Rifampin 300 mg q.d. for 4 days	1,200 mg b.i.d. for 4 days	11	↓ 70 (↓ 76 to ↓ 62)	↓ 82 (↓ 84 to ↓ 78)	↓ 92 (↓ 95 to ↓ 89)
Saquinavir 800 mg t.i.d. for 2 weeks (fed)	750 or 800 mg t.i.d. for 2 weeks (fed)	7	↓ 37 (↓ 54 to ↓ 14)	↓ 32 (↓ 49 to ↓ 9)	↓ 14 (↓ 52 to ↑ 54)
Zidovudine 300 mg single dose	600 mg single dose	12	↔	↑ 13 (↓ 2 to ↑ 31)	NA

*Median percent change; confidence interval not reported.
↑ = Increase; ↓ = Decrease; ↔ = No change (↑ or ↓ <10%); NA = C_{min} not calculated for single-dose study.

Table 5. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the Presence of Amprenavir After Administration of LEXIVA

Coadministered Drug(s) and Dose(s)	Dose of **LEXIVA***	n	% Change in Pharmacokinetic Parameters of **Coadministered Drug** (90% CI) C_{max}	AUC	C_{min}
Atazanavir 300 mg q.d. for 10 days†	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 10 days	21	↓ 24 (↓ 39 to ↓ 6)	↓ 22 (↓ 34 to ↓ 9)	↔
Atorvastatin 10 mg q.d. for 4 days	1,400 mg b.i.d. for 2 weeks	16	↑ 304 (↑ 205 to ↑ 437)	↑ 130 (↑ 100 to ↑ 164)	↓ 10 (↓ 27 to ↑ 12)
Atorvastatin 10 mg q.d. for 4 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	16	↑ 184 (↑ 126 to ↑ 257)	↑ 153 (↑ 115 to ↑ 199)	↑ 73 (↑ 45 to ↑ 108)
Esomeprazole 20 mg q.d. for 2 weeks	1,400 mg b.i.d. for 2 weeks	25	↔	↑ 55 (↑ 39 to ↑ 73)	ND
Esomeprazole 20 mg q.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	23	↔	↔	ND
Ethinyl estradiol‡ 0.035 mg q.d. for 21 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 21 days	25	↓ 28 (↓ 21 to ↓ 35)	↓ 37 (↓ 30 to ↓ 42)	ND
Ketoconazole§ 200 mg q.d. for 4 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 4 days	15	↑ 25 (↑ 0 to ↑ 56)	↑ 169 (↑ 108 to ↑ 248)	ND
Lopinavir/ritonavir‖ 533 mg/133 mg b.i.d. for 2 weeks	1,400 mg b.i.d. for 2 weeks	18	See following section: **HIV Protease Inhibitors**		
Lopinavir/ritonavir‖ 400 mg/100 mg b.i.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	18	↑ 30 (↓ 15 to ↑ 47)	↑ 37 (↓ 20 to ↑ 55)	↑ 52 (↓ 28 to ↑ 82)
Nevirapine 200 mg b.i.d. for 2 weeks¶	1,400 mg b.i.d. for 2 weeks	17	↑ 25 (↑ 14 to ↑ 37)	↑ 29 (↑ 19 to ↑ 40)	↑ 34 (↑ 20 to ↑ 49)
Nevirapine 200 mg b.i.d. for 2 weeks¶	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	17	↑ 13 (↑ 3 to ↑ 24)	↑ 14 (↑ 5 to ↑ 24)	↑ 22 (↑ 9 to ↑ 35)
Norethindrone‡ 0.5 mg q.d.for 21 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 21 days	25	↓ 38 (↓ 32 to ↓ 44)	↓ 34 (↓ 30 to ↓ 37)	↓ 26 (↓ 20 to ↓ 32)
Rifabutin 150 mg every other day for 2 weeks# (25-O-desacetylrifabutin metabolite) Rifabutin + 25-O-desacetylrifabutin metabolite	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	15	↓ 14 (↓ 28 to ↑ 4) ↑ 579 (↑ 479 to ↑ 698) NA	↔ ↑ 1,120 (↑ 965 to ↑ 1,300) ↑ 64 (↑ 46 to ↑ 84)	↑ 28 (↑ 12 to ↑ 46) ↑ 2,510 (↑ 1,910 to 3,300) NA

* Concomitant medication is also shown in this column where appropriate.
† Comparison arm of atazanavir 300 mg q.d. plus ritonavir 100 mg q.d. for 10 days.
‡ Administered as a combination oral contraceptive tablet: ethinyl estradial 0.035 mg/norethindrone 0.5 mg.
§ Patients were receiving LEXIVA/ritonavir for 10 days prior to the 4-day treatment period with both ketoconazole and LEXIVA/ritonavir.
‖ Data represent lopinavir concentrations.
¶ Patients were receiving nevirapine for at least 12 weeks prior to study.
# Comparison arm of rifabutin 300 mg q.d. for 2 weeks. AUC is $AUC_{(0\text{-}48\ hr)}$.
↑ = Increase; ↓ = Decrease; ↔ = No change (↑ or ↓ <10%).
ND = Interaction cannot be determined as C_{min} was below the lower limit of quantitation.

Table 6. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the Presence of Amprenavir After Administration of AGENERASE

Coadministered Drug(s) and Dose(s)	Dose of **AGENERASE**	n	% Change in Pharmacokinetic Parameters of **Coadministered Drug** (90% CI) C_{max}	AUC	C_{min}
Clarithromycin 500 mg b.i.d. for 4 days	1,200 mg b.i.d. for 4 days	12	↓ 10 (↓ 24 to ↑ 7)	↔	↔
Delavirdine 600 mg b.i.d. for 10 days	600 mg b.i.d. for 10 days	9	↓ 47*	↓ 61*	↓ 88*

Table 6. (Cont.)

Coadministered Drug(s) and Dose(s)	Dose of **AGENERASE**	n	% Change in Pharmacokinetic Parameters of **Coadministered Drug** (90% CI) C_{max}	AUC	C_{min}
Ethinyl estradiol 0.035 mg for 1 cycle	1,200 mg b.i.d. for 28 days	10	↔	↔	↑ 32 (↓ 3 to ↑ 79)
Ketoconazole 400 mg single dose	1,200 mg single dose	12	↑ 19 (↑ 8 to ↑ 33)	↑ 44 (↑ 31 to ↑ 59)	NA
Lamivudine 150 mg single dose	600 mg single dose	11	↔	↔	NA
Methadone 44 to 100 mg q.d. for >30 days	1,200 mg b.i.d. for 10 days	16		R-Methadone (active)	
			↓ 25 (↓ 32 to ↓ 18)	↓ 13 (↓ 21 to ↓ 5)	↓ 21 (↓ 32 to ↓ 9)
				S-Methadone (inactive)	
			↓ 48 (↓ 55 to ↓ 40)	↓ 40 (↓ 46 to ↓ 32)	↓ 53 (↓ 60 to ↓ 43)
Norethindrone 1 mg for 1 cycle	1,200 mg b.i.d. for 28 days	10	↔	↑ 18 ↑ 1 to ↑ 38	↑ 45 ↑ 13 to ↑ 88
Rifabutin 300 mg q.d. for 10 days	1,200 mg b.i.d. for 10 days	5	↑ 119 (↑ 82 to ↑ 164)	↑ 193 (↑ 156 to ↑ 235)	↑ 271 (↑ 171 to ↑ 409)
Rifampin 300 mg q.d. for 4 days	1,200 mg b.i.d. for 4 days	11	↔	↔	ND
Zidovudine 300 mg single dose	600 mg single dose	12	↑ 40 (↑ 14 to ↑ 71)	↑ 31 (↑ 19 to ↑ 45)	NA

*Median percent change; confidence interval not reported.
↑ = Increase; ↓ = Decrease; ↔ = No change (↑ or ↓ <10%); NA = C_{min} not calculated for single-dose study;
ND = Interaction cannot be determined as C_{min} was below the lower limit of quantitation.

Nucleoside Reverse Transcriptase Inhibitors: There was no clinically significant effect of amprenavir after administration of AGENERASE on abacavir in subjects receiving both agents based on historical data.

In a Phase III clinical trial (APV30003), plasma amprenavir trough concentrations were similar for subjects receiving tenofovir disoproxil fumarate in combination with LEXIVA and ritonavir as compared to subjects not receiving tenofovir.

HIV Protease Inhibitors: In a 3-arm, randomized, cross-over study involving healthy volunteers, amprenavir pharmacokinetics were compared after administration of LEXIVA 1,400 mg twice daily plus lopinavir/ritonavir 533 mg/133 mg twice daily for 2 weeks versus LEXIVA 700 mg twice daily plus ritonavir 100 mg twice daily for 2 weeks. Amprenavir concentrations were lower with the regimen containing lopinavir/ritonavir: C_{max} was 13% lower, AUC was 26% lower, and C_{min} was 42% lower. In the same study, lopinavir pharmacokinetics were compared after administration of LEXIVA 1,400 mg twice daily plus lopinavir/ritonavir 533 mg/133 mg twice daily for 2 weeks versus lopinavir/ritonavir 400 mg/100 mg twice daily for 2 weeks. Lopinavir concentrations were similar (less than 10% change in C_{max}, AUC, and C_{min} values) with these 2 regimens.

The effect of amprenavir after administration of AGENERASE Capsules on concentrations of other HIV protease inhibitors in subjects receiving both agents was evaluated using comparisons to historical data. Indinavir steady-state C_{max}, AUC, and C_{min} were decreased by 22%, 38%, and 27%, respectively, by concomitant amprenavir. Similar decreases in C_{max} and AUC were seen after the first dose. Saquinavir steady-state C_{max}, AUC, and C_{min} were increased 21%, decreased 19%, and decreased 48%, respectively, by concomitant amprenavir. Nelfinavir steady-state C_{max}, AUC, and C_{min} were increased by 12%, 15%, and 14%, respectively, by concomitant amprenavir.

Methadone: Coadministration of amprenavir and methadone can decrease plasma levels of methadone.

Coadministration of amprenavir and methadone as compared to a non-matched historical control group resulted in a 30%, 27%, and 25% decrease in serum amprenavir AUC, C_{max}, and C_{min}, respectively.

INDICATIONS AND USAGE

LEXIVA is indicated in combination with other antiretroviral agents for the treatment of HIV infection in adults.

The following points should be considered when initiating therapy with LEXIVA/ritonavir in protease inhibitor-experienced patients (see Description of Clinical Studies).

• The protease inhibitor-experienced patient study was not large enough to reach a definitive conclusion that LEXIVA/ritonavir and lopinavir/ritonavir are clinically equivalent.

• Once-daily administration of LEXIVA plus ritonavir is not recommended for protease inhibitor-experienced patients.

Description of Clinical Studies: ***Therapy-Naive Patients: Study APV30001:*** APV30001 was a randomized, open-label study, comparing treatment with LEXIVA Tablets (1,400 mg twice daily) versus nelfinavir (1,250 mg twice daily) in 249 antiretroviral treatment-naive patients. Both groups of patients also received abacavir (300 mg twice daily) and lamivudine (150 mg twice daily).

The mean age of the patients in this study was 37 years (range 17 to 70 years), 69% of the patients were males, 20% were CDC Class C (AIDS), 24% were Caucasian, 32% were black, and 44% were Hispanic. At baseline, the median CD4+ cell count was 212 cells/mm^3 (range: 2 to 1,136 cells/mm^3; 18% of patients had a CD4+ cell count of <50 cells/mm^3 and 30% were in the range of 50 to <200 cells/mm^3). Baseline median HIV-1 RNA was 4.83 $\log_{10}$ copies/mL (range: 1.69 to 7.41 $\log_{10}$ copies/mL; 45% of patients had >100,000 copies/mL).

The outcomes of randomized treatment are provided in Table 7.

Table 7. Outcomes of Randomized Treatment Through Week 48 (APV30001)

Outcome (Rebound or discontinuation = failure)	LEXIVA 1,400 mg b.i.d. (n = 166)	Nelfinavir 1,250 mg b.i.d. (n = 83)
Responder*	66% (57%)	52% (42%)
Virologic failure	19%	32%
Rebound	16%	19%
Never suppressed through Week 48	3%	13%
Clinical progression	1%	1%
Death	0%	1%
Discontinued due to adverse reactions	4%	2%
Discontinued due to other reasons†	10%	10%

* Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL (<50 copies/mL) through Week 48 (Roche AMPLICOR HIV-1 MONITOR Assay Version 1.5).
† Includes consent withdrawn, lost to follow up, protocol violations, those with missing data, and other reasons.

Treatment response by viral load strata is shown in Table 8.

Table 8. Proportions of Responders Through Week 48 by Screening Viral Load (APV30001)

Screening Viral Load HIV-1 RNA	LEXIVA 1,400 mg b.i.d.		Nelfinavir 1,250 mg b.i.d.	
(copies/mL)	<400 copies/mL	n	<400 copies/mL	n
≤100,000	65%	93	65%	46
>100,000	67%	73	36%	37

Through 48 weeks of therapy, the median increases from baseline in CD4+ cell counts were 201 cells/mm^3 in the group receiving LEXIVA and 216 cells/mm^3 in the nelfinavir group.

Study APV30002: APV30002 was a randomized, open-label study, comparing treatment with LEXIVA Tablets (1,400 mg once daily) plus ritonavir (200 mg once daily) versus nelfinavir (1,250 mg twice daily) in 649 treatment-naive patients. Both treatment groups also received abacavir (300 mg twice daily) and lamivudine (150 mg twice daily).

The mean age of the patients in this study was 37 years (range 18 to 69 years), 73% of the patients were males, 22% were CDC Class C, 53% were Caucasian, 36% were black, and 8% were Hispanic. At baseline, the median CD4+ cell count was 170 cells/mm^3 (range: 1 to 1,055 cells/mm^3; 20% of patients had a CD4+ cell count of <50 cells/mm^3 and 35% were in the range of 50 to <200 cells/mm^3). Baseline median HIV-1 RNA was 4.81 $\log_{10}$ copies/mL (range: 2.65 to 7.29 $\log_{10}$ copies/mL; 43% of patients had >100,000 copies/mL).

The outcomes of randomized treatment are provided in Table 9.

Table 9. Outcomes of Randomized Treatment Through Week 48 (APV30002)

Outcome (Rebound or discontinuation = failure)	LEXIVA 1,400 mg q.d./ Ritonavir 200 mg q.d. (n = 322)	Nelfinavir 1,250 mg b.i.d. (n = 327)
Responder*	69% (58%)	68% (55%)
Virologic failure	6%	16%
Rebound	5%	8%
Never suppressed through Week 48	1%	8%
Death	1%	0%
Discontinued due to adverse reactions	9%	6%
Discontinued due to other reasons†	15%	10%

* Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL (<50 copies/mL) through Week 48 (Roche AMPLICOR HIV-1 MONITOR Assay Version 1.5).
† Includes consent withdrawn, lost to follow up, protocol violations, those with missing data, and other reasons.

Treatment response by viral load strata is shown in Table 10.

Table 10. Proportions of Responders Through Week 48 by Screening Viral Load (APV30002)

Screening Viral Load HIV-1 RNA (copies/mL)	LEXIVA 1,400 mg q.d./ Ritonavir 200 mg q.d.		Nelfinavir 1,250 mg b.i.d.	
	<400 copies/mL	n	<400 copies/mL	n
≤100,000	72%	197	73%	194
>100,000	66%	125	64%	133

Through 48 weeks of therapy, the median increases from baseline in CD4+ cell counts were 203 cells/mm^3 in the group receiving LEXIVA and 207 cells/mm^3 in the nelfinavir group.

Protease Inhibitor-Experienced Patients: Study APV30003: APV30003 was a randomized, open-label, multicenter study comparing 2 different regimens of LEXIVA plus ritonavir (LEXIVA Tablets 700 mg twice daily plus ritonavir 100 mg twice daily or LEXIVA Tablets 1,400 mg once daily plus ritonavir 200 mg once daily) versus lopinavir/ritonavir (400 mg/100 mg twice daily) in 315 patients who had experienced virologic failure to 1 or 2 prior protease inhibitor-containing regimens.

The mean age of the patients in this study was 42 years (range 24 to 72 years), 85% were male, 33% were CDC Class C, 67% were Caucasian, 24% were black, and 9% were Hispanic. The median CD4+ cell count at baseline was 263 cells/mm^3 (range: 2 to 1,171 cells/mm^3). Baseline median plasma HIV-1 RNA level was 4.14 $\log_{10}$ copies/mL (range: 1.69 to 6.41 $\log_{10}$ copies/mL).

The median durations of prior exposure to NRTIs were 257 weeks for patients receiving LEXIVA/ritonavir twice daily (79% had ≥3 prior NRTIs) and 210 weeks for patients receiving lopinavir/ritonavir (64% had ≥3 prior NRTIs). The median durations of prior exposure to protease inhibitors were 149 weeks for patients receiving LEXIVA/ritonavir twice daily (49% received ≥2 prior PIs) and 130 weeks for patients receiving lopinavir/ritonavir (40% received ≥2 prior PIs).

The time-averaged changes in plasma HIV-1 RNA from baseline (AAUCMB) at 48 weeks (the endpoint on which the study was powered) were -1.4 $\log_{10}$ copies/mL for twice-daily LEXIVA/ritonavir and -1.67 $\log_{10}$ copies/mL for the lopinavir/ritonavir group.

The proportions of patients who achieved and maintained confirmed HIV-1 RNA <400 copies/mL (secondary efficacy endpoint) were 58% with twice-daily LEXIVA/ritonavir and 61% with lopinavir/ritonavir (95% CI for the difference -16.6, 10.1). The proportions of patients with HIV-1 RNA <50 copies/mL with twice-daily LEXIVA/ritonavir and with lopinavir/ritonavir were 46% and 50%, respectively (95% CI for the difference -18.3, 8.9). The proportions of patients who were virologic failures were 29% with twice-daily LEXIVA/ritonavir and 27% with lopinavir/ritonavir.

The frequency of discontinuations due to adverse events and other reasons, and deaths were similar between treatment arms.

Through 48 weeks of therapy, the median increases from baseline in CD4+ cell counts were 81 cells/mm^3 with twice-daily LEXIVA/ritonavir and 91 cells/mm^3 with lopinavir/ritonavir.

This study was not large enough to reach a definitive conclusion that LEXIVA/ritonavir and lopinavir/ritonavir are clinically equivalent.

Once-daily administration of LEXIVA plus ritonavir is **not recommended** for protease inhibitor-experienced patients. Through Week 48, 50% and 37% of patients receiving LEXIVA/ritonavir once daily had plasma HIV-1 RNA <400 copies/mL and <50 copies/mL, respectively.

CONTRAINDICATIONS

LEXIVA is contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of this product or to amprenavir.

Coadministration of LEXIVA with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. These drugs are listed in Table 11.

Table 11. Drugs That Are Contraindicated With LEXIVA

Drug Class	Drugs Within Class That Are CONTRAINDICATED with LEXIVA
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agent	Cisapride
Neuroleptic	Pimozide
Sedatives/hypnotics	Midazolam, triazolam

If LEXIVA is coadministered with ritonavir, the antiarrhythmic agents flecainide and propafenone are also contraindicated. Also, refer to the full prescribing information for NORVIR® (ritonavir) for other potential drug interactions.

WARNINGS

Serious and/or life-threatening drug interactions could occur between LEXIVA and amiodarone, lidocaine (systemic), tricyclic antidepressants, and quinidine. Concentration monitoring of these agents is recommended if these agents are used concomitantly with LEXIVA (see CONTRAINDICATIONS).

Severe and life-threatening skin reactions, including Stevens-Johnson syndrome, have occurred in patients treated with amprenavir (see ADVERSE REACTIONS). Acute hemolytic anemia has been reported in a patient treated with amprenavir.

Rifampin should not be used in combination with LEXIVA because it reduces plasma concentrations of amprenavir by about 90%. The effect of rifampin on amprenavir concentrations when rifampin is administered with LEXIVA plus ritonavir is not known.

A drug interaction study in healthy subjects has shown that ritonavir significantly increases plasma fluticasone propionate exposures, resulting in significantly decreased serum cortisol concentrations. Concomitant use of LEXIVA with ritonavir and fluticasone propionate is expected to produce the same effects. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported during postmarketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. Therefore, the coadministration of fluticasone propionate and LEXIVA/ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects (see PRECAUTIONS: Drug Interactions).

Concomitant use of LEXIVA and St. John's wort (hypericum perforatum) or products containing St. John's wort is not recommended. Coadministration of protease inhibitors, including LEXIVA, with St. John's wort is expected to substantially decrease protease inhibitor concentrations and may result in suboptimal levels of amprenavir and lead to loss of virologic response and possible resistance to LEXIVA or to the class of protease inhibitors.

Concomitant use of LEXIVA with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including LEXIVA, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (e.g., atorvastatin). The risk of myopathy, including rhabdomyolysis, may be increased when HIV protease inhibitors, including LEXIVA, are used in combination with these drugs.

Particular caution should be used when prescribing phosphodiesterase (PDE5) inhibitors for erectile dysfunction (e.g., sildenafil or vardenafil) in patients receiving protease inhibitors, including LEXIVA. Coadministration of a protease inhibitor with a PDE5 inhibitor is expected to substantially increase the PDE5 inhibitor concentration and may result in an increase in PDE5 inhibitor-associated adverse events, including hypotension, visual changes, and priapism (see PRECAUTIONS: Drug Interactions and Information for Patients, and the complete specific PDE5 inhibitor prescribing information).

Concomitant use of LEXIVA with ritonavir and oral contraceptives is not recommended. LEXIVA with ritonavir and oral contraceptives may result in clinically significant hepatic transaminase elevations. Therefore, alternate methods of non-hormonal contraception are recommended (see PRECAUTIONS: Drug Interactions).

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during post-marketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and causal relationships between protease inhibitor therapy and these events have not been established.

PRECAUTIONS

Sulfa Allergy: LEXIVA should be used with caution in patients with a known sulfonamide allergy. Fosamprenavir contains a sulfonamide moiety. The potential for cross-sensitivity between drugs in the sulfonamide class and fosamprenavir is unknown. In a clinical study of LEXIVA used as the sole protease inhibitor, rash occurred in 2 of 10 patients (20%) with a history of sulfonamide allergy compared with 42 of 126 patients (33%) with no history of sulfonamide allergy. In 2 clinical studies of LEXIVA plus low-dose ritonavir, rash occurred in 8 of 50 patients (16%) with a history of sulfonamide allergy compared with 50 of 412 patients (12%) with no history of sulfonamide allergy.

Hepatic Impairment and Toxicity: LEXIVA is principally metabolized by the liver; therefore, caution should be exercised when administering LEXIVA to patients with hepatic impairment because amprenavir concentrations may be increased (see CLINICAL PHARMACOLOGY: Special Populations: Hepatic Insufficiency). Patients with impaired hepatic function receiving LEXIVA without concurrent ritonavir may require dose reduction (see DOSAGE AND ADMINISTRATION). There are no data on the use of LEXIVA in combination with ritonavir in patients with any degree of hepatic impairment.

Patients with underlying hepatitis B or C or marked elevations in transaminases prior to treatment may be at increased risk for developing transaminase elevations. Appropriate laboratory testing should be conducted prior to initiating therapy with LEXIVA and patients should be monitored closely during treatment.

Use of LEXIVA with ritonavir at higher-than-recommended dosages may result in transaminase elevations and should not be used (see OVERDOSAGE and DOSAGE AND ADMINISTRATION).

Patients With Hemophilia: There have been reports of spontaneous bleeding in patients with hemophilia A and B treated with protease inhibitors. In some patients, additional factor VIII was required. In many of the reported cases, treatment with protease inhibitors was continued or restarted. A causal relationship between protease inhibitor therapy and these episodes has not been established.

Immune Reconstitution Syndrome: Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including LEXIVA. 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.

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, including LEXIVA. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Lipid Elevations: Treatment with LEXIVA plus ritonavir has resulted in increases in the concentration of triglycerides (see Tables 16 and 17). Triglyceride and cholesterol testing should be performed prior to initiating therapy with LEXIVA and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate. (See PRECAUTIONS: Table 12. Drugs That Should Not Be Coadministered with LEXIVA and Table 13: Established and Other Potentially Significant Drug Interactions for additional information on potential drug interactions with LEXIVA and HMG-CoA reductase inhibitors.)

Resistance/Cross-Resistance: Because the potential for HIV cross-resistance among protease inhibitors has not been fully explored, it is unknown what effect therapy with LEXIVA will have on the activity of subsequently administered protease inhibitors. LEXIVA has been studied in patients who have experienced treatment failure with protease inhibitors (see INDICATIONS AND USAGE: Description of Clinical Studies).

Information for Patients: A statement to patients and healthcare providers is included on the product's bottle label: ALERT: Find out about medicines that should NOT be taken with LEXIVA. **A Patient Information Sheet for LEXIVA Tablets is available for patient information.**

Patients should be informed that LEXIVA is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of LEXIVA are unknown at this time. Patients should be told that there are currently no data demonstrating that therapy with LEXIVA can reduce the risk of transmitting HIV to others.

Patients should be told that sustained decreases in plasma HIV-1 RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using LEXIVA. Patients should be advised to take LEXIVA every day as prescribed. LEXIVA must always be used in combination with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting their physician. If a dose is missed, patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped, the patient should not double the next dose.

Patients should inform their healthcare provider if they have a sulfa allergy. The potential for cross-sensitivity between drugs in the sulfonamide class and fosamprenavir is unknown.

LEXIVA may interact with many drugs; therefore, patients should be advised to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, particularly St. John's wort.

Patients receiving PDE5 inhibitors should be advised that they may be at an increased risk of PDE5 inhibitor-associated adverse events, including hypotension, visual changes, and priapism, and should promptly report any symptoms to their healthcare provider.

Patients receiving hormonal contraceptives should be instructed to use alternate contraceptive measures during therapy with LEXIVA because hormonal levels may be altered, and if used in combination with LEXIVA and ritonavir, liver enzyme elevations may occur.

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

Drug Interactions: See also CONTRAINDICATIONS, WARNINGS, and CLINICAL PHARMACOLOGY: Drug Interactions.

Amprenavir, the active metabolite of fosamprenavir, is an inhibitor of cytochrome P450 3A4 metabolism and therefore should not be administered concurrently with medications with narrow therapeutic windows that are substrates of CYP3A4. Data also suggest that amprenavir induces CYP3A4.

Amprenavir is metabolized by CYP3A4. Coadministration of LEXIVA and drugs that induce CYP3A4, such as rifampin, may decrease amprenavir concentrations and reduce its therapeutic effect. Coadministration of LEXIVA and drugs that inhibit CYP3A4 may increase amprenavir concentrations and increase the incidence of adverse effects.

The potential for drug interactions with LEXIVA changes when LEXIVA is coadministered with the potent CYP3A4 inhibitor ritonavir. The magnitude of CYP3A4-mediated drug interactions (effect on amprenavir or effect on coadministered drug) may change when LEXIVA is coadministered with ritonavir. Because ritonavir is a CYP2D6 inhibitor, clinically significant interactions with drugs metabolized by CYP2D6 are possible when coadministered with LEXIVA plus ritonavir.

There are other agents that may result in serious and/or life-threatening drug interactions (see CONTRAINDICATIONS and WARNINGS).

Table 12. Drugs That Should Not Be Coadministered With LEXIVA

Drug Class/Drug Name	Clinical Comment
Antiarrhythmics: Flecainide, propafenone	**CONTRAINDICATED** if LEXIVA is co-prescribed with **ritonavir** due to potential for serious and/or life threatening reactions such as cardiac arrhythmias secondary to increases in plasma concentrations of antiarrhythmics.
Antimycobacterials: Rifampin*	May lead to loss of virologic response and possible resistance to LEXIVA or to the class of protease inhibitors.
Ergot derivatives: Dihydroergotamine, ergonovine, ergotamine, methylergonovine	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI motility agents: Cisapride	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal products: St. John's wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to LEXIVA or to the class of protease inhibitors.
HMG co-reductase inhibitors: Lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic: Pimozide	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Non-nucleoside reverse transcriptase inhibitor: Delavirdine*	May lead to loss of virologic response and possible resistance to delavirdine.
Sedative/hypnotics: Midazolam, triazolam	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
Oral contraceptives: Ethinyl estradiol/norethindrone*	Alternative methods of non-hormonal contraception are recommended. **LEXIVA/ritonavir:** Increased risk of transaminase elevations. No data are available on the use of LEXIVA/ritonavir with other hormonal therapies, such as HRT for postmenopausal women (see WARNINGS). **LEXIVA without ritonavir:** May lead to loss of virologic response (see CLINICAL PHARMACOLOGY, Table 5).

*See CLINICAL PHARMACOLOGY Tables 3, 4, 5, or 6 for magnitude of interaction.

Table 13. Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction (Information in the table applies to LEXIVA with or without ritonavir, unless otherwise indicated.)

Concomitant Drug Class: Drug Name	Effect on Concentration of Amprenavir or Concomitant Drug	Clinical Comment
	HIV-Antiviral Agents	
Non-nucleoside reverse transcriptase inhibitor: Efavirenz	**LEXIVA:** ↓ Amprenavir **LEXIVA/ritonavir:** ↓ Amprenavir	Appropriate doses of the combinations with respect to safety and efficacy have not been established. An additional 100 mg/day (300 mg total) of ritonavir is recommended when efavirenz is administered with LEXIVA/ritonavir once daily. No change in the ritonavir dose is required when efavirenz is administered with LEXIVA plus ritonavir twice daily.
Non-nucleoside reverse transcriptase inhibitor: Nevirapine*	**LEXIVA:** ↓ Amprenavir ↑ Nevirapine **LEXIVA/ritonavir:** ↓ Amprenavir ↑ Nevirapine	Coadministration of nevirapine and LEXIVA without ritonavir is not recommended. No dosage adjustment required when nevirapine is administered with LEXIVA/ritonavir twice daily. The combination of nevirapine administered with LEXIVA/ritonavir once-daily regimen has not been studied.
HIV protease inhibitor: Atazanavir*	**LEXIVA:** Interaction has not been evaluated **LEXIVA/ritonavir:** ↓ Atazanavir ↔Amprenavir	Appropriate doses of the combinations with respect to safety and efficacy have not been established.
HIV protease inhibitors: Indinavir,* nelfinavir*	**LEXIVA:** ↑ Amprenavir Effect on indinavir and nelfinavir is not well established. **LEXIVA/ritonavir:** Interaction has not been evaluated.	Appropriate doses of the combinations with respect to safety and efficacy have not been established.

Table 3. (Cont.)

Concomitant Drug Class: Drug Name	Effect on Concentration of Amprenavir or Concomitant Drug	Clinical Comment
	HIV-Antiviral Agents	
HIV protease inhibitors: Lopinavir/ritonavir*	↓ Amprenavir ↓ Lopinavir	An increased rate of adverse events has been observed with coadministration of these medications. Appropriate doses of the combinations with respect to safety and efficacy have not been established.
HIV protease inhibitor: Saquinavir*	**LEXIVA:** ↓ Amprenavir Effect on saquinavir is not well established. **LEXIVA/ritonavir:** Interaction has not been evaluated.	Appropriate doses of the combination with respect to safety and efficacy have not been established.
	Other Agents	
Antiarrhythmics: Amiodarone, lidocaine (systemic), and quinidine	↑ Antiarrhythmics	Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when coadministered with LEXIVA.
Antiarrhythmic: Bepridil	↑ Bepridil	Use with caution. Increased bepridil exposure may be associated with life-threatening reactions such as cardiac arrhythmias.
Anticoagulant: Warfarin		Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.
Anticonvulsants: Carbamazepine, phenobarbital, phenytoin	↓ Amprenavir	Use with caution. LEXIVA may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly.
Antidepressant: Trazodone	↑ Trazodone	Concomitant use of trazodone and LEXIVA with or without ritonavir may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension, and syncope have been observed following coadministration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as LEXIVA, the combination should be used with caution and a lower dose of trazodone should be considered.
Antifungals: Ketoconazole,* itraconazole	↑ Ketoconazole ↑ Itraconazole	Increase monitoring for adverse events due to ketoconazole or itraconazole. **LEXIVA:** Dose reduction of ketoconazole or itraconazole may be needed for patients receiving more than 400 mg ketoconazole or itraconazole per day. **LEXIVA/ritonavir:** High doses of ketoconazole or itraconazole (>200 mg/day) are not recommended.
Antimycobacterial: Rifabutin*	↑ Rifabutin and rifabutin metabolite	A complete blood count should be performed weekly and as clinically indicated in order to monitor for neutropenia in patients receiving LEXIVA and rifabutin. **LEXIVA:** A dosage reduction of rifabutin by at least half the recommended dose is required. **LEXIVA/ritonavir:** Dosage reduction of rifabutin by at least 75% of the usual dose of 300 mg/day is recommended (a maximum dose of 150 mg every other day or 3 times per week).
Benzodiazepines: Alprazolam, clorazepate, diazepam, flurazepam	↑ Benzodiazepines	Clinical significance is unknown; however, a decrease in benzodiazepine dose may be needed.
Calcium channel blockers: Diltiazem, felodipine, nifedipine, nicardipine, nimodipine, verapamil, amlodipine, nisoldipine, isradipine	↑ Calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: Dexamethasone	↓ Amprenavir	Use with caution. LEXIVA may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly.
Histamine H_2-receptor antagonists: Cimetidine, famotidine, nizatidine, ranitidine*	**LEXIVA:** ↓ Amprenavir **LEXIVA/ritonavir:** Interaction not evaluated	Use with caution. LEXIVA may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly.
HMG-CoA reductase inhibitor: Atorvastatin*	↑ Atorvastatin	Use ≤20 mg/day of atorvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as fluvastatin, pravastatin, or rosuvastatin in combination with LEXIVA.
Immunosuppressants: Cyclosporine, tacrolimus, rapamycin	↑ Immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with LEXIVA.
Inhaled/nasal steroid: Fluticasone	**LEXIVA:** ↑ Fluticasone **LEXIVA/ritonavir:** ↑ Fluticasone	Concomitant use of fluticasone propionate and LEXIVA (without ritonavir) may increase plasma concentrations of fluticasone propionate. Use with caution. Consider alternatives to fluticasone propionate, particularly for long-term use. Concomitant use of fluticasone propionate and LEXIVA/ritonavir may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Coadministration of fluticasone propionate and LEXIVA/ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects (see WARNINGS).
Narcotic analgesic: Methadone	↓ Methadone	Dosage of methadone may need to be increased when coadministered with LEXIVA.
PDE5 inhibitors: Sildenafil, vardenafil	↑ Sildenafil ↑ Vardenafil	Use sildenafil with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events. **LEXIVA:** Use vardenafil with caution at reduced doses of no more than 2.5 mg every 24 hours with increased monitoring for adverse events. **LEXIVA/ritonavir:** Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring for adverse events.
Proton pump inhibitors: Esomeprazole*, lansoprazole, omeprazole, pantoprazole, rabeprazole	**LEXIVA:** ↔Amprenavir ↑ Esomeprazole **LEXIVA/ritonavir:** ↔Amprenavir ↔Esomeprazole	Proton pump inhibitors can be administered at the same time as a dose of LEXIVA with no change in plasma amprenavir concentrations.
Tricyclic antidepressants: Amitriptyline, imipramine	↑ Tricyclics	Therapeutic concentration monitoring is recommended for tricyclic antidepressants when coadministered with LEXIVA.

*See CLINICAL PHARMACOLOGY Tables 3, 4, 5, or 6 for magnitude of interaction.

Carcinogenesis and Mutagenesis: In long-term carcinogenicity studies, fosamprenavir was administered orally for up to 104 weeks at doses of 250, 400, or 600 mg/kg/day in mice and at doses of 300, 825, or 2,250 mg/kg/day in rats. Exposures at these doses were 0.3- to 0.7-fold (mice) and 0.7- to 1.4-fold (rats) those in humans given 1,400 mg twice daily of fosamprenavir alone, and 0.2- to 0.3-fold (mice) and 0.3- to 0.7-fold (rats) those in humans given 1,400 mg once daily of fosamprenavir plus 200 mg ritonavir once daily. Exposures in the carcinogenicity studies were 0.1- to 0.3-fold (mice) and 0.3- to 0.6-fold (rats) those in humans given 700 mg of fosamprenavir plus 100 mg ritonavir twice daily. There was an increase in hepatocellular adenomas and hepatocellular carcinomas at all doses in male mice and at 600 mg/kg/day in female mice, and in hepatocellular adenomas and thyroid follicular cell adenomas at all doses in male rats, and at 835 mg/kg/day and 2,250 mg/kg/day in female rats. The relevance of the hepatocellular findings in the rodents for humans is uncertain. Repeat dose studies with fosamprenavir in rats produced effects consistent with enzyme induction, which predisposes rats, but not humans, to thyroid neoplasms. In addition, in rats only there was an increase in interstitial cell hyperplasia at 825 mg/kg/day and 2,250 mg/kg/day, and an increase in uterine endometrial adenocarcinoma at 2,250 mg/kg/day. The incidence of endometrial findings was slightly increased over concurrent controls, but was within background range for female rats. The relevance of the uterine endometrial adenocarcinoma findings in rats for humans is uncertain.

Fosamprenavir was not mutagenic or genotoxic in a battery of in vitro and in vivo assays. These assays included bacterial reverse mutation (Ames), mouse lymphoma, rat micronucleus, and chromosome aberrations in human lymphocytes.

Impairment of Fertility: The effects of fosamprenavir on fertility and general reproductive performance were investigated in male (treated for 4 weeks before mating) and female rats (treated for 2 weeks before mating through postpartum day 6). Systemic exposures ($AUC_{0\text{-}24\ hr}$) to amprenavir in these studies were 3 (males) to 4 (females) times higher than exposures in humans following administration of the maximum recommended human dose (MRHD) of fosamprenavir alone or similar to those seen in humans following administration of fosamprenavir in combination with ritonavir. Fosamprenavir did not impair mating or fertility of male or female rats and did not affect the development and maturation of sperm from treated rats.

Pregnancy and Reproduction: Pregnancy Category C. Embryo/fetal development studies were conducted in rats (dosed from day 6 to day 17 of gestation) and rabbits (dosed from day 7 to day 20 of gestation). Administration of fosamprenavir to pregnant rats and rabbits produced no major effects on embryo-fetal development; however, the incidence of abortion was increased in rabbits that were administered fosamprenavir. Systemic exposures ($AUC_{0\text{-}24\ hr}$) to amprenavir at these dosages were 0.8 (rabbits) to 2 (rats) times the exposures in humans following administration of the MRHD of fosamprenavir alone or 0.3 (rabbits) to 0.7 (rats) times the exposures in humans following administration of the MRHD of fosamprenavir in combination with ritonavir. In contrast, administration of amprenavir was associated with abortions and an increased incidence of minor skeletal variations resulting from deficient ossification of the femur, humerus, and trochlea, in pregnant rabbits at the tested dose; approximately one twentieth the exposure seen at the recommended human dose.

The mating and fertility of the F_1 generation born to female rats given fosamprenavir was not different from control animals; however, fosamprenavir did cause a reduction in both pup survival and body weights. Surviving F_1 female rats showed an increased time to successful mating, an increased length of gestation, a reduced number of uterine implantation sites per litter, and reduced gestational body weights compared to control animals. Systemic exposure ($AUC_{0\text{-}24\ hr}$) to amprenavir in the F_0 pregnant rats was approximately 2 times higher than exposures in humans following administration of the MRHD of fosamprenavir alone or approximately the same as those seen in humans following administration of the MRHD of fosamprenavir in combination with ritonavir.

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

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

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Although it is not known if amprenavir is excreted in human milk, amprenavir is secreted into the milk of lactating rats. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving LEXIVA.**

Pediatric Use: The safety and efficacy of LEXIVA Tablets have not been established in pediatric patients.

Geriatric Use: Clinical studies of LEXIVA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger adults. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

LEXIVA was studied in 700 patients in Phase III controlled clinical studies. The most common treatment-emergent adverse events in clinical studies of LEXIVA were diarrhea, nausea, vomiting, headache, and rash and were generally mild to moderate in severity. Treatment discontinuation due to adverse events occurred in 6.4% of patients receiving LEXIVA and in 5.9% of patients receiving comparator treatments.

Severe or life-threatening skin reactions, including 1 case of Stevens-Johnson syndrome among 700 patients treated with LEXIVA, were reported in <1% of patients treated with LEXIVA in the clinical studies. Treatment with LEXIVA should be discontinued for severe or life-threatening rashes and for moderate rashes accompanied by systemic symptoms.

Skin rash (without regard to causality) occurred in approximately 19% of patients treated with LEXIVA in the pivotal efficacy studies. Rashes were usually maculopapular and of mild or moderate intensity, some with pruritus. Rash had a median onset of 11 days after initiation of LEXIVA and had a median duration of 13 days. Skin rash led to discontinuation of LEXIVA in <1% of patients. In some patients with mild or moderate rash, dosing with LEXIVA was often continued without interruption; if interrupted, reintroduction of LEXIVA generally did not result in rash recurrence.

Selected adverse events reported during the clinical efficacy studies of LEXIVA are shown in Tables 14 and 15. Each table presents drug-related adverse events of moderate or severe intensity and adverse events of all grades regardless of causality in patients treated with combination therapy for up to 48 weeks.

Table 14. Selected Clinical Adverse Events Reported in Antiretroviral-Naive Patients

	APV30001*				APV30002*			
	LEXIVA 1,400 mg b.i.d. (n = 166)		Nelfinavir 1,250 mg b.i.d. (n = 83)		LEXIVA 1,400 mg q.d./Ritonavir 200 mg q.d. (n = 322)		Nelfinavir/ 1,250 mg b.i.d. (n = 327)	
Adverse Event	Moderate/ Severe Drug-Related	All Grades†	Moderate/ Severe Drug-Related	All Grades†	Moderate/ Severe Drug-Related	All Grades†	Moderate/ Severe Drug-Related	All Grades†
Gastrointestinal								
Diarrhea	5%	34%	18%	63%	10%	52%	18%	72%
Nausea	7%	39%	4%	24%	7%	37%	5%	27%
Vomiting	2%	16%	4%	17%	6%	20%	4%	13%
Abdominal pain	1%	5%	0%	8%	2%	11%	2%	11%
Skin								
Pruritus	0%	7%	0%	11%	<1%	7%	1%	9%
Rash	8%	35%	2%	19%	3%	17%	2%	21%
General disorders								
Fatigue	2%	10%	1%	7%	4%	18%	2%	13%
Nervous system								
Depressive/ mood disorders	1%	8%	0%	8%	<1%	8%	0%	6%
Headache	2%	19%	4%	20%	3%	21%	3%	27%
Paresthesia, oral	0%	2%	0%	0%	<1%	10%	0%	<1%

*All patients also received abacavir and lamivudine twice daily.
† Includes adverse events of all grades regardless of causality reported in >5% of patients.

Table 15. Selected Clinical Adverse Events Reported in Protease Inhibitor-Experienced Patients (Study APV30003)

	LEXIVA 700 mg b.i.d./ Ritonavir 100 mg b.i.d.* (n = 106)		Lopinavir 400 mg b.i.d./ Ritonavir 100 mg b.i.d.* (n = 103)	
Adverse Event	Moderate/Severe Drug-Related	All Grades†	Moderate/Severe Drug-Related	All Grades†
Gastrointestinal				
Diarrhea	13%	38%	11%	47%
Nausea	3%	20%	9%	31%
Vomiting	3%	10%	5%	17%
Abdominal pain	<1%	11%	2%	9%
Skin				
Pruritus	<1%	8%	0%	3%
Rash	3%	9%	0%	22%
General disorders				
Fatigue	<1%	9%	<1%	14%
Nervous system				
Depressive/mood disorders	<1%	11%	<1%	10%
Headache	4%	27%	2%	20%
Paresthesia, oral	0%	<1%	0%	0%

* All patients also received 2 reverse transcriptase inhibitors.
† Includes adverse events of all grades regardless of causality in >5% of patients.

The percentages of patients with Grade 3 or 4 laboratory abnormalities in the clinical efficacy studies of LEXIVA are presented in Tables 16 and 17.

Table 16. Grade 3/4 Laboratory Abnormalities Reported in ≥2% of Antiretroviral-Naive Adult Patients in Studies APV30001 and APV30002

	APV30001*		APV30002*	
Laboratory Abnormality	LEXIVA 1,400 mg b.i.d. (n = 166)	Nelfinavir 1,250 mg b.i.d. (n = 83)	LEXIVA 1,400 mg q.d./ Ritonavir 200 mg q.d. (n = 322)	Nelfinavir 1,250 mg b.i.d. (n = 327)
ALT (>5 x ULN)	6%	5%	8%	8%
AST (>5 x ULN)	6%	6%	6%	7%
Serum lipase (>2 x ULN)	8%	4%	6%	4%
Hypertriglyceridemia† (>750 mg/dL)	0%	1%	6%	2%
Neutropenia (<750 cells/mm^3)	3%	6%	3%	4%

* All patients also received abacavir and lamivudine twice daily.
† Fasting specimens.
ULN = Upper limit of normal.

The incidence of Grade 3 or 4 hyperglycemia in antiretroviral-naive patients who received LEXIVA in the pivotal studies was <1%.

Table 17. Grade 3/4 Laboratory Abnormalities Reported in ≥2% of Protease Inhibitor-Experienced Adult Patients in Study APV30003

Laboratory Abnormality	LEXIVA 700 mg b.i.d./ Ritonavir 100 mg b.i.d.* (n = 104)	Lopinavir 400 mg b.i.d./ Ritonavir 100 mg b.i.d.* (n = 103)
Hypertriglyceridemia† (>750 mg/dL)	11%‡	6%‡
Serum lipase (>2 x ULN)	5%	12%
ALT (>5 x ULN)	4%	4%
AST (>5 x ULN)	4%	2%
Hyperglycemia (>251 mg/dL)	2%‡	2%‡

* All patients also received 2 reverse transcriptase inhibitors.
† Fasting specimens.
‡ n = 100 for LEXIVA/ritonavir, n = 98 for lopinavir/ritonavir.
ULN = Upper limit of normal.

OVERDOSAGE

In a healthy volunteer repeat-dose pharmacokinetic study evaluating high-dose combinations of LEXIVA plus ritonavir, an increased frequency of Grade 2/3 ALT elevations (>2.5 x ULN) was observed with LEXIVA 1,400 mg twice daily plus ritonavir 200 mg twice daily (4 of 25 subjects). Concurrent Grade 1/2 elevations in AST (>1.25 x ULN) were noted in 3 of these 4 subjects. These transaminase elevations resolved following discontinuation of dosing.

There is no known antidote for LEXIVA. It is not known whether amprenavir can be removed by peritoneal dialysis or hemodialysis. If overdosage occurs, the patient should be monitored for evidence of toxicity and standard supportive treatment applied as necessary.

DOSAGE AND ADMINISTRATION

LEXIVA Tablets may be taken with or without food.

The recommended oral dose of LEXIVA, alone or in combination with ritonavir, is as follows:

Therapy-Naive Patients:

- LEXIVA 1,400 mg twice daily (without ritonavir)
- LEXIVA 1,400 mg once daily plus ritonavir 200 mg once daily
- LEXIVA 700 mg twice daily plus ritonavir 100 mg twice daily

The twice-daily plus ritonavir dose is supported by pharmacokinetic and safety data (see CLINICAL PHARMACOLOGY and ADVERSE REACTIONS).

Protease Inhibitor-Experienced Patients:

- LEXIVA 700 mg twice daily plus ritonavir 100 mg twice daily

Once-daily administration of LEXIVA plus ritonavir is not recommended in protease inhibitor-experienced patients (see Description of Clinical Studies).

Adjustment of Ritonavir Dose When LEXIVA Plus Ritonavir are Administered With Efavirenz: An additional 100 mg/day (300 mg total) of ritonavir is recommended when efavirenz is administered with LEXIVA plus ritonavir once daily (see Table 13. Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction).

Prescribers should consult the full prescribing information for NORVIR (ritonavir) when using this agent.

High-Dose Combinations of LEXIVA Plus Ritonavir: Higher-than-approved dose combinations of LEXIVA plus ritonavir are not recommended for use (see PRECAUTIONS and OVERDOSAGE).

Patients with Hepatic Impairment: LEXIVA Tablets should be used with caution, at a reduced dosage of 700 mg twice daily in patients with mild or moderate hepatic impairment (Child-Pugh score ranging from 5 to 8) receiving LEXIVA without concurrent ritonavir (see CLINICAL PHARMACOLOGY: Hepatic Insufficiency). LEXIVA should not be used in patients with severe hepatic impairment (Child-Pugh score ranging from 9 to 12) because the dose cannot be reduced below 700 mg. There are no data on the use of LEXIVA in combination with ritonavir in patients with any degree of hepatic impairment.

HOW SUPPLIED

LEXIVA Tablets, 700 mg, are pink, film-coated, capsule-shaped, biconvex tablets, with "GX LL7" debossed on one face.

Bottles of 60 with child-resistant closures (NDC 0173-0721-00).

Store at controlled room temperature of 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature). Keep container tightly closed.

PHARMACIST—DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT INFORMATION
LEXIVA®

(lex-EE-vah)

(fosamprenavir calcium) Tablets

Read the Patient Information that comes with LEXIVA before you start taking it 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 treatment. It is important to remain under a healthcare provider's care while taking LEXIVA. **Do not change or stop treatment without first talking with your healthcare provider.** Talk to your healthcare provider or pharmacist if you have any questions about LEXIVA.

What is the most important information I should know about LEXIVA?

LEXIVA can cause dangerous and life-threatening interactions if taken with certain other medicines. Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

- Some medicines cannot be taken at all with LEXIVA.
- Some medicines will require dose changes if taken with LEXIVA.
- Some medicines will require close monitoring if you take them with LEXIVA.

Know all the medicines you take, including prescription and nonprescription medicines, vitamins and herbal supplements. Keep a list of the medicines you take. Show this list to all your healthcare providers and pharmacists anytime you get a new medicine or refill. Your healthcare providers and pharmacists must know all the medicines you take. They will tell you if you can take other medicines with LEXIVA. **Do not start any new medicines while you are taking LEXIVA without talking with your healthcare provider or pharmacist.** You can ask your healthcare provider or pharmacist for a list of medicines that can interact with LEXIVA.

What is LEXIVA?

LEXIVA is a medicine you take by mouth to treat HIV infection. HIV is the virus that causes AIDS (acquired immune deficiency syndrome.) LEXIVA belongs to a class of anti-HIV medicines called protease inhibitors. LEXIVA is always used with other anti-HIV medicines. When used in combination therapy, LEXIVA may help lower the amount of HIV found in your blood, raise CD4+ (T) cell counts, and keep your immune system as healthy as possible, so it can help fight infection. However, LEXIVA does not work in all patients with HIV.

LEXIVA does not:

- cure HIV infection or AIDS. We do not know if LEXIVA will help you live longer or have fewer of the medical problems (opportunistic infections) that people get with HIV or AIDS. Opportunistic infections are infections that develop because the immune system is weak. Some of these conditions are pneumonia, herpes virus infections, and *Mycobacterium avium* complex (MAC) infections. **It is very important that you see your healthcare provider regularly while you are taking LEXIVA.** The long-term effects of LEXIVA are not known.
- lower the risk of passing HIV to other people through sexual contact, sharing needles, or being exposed to your blood. For your health and the health of others, it is important to always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood. Never use or share dirty needles.

LEXIVA has not been fully studied in children under the age of 18 or in adults over the age of 65.

Who should not take LEXIVA?

Do not take LEXIVA Tablets if you:

- are taking certain other medicines. Read the section **"What is the most important information I should know about LEXIVA?"** Do **not** take the following medicines* with LEXIVA. You could develop serious or life-threatening problems.
  - HALCION® (triazolam; used for insomnia)
  - Ergot medicines: dihydroergotamine, ergonovine, ergotamine, and methylergonovine such as CAFERGOT®, MIGRANAL®, D.H.E. 45®, ergotrate maleate, METHERGINE®, and others (used for migraine headaches)
  - PROPULSID® (cisapride), used for certain stomach problems
  - VERSED® (midazolam); used for sedation
  - ORAP® (pimozide); used for Tourette's disorder

  Do **not** take the following medicines if you are taking LEXIVA and NORVIR® (ritonavir) together. You could develop serious or life-threatening problems.
  - TAMBOCOR® (flecainide); used for certain abnormal heart rhythms
  - RYTHMOL® (propafenone); used for certain abnormal heart rhythms
- **are allergic to LEXIVA or any of its ingredients.** The active ingredient is fosamprenavir calcium. See the end of this leaflet for a list of all the ingredients in LEXIVA.
- **are allergic to AGENERASE® (amprenavir).**

You should not take AGENERASE® (amprenavir) and LEXIVA at the same time.

Before taking LEXIVA, tell your healthcare provider about all your medical conditions including if you:

- **are pregnant or planning to become pregnant. It is not known if LEXIVA can harm your unborn baby. You and your healthcare provider will need to decide if LEXIVA is right for you. If you use LEXIVA while you are pregnant, talk to your healthcare provider about how you can be on the Antiretroviral Pregnancy Registry.**
- **are breastfeeding.** You should not breastfeed if you are HIV-positive because of the chance of passing the HIV virus to your baby through your milk. Also, it is not known if LEXIVA can pass into your breast milk and if it can harm your baby. If you are a woman who has or will have a baby, talk with your healthcare provider about the best way to feed your baby.
- **have liver problems.** You may be given a lower dose of LEXIVA or LEXIVA may not be right for you.
- **have kidney problems**
- **have diabetes.** You may need dose changes in your insulin or other diabetes medicines.
- **have hemophilia**
- **are allergic to sulfa medicines**

Before taking LEXIVA, tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. LEXIVA can cause dangerous and life-threatening interactions if taken with certain other medicines. You may need dose changes in some of your medicines or closer monitoring with some medicines if you also take LEXIVA (see **"What is the most important information I should know about LEXIVA."**). **Know all the medicines that you take and keep a list of them with you to show healthcare providers and pharmacists.**

Women who use birth control pills should choose a different kind of contraception. The use of LEXIVA with NORVIR (ritonavir) in combination with birth control pills may be harmful to your liver. The use of LEXIVA with or without NORVIR may decrease the effectiveness of birth control pills. Talk to your healthcare provider about choosing an effective contraceptive.

How should I take LEXIVA?

- Take LEXIVA Tablets exactly as your healthcare provider prescribed.
- **Do not take more or less than your prescribed dose of LEXIVA Tablets at any one time.** Do not change your dose or stop taking LEXIVA without talking with your healthcare provider.
- You can take LEXIVA Tablets with or without food.
- When your supply of LEXIVA or other anti-HIV medicine starts to run low, get more from your healthcare provider or pharmacy. The amount of HIV virus in your blood may increase if one or more of the medicines are stopped, even for a short time.
- Stay under the care of a healthcare provider while using LEXIVA.
- It is important that you do not miss any doses. If you miss a dose of LEXIVA by more than 4 hours, wait and take the next dose at the regular time. However, if you miss a dose by fewer than 4 hours, take your missed dose right away. Then take your next dose at the regular time.
- If you take too much LEXIVA, call your healthcare provider or poison control center right away.

What should I avoid while taking LEXIVA?

- **Do not use certain medicines while you are taking LEXIVA.** See "What is the most important information I should know about LEXIVA" and "Who should not take LEXIVA?"
- **Do not breastfeed. See "Before taking LEXIVA, tell your healthcare provider". Talk with your healthcare provider about the best way to feed your baby.**
- **Avoid doing things that can spread HIV infection** since LEXIVA doesn't stop you from passing the HIV infection to others.
- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes or razor blades.**
- **Do not have any kind of sex without protection.** Always practice safer sex by using a latex or polyurethane condom, to lower the chance of sexual contact with semen, vaginal secretions, or blood.

What are the possible side effects of LEXIVA?

LEXIVA may cause the following side effects:

- **skin rash.** Skin rashes, some with itching have happened in patients taking LEXIVA. Tell your healthcare provider if you get a rash after starting LEXIVA.
- **diabetes and high blood sugar (hyperglycemia).** Some patients had diabetes before taking LEXIVA while others did not. Some patients may need changes in their diabetes medicine. Others may need a new diabetes medicine.
- **increased bleeding problems in some patients with hemophilia.**
- **worse liver disease.** Patients with liver problems, including hepatitis B or C, are more likely to get worse liver disease when they take anti-HIV medicines like LEXIVA.
- **changes in blood tests.** Some people have changes in blood tests while taking LEXIVA. These include increases seen in liver function tests and blood fat levels, and decreases in white blood cells. Your healthcare provider may do regular blood tests to see if LEXIVA is affecting your body.
- **changes in body fat.** These changes have happened in patients taking antiretroviral medicines like LEXIVA. The changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the trunk. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

Common side effects of LEXIVA are nausea, vomiting, and diarrhea. **Tell your healthcare provider about any side effects that bother you or that won't go away.**

This list of side effects of LEXIVA is not complete. For more information, ask your healthcare provider or pharmacist.

How should I store LEXIVA Tablets?

- Store LEXIVA Tablets at room temperature between 59° and 86° F (15° to 30° C). Keep the container tightly closed.
- **Keep LEXIVA and all medicines out of the reach of children.**
- Do not keep medicine that is out of date or that you no longer need. Be sure that if you throw any medicine away, it is out of the reach of children.

General information about LEXIVA

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use LEXIVA for a condition for which it was not prescribed. Do not give LEXIVA to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about LEXIVA. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about LEXIVA that is written for health professionals. For more information you can call toll-free 888-825-5249 or visit www.LEXIVA.com.

What are the ingredients in LEXIVA?

Active Ingredient: fosamprenavir calcium.

Inactive Ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and povidone K30. The tablet film-coating contains the inactive ingredients hypromellose, iron oxide red, titanium dioxide, and triacetin.

LEXIVA Tablets, 700 mg, are pink in color and are capsule-shaped, with the letters "GX LL7" printed on one side of the tablet.

R_x **only**

LEXIVA is a registered trademark of GlaxoSmithKline.

* The brands listed are trademarks of their respective owners and are not trademarks of GlaxoSmithKline. The makers of these brands are not affiliated with and do not endorse GlaxoSmithKline or its products.

GlaxoSmithKline
Research Triangle Park, NC 27709

VERTEX™
Vertex Pharmaceuticals Incorporated
Cambridge, MA 02139

February 2007 RL-2365

RETROVIR® (zidovudine) Tablets
RETROVIR® (zidovudine) Capsules
RETROVIR® (zidovudine) Syrup

PRESCRIBING INFORMATION

WARNING

RETROVIR (ZIDOVUDINE) HAS BEEN ASSOCIATED WITH HEMATOLOGIC TOXICITY INCLUDING NEUTROPENIA AND SEVERE ANEMIA PARTICULARLY IN PATIENTS WITH ADVANCED HUMAN IMMUNODEFICIENCY VIRUS (HIV) DISEASE (SEE WARNINGS). PROLONGED USE OF RETROVIR HAS BEEN ASSOCIATED WITH SYMPTOMATIC MYOPATHY.

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING RETROVIR AND OTHER ANTIRETROVIRALS (SEE WARNINGS).

DESCRIPTION

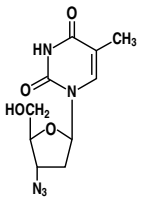
RETROVIR is the brand name for zidovudine (formerly called azidothymidine [AZT]), a pyrimidine nucleoside analogue active against HIV.

Tablets: RETROVIR Tablets are for oral administration. Each film-coated tablet contains 300 mg of zidovudine and the inactive ingredients hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide.

Capsules: RETROVIR Capsules are for oral administration. Each capsule contains 100 mg of zidovudine and the inactive ingredients corn starch, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The 100-mg empty hard gelatin capsule, printed with edible black ink, consists of black iron oxide, dimethylpolysiloxane, gelatin, pharmaceutical shellac, soya lecithin, and titanium dioxide.

Syrup: RETROVIR Syrup is for oral administration. Each teaspoonful (5 mL) of RETROVIR Syrup contains 50 mg of zidovudine and the inactive ingredients sodium benzoate 0.2% (added as a preservative), citric acid, flavors, glycerin, and liquid sucrose. Sodium hydroxide may be added to adjust pH.

The chemical name of zidovudine is 3′-azido-3′-deoxythymidine; it has the following structural formula:



Zidovudine is a white to beige, odorless, crystalline solid with a molecular weight of 267.24 and a solubility of 20.1 mg/mL in water at 25°C. The molecular formula is $C_{10}H_{13}N_5O_4$.

MICROBIOLOGY

Mechanism of Action: Zidovudine is a synthetic nucleoside analogue. Intracellularly, zidovudine is phosphorylated to its active 5′-triphosphate metabolite, zidovudine triphosphate (ZDV-TP). The principal mode of action of ZDV-TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue. ZDV-TP is a weak inhibitor of the cellular DNA polymerases α and γ and has been reported to be incorporated into the DNA of cells in culture.

Antiviral Activity: The antiviral activity of zidovudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes). The EC_{50} and EC_{90} values for zidovudine were 0.01 to 0.49 μM (1 μM = 0.27 mcg/mL) and 0.1 to 9 μM, respectively. HIV from therapy-naive subjects with no mutations associated with resistance gave median EC_{50} values of 0.011 μM (range: 0.005 to 0.110 μM) from Virco (n = 93 baseline samples from COLA40263) and 0.02 μM (0.01 to 0.03 μM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC_{50} values of zidovudine against different HIV-1 clades (A-G) ranged from 0.00018 to 0.02 μM, and against HIV-2 isolates from 0.00049 to 0.004 μM. In cell culture drug combination studies, zidovudine demonstrates synergistic activity with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir, didanosine, lamivudine, and zalcitabine; the non-nucleoside reverse transcriptase inhibitors (NNRTIs) delavirdine and nevirapine; and the protease inhibitors (PIs) indinavir, nelfinavir, ritonavir, and saquinavir; and additive activity with interferon alfa. Ribavirin has been found to inhibit the phosphorylation of zidovudine in cell culture.

Resistance: Genotypic analyses of the isolates selected in cell culture and recovered from zidovudine-treated patients showed mutations in the HIV-1 RT gene resulting in 6 amino acid substitutions (M41L, D67N, K70R, L210W, T215Y or F, and K219Q) that confer zidovudine resistance. In general, higher levels of resistance were associated with greater number of mutations. In some patients harboring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

Cross-Resistance: In a study of 167 HIV-infected patients, isolates (n = 2) with multi-drug resistance to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine were recovered from patients treated for ≥1 year with zidovudine plus didanosine or zidovudine plus zalcitabine. The pattern of resistance-associated mutations with such combination therapies was different (A62V, V75I, F77L, F116Y, Q151M) from the pattern with zidovudine monotherapy, with the Q151M mutation being most commonly associated with multi-drug resistance. The mutation at codon 151 in combination with mutations at 62, 75, 77, and 116 results in a virus with reduced susceptibility to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine. Thymidine analogue mutations (TAMs) are selected by zidovudine and confer cross-resistance to abacavir, didanosine, stavudine, tenofovir, and zalcitabine.

CLINICAL PHARMACOLOGY

Pharmacokinetics: ***Adults:*** The pharmacokinetic properties of zidovudine in fasting patients are summarized in Table 1. Following oral administration, zidovudine is rapidly absorbed and extensively distributed, with peak serum concentrations occurring within 0.5 to 1.5 hours. Binding to plasma protein is low. Zidovudine is primarily eliminated by hepatic metabolism. The major metabolite of zidovudine is 3′-azido-3′-deoxy-5′-*O*-β-*D*-glucopyranuronosylthymidine (GZDV). GZDV area under the curve (AUC) is about 3-fold greater than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 14% and 74%, respectively, of the dose following oral administration. A second metabolite, 3′-amino-3′-deoxythymidine (AMT), has been identified in the plasma following single-dose intravenous (IV) administration of zidovudine. The AMT AUC was one fifth of the zidovudine AUC. Pharmacokinetics of zidovudine were dose independent at oral dosing regimens ranging from 2 mg/kg every 8 hours to 10 mg/kg every 4 hours.

The extent of absorption (AUC) was equivalent when zidovudine was administered as RETROVIR Tablets or Syrup compared to RETROVIR Capsules.

Table 1. Zidovudine Pharmacokinetic Parameters in Fasting Adult Patients

Parameter	Mean ± SD (except where noted)
Oral bioavailability (%)	64 ± 10 (n = 5)
Apparent volume of distribution (L/kg)	1.6 ± 0.6 (n = 8)
Plasma protein binding (%)	<38
CSF: plasma ratio*	0.6 [0.04 to 2.62] (n = 39)
Systemic clearance (L/hr/kg)	1.6 ± 0.6 (n = 6)
Renal clearance (L/hr/kg)	0.34 ± 0.05 (n = 9)
Elimination half-life (hr)†	0.5 to 3 (n = 19)

*Median [range].
†Approximate range.

Adults With Impaired Renal Function: Zidovudine clearance was decreased resulting in increased zidovudine and GZDV half-life and AUC in patients with impaired renal function (n = 14) following a single 200-mg oral dose (Table 2). Plasma concentrations of AMT were not determined. A dose adjustment should not be necessary for patients with creatinine clearance (CrCl) ≥ 15 mL/min.

Table 2. Zidovudine Pharmacokinetic Parameters in Patients With Severe Renal Impairment*

Parameter	Control Subjects (Normal Renal Function) (n = 6)	Patients With Renal Impairment (n = 14)
CrCl (mL/min)	120 ± 8	18 ± 2
Zidovudine AUC (ng•hr/mL)	1,400 ± 200	3,100 ± 300
Zidovudine half-life (hr)	1.0 ± 0.2	1.4 ± 0.1

*Data are expressed as mean ± standard deviation.

The pharmacokinetics and tolerance of zidovudine were evaluated in a multiple-dose study in patients undergoing hemodialysis (n = 5) or peritoneal dialysis (n = 6) receiving escalating doses up to 200 mg 5 times daily for 8 weeks. Daily doses of 500 mg or less were well tolerated despite significantly elevated GZDV plasma concentrations. Apparent zidovudine oral clearance was approximately 50% of that reported in patients with normal renal function. Hemodialysis and peritoneal dialysis appeared to have a negligible effect on the removal of zidovudine, whereas GZDV elimination was enhanced. A dosage adjustment is recommended for patients undergoing hemodialysis or peritoneal dialysis (see DOSAGE AND ADMINISTRATION: Dose Adjustment).

Adults With Impaired Hepatic Function: Data describing the effect of hepatic impairment on the pharmacokinetics of zidovudine are limited. However, because zidovudine is eliminated primarily by hepatic metabolism, it is expected that zidovudine clearance would be decreased and plasma concentrations would be increased following administration of the recommended adult doses to patients with hepatic impairment (see DOSAGE AND ADMINISTRATION: Dose Adjustment).

Pediatrics: Zidovudine pharmacokinetics have been evaluated in HIV-infected pediatric patients (Table 3).

Patients From 3 Months to 12 Years of Age: Overall, zidovudine pharmacokinetics in pediatric patients greater than 3 months of age are similar to those in adult patients. Proportional increases in plasma zidovudine concentrations were observed following administration of oral solution from 90 to 240 mg/m^2 every 6 hours. Oral bioavailability, terminal half-life, and oral clearance were comparable to adult values. As in adult patients, the major route of elimination was by metabolism to GZDV. After intravenous dosing, about 29% of the dose was excreted in the urine unchanged, and about 45% of the dose was excreted as GZDV (see DOSAGE AND ADMINISTRATION: Pediatrics).

Patients Younger Than 3 Months of Age: Zidovudine pharmacokinetics have been evaluated in pediatric patients from birth to 3 months of life. Zidovudine elimination was determined immediately following birth in 8 neonates who were exposed to zidovudine in utero. The half-life was 13.0 ± 5.8 hours. In neonates ≤ 14 days old, bioavailability was greater, total body clearance was slower, and half-life was longer than in pediatric patients >14 days old. For dose recommendations for neonates, see DOSAGE AND ADMINISTRATION: Neonatal Dosing.

Table 3. Zidovudine Pharmacokinetic Parameters in Pediatric Patients*

Parameter	Birth to 14 Days of Age	14 Days to 3 Months of Age	3 Months to 12 Years of Age
Oral bioavailability (%)	89 ± 19 (n = 15)	61 ± 19 (n = 17)	65 ± 24 (n = 18)
CSF: plasma ratio	no data	no data	0.68 [0.03 to 3.25]† (n = 38)
CL (L/hr/kg)	0.65 ± 0.29 (n = 18)	1.14 ± 0.24 (n = 16)	1.85 ± 0.47 (n = 20)
Elimination half-life (hr)	3.1 ± 1.2 (n = 21)	1.9 ± 0.7 (n = 18)	1.5 ± 0.7 (n = 21)

* Data presented as mean ± standard deviation except where noted.
† Median [range].

Pregnancy: Zidovudine pharmacokinetics have been studied in a Phase 1 study of 8 women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation. Zidovudine pharmacokinetics were similar to those of nonpregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery. Although data are limited, methadone maintenance therapy in 5 pregnant women did not appear to alter zidovudine pharmacokinetics. However, in another patient population, a potential for interaction has been identified (see PRECAUTIONS).

Nursing Mothers: **The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV.** After administration of a single dose of 200 mg zidovudine to 13 HIV-infected women, the mean concentration of zidovudine was similar in human milk and serum (see PRECAUTIONS: Nursing Mothers).

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

Gender: A pharmacokinetic study in healthy male (n = 12) and female (n = 12) subjects showed no differences in zidovudine exposure (AUC) when a single dose of zidovudine was administered as the 300-mg RETROVIR Tablet.

Effect of Food on Absorption: RETROVIR may be administered with or without food. The extent of zidovudine absorption (AUC) was similar when a single dose of zidovudine was administered with food.

Drug Interactions: See Table 4 and PRECAUTIONS: Drug Interactions.

Zidovudine Plus Lamivudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg every 12 hours).

Table 4. Effect of Coadministered Drugs on Zidovudine AUC*

Note: ROUTINE DOSE MODIFICATION OF ZIDOVUDINE IS NOT WARRANTED WITH COADMINISTRATION OF THE FOLLOWING DRUGS.

Coadministered Drug and Dose	Zidovudine Dose	n	Zidovudine Concentrations		Concentration of Coadministered Drug
			AUC	Variability	
Atovaquone 750 mg q 12 hr with food	200 mg q 8 hr	14	↑ AUC 31%	Range 23% to 78%†	↔
Fluconazole 400 mg daily	200 mg q 8 hr	12	↑ AUC 74%	95% CI: 54% to 98%	Not Reported
Methadone 30 to 90 mg daily	200 mg q 4 hr	9	↑ AUC 43%	Range 16% to 64%†	↔
Nelfinavir 750 mg q 8 hr x 7 to 10 days	single 200 mg	11	↓ AUC 35%	Range 28% to 41%	↔
Probenecid 500 mg q 6 hr x 2 days	2 mg/kg q 8 hr x 3 days	3	↑ AUC 106%	Range 100% to 170%†	Not Assessed
Rifampin 600 mg daily x 14 days	200 mg q 8 hr x 14 days	8	↓ AUC 47%	90% CI: 41% to 53%	Not Assessed
Ritonavir 300 mg q 6 hr x 4 days	200 mg q 8 hr x 4 days	9	↓ AUC 25%	95% CI: 15% to 34%	↔
Valproic acid 250 mg or 500 mg q 8 hr x 4 days	100 mg q 8 hr x 4 days	6	↑ AUC 80%	Range 64% to 130%†	Not Assessed

↑ = Increase; ↓ = Decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; CI = confidence interval.
* This table is not all inclusive.
† Estimated range of percent difference.

Ribavirin: In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were co-administered as part of a multi-drug regimen to HIV/HCV co-infected patients (see WARNINGS).

INDICATIONS AND USAGE

RETROVIR in combination with other antiretroviral agents is indicated for the treatment of HIV infection.

Maternal-Fetal HIV Transmission: RETROVIR is also indicated for the prevention of maternal-fetal HIV transmission as part of a regimen that includes oral RETROVIR beginning between 14 and 34 weeks of gestation, intravenous RETROVIR during labor, and administration of RETROVIR Syrup to the neonate after birth. The efficacy of this regimen for preventing HIV transmission in women who have received RETROVIR for a prolonged period before pregnancy has not been evaluated. The

safety of RETROVIR for the mother or fetus during the first trimester of pregnancy has not been assessed (see Description of Clinical Studies).

Description of Clinical Studies: Therapy with RETROVIR has been shown to prolong survival and decrease the incidence of opportunistic infections in patients with advanced HIV disease and to delay disease progression in asymptomatic HIV-infected patients.

Combination Therapy in Adults: RETROVIR in combination with other antiretroviral agents has been shown to be superior to monotherapy for one or more of the following endpoints: delaying death, delaying development of AIDS, increasing CD4+ cell counts, and decreasing plasma HIV-1 RNA. The clinical efficacy of a combination regimen that includes RETROVIR was demonstrated in study ACTG320. This study was a multi-center, randomized, double-blind, placebo-controlled trial that compared RETROVIR 600 mg/day plus EPIVIR 300 mg/day to RETROVIR plus EPIVIR plus indinavir 800 mg t.i.d. The incidence of AIDS-defining events or death was lower in the triple-drug–containing arm compared to the 2-drug–containing arm (6.1% versus 10.9%, respectively).

The complete prescribing information for each drug should be consulted before combination therapy that includes RETROVIR is initiated.

Monotherapy in Adults: In controlled studies of treatment-naive patients conducted between 1986 and 1989, monotherapy with RETROVIR, as compared to placebo, reduced the risk of HIV disease progression, as assessed using endpoints that included the occurrence of HIV-related illnesses, AIDS-defining events, or death. These studies enrolled patients with advanced disease (BW002), and asymptomatic or mildly symptomatic disease in patients with CD4+ cell counts between 200 and 500 cells/mm^3 (ACTG016 and ACTG019). A survival benefit for monotherapy with RETROVIR was not demonstrated in the latter 2 studies. Subsequent studies showed that the clinical benefit of monotherapy with RETROVIR was time limited.

Pediatric Patients: ACTG300 was a multi-center, randomized, double-blind study that provided for comparison of EPIVIR plus RETROVIR to didanosine monotherapy. A total of 471 symptomatic, HIV-infected therapy-naive pediatric patients were enrolled in these 2 treatment arms. The median age was 2.7 years (range 6 weeks to 14 years), the mean baseline CD4+ cell count was 868 cells/mm^3, and the mean baseline plasma HIV-1 RNA was 5.0 $\log_{10}$ copies/mL. The median duration that patients remained on study was approximately 10 months. Results are summarized in Table 5.

Table 5. Number of Patients (%) Reaching a Primary Clinical Endpoint (Disease Progression or Death)

Endpoint	EPIVIR plus RETROVIR (n = 236)	Didanosine (n = 235)
HIV disease progression or death (total)	15 (6.4%)	37 (15.7%)
Physical growth failure	7 (3.0%)	6 (2.6%)
Central nervous system deterioration	4 (1.7%)	12 (5.1%)
CDC Clinical Category C	2 (0.8%)	8 (3.4%)
Death	2 (0.8%)	11 (4.7%)

Pregnant Women and Their Neonates: The utility of RETROVIR for the prevention of maternal-fetal HIV transmission was demonstrated in a randomized, double-blind, placebo-controlled trial (ACTG076) conducted in HIV-infected pregnant women with CD4+ cell counts of 200 to 1,818 cells/mm^3 (median in the treated group: 560 cells/mm^3) who had little or no previous exposure to RETROVIR. Oral RETROVIR was initiated between 14 and 34 weeks of gestation (median 11 weeks of therapy) followed by IV administration of RETROVIR during labor and delivery. Following birth, neonates received oral RETROVIR Syrup for 6 weeks. The study showed a statistically significant difference in the incidence of HIV infection in the neonates (based on viral culture from peripheral blood) between the group receiving RETROVIR and the group receiving placebo. Of 363 neonates evaluated in the study, the estimated risk of HIV infection was 7.8% in the group receiving RETROVIR and 24.9% in the placebo group, a relative reduction in transmission risk of 68.7%. RETROVIR was well tolerated by mothers and infants. There was no difference in pregnancy-related adverse events between the treatment groups.

CONTRAINDICATIONS

RETROVIR Tablets, Capsules, and Syrup are contraindicated for patients who have potentially life-threatening allergic reactions to any of the components of the formulations.

WARNINGS

COMBIVIR and TRIZIVIR are combination product tablets that contain zidovudine as one of their components. RETROVIR should not be administered concomitantly with COMBIVIR or TRIZIVIR.

The incidence of adverse reactions appears to increase with disease progression; patients should be monitored carefully, especially as disease progression occurs.

Bone Marrow Suppression: RETROVIR should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count <1,000 cells/mm^3 or hemoglobin <9.5 g/dL. In patients with advanced symptomatic HIV disease, anemia and neutropenia were the most significant adverse events observed. There have been reports of pancytopenia associated with the use of RETROVIR, which was reversible in most instances after discontinuance of the drug. However, significant anemia, in many cases requiring dose adjustment, discontinuation of RETROVIR, and/or blood transfusions, has occurred during treatment with RETROVIR alone or in combination with other antiretrovirals.

Frequent blood counts are strongly recommended in patients with advanced HIV disease who are treated with RETROVIR. For HIV-infected individuals and patients with asymptomatic or early HIV disease, periodic blood counts are recommended. If anemia or neutropenia develops, dosage adjustments may be necessary (see DOSAGE AND ADMINISTRATION).

Myopathy: Myopathy and myositis with pathological changes, similar to that produced by HIV disease, have been associated with prolonged use of RETROVIR.

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 zidovudine and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged exposure to antiretroviral nucleoside analogues may be risk factors. Particular caution should be exercised when administering RETROVIR 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 RETROVIR 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).

Use With Interferon- and Ribavirin-Based Regimens: In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as zidovudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV/HCV virologic suppression) was seen when ribavirin was coadministered with zidovudine in HIV/HCV co-infected patients (see CLINICAL PHARMACOLOGY: Drug Interactions), **hepatic decompensation (some fatal) has occurred in HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon alfa with or without ribavirin.** Patients receiving interferon alfa with or without ribavirin and RETROVIR should be closely monitored for treatment-associated toxicities, especially hepatic decompensation, neutropenia, and anemia. Discontinuation of RETROVIR should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Childs Pugh >6) (see the complete prescribing information for interferon and ribavirin).

PRECAUTIONS

General: Zidovudine is eliminated from the body primarily by renal excretion following metabolism in the liver (glucuronidation). In patients with severely impaired renal function (CrCl<15 mL/min), dosage reduction is recommended. Although the data are limited, zidovudine concentrations appear to be increased in patients with severely impaired hepatic function which may increase the risk of hematologic toxicity (see CLINICAL PHARMACOLOGY: Pharmacokinetics and DOSAGE AND ADMINISTRATION).

Immune Reconstitution Syndrome: Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including RETROVIR. 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.

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.

Information for Patients: RETROVIR is not a cure for HIV infection, and patients may continue to acquire illnesses associated with HIV infection, including opportunistic infections. Therefore, patients should be advised to seek medical care for any significant change in their health status.

The safety and efficacy of RETROVIR in women, intravenous drug users, and racial minorities is not significantly different than that observed in white males.

Patients should be informed that the major toxicities of RETROVIR are neutropenia and/or anemia. The frequency and severity of these toxicities are greater in patients with more advanced disease and in those who initiate therapy later in the course of their infection. They should be told that if toxicity develops, they may require transfusions or drug discontinuation. They should be told of the extreme importance of having their blood counts followed closely while on therapy, especially for patients with advanced symptomatic HIV disease. They should be cautioned about the use of other medications, including ganciclovir and interferon alfa, which may exacerbate the toxicity of RETROVIR (see PRECAUTIONS: Drug Interactions). Patients should be informed that other adverse effects of RETROVIR include nausea and vomiting. Patients should also be encouraged to contact their physician if they experience muscle weakness, shortness of breath, symptoms of hepatitis or pancreatitis, or any other unexpected adverse events while being treated with RETROVIR.

RETROVIR Tablets, Capsules, and Syrup are for oral ingestion only. Patients should be told of the importance of taking RETROVIR exactly as prescribed. They should be told not to share medication and not to exceed the recommended dose. Patients should be told that the long-term effects of RETROVIR are unknown at this time.

Pregnant women considering the use of RETROVIR during pregnancy for prevention of HIV transmission to their infants should be advised that transmission may still occur in some cases despite therapy. The long-term consequences of in utero and infant exposure to RETROVIR are unknown, including the possible risk of cancer.

HIV-infected pregnant women should be advised not to breastfeed to avoid postnatal transmission of HIV to a child who may not yet be infected.

Patients should be advised that therapy with RETROVIR 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 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.

Drug Interactions: See CLINICAL PHARMACOLOGY section (Table 4) for information on zidovudine concentrations when coadministered with other drugs. For patients experiencing pronounced anemia or other severe zidovudine-associated events while receiving chronic administration of zidovudine and some of the drugs (e.g., fluconazole, valproic acid) listed in Table 4, zidovudine dose reduction may be considered.

Antiretroviral Agents: Concomitant use of zidovudine with stavudine should be avoided since an antagonistic relationship has been demonstrated in vitro.

Some nucleoside analogues affecting DNA replication, such as ribavirin, antagonize the in vitro antiviral activity of RETROVIR against HIV; concomitant use of such drugs should be avoided.

Doxorubicin: Concomitant use of zidovudine with doxorubicin should be avoided since an antagonistic relationship has been demonstrated in vitro (see CLINICAL PHARMACOLOGY for additional drug interactions).

Phenytoin: Phenytoin plasma levels have been reported to be low in some patients receiving RETROVIR, while in one case a high level was documented. However, in a pharmacokinetic interaction study in which 12 HIV-positive volunteers received a single 300-mg phenytoin dose alone and during steady-state zidovudine conditions (200 mg every 4 hours), no change in phenytoin kinetics was observed. Although not designed to optimally assess the effect of phenytoin on zidovudine kinetics, a 30% decrease in oral zidovudine clearance was observed with phenytoin.

Overlapping Toxicities: Coadministration of ganciclovir, interferon alfa, and other bone marrow suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Zidovudine was administered orally at 3 dosage levels to separate groups of mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60, and 120 mg/kg/day in mice and 80, 220, and 600 mg/kg/day in rats. The doses in mice were reduced to 20, 30, and 40 mg/kg/day after day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg/kg/day on day 91 and then to 300 mg/kg/day on day 279.

In mice, 7 late-appearing (after 19 months) vaginal neoplasms (5 nonmetastasizing squamous cell carcinomas, 1 squamous cell papilloma, and 1 squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of a middle-dose animal. No vaginal tumors were found at the lowest dose.

In rats, 2 late-appearing (after 20 months), nonmetastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle dose in rats. No other drug-related tumors were observed in either sex of either species.

At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 3 times (mouse) and 24 times (rat) the estimated human exposure at the recommended therapeutic dose of 100 mg every 4 hours.

Two transplacental carcinogenicity studies were conducted in mice. One study administered zidovudine at doses of 20 mg/kg/day or 40 mg/kg/day from gestation day 10 through parturition and lactation with dosing continuing in offspring for 24 months postnatally. The doses of zidovudine employed in this study produced zidovudine exposures approximately 3 times the estimated human exposure at recommended doses. After 24 months, an increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in either gender. These findings are consistent with results of the standard oral carcinogenicity study in mice, as described earlier. A second study administered zidovudine at maximum tolerated doses of 12.5 mg/day or 25 mg/day (~1,000 mg/kg nonpregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from days 12 through 18 of gestation. There was an increase in the number of tumors in the lung, liver, and female reproductive tracts in the offspring of mice receiving the higher dose level of zidovudine.

It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Zidovudine was mutagenic in a 5178Y/TK$^{+/-}$ mouse lymphoma assay, positive in an in vitro cell transformation assay, clastogenic in a cytogenetic assay using cultured human lymphocytes, and positive in mouse and rat micronucleus tests after repeated doses. It was negative in a cytogenetic study in rats given a single dose.

Zidovudine, administered to male and female rats at doses up to 7 times the usual adult dose based on body surface area considerations, had no effect on fertility judged by conception rates.

Pregnancy: Pregnancy Category C. Oral teratology studies in the rat and in the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal toxicity as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one half of the daily dose) in rats 66 to 226 times, and in rabbits 12 to 87 times, mean steady-state peak human plasma concentrations (after one sixth of the daily dose) achieved with the recommended daily dose (100 mg every 4 hours). In an in vitro experiment with fertilized mouse oocytes, zidovudine exposure resulted in a dose-dependent reduction in blastocyst formation. In an additional teratology study in rats, a dose of 3,000 mg/kg/day (very near the oral median lethal dose in rats of 3,683 mg/kg) caused marked maternal toxicity and an increase in the incidence of fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations. (Estimated area under the curve [AUC] in rats at this dose level was 300 times the daily AUC in humans given 600 mg/day.) No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg/day or less.

Two rodent transplacental carcinogenicity studies were conducted (see Carcinogenesis, Mutagenesis, Impairment of Fertility).

A randomized, double-blind, placebo-controlled trial was conducted in HIV-infected pregnant women to determine the utility of RETROVIR for the prevention of maternal-fetal HIV-transmission (see INDICATIONS AND USAGE: Description of Clinical Studies). Congenital abnormalities occurred with similar frequency between neonates born to mothers who received RETROVIR and neonates born to mothers who received placebo. Abnormalities were either problems in embryogenesis (prior to 14 weeks) or were recognized on ultrasound before or immediately after initiation of study drug.

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

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Zidovudine is excreted in human milk (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Nursing Mothers). Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving RETROVIR** (see Pediatric Use and INDICATIONS AND USAGE: Maternal-Fetal HIV Transmission).

Pediatric Use: RETROVIR has been studied in HIV-infected pediatric patients over 3 months of age who had HIV-related symptoms or who were asymptomatic with abnormal laboratory values indicating significant HIV-related immunosuppression. RETROVIR has also been studied in neonates perinatally exposed to HIV (see ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, INDICATIONS AND USAGE: Description of Clinical Studies, and CLINICAL PHARMACOLOGY: Pharmacokinetics).

Geriatric Use: Clinical studies of RETROVIR did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Adults: The frequency and severity of adverse events associated with the use of RETROVIR are greater in patients with more advanced infection at the time of initiation of therapy.

Table 6 summarizes events reported at a statistically significant greater incidence for patients receiving RETROVIR in a monotherapy study:

Table 6. Percentage (%) of Patients with Adverse Events* in Asymptomatic HIV Infection (ACTG019)

Adverse Event	RETROVIR 500 mg/day (n = 453)	Placebo (n = 428)
Body as a whole		
Asthenia	8.6%†	5.8%
Headache	62.5%	52.6%
Malaise	53.2%	44.9%
Gastrointestinal		
Anorexia	20.1%	10.5%
Constipation	6.4%†	3.5%
Nausea	51.4%	29.9%
Vomiting	17.2%	9.8%

* Reported in ≥5% of study population.
† Not statistically significant versus placebo.

In addition to the adverse events listed in Table 6, other adverse events observed in clinical studies were abdominal cramps, abdominal pain, arthralgia, chills, dyspepsia, fatigue, hyperbilirubinemia, insomnia, musculoskeletal pain, myalgia, and neuropathy.

Selected laboratory abnormalities observed during a clinical study of monotherapy with RETROVIR are shown in Table 7.

Table 7. Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Patients with Asymptomatic HIV Infection (ACTG019)

Adverse Event	RETROVIR 500 mg/day (n = 453)	Placebo (n = 428)
Anemia (Hgb<8 g/dL)	1.1%	0.2%
Granulocytopenia (<750 cells/mm^3)	1.8%	1.6%
Thrombocytopenia (platelets<50,000/mm^3)	0%	0.5%
ALT (>5 x ULN)	3.1%	2.6%
AST (>5 x ULN)	0.9%	1.6%
Alkaline phosphatase (>5 x ULN)	0%	0%

ULN = Upper limit of normal.

Pediatrics: ***Study ACTG300:*** Selected clinical adverse events and physical findings with a ≥ 5% frequency during therapy with EPIVIR 4 mg/kg twice daily plus RETROVIR 160 mg/m^2 3 times daily compared with didanosine in therapy-naive (≤ 56 days of antiretroviral therapy) pediatric patients are listed in Table 8.

Table 8. Selected Clinical Adverse Events and Physical Findings (≥5% Frequency) in Pediatric Patients in Study ACTG300

Adverse Event	EPIVIR plus RETROVIR (n = 236)	Didanosine (n = 235)
Body as a whole		
Fever	25%	32%
Digestive		
Hepatomegaly	11%	11%
Nausea & vomiting	8%	7%
Diarrhea	8%	6%
Stomatitis	6%	12%
Splenomegaly	5%	8%
Respiratory		
Cough	15%	18%
Abnormal breath sounds/wheezing	7%	9%
Ear, Nose, and Throat		
Signs or symptoms of ears*	7%	6%
Nasal discharge or congestion	8%	11%
Other		
Skin rashes	12%	14%
Lymphadenopathy	9%	11%

*Includes pain, discharge, erythema, or swelling of an ear.

Selected laboratory abnormalities experienced by therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in Table 9.

Table 9. Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Pediatric Patients in Study ACTG300

Test (Abnormal Level)	EPIVIR plus RETROVIR	Didanosine
Neutropenia (ANC<400 cells/mm^3)	8%	3%
Anemia (Hgb<7.0 g/dL)	4%	2%
Thrombocytopenia (platelets<50,000/mm^3)	1%	3%
ALT (>10 x ULN)	1%	3%
AST (>10 x ULN)	2%	4%
Lipase (>2.5 x ULN)	3%	3%
Total amylase (>2.5 x ULN)	3%	3%

ULN = Upper limit of normal.
ANC = Absolute neutrophil count.

Additional adverse events reported in open-label studies in pediatric patients receiving RETROVIR 180 mg/m^2 every 6 hours were congestive heart failure, decreased reflexes, ECG abnormality, edema, hematuria, left ventricular dilation, macrocytosis, nervousness/irritability, and weight loss.

The clinical adverse events reported among adult recipients of RETROVIR may also occur in pediatric patients.

Use for the Prevention of Maternal-Fetal Transmission of HIV: In a randomized, double-blind, placebo-controlled trial in HIV-infected women and their neonates conducted to determine the utility of RETROVIR for the prevention of maternal-fetal HIV transmission, RETROVIR Syrup at 2 mg/kg was administered every 6 hours for 6 weeks to neonates beginning within 12 hours following birth. The most commonly reported adverse experiences were anemia (hemoglobin <9.0 g/dL) and neutropenia (<1,000 cells/mm^3). Anemia occurred in 22% of the neonates who received RETROVIR and in 12% of the neonates who received placebo. The mean difference in hemoglobin values was less than 1.0 g/dL for neonates receiving RETROVIR compared to neonates receiving placebo. No neonates with anemia required transfusion and all hemoglobin values spontaneously returned to normal within 6 weeks after completion of therapy with RETROVIR. Neutropenia was reported with similar frequency in the group that received RETROVIR (21%) and in the group that received placebo (27%). The long-term consequences of in utero and infant exposure to RETROVIR are unknown.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during use of RETROVIR in clinical practice. 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 either their seriousness, frequency of reporting, potential causal connection to RETROVIR, or a combination of these factors.

Body as a Whole: Back pain, chest pain, flu-like syndrome, generalized pain, redistribution/accumulation of body fat (see PRECAUTIONS: Fat Redistribution).

Cardiovascular: Cardiomyopathy, syncope.

Endocrine: Gynecomastia.

Eye: Macular edema.

Gastrointestinal: Constipation, dysphagia, flatulence, oral mucosa pigmentation, mouth ulcer.

General: Sensitization reactions including anaphylaxis and angioedema, vasculitis.

Hemic and Lymphatic: Aplastic anemia, hemolytic anemia, leukopenia, lymphadenopathy, pancytopenia with marrow hypoplasia, pure red cell aplasia.

Hepatobiliary Tract and Pancreas: Hepatitis, hepatomegaly with steatosis, jaundice, lactic acidosis, pancreatitis.

Musculoskeletal: Increased CPK, increased LDH, muscle spasm, myopathy and myositis with pathological changes (similar to that produced by HIV disease), rhabdomyolysis, tremor.

Nervous: Anxiety, confusion, depression, dizziness, loss of mental acuity, mania, paresthesia, seizures, somnolence, vertigo.

Respiratory: Cough, dyspnea, rhinitis, sinusitis.

Skin: Changes in skin and nail pigmentation, pruritus, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, sweat, urticaria.

Special Senses: Amblyopia, hearing loss, photophobia, taste perversion.

Urogenital: Urinary frequency, urinary hesitancy.

OVERDOSAGE

Acute overdoses of zidovudine have been reported in pediatric patients and adults. These involved exposures up to 50 grams. No specific symptoms or signs have been identified following acute overdosage with zidovudine apart from those listed as adverse events such as fatigue, headache, vomiting, and occasional reports of hematological disturbances. All patients recovered without permanent sequelae. Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine while elimination of its primary metabolite, GZDV, is enhanced.

DOSAGE AND ADMINISTRATION

Adults: The recommended oral dose of RETROVIR is 600 mg per day in divided doses in combination with other antiretroviral agents.

Pediatrics: The recommended dose in pediatric patients 6 weeks to 12 years of age is 160 mg/m^2 every 8 hours (480 mg/m^2/day up to a maximum of 200 mg every 8 hours) in combination with other antiretroviral agents.

Maternal-Fetal HIV Transmission: The recommended dosing regimen for administration to pregnant women (>14 weeks of pregnancy) and their neonates is:

Maternal Dosing: 100 mg orally 5 times per day until the start of labor (see INDICATIONS AND USAGE: Description of Clinical Studies). During labor and delivery, intravenous RETROVIR should be administered at 2 mg/kg (total body weight) over 1 hour followed by a continuous intravenous infusion of 1 mg/kg/hour (total body weight) until clamping of the umbilical cord.

Neonatal Dosing: 2 mg/kg orally every 6 hours starting within 12 hours after birth and continuing through 6 weeks of age. Neonates unable to receive oral dosing may be administered RETROVIR intravenously at 1.5 mg/kg, infused over 30 minutes, every 6 hours. (See PRECAUTIONS if hepatic disease or renal insufficiency is present.)

Monitoring of Patients: Hematologic toxicities appear to be related to pretreatment bone marrow reserve and to dose and duration of therapy. In patients with poor bone marrow reserve, particularly in patients with advanced symptomatic HIV disease, frequent monitoring of hematologic indices is recommended to detect serious anemia or neutropenia (see WARNINGS). In patients who experience hematologic toxicity, reduction in hemoglobin may occur as early as 2 to 4 weeks, and neutropenia usually occurs after 6 to 8 weeks.

Dose Adjustment: ***Anemia:*** Significant anemia (hemoglobin of <7.5 g/dL or reduction of >25% of baseline) and/or significant neutropenia (granulocyte count of <750 cells/mm^3 or reduction of >50% from baseline) may require a dose interruption until evidence of marrow recovery is observed (see WARNINGS). In patients who develop significant anemia, dose interruption does not necessarily eliminate the need for transfusion. If marrow recovery occurs following dose interruption, resumption in dose may be appropriate using adjunctive measures such as epoetin alfa at recommended doses, depending on hematologic indices such as serum erythropoetin level and patient tolerance.

For patients experiencing pronounced anemia while receiving chronic coadministration of zidovudine and some of the drugs (e.g., fluconazole, valproic acid) listed in Table 4, zidovudine dose reduction may be considered.

End-Stage Renal Disease: In patients maintained on hemodialysis or peritoneal dialysis, recommended dosing is 100 mg every 6 to 8 hours (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

Hepatic Impairment: There are insufficient data to recommend dose adjustment of RETROVIR in patients with mild to moderate impaired hepatic function or liver cirrhosis. Since RETROVIR is primarily eliminated by hepatic metabolism, a reduction in the daily dose may be necessary in these patients. Frequent monitoring for hematologic toxicities is advised (see CLINICAL PHARMACOLOGY: Pharmacokinetics and PRECAUTIONS: General).

HOW SUPPLIED

RETROVIR Tablets 300 mg (biconvex, white, round, film-coated) containing 300 mg zidovudine, one side engraved "GX CW3" and "300" on the other side.

Bottle of 60 (NDC 0173-0501-00).

Store at 15° to 25°C (59° to 77°F).

RETROVIR Capsules 100 mg (white, opaque cap and body) containing 100 mg zidovudine and printed with "Wellcome" and unicorn logo on cap and "Y9C" and "100" on body.

Bottles of 100 (NDC 0173-0108-55).

Unit Dose Pack of 100 (NDC 0173-0108-56).

Store at 15° to 25°C (59° to 77°F) and protect from moisture.

RETROVIR Syrup (colorless to pale yellow, strawberry-flavored) containing 50 mg zidovudine in each teaspoonful (5 mL).

Bottle of 240 mL (NDC 0173-0113-18) with child-resistant cap.

Store at 15° to 25°C (59° to 77°F).

GlaxoSmithKline
Research Triangle Park, NC 27709

November 2006 RL-2325

TRIZIVIR®
(abacavir sulfate, lamivudine, and zidovudine) Tablets

WARNINGS

TRIZIVIR contains 3 nucleoside analogues (abacavir sulfate, lamivudine, and zidovudine) and is intended only for patients whose regimen would otherwise include these 3 components.

Hypersensitivity Reactions: Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate, a component of TRIZIVIR. Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups: (1) fever, (2) rash, (3) gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain), (4) constitutional (including generalized malaise, fatigue, or achiness), and (5) respiratory (including dyspnea, cough, or pharyngitis). Discontinue TRIZIVIR as soon as a hypersensitivity reaction is suspected. Permanently discontinue TRIZIVIR if hypersensitivity cannot be ruled out, even when other diagnoses are possible.

Following a hypersensitivity reaction to abacavir, NEVER restart TRIZIVIR or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.

Reintroduction of TRIZIVIR or any other abacavir-containing product, even in patients who have no identified history or unrecognized symptoms of hypersensitivity to abacavir therapy, can result in serious or fatal hypersensitivity reactions. Such reactions can occur within hours (see WARNINGS and PRECAUTIONS: Information for Patients).

Hematologic Toxicity: Zidovudine has been associated with hematologic toxicity including neutropenia and severe anemia, particularly in patients with advanced Human Immunodeficiency Virus (HIV) disease (see WARNINGS). Prolonged use of zidovudine has been associated with symptomatic myopathy.

Lactic Acidosis and Severe Hepatomegaly: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir, lamivudine, zidovudine, and other antiretrovirals (see WARNINGS).

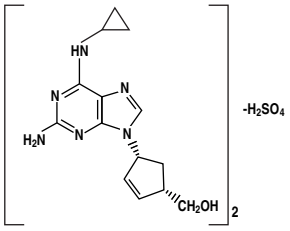
Exacerbations of Hepatitis B: Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV) and have discontinued lamivudine, which is one component of TRIZIVIR. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue TRIZIVIR and are co-infected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted (see WARNINGS).

DESCRIPTION

TRIZIVIR: TRIZIVIR Tablets contain the following 3 synthetic nucleoside analogues: abacavir sulfate (ZIAGEN®), lamivudine (also known as EPIVIR® or 3TC), and zidovudine (also known as RETROVIR®, azidothymidine, or ZDV) with inhibitory activity against HIV.

TRIZIVIR Tablets are for oral administration. Each film-coated tablet contains the active ingredients 300 mg of abacavir as abacavir sulfate, 150 mg of lamivudine, and 300 mg of zidovudine, and the inactive ingredients magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablets are coated with a film (Opadry® green 03B11434) that is made of FD&C Blue No. 2, hypromellose, polyethylene glycol, titanium dioxide, and yellow iron oxide.

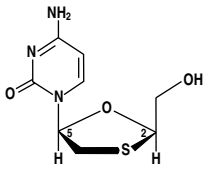
Abacavir Sulfate: The chemical name of abacavir sulfate is (1*S,cis*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1). Abacavir sulfate is the enantiomer with *1S, 4R* absolute configuration on the cyclopentene ring. It has a molecular formula of $(C_{14}H_{18}N_6O)_2 \cdot H_2SO_4$ and a molecular weight of 670.76 daltons. It has the following structural formula:



Abacavir sulfate is a white to off-white solid with a solubility of approximately 77 mg/mL in distilled water at 25ºC.

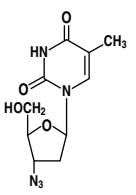
In vivo, abacavir sulfate dissociates to its free base, abacavir. In this insert, all dosages for ZIAGEN (abacavir sulfate) are expressed in terms of abacavir.

Lamivudine: The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2´,3´-dideoxy, 3´-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.3 daltons. It has the following structural formula:



Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg/mL in water at 20ºC.

Zidovudine: The chemical name of zidovudine is 3´-azido-3´-deoxythymidine. It has a molecular formula of $C_{10}H_{13}N_5O_4$ and a molecular weight of 267.24 daltons. It has the following structural formula:



Zidovudine is a white to beige, crystalline solid with a solubility of 20.1 mg/mL in water at 25°C.

MICROBIOLOGY

Mechanism of Action:

Abacavir: Abacavir is a carbocyclic synthetic nucleoside analogue. Abacavir is converted by cellular enzymes to the active metabolite, carbovir triphosphate (CBV-TP), an analogue of deoxyguanosine-5´-triphosphate (dGTP). CBV-TP inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation into viral DNA. The lack of a 3´-OH group in the incorporated nucleotide analogue prevents the formation of the 5´ to 3´ phosphodiester linkage essential for DNA chain elongation, and therefore, the viral DNA growth is terminated. CBV-TP is a weak inhibitor of cellular DNA polymerases α, β, and γ.

Lamivudine: Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5´-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue. 3TC-TP is a weak inhibitor of cellular DNA polymerases α, β, and γ.

Zidovudine: Zidovudine is a synthetic nucleoside analogue. Intracellularly, zidovudine is phosphorylated to its active 5´-triphosphate metabolite, zidovudine triphosphate (ZDV-TP). The principal mode of action of ZDV-TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue. ZDV-TP is a weak inhibitor of the cellular DNA polymerases α and γ and has been reported to be incorporated into the DNA of cells in culture.

Antiviral Activity:

Abacavir: The antiviral activity of abacavir against HIV-1 was evaluated against a T-cell tropic laboratory strain HIV-1_{IIIB} in lymphoblastic cell lines, a monocyte/macrophage tropic laboratory strain HIV-1_{BaL} in primary monocytes/macrophages, and clinical isolates in peripheral blood mononuclear cells. The concentration of drug necessary to effect viral replication by 50 percent (EC_{50}) ranged from 3.7 to 5.8 μM (1 μM = 0.28 mcg/mL) and 0.07 to 1.0 μM against HIV-1_{IIIB} and HIV-1_{BaL}, respectively, and was 0.26 ± 0.18 μM against 8 clinical isolates. The EC_{50} values of abacavir against different HIV-1 clades (A-G) ranged from 0.0015 to 1.05 μM, and against HIV-2 isolates, from 0.024 to 0.49 μM. Abacavir had synergistic activity in cell culture in combination with the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, and the protease inhibitor (PI) amprenavir; and additive activity in combination with the NRTIs didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine. Ribavirin (50 μM) had no effect on the anti–HIV-1 activity of abacavir in cell culture.

Lamivudine: The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. EC_{50} values were in the range of 0.003 to 15 μM (1 μM = 0.23 mcg/mL). HIV from therapy-naive subjects with no mutations associated with resistance gave median EC_{50} values of 0.426 μM (range: 0.200 to 2.007 μM) from Virco (n = 93 baseline samples from COLA40263) and 2.35 μM (1.44 to 4.08 μM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC_{50} values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120 μM, and against HIV-2 isolates from 0.003 to 0.120 μM in peripheral blood mononuclear cells. Ribavirin (50 μM) decreased the anti-HIV-1 activity of lamivudine by 3.5 fold in MT-4 cells.

Zidovudine: The antiviral activity of zidovudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes). The EC_{50} and EC_{90} values for zidovudine were 0.01 to 0.49 μM (1 μM = 0.27 mcg/mL) and 0.1 to 9 μM, respectively. HIV from therapy-naive subjects with no mutations associated with resistance gave median EC_{50} values of 0.011 μM (range: 0.005 to 0.110 μM) from Virco (n = 93 baseline samples from COLA40263) and 0.02 μM (0.01 to 0.03 μM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC_{50} values of zidovudine against different HIV-1 clades (A-G) ranged from 0.00018 to 0.02 μM, and against HIV-2 isolates from 0.00049 to 0.004 μM. In cell culture drug combination studies, zidovudine demonstrates synergistic activity with the NRTIs abacavir, didanosine, lamivudine, and zalcitabine; the NNRTIs delavirdine and nevirapine; and the PIs indinavir, nelfinavir, ritonavir, and saquinavir; and additive activity with interferon alfa. Ribavirin has been found to inhibit the phosphorylation of zidovudine in cell culture.

Resistance:

HIV-1 isolates with reduced sensitivity to abacavir, lamivudine, or zidovudine have been selected in cell culture and were also obtained from patients treated with abacavir, lamivudine, and zidovudine, or the combination of lamivudine and zidovudine.

Abacavir: Genotypic analysis of isolates selected in cell culture and recovered from abacavir-treated patients demonstrated that amino acid substitutions K65R, L74V, Y115F, and M184V/I in RT contributed to abacavir resistance. In a study of subjects receiving abacavir once or twice daily in combination with lamivudine and efavirenz once daily, 39% (7/18) of the isolates from patients who experienced virologic failure in the abacavir once-daily arm had a >2.5-fold decrease in abacavir susceptibility with a median-fold decrease of 1.3 (range 0.5 to 11) compared with 29% (5/17) of the failure isolates in the twice-daily arm with a median-fold decrease of 0.92 (range 0.7 to 13).

Lamivudine: Genotypic analysis of isolates selected in cell culture and recovered from lamivudine-treated patients showed that the resistance was due to a specific amino acid substitution in the HIV-1 reverse transcriptase at codon 184 changing the methionine to either isoleucine or valine (M184V/I).

Zidovudine: Genotypic analyses of the isolates selected in cell culture and recovered from zidovudine-treated patients showed mutations in the HIV-1 RT gene resulting in 6 amino acid substitutions (M41L, D67N, K70R, L210W, T215Y or F, and K219Q) that confer zidovudine resistance. In general, higher levels of resistance were associated with greater number of mutations. In some patients harboring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

Cross-Resistance:

Cross-resistance has been observed among NRTIs.

Abacavir: Isolates containing abacavir resistance-associated mutations, namely, K65R, L74V, Y115F, and M184V, exhibited cross-resistance to didanosine, emtricitabine, lamivudine, tenofovir, and zalcitabine in cell culture and in patients. The K65R mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine; the L74V mutation can confer resistance to abacavir, didanosine, and zalcitabine; and the M184V mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, and zalcitabine. An increasing number of thymidine analogue mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219E/R/H/Q/N) is associated with a progressive reduction in abacavir susceptibility.

Lamivudine: Cross-resistance to abacavir, didanosine, tenofovir, and zalcitabine has been observed in some patients harboring lamivudine-resistant HIV-1 isolates. In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple drugs, including lamivudine, have emerged (see under Zidovudine below). Cross-resistance between lamivudine and zidovudine has not been reported.

Zidovudine: In a study of 167 HIV-infected patients, isolates (n = 2) with multi-drug resistance to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine were recovered from patients treated for ≥1 year with zidovudine plus didanosine or zidovudine plus zalcitabine. The pattern of resistance-associated mutations with such combination therapies was different (A62V, V75I, F77L, F116Y, Q151M) from the pattern with zidovudine monotherapy, with the Q151M mutation being most commonly associated with multi-drug resistance. The mutation at codon 151 in combination with mutations at 62, 75, 77, and 116 results in a virus with reduced susceptibility to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine. TAMs are selected by zidovudine and confer cross-resistance to abacavir, didanosine, stavudine, tenofovir, and zalcitabine.

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults:

TRIZIVIR: In a single-dose, 3-way crossover bioavailability study of 1 TRIZIVIR Tablet versus 1 ZIAGEN Tablet (300 mg), 1 EPIVIR Tablet (150 mg), plus 1 RETROVIR Tablet (300 mg) administered simultaneously in healthy subjects (n = 24), there was no difference in the extent of absorption, as measured by the area under the plasma concentration-time curve (AUC) and maximal peak concentration (C_{max}), of all 3 components. One TRIZIVIR Tablet was bioequivalent to 1 ZIAGEN Tablet (300 mg), 1 EPIVIR Tablet (150 mg), plus 1 RETROVIR Tablet (300 mg) following single-dose administration to fasting healthy subjects (n = 24).

Abacavir: Following oral administration, abacavir is rapidly absorbed and extensively distributed. Binding of abacavir to human plasma proteins is approximately 50%. Binding of abacavir to plasma proteins was independent of concentration. Total blood and plasma drug-related radioactivity concentrations are identical, demonstrating that abacavir readily distributes into erythrocytes. The primary routes of elimination of abacavir are metabolism by alcohol dehydrogenase to form the 5´-carboxylic acid and glucuronyl transferase to form the 5´-glucuronide.

Lamivudine: Following oral administration, lamivudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low. Approximately 70% of an intravenous dose of lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite is the transsulfoxide metabolite (approximately 5% of an oral dose after 12 hours).

Zidovudine: Following oral administration, zidovudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low. Zidovudine is eliminated primarily by hepatic metabolism. The major metabolite of zidovudine is 3´-azido-3´-deoxy-5´-*O*-β-*D*-glucopyranuronosylthymidine (GZDV). GZDV area under the curve (AUC) is about 3-fold greater than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 14% and 74% of the dose following oral administration, respectively. A second metabolite, 3´-amino-3´-deoxythymidine (AMT), has been identified in plasma. The AMT AUC was one fifth of the zidovudine AUC.

In humans, abacavir, lamivudine, and zidovudine are not significantly metabolized by cytochrome P450 enzymes.

The pharmacokinetic properties of abacavir, lamivudine, and zidovudine in fasting patients are summarized in Table 1.

Table 1. Pharmacokinetic Parameters* for Abacavir, Lamivudine, and Zidovudine in Adults

Parameter	Abacavir		Lamivudine		Zidovudine	
Oral bioavailability (%)	86 ± 25	n = 6	86 ± 16	n = 12	64 ± 10	n = 5
Apparent volume of distribution (L/kg)	0.86 ± 0.15	n = 6	1.3 ± 0.4	n = 20	1.6 ± 0.6	n = 8
Systemic clearance (L/hr/kg)	0.80 ± 0.24	n = 6	0.33 ± 0.06	n = 20	1.6 ± 0.6	n = 6
Renal clearance (L/hr/kg)	.007 ± .008	n = 6	0.22 ± 0.06	n = 20	0.34 ± 0.05	n = 9
Elimination half-life (hr)†	1.45 ± 0.32	n = 20	5 to 7		0.5 to 3	

* Data presented as mean ± standard deviation except where noted.

† Approximate range.

Continued

Effect of Food on Absorption of TRIZIVIR:

TRIZIVIR may be administered with or without food. Administration with food in a single-dose bioavailability study resulted in lower C_{max}, similar to results observed previously for the reference formulations. The average [90% CI] decrease in abacavir, lamivudine, and zidovudine C_{max} was 32% [24% to 38%], 18% [10% to 25%], and 28% [13% to 40%], respectively, when administered with a high-fat meal, compared to administration under fasted conditions. Administration of TRIZIVIR with food did not alter the extent of abacavir, lamivudine, and zidovudine absorption (AUC), as compared to administration under fasted conditions (n = 24).

Special Populations:

Impaired Renal Function:

TRIZIVIR: Because lamivudine and zidovudine require dose adjustment in the presence of renal insufficiency, TRIZIVIR is not recommended for use in patients with creatinine clearance <50 mL/min (see PRECAUTIONS).

Impaired Hepatic Function:

TRIZIVIR: A reduction in the daily dose of zidovudine may be necessary in patients with mild to moderate impaired hepatic function or liver cirrhosis. Abacavir is contraindicated in patients with moderate to severe hepatic impairment and dose reduction is required in patients with mild hepatic impairment. Because TRIZIVIR is a fixed-dose combination that cannot be adjusted for this patient population, TRIZIVIR is contraindicated for patients with impaired hepatic function.

Pregnancy: See PRECAUTIONS: Pregnancy.

Abacavir and Lamivudine: No data are available on the pharmacokinetics of abacavir or lamivudine during pregnancy.

Zidovudine: Zidovudine pharmacokinetics have been studied in a Phase 1 study of 8 women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation. The pharmacokinetics of zidovudine were similar to that of nonpregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery. Although data are limited, methadone maintenance therapy in 5 pregnant women did not appear to alter zidovudine pharmacokinetics. In a nonpregnant adult population, a potential for interaction has been identified (see CLINICAL PHARMACOLOGY: Drug Interactions).

Nursing Mothers: See PRECAUTIONS: Nursing Mothers.

Abacavir: No data are available on the pharmacokinetics of abacavir in nursing mothers.

Lamivudine: Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

Zidovudine: After administration of a single dose of 200 mg zidovudine to 13 HIV-infected women, the mean concentration of zidovudine was similar in human milk and serum.

Pediatric Patients:

TRIZIVIR: TRIZIVIR is not intended for use in pediatric patients. TRIZIVIR should not be administered to adolescents who weigh less than 40 kg because it is a fixed-dose tablet that cannot be dose adjusted for this patient population (see PRECAUTIONS: Pediatric Use).

Geriatric Patients: The pharmacokinetics of abacavir, lamivudine, and zidovudine have not been studied in patients over 65 years of age.

Gender:

Abacavir: A population pharmacokinetic analysis in HIV-infected male (n = 304) and female (n = 67) patients showed no gender differences in abacavir AUC normalized for lean body weight.

Lamivudine and Zidovudine: A pharmacokinetic study in healthy male (n = 12) and female (n = 12) subjects showed no gender differences in zidovudine exposure (AUC∞) or lamivudine (AUC∞) normalized for body weight.

Race:

Abacavir: There are no significant differences between blacks and Caucasians in abacavir pharmacokinetics.

Lamivudine: There are no significant racial differences in lamivudine pharmacokinetics.

Zidovudine: The pharmacokinetics of zidovudine with respect to race have not been determined.

Drug Interactions: See PRECAUTIONS: Drug Interactions. The drug interactions described are based on studies conducted with the individual nucleoside analogues. In humans, abacavir, lamivudine, and zidovudine are not significantly metabolized by cytochrome P450 enzymes; therefore, it is unlikely that clinically significant drug interactions will occur with drugs metabolized through these pathways.

Abacavir: Due to the common metabolic pathways of abacavir and zidovudine via glucuronyl transferase, 15 HIV-infected patients were enrolled in a crossover study evaluating single doses of abacavir (600 mg), lamivudine (150 mg), and zidovudine (300 mg) alone or in combination. Analysis showed no clinically relevant changes in the pharmacokinetics of abacavir with the addition of lamivudine or zidovudine or the combination of lamivudine and zidovudine. Lamivudine exposure (AUC decreased 15%) and zidovudine exposure (AUC increased 10%) did not show clinically relevant changes with concurrent abacavir.

In a study of 11 HIV-infected patients receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of ZIAGEN twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI 6% to 42%). This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients.

Lamivudine and Zidovudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q 12 hr).

Table 2. Effect of Coadministered Drugs on Abacavir, Lamivudine, and Zidovudine AUC*

Note: ROUTINE DOSE MODIFICATION OF ABACAVIR, LAMIVUDINE, AND ZIDOVUDINE IS NOT WARRANTED WITH COADMINISTRATION OF THE FOLLOWING DRUGS.

Drugs That May Alter Lamivudine Blood Concentrations					
Coadministered Drug and Dose	Lamivudine Dose	n	Lamivudine Concentrations AUC	Lamivudine Concentrations Variability	Concentration of Coadministered Drug
Nelfinavir 750 mg q 8 hr x 7 to 10 days	single 150 mg	11	↑10%	95% CI: 1% to 20%	↔
Trimethoprim 160 mg/ Sulfamethoxazole 800 mg daily x 5 days	single 300 mg	14	↑43%	90% CI: 32% to 55%	↔
Drugs That May Alter Zidovudine Blood Concentrations					
Coadministered Drug and Dose	Zidovudine Dose	n	Zidovudine Concentrations AUC	Zidovudine Concentrations Variability	Concentration of Coadministered Drug
Atovaquone 750 mg q 12 hr with food	200 mg q 8 hr	14	↑31%	Range 23% to 78%†	↔
Fluconazole 400 mg daily	200 mg q 8 hr	12	↑74%	95% CI: 54% to 98%	Not Reported
Methadone 30 to 90 mg daily	200 mg q 4 hr	9	↑43%	Range 16% to 64%†	↔
Nelfinavir 750 mg q 8 hr x 7 to 10 days	single 200 mg	11	↓35%	Range 28% to 41%	↔
Probenecid 500 mg q 6 hr x 2 days	2 mg/kg q 8 hr x 3 days	3	↑106%	Range 100% to 170%†	Not Assessed
Ritonavir 300 mg q 6 hr x 4 days	200 mg q 8 hr x 4 days	9	↓25%	95% CI: 15% to 34%	↔
Valproic acid 250 mg or 500 mg q 8 hr x 4 days	100 mg q 8 hr x 4 days	6	↑80%	Range 64% to 130%†	Not Assessed

Table 2. Effect of Coadministered Drugs on Abacavir, Lamivudine, and Zidovudine AUC*

Note: ROUTINE DOSE MODIFICATION OF ABACAVIR, LAMIVUDINE, AND ZIDOVUDINE IS NOT WARRANTED WITH COADMINISTRATION OF THE FOLLOWING DRUGS. (cont'd)

Drugs That May Alter Abacavir Blood Concentrations					
Coadministered Drug and Dose	Abacavir Dose	n	Abacavir Concentrations AUC	Abacavir Concentrations Variability	Concentration of Coadministered Drug
Ethanol 0.7 g/kg	single 600 mg	24	↑41%	90% CI: 35% to 48%	↔

↑= Increase; ↓= Decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; CI = confidence interval.

* See PRECAUTIONS: Drug Interactions for additional information on drug interactions.

† Estimated range of percent difference.

Ribavirin: In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV/HCV co-infected patients (see WARNINGS).

INDICATIONS AND USAGE

TRIZIVIR is indicated in combination with other antiretrovirals or alone for the treatment of HIV-1 infection.

Additional important information on the use of TRIZIVIR for treatment of HIV-1 infection:

- TRIZIVIR is one of multiple products containing abacavir. Before starting TRIZIVIR, review medical history for prior exposure to any abacavir-containing product in order to avoid reintroduction in a patient with a history of hypersensitivity to abacavir.
- Limited data exist on the use of TRIZIVIR alone in patients with higher baseline viral load levels (>100,000 copies/mL, see Description of Clinical Studies).

Description of Clinical Studies:

TRIZIVIR: The following study was conducted with the individual components of TRIZIVIR (see CLINICAL PHARMACOLOGY for information about bioequivalence of TRIZIVIR).

CNA3005 was a multicenter, double-blind, controlled study in which 562 HIV-infected, therapy-naive adults were randomized to receive either ZIAGEN (300 mg twice daily) plus COMBIVIR® (lamivudine 150 mg/zidovudine 300 mg twice daily), or indinavir (800 mg 3 times a day) plus COMBIVIR twice daily. The study was stratified at randomization by pre-entry plasma HIV-1 RNA 10,000 to 100,000 copies/mL and plasma HIV-1 RNA >100,000 copies/mL. Study participants were male (87%), Caucasian (73%), black (15%), and Hispanic (9%). At baseline the median age was 36 years, the median pretreatment CD4+ cell count was 360 cells/mm^3, and median plasma HIV-1 RNA was 4.8 $\log_{10}$ copies/mL. Proportions of patients with plasma HIV-1 RNA <400 copies/mL (using Roche AMPLICOR HIV-1 MONITOR® Test) through 48 weeks of treatment are summarized in Table 3.

Table 3. Outcomes of Randomized Treatment Through Week 48 (CNA3005)

Outcome	ZIAGEN plus Lamivudine/Zidovudine (n = 262)	Indinavir plus Lamivudine/Zidovudine (n = 265)
Responder*	49%	50%
Virologic failure†	31%	28%
Discontinued due to adverse reactions	10%	12%
Discontinued due to other reasons‡	11%	10%

* Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL.

† Includes viral rebound and failure to achieve confirmed <400 copies/mL by Week 48.

‡ Includes consent withdrawn, lost to follow up, protocol violations, those with missing data, clinical progression, and other.

Treatment response by plasma HIV-1 RNA strata is shown in Table 4.

Table 4. Proportions of Responders Through Week 48 By Screening Plasma HIV-1 RNA Levels (CNA3005)

Screening HIV-1 RNA (copies/mL)	ZIAGEN plus Lamivudine/Zidovudine (n = 262) <400 copies/mL	n	Indinavir plus Lamivudine/Zidovudine (n = 265) <400 copies/mL	n
≥10,000 - ≤100,000	50%	166	48%	165
>100,000	48%	96	52%	100

In subjects with baseline viral load >100,000 copies/mL, percentages of patients with HIV-1 RNA levels <50 copies/mL were 31% in the group receiving abacavir vs. 45% in the group receiving indinavir.

Through Week 48, an overall mean increase in CD4+ cell count of about 150 cells/mm^3 was observed in both treatment arms. Through Week 48, 9 subjects (3.4%) in the group receiving abacavir sulfate (6 CDC classification C events and 3 deaths) and 3 subjects (1.5%) in the group receiving indinavir (2 CDC classification C events and 1 death) experienced clinical disease progression.

CONTRAINDICATIONS

TRIZIVIR Tablets are contraindicated in patients with previously demonstrated hypersensitivity to abacavir or to any other component of the product (see WARNINGS).

Following a hypersensitivity reaction to abacavir, NEVER restart TRIZIVIR or any other abacavir-containing product. Fatal rechallenge reactions have been associated with readministration of abacavir to patients with a prior history of a hypersensitivity reaction to abacavir (see WARNINGS and PRECAUTIONS).

TRIZIVIR Tablets are contraindicated in patients with hepatic impairment (see CLINICAL PHARMACOLOGY).

WARNINGS

Hypersensitivity Reaction: Serious and sometimes fatal hypersensitivity reactions have been associated with TRIZIVIR and other abacavir-containing products. To minimize the risk of a life-threatening hypersensitivity reaction, permanently discontinue TRIZIVIR if hypersensitivity cannot be ruled out, even when other diagnoses are possible. Important information on signs and symptoms of hypersensitivity, as well as clinical management, is presented below.

Signs and Symptoms of Hypersensitivity: Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups.

Group 1: Fever

Group 2: Rash

Group 3: Gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain)

Group 4: Constitutional (including generalized malaise, fatigue, or achiness)

Group 5: Respiratory (including dyspnea, cough, or pharyngitis)

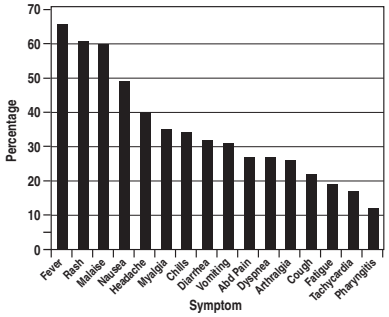
Hypersensitivity to abacavir following the presentation of a single sign or symptom has been reported infrequently.

Hypersensitivity to abacavir was reported in approximately 8% of 2,670 patients (n = 206) in 9 clinical trials (range: 2% to 9%) with enrollment from November 1999 to February 2002. Data on time to onset and symptoms of suspected hypersensitivity were collected on a detailed data collection module. The frequencies of symptoms are shown in Figure 1. Symptoms usually appeared within the first 6 weeks of treatment with abacavir, although the reaction may occur at any time during therapy. Median time to onset was 9 days; 89% appeared within the first 6 weeks; 95% of patients reported symptoms from 2 or more of the 5 groups listed above.

A recent study with ZIAGEN used double-blind ascertainment of suspected hypersensitivity reactions. During the blinded portion of the study, suspected hypersensitivity to abacavir was reported by investigators in 9% of 324 patients in the abacavir group and 3% of 325 patients in the zidovudine group.

Continued

Figure 1: Hypersensitivity-Related Symptoms Reported with ≥10% Frequency in Clinical Trials (n = 206 Patients)



Other less common signs and symptoms of hypersensitivity include lethargy, myolysis, edema, abnormal chest x-ray findings (predominantly infiltrates, which can be localized), and paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure, and death have occurred in association with hypersensitivity reactions.

Physical findings associated with hypersensitivity to abacavir in some patients include lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and rash. The rash usually appears maculopapular or urticarial, but may be variable in appearance. There have been reports of erythema multiforme. Hypersensitivity reactions have occurred without rash.

Laboratory abnormalities associated with hypersensitivity to abacavir in some patients include elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, and lymphopenia.

Clinical Management of Hypersensitivity: **Discontinue TRIZIVIR as soon as a hypersensitivity reaction is suspected. To minimize the risk of a life-threatening hypersensitivity reaction, permanently discontinue TRIZIVIR if hypersensitivity cannot be ruled out, even when other diagnoses are possible (e.g., acute onset respiratory diseases such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions to other medications).**

Following a hypersensitivity reaction to abacavir, NEVER restart TRIZIVIR or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.

When therapy with TRIZIVIR has been discontinued for reasons other than symptoms of a hypersensitivity reaction, and if reinitiation of abacavir is under consideration, carefully evaluate the reason for discontinuation to ensure that the patient did not have symptoms of a hypersensitivity reaction. If hypersensitivity cannot be ruled out, DO NOT reintroduce abacavir. If symptoms consistent with hypersensitivity are not identified, reintroduction can be undertaken with continued monitoring for symptoms of a hypersensitivity reaction. Make patients aware that a hypersensitivity reaction can occur with reintroduction of abacavir and that abacavir reintroduction needs to be undertaken only if medical care can be readily accessed by the patient or others.

Abacavir Hypersensitivity Reaction Registry: To facilitate reporting of hypersensitivity reactions and collection of information on each case, an Abacavir Hypersensitivity Registry has been established. Physicians should register patients by calling 1-800-270-0425.

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 abacavir, lamivudine, zidovudine, 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 TRIZIVIR 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 TRIZIVIR 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).

Bone Marrow Suppression: Since TRIZIVIR contains zidovudine, TRIZIVIR should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count <1,000 cells/mm^3 or hemoglobin <9.5 g/dL. Frequent blood counts are strongly recommended in patients with advanced HIV disease who are treated with TRIZIVIR. For HIV-infected individuals and patients with asymptomatic or early HIV disease, periodic blood counts are recommended.

Myopathy: Myopathy and myositis, with pathological changes similar to that produced by HIV disease, have been associated with prolonged use of zidovudine, and therefore may occur with therapy with TRIZIVIR.

Posttreatment Exacerbations of Hepatitis: In clinical trials in non-HIV-infected patients treated with lamivudine for chronic HBV, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence of HBV DNA. Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from post-marketing experience after changes from lamivudine-containing HIV treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. There is insufficient evidence to determine whether reinitiation of lamivudine alters the course of posttreatment exacerbations of hepatitis.

Use With Interferon- and Ribavirin-Based Regimens: In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine and zidovudine, components of TRIZIVIR. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine or zidovudine in HIV/HCV co-infected patients (see CLINICAL PHARMACOLOGY: Drug Interactions), **hepatic decompensation (some fatal) has occurred in HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon alfa with or without ribavirin.** Patients receiving interferon alfa with or without ribavirin and TRIZIVIR should be closely monitored for treatment-associated toxicities, especially hepatic decompensation, neutropenia, and anemia. Discontinuation of TRIZIVIR should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Childs Pugh >6) (see the complete prescribing information for interferon and ribavirin).

Other: TRIZIVIR contains fixed doses of 3 nucleoside analogues: abacavir, lamivudine, and zidovudine and should not be administered concomitantly with abacavir, lamivudine, emtricitabine, or zidovudine. TRIZIVIR should also not be administered concomitantly with the fixed-dose combination drugs: lamivudine/zidovudine (COMBIVIR), abacavir and lamivudine (EPZICOM™), or emtricitabine and tenofovir (TRUVADA®).

Because TRIZIVIR is a fixed-dose tablet, it should not be prescribed for adolescents who weigh less than 40 kg or other patients requiring dosage adjustment.

The complete prescribing information for all agents being considered for use with TRIZIVIR should be consulted before combination therapy with TRIZIVIR is initiated.

PRECAUTIONS

Therapy-Experienced Patients:

Abacavir: In clinical trials, patients with prolonged prior NRTI exposure or who had HIV-1 isolates that contained multiple mutations conferring resistance to NRTIs had limited response to abacavir. The potential for cross-resistance between abacavir and other NRTIs should be considered when choosing new therapeutic regimens in therapy-experienced patients (see MICROBIOLOGY: Cross-Resistance).

Patients With HIV and Hepatitis B Virus Co-infection:

Lamivudine: Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients dually infected with HIV and HBV. In non-HIV-infected patients treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected and has been associated with diminished treatment response (see EPIVIR-HBV® package insert for additional information). Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

Patients With Impaired Renal Function:

TRIZIVIR: Since TRIZIVIR is a fixed-dose tablet and the dosage of the individual components cannot be altered, patients with creatinine clearance <50 mL/min should not receive TRIZIVIR.

Patients With Impaired Hepatic Function:

TRIZIVIR: TRIZIVIR is contraindicated in patients with hepatic impairment since it is a fixed-dose tablet and the dosage of the individual components cannot be altered.

Immune Reconstitution Syndrome: Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including TRIZIVIR. 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.

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.

Information for Patients:

Abacavir: Hypersensitivity Reaction: Inform patients:

- **that a Medication Guide and Warning Card summarizing the symptoms of the abacavir hypersensitivity reaction and other product information will be dispensed by the pharmacist with each new prescription and refill of TRIZIVIR, and encourage the patient to read the Medication Guide and Warning Card every time to obtain any new information that may be present about TRIZIVIR. (The complete text of the Medication Guide is reprinted at the end of this document.)**
- **to carry the Warning Card with them.**
- how to identify a hypersensitivity reaction (see WARNINGS and MEDICATION GUIDE).
- that if they develop symptoms consistent with a hypersensitivity reaction to discontinue treatment with TRIZIVIR and seek medical evaluation immediately.
- that a hypersensitivity reaction can worsen and lead to hospitalization or death if TRIZIVIR is not immediately discontinued.
- **to not restart TRIZIVIR or any other abacavir-containing product following a hypersensitivity reaction because more severe symptoms can occur within hours and may include life-threatening hypotension and death.**
- that a hypersensitivity reaction is usually reversible if it is detected promptly and TRIZIVIR is stopped right away.
- that if they have interrupted TRIZIVIR for reasons other than symptoms of hypersensitivity (for example, those who have an interruption in drug supply), a serious or fatal hypersensitivity reaction may occur with reintroduction of abacavir.
- to not restart TRIZIVIR or any other abacavir-containing product without medical consultation and that restarting abacavir needs to be undertaken only if medical care can be readily accessed by the patient or others.
- TRIZIVIR should not be coadministered with COMBIVIR, EMTRIVA™, EPIVIR, EPIVIR-HBV, EPZICOM, RETROVIR, TRUVADA, or ZIAGEN.

Lamivudine: Patients co-infected with HIV and HBV should be informed that deterioration of liver disease has occurred in some cases when treatment with lamivudine was discontinued. Patients should be advised to discuss any changes in regimen with their physician.

Zidovudine: Patients should be informed that the important toxicities associated with zidovudine are neutropenia and/or anemia. They should be told of the extreme importance of having their blood counts followed closely while on therapy, especially for patients with advanced HIV disease.

TRIZIVIR: Inform patients that some HIV medicines, including TRIZIVIR can cause a rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly).

TRIZIVIR is not a cure for HIV infection and patients may continue to experience illnesses associated with HIV infection, including opportunistic infections. Patients should remain under the care of a physician when using TRIZIVIR. Advise patients that the use of TRIZIVIR has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Inform patients 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.

TRIZIVIR Tablets are for oral ingestion only.

Patients should be advised of the importance of taking TRIZIVIR exactly as it is prescribed.

Drug Interactions:

TRIZIVIR: No clinically significant changes to pharmacokinetic parameters were observed for abacavir, lamivudine, or zidovudine when administered together.

Abacavir: Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol decreases the elimination of abacavir causing an increase in overall exposure (see CLINICAL PHARMACOLOGY: Drug Interactions).

The addition of methadone has no clinically significant effect on the pharmacokinetic properties of abacavir. In a study of 11 HIV-infected patients receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of ZIAGEN twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI 6% to 42%). This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients.

Lamivudine: Trimethoprim (TMP) 160 mg/sulfamethoxazole (SMX) 800 mg once daily has been shown to increase lamivudine exposure (AUC). The effect of higher doses of TMP/SMX on lamivudine pharmacokinetics has not been investigated (see CLINICAL PHARMACOLOGY).

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of TRIZIVIR in combination with zalcitabine is not recommended.

Zidovudine: Coadministration of ganciclovir, interferon-alfa, and other bone marrow suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine. Concomitant use of zidovudine with stavudine should be avoided since an antagonistic relationship has been demonstrated in vitro. In addition, concomitant use of zidovudine with doxorubicin or ribavirin should be avoided because an antagonistic relationship has also been demonstrated in vitro.

See CLINICAL PHARMACOLOGY for additional drug interactions.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

Carcinogenicity:

Abacavir: Abacavir was administered orally at 3 dosage levels to separate groups of mice and rats in 2-year carcinogenicity studies. Results showed an increase in the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver of female rats. In addition, non-malignant tumors also occurred in the liver and thyroid gland of female rats.

Lamivudine: Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at the recommended therapeutic dose for HIV infection.

Zidovudine: Zidovudine was administered orally at 3 dosage levels to separate groups of mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60, and 120 mg/kg/day in mice and 80, 220, and 600 mg/kg/day in rats. The doses in mice were reduced to 20, 30, and 40 mg/kg/day after day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg/kg per day on day 91 and then to 300 mg/kg/day on day 279.

In mice, 7 late-appearing (after 19 months) vaginal neoplasms (5 nonmetastasizing squamous cell carcinomas, 1 squamous cell papilloma, and 1 squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of a middle-dose animal. No vaginal tumors were found at the lowest dose.

In rats, 2 late-appearing (after 20 months), nonmetastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle dose in rats. No other drug-related tumors were observed in either sex of either species.

At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 3 times (mouse) and 24 times (rat) the estimated human exposure at the recommended therapeutic dose of 100 mg every 4 hours.

Two transplacental carcinogenicity studies were conducted in mice. One study administered zidovudine at doses of 20 mg/kg/day or 40 mg/kg/day from gestation day 10 through parturition and lactation with dosing continuing in offspring for 24 months postnatally. At these doses, exposures were approximately 3 times the estimated human exposure at the recommended doses. After 24 months at the 40-mg/kg/day dose, an increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in either gender. These findings are consistent with results of the standard oral carcinogenicity study in mice, as described earlier. A second study administered zidovudine at maximum tolerated doses of 12.5 mg/day or 25 mg/day (~1,000 mg/kg nonpregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from days 12 through 18 of gestation. There was an increase in the number of tumors in the lung, liver, and female reproductive tracts in the offspring of mice receiving the higher dose level of zidovudine.

It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Mutagenicity:

Abacavir: Abacavir induced chromosomal aberrations both in the presence and absence of metabolic activation in an in vitro cytogenetic study in human lymphocytes. Abacavir was mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence of metabolic activation in an L5178Y/TK$^{+/-}$ mouse lymphoma assay. Abacavir was clastogenic in males and not clastogenic in females in an in vivo mouse bone marrow micronucleus assay. Abacavir was not mutagenic in bacterial mutagenicity assays in the presence and absence of metabolic activation.

Continued

Lamivudine: Lamivudine was mutagenic in an L5178Y/TK$^{+/-}$ mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was negative in a microbial mutagenicity assay, in an in vitro cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver.

Zidovudine: Zidovudine was mutagenic in an L5178Y/TK$^{+/-}$ mouse lymphoma assay, positive in an in vitro cell transformation assay, clastogenic in a cytogenetic assay using cultured human lymphocytes, and positive in mouse and rat micronucleus tests after repeated doses. It was negative in a cytogenetic study in rats given a single dose.

Impairment of Fertility:

Abacavir: Abacavir had no adverse effects on the mating performance or fertility of male and female rats at a dose approximately 8 times the human exposure at the recommended dose based on body surface area comparisons.

Lamivudine: In a study of reproductive performance, lamivudine, administered to male and female rats at doses up to 130 times the usual adult dose based on body surface area considerations, revealed no evidence of impaired fertility judged by conception rates and no effect on the survival, growth, and development to weaning of the offspring.

Zidovudine: Zidovudine, administered to male and female rats at doses up to 7 times the usual adult dose based on body surface area considerations, had no effect on fertility judged by conception rates.

Pregnancy: Pregnancy Category C. There are no adequate and well-controlled studies of TRIZIVIR in pregnant women. Reproduction studies with abacavir, lamivudine, and zidovudine have been performed in animals (see Abacavir, Lamivudine, and Zidovudine sections below). TRIZIVIR should be used during pregnancy only if the potential benefits outweigh the risks.

Abacavir: Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. Fetal malformations (increased incidences of fetal anasarca and skeletal malformations) and developmental toxicity (depressed fetal body weight and reduced crown-rump length) were observed in rats at a dose which produced 35 times the human exposure, based on AUC. Embryonic and fetal toxicities (increased resorptions, decreased fetal body weights) and toxicities to the offspring (increased incidence of stillbirth and lower body weights) occurred at half of the above-mentioned dose in separate fertility studies conducted in rats. In the rabbit, no developmental toxicity and no increases in fetal malformations occurred at doses that produced 8.5 times the human exposure at the recommended dose based on AUC.

Lamivudine: Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta. Reproduction studies with orally administered lamivudine have been performed in rats and rabbits at doses up to 4,000 mg/kg/day and 1,000 mg/kg/day, respectively, producing plasma levels up to approximately 35 times that for the adult HIV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryolethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 35 times those in humans.

Zidovudine: Reproduction studies with orally administered zidovudine in the rat and in the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal toxicity as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one half of the daily dose) in rats 66 to 226 times, and in rabbits 12 to 87 times, mean steady-state peak human plasma concentrations (after one sixth of the daily dose) achieved with the recommended daily dose (100 mg every 4 hours). In an additional teratology study in rats, a dose of 3,000 mg/kg/day (very near the oral median lethal dose in rats of approximately 3,700 mg/kg) caused marked maternal toxicity and an increase in the incidence of fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations. No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg/day or less. Two rodent carcinogenicity studies were conducted (see Carcinogenesis, Mutagenesis, and Impairment of Fertility).

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

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV infection.

Abacavir, Lamivudine, and Zidovudine: Lamivudine and zidovudine are excreted in human breast milk; abacavir and lamivudine are secreted into the milk of lactating rats.

Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving TRIZIVIR.**

Pediatric Use: TRIZIVIR is not intended for use in pediatric patients. TRIZIVIR should not be administered to adolescents who weigh less than 40 kg because it is a fixed-dose tablet that cannot be adjusted for this patient population.

Therapy-Experienced Pediatric Patients: A randomized, double-blind study, CNA3006, compared ZIAGEN plus lamivudine and zidovudine versus lamivudine and zidovudine in pediatric patients, most of whom were extensively pretreated with nucleoside analogue antiretroviral agents. Patients in this study had a limited response to abacavir.

Geriatric Use: Clinical studies of abacavir, lamivudine, and zidovudine did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. TRIZIVIR is not recommended for patients with impaired renal function (i.e., creatinine clearance <50 mL/min; see PRECAUTIONS: Patients with Impaired Renal Function and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Hypersensitivity Reaction: Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate, a component of TRIZIVIR (see WARNINGS and PRECAUTIONS: Information for Patients).

Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a ≥5% frequency during therapy with abacavir 300 mg twice daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily compared with indinavir 800 mg 3 times daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily from CNA3005 are listed in Table 5.

Table 5. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Naive Adults (CNA3005) Through 48 Weeks of Treatment

Adverse Reaction	ZIAGEN plus Lamivudine/Zidovudine (n = 262)	Indinavir plus Lamivudine/Zidovudine (n = 264)
Nausea	19%	17%
Headache	13%	9%
Malaise and fatigue	12%	12%
Nausea and vomiting	10%	10%
Hypersensitivity reaction	8%	2%
Diarrhea	7%	5%
Fever and/or chills	6%	3%
Depressive disorders	6%	4%
Musculoskeletal pain	5%	7%
Skin rashes	5%	4%
Ear/nose/throat infections	5%	4%
Viral respiratory infections	5%	5%
Anxiety	5%	3%
Renal signs/symptoms	<1%	5%
Pain (non-site-specific)	<1%	5%

Five patients receiving abacavir in study CNA3005 experienced worsening of pre-existing depression compared to none in the indinavir arm. The background rates of pre-existing depression were similar in the 2 treatment arms.

Laboratory Abnormalities: Laboratory abnormalities in study CNA3005 are listed in Table 6.

Table 6. Treatment-Emergent Laboratory Abnormalities (Grades 3-4) in Study CNA3005

Grade 3/4 Laboratory Abnormalities	Number of Subjects by Treatment Group	
	ZIAGEN plus Lamivudine/Zidovudine (n = 262)	Indinavir plus Lamivudine/Zidovudine (n = 264)
Elevated CPK (>4 x ULN)	18 (7%)	18 (7%)
ALT (>5.0 x ULN)	16 (6%)	16 (6%)
Neutropenia (<750/mm^3)	13 (5%)	13 (5%)
Hypertriglyceridemia (>750 mg/dL)	5 (2%)	3 (1%)
Hyperamylasemia (>2.0 x ULN)	5 (2%)	1 (<1%)
Hyperglycemia (>13.9 mmol/L)	2 (<1%)	2 (<1%)
Anemia (Hgb ≤6.9 g/dL)	0 (0%)	3 (1%)

ULN = Upper limit of normal.

n = Number of patients assessed.

Other Adverse Events: In addition to adverse reactions in Tables 5 and 6, other adverse events observed in the expanded access program for abacavir were pancreatitis and increased GGT.

Observed During Clinical Practice: The following events have been identified during post-approval use of abacavir, lamivudine, and/or zidovudine. 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 a combination of their seriousness, frequency of reporting, or potential causal connection to lamivudine and/or zidovudine.

Abacavir: Suspected Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients receiving abacavir primarily in combination with medications known to be associated with SJS and TEN, respectively. Because of the overlap of clinical signs and symptoms between hypersensitivity to abacavir and SJS and TEN, and the possibility of multiple drug sensitivities in some patients, abacavir should be discontinued and not restarted in such cases.

There have also been reports of erythema multiforme with abacavir use.

Abacavir, Lamivudine, and/or Zidovudine:

Body as a Whole: Redistribution/accumulation of body fat (see PRECAUTIONS: Fat Redistribution).

Cardiovascular: Cardiomyopathy.

Digestive: Stomatitis.

Endocrine and Metabolic: Gynecomastia, hyperglycemia.

Gastrointestinal: Anorexia and/or decreased appetite, abdominal pain, dyspepsia, oral mucosal pigmentation.

General: Vasculitis, weakness.

Hemic and Lymphatic: Aplastic anemia, anemia (including pure red cell aplasia and severe anemias progressing on therapy), lymphadenopathy, splenomegaly, thrombocytopenia.

Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis, elevated bilirubin, elevated transaminases, pancreatitis, posttreatment exacerbation of hepatitis B (see WARNINGS).

Hypersensitivity: Sensitization reactions (including anaphylaxis), urticaria.

Musculoskeletal: Arthralgia, myalgia, muscle weakness, CPK elevation, rhabdomyolysis.

Nervous: Dizziness, paresthesia, peripheral neuropathy, seizures.

Psychiatric: Insomnia and other sleep disorders.

Respiratory: Abnormal breath sounds/wheezing.

Skin: Alopecia, erythema multiforme, Stevens-Johnson syndrome.

OVERDOSAGE

Abacavir: There is no known antidote for abacavir. It is not known whether abacavir can be removed by peritoneal dialysis or hemodialysis.

Lamivudine: One case of an adult ingesting 6 grams of lamivudine was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event.

Zidovudine: Acute overdoses of zidovudine have been reported in pediatric patients and adults. These involved exposures up to 50 grams. The only consistent findings were nausea and vomiting. Other reported occurrences included headache, dizziness, drowsiness, lethargy, and confusion. Hematologic changes were transient. All patients recovered. Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine, while elimination of its primary metabolite, GZDV, is enhanced.

DOSAGE AND ADMINISTRATION

A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill. To facilitate reporting of hypersensitivity reactions and collection of information on each case, an Abacavir Hypersensitivity Registry has been established. Physicians should register patients by calling 1-800-270-0425.

The recommended oral dose of TRIZIVIR for adults and adolescents is 1 tablet twice daily. TRIZIVIR is not recommended in adolescents who weigh less than 40 kg because it is a fixed-dose tablet.

Dose Adjustment: Because it is a fixed-dose tablet, TRIZIVIR should not be prescribed for patients requiring dosage adjustment such as those with creatinine clearance <50 mL/min, patients with hepatic impairment, or patients experiencing dose-limiting adverse events.

HOW SUPPLIED

TRIZIVIR is available as tablets. Each tablet contains 300 mg of abacavir as abacavir sulfate, 150 mg of lamivudine, and 300 mg of zidovudine. The tablets are blue-green capsule-shaped, film-coated, and imprinted with GX LL1 on one side with no markings on the reverse side. They are packaged as follows:

Bottles of 60 Tablets (NDC 0173-0691-00).

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature).

ANIMAL TOXICOLOGY

Myocardial degeneration was found in mice and rats following administration of abacavir for 2 years. The systemic exposures were equivalent to 7 to 24 times the expected systemic exposure in humans. The clinical relevance of this finding has not been determined.

MEDICATION GUIDE

TRIZIVIR® (TRY-zih-veer) Tablets

Generic name: abacavir sulfate, lamivudine, and zidovudine

Read the Medication Guide that comes with Trizivir before you start taking it and each time you get a refill because there may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment. Be sure to carry your Trizivir Warning Card with you at all times.

What is the most important information I should know about Trizivir?

- **Serious Allergic Reaction to Abacavir.** Trizivir contains abacavir (also contained in Ziagen® and Epzicom™). Patients taking Trizivir may have a serious allergic reaction (hypersensitivity reaction) that can cause death. **If you get a symptom from 2 or more of the following groups while taking Trizivir, stop taking Trizivir and call your doctor right away.**

	Symptom(s)
Group 1	**Fever**
Group 2	**Rash**
Group 3	**Nausea, vomiting, diarrhea, abdominal (stomach area) pain**
Group 4	**Generally ill feeling, extreme tiredness, or achiness**
Group 5	**Shortness of breath, cough, sore throat**

A list of these symptoms is on the Warning Card your pharmacist gives you. Carry this Warning Card with you.

If you stop Trizivir because of an allergic reaction, NEVER take Trizivir (abacavir sulfate, lamivudine, and zidovudine) **or any other abacavir-containing medicine (Ziagen, Epzicom) again.** If you take Trizivir or any other abacavir-containing medicine again after you have had an allergic reaction, **WITHIN HOURS** you may get life-threatening symptoms that may include **very low blood pressure or death**.

If you stop Trizivir, for any other reason, even for a few days, and you are not allergic to abacavir, talk with your doctor before taking it again. Taking Trizivir again can cause a serious or life-threatening reaction, even if you never had an allergic reaction to it before. If your doctor tells you that you can take Trizivir again, **start taking it when you are around medical help or people who can call a doctor if you need one.**

- **Blood problems.** Retrovir®, one of the medicines in Trizivir, can cause serious blood cell problems. These include reduced numbers of white blood cells (neutropenia) and extremely reduced numbers of red blood cells (anemia). These blood cell problems are especially likely to happen in patients with advanced HIV disease or AIDS. Your doctor should be checking your blood cell counts regularly while you are taking Trizivir. This is especially important if you have advanced HIV or AIDS. This is to make sure that any blood cell problems are found quickly.
- **Lactic Acidosis.** Some HIV medicines, including Trizivir, can cause a rare but serious condition called lactic acidosis with liver enlargement (hepatomegaly). Nausea and tiredness that don't get better may be symptoms of lactic acidosis. In some cases this condition can cause death. Women, overweight people, and people who have

Continued

taken HIV medicines like Trizivir for a long time have a higher chance of getting lactic acidosis and liver enlargement. Lactic acidosis is a medical emergency and must be treated in the hospital.

- **Worsening of hepatitis B virus (HBV) infection.** Patients with HBV infection who take Trizivir and then stop it, may get "flare-ups" of their hepatitis. "Flare-up" is when the disease suddenly returns in a worse way than before. If you have HBV infection, your doctor should closely monitor your liver function for several months after stopping Trizivir. You may need to take anti-HBV medicines.
- **Muscle weakness (myopathy).** Retrovir, one of the medicines in Trizivir, can cause muscle weakness. This can be a serious problem.
- **Use with interferon- and ribavirin-based regimens.** Worsening of liver disease (sometimes resulting in death) has occurred in patients infected with both HIV and hepatitis C virus who are taking anti-HIV medicines and are also being treated for hepatitis C with interferon with or without ribavirin. If you are taking Trizivir as well as interferon with or without ribavirin and you experience side effects, be sure to tell your doctor.

Trizivir can have other serious side effects. Be sure to read the section below entitled "What are the possible side effects of Trizivir?"

What is Trizivir?

Trizivir is a prescription medicine used to treat HIV infection. Trizivir includes 3 medicines: Ziagen (abacavir), Epivir® (lamivudine or 3TC), and Retrovir® (zidovudine, AZT, or ZDV). See the end of this Medication Guide for a complete list of ingredients in Trizivir. All 3 of these medicines are called nucleoside analogue reverse transcriptase inhibitors (NRTIs). When used together, they help lower the amount of HIV in your blood. This helps to keep your immune system as healthy as possible so it can fight infection.

Different combinations of medicines are used to treat HIV infection. You and your doctor should discuss which combination of medicines is best for you.

- **Trizivir does not cure HIV infection or AIDS.** We do not know if Trizivir will help you live longer or have fewer of the medical problems that people get with HIV or AIDS. It is very important that you see your doctor regularly while you are taking Trizivir.
- **Trizivir does not lower the risk of passing HIV to other people through sexual contact, sharing needles, or being exposed to your blood.** For your health and the health of others, it is important to always practice safe sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood. Never use or share dirty needles.

Who should not take Trizivir?

Do not take Trizivir if you:

- **have ever had a serious allergic reaction (a hypersensitivity reaction) to Trizivir or any other medicine (Ziagen, Epzicom) that has abacavir as an ingredient.** See the end of this Medication Guide for a complete list of ingredients in Trizivir. If you have had such a reaction, return all of your unused Trizivir to your doctor or pharmacist.
- **have a liver that does not function properly.**
- **are an adolescent who weighs less than 90 pounds.**

Before starting Trizivir, tell your doctor about all your medical problems, including if you:

- **are pregnant or planning to become pregnant.** We do not know if Trizivir will harm your unborn child. You and your doctor will need to decide if Trizivir is right for you. If you use Trizivir while you are pregnant, talk to your doctor about how you can be on the Antiviral Pregnancy Registry for Trizivir.
- **are breastfeeding.** Some of the ingredients in Trizivir can be passed to your baby in your breast milk. It is not known if they could harm your baby. Also, mothers with HIV should not breastfeed because HIV can be passed to the baby in the breast milk.
- **have liver problems including hepatitis B virus infection.**
- **have kidney problems.**
- **have low blood cell counts (bone marrow problem).** Ask your doctor if you are not sure.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Especially tell your doctor if you take:

- **methadone.**
- **trimethoprim (TMP/sulfamethoxazole [SMX] [Bactrim®, Septra®]).**
- **ganciclovir (Cytovene®, DHPG).**
- **interferon-alfa.**
- **doxorubicin (Adriamycin®).**
- **ribavirin (Copegus®, Rebetol®, Virazole®).**
- **any bone marrow suppressive medicines or cytotoxic medicines.** Ask your doctor if you are not sure.
- **any of the following anti-HIV medicines: Combivir®** (lamivudine and zidovudine), **Emtriva™** (emtricitabine), **Epivir or Epivir-HBV®** (lamivudine, 3TC), **Epzicom** (abacavir sulfate and lamivudine), **Hivid®** (zalcitabine, ddC), **Retrovir** (zidovudine, AZT, or ZDV), **Truvada®** (emtricitabine and tenofovir), **Zerit®** (stavudine, d4T), or **Ziagen** (abacavir sulfate).

How should I take Trizivir?

Take Trizivir by mouth exactly as your doctor prescribes it. The usual dosage is 1 tablet twice a day. Do not skip doses.

- **You can take Trizivir with or without food.**
- **If you miss a dose of Trizivir, take the missed dose right away.** Then, take the next dose at the usual scheduled time.
- **Do not let your Trizivir run out.** If you stop your anti-HIV medicines, even for a short time, the amount of virus in your blood may increase and the virus may become harder to treat.
- **Starting Trizivir again can cause a serious allergic reaction or life-threatening reaction, even if you have never had an allergic reaction to it before.** If you run out of Trizivir even for a few days, you must ask your doctor if you can start Trizivir again. If your doctor tells you that you can take Trizivir again, start taking it when you are around medical help or people who can call a doctor if you need one.
- **If you take too much Trizivir, call your doctor or poison control center right away.**

What should I avoid while taking Trizivir?

Do not take **Combivir** (lamivudine and zidovudine), **Epivir** (lamivudine, 3TC), **Epzicom** (abacavir sulfate and lamivudine), **Retrovir** (zidovudine, AZT, or ZDV), or **Ziagen** (abacavir sulfate) while taking Trizivir. These medicines are already in Trizivir.

Avoid doing things that can spread HIV infection, as Trizivir does not stop you from passing the HIV infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** Some of the medicines in Trizivir can be passed to babies in breast milk and could harm the baby. Also, mothers with HIV should not breastfeed because HIV can be passed to the baby in the breast milk.

What are the possible side effects of Trizivir?

Trizivir can cause the following serious side effects. See "What is the most important information I should know about Trizivir?" at the beginning of this Medication Guide.

- **Serious allergic reaction that can cause death.**
- **Lactic acidosis with liver enlargement (hepatomegaly) that can cause death.**
- **Blood problems.**
- **Muscle weakness.**
- **Changes in immune system.** When you start taking HIV medicines, your immune system may get stronger and could begin to fight infections that have been hidden in your body, such as pneumonia, herpes virus, or tuberculosis. If you have new symptoms after starting your HIV medicines, be sure to tell your doctor.
- **Changes in body fat.** These changes have happened in patients taking antiretroviral medicines like Trizivir. The changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the back, chest, and stomach area. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known.

The most common adverse events (≥5%) of at least moderate intensity associated with the use of Trizivir include nausea, headache, weakness or tiredness, vomiting, hypersensitivity reaction, diarrhea, fever and/or chills, depression, muscle and joint pain, skin rashes, ear/nose/throat infections, cold symptoms, and nervousness.

This list of side effects is not complete. Ask your doctor or pharmacist for more information.

How should I store Trizivir?

- Store Trizivir between 59º to 86ºF (15º to 30ºC).
- **Keep Trizivir and all medicines out of the reach of children.**

General information for safe and effective use of Trizivir

Medicines are sometimes prescribed for conditions that are not mentioned in Medication Guides. Do not use Trizivir for a condition for which it was not prescribed. Do not give Trizivir to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Trizivir. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for the information that is written for healthcare professionals or call 1-888-825-5249.

What are the ingredients in Trizivir?

Active ingredients: abacavir sulfate, lamivudine, and zidovudine

Inactive ingredients: Each film-coated Trizivir Tablet contains the inactive ingredients magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablets are coated with a film (Opadry® green 03B11434) that is made of FD&C Blue No. 2, hypromellose, polyethylene glycol, titanium dioxide, and yellow iron oxide.

March 2006 MG-038

This Medication Guide has been approved by the US Food and Drug Administration.

GlaxoSmithKline
Research Triangle Park, NC 27709

Lamivudine is manufactured under agreement from
Shire Pharmaceuticals Group plc
Basingstoke, UK

October 2006 RL-2318

ZIAGEN®
(abacavir sulfate)
Tablets

ZIAGEN®
(abacavir sulfate)
Oral Solution

WARNINGS

Hypersensitivity Reactions: Serious and sometimes fatal hypersensitivity reactions have been associated with ZIAGEN (abacavir sulfate). Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups: (1) fever, (2) rash, (3) gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain), (4) constitutional (including generalized malaise, fatigue, or achiness), and (5) respiratory (including dyspnea, cough, or pharyngitis). Discontinue ZIAGEN as soon as a hypersensitivity reaction is suspected. Permanently discontinue ZIAGEN if hypersensitivity cannot be ruled out, even when other diagnoses are possible.

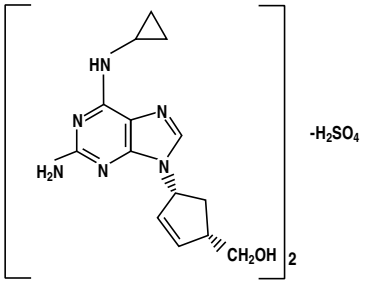
Following a hypersensitivity reaction to abacavir, NEVER restart ZIAGEN or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.

Reintroduction of ZIAGEN or any other abacavir-containing product, even in patients who have no identified history or unrecognized symptoms of hypersensitivity to abacavir therapy, can result in serious or fatal hypersensitivity reactions. Such reactions can occur within hours (see WARNINGS and PRECAUTIONS: Information for Patients).

Lactic Acidosis and Severe Hepatomegaly: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including ZIAGEN and other antiretrovirals (see WARNINGS).

DESCRIPTION

ZIAGEN is the brand name for abacavir sulfate, a synthetic carbocyclic nucleoside analogue with inhibitory activity against human immunodeficiency virus (HIV). The chemical name of abacavir sulfate is *(1S,cis)*-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1). Abacavir sulfate is the enantiomer with *1S, 4R* absolute configuration on the cyclopentene ring. It has a molecular formula of $(C_{14}H_{18}N_6O)_2 \cdot H_2SO_4$ and a molecular weight of 670.76 daltons. It has the following structural formula:



Abacavir sulfate is a white to off-white solid with a solubility of approximately 77 mg/mL in distilled water at 25°C. It has an octanol/water (pH 7.1 to 7.3) partition coefficient (log *P*) of approximately 1.20 at 25°C.

ZIAGEN Tablets are for oral administration. Each tablet contains abacavir sulfate equivalent to 300 mg of abacavir as active ingredient and the following inactive ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablets are coated with a film that is made of hypromellose, polysorbate 80, synthetic yellow iron oxide, titanium dioxide, and triacetin.

ZIAGEN Oral Solution is for oral administration. Each milliliter (1 mL) of ZIAGEN Oral Solution contains abacavir sulfate equivalent to 20 mg of abacavir (i.e., 20 mg/mL) as active ingredient and the following inactive ingredients: artificial strawberry and banana flavors, citric acid (anhydrous), methylparaben and propylparaben (added as preservatives), propylene glycol, saccharin sodium, sodium citrate (dihydrate), sorbitol solution, and water.

In vivo, abacavir sulfate dissociates to its free base, abacavir. All dosages for ZIAGEN are expressed in terms of abacavir.

MICROBIOLOGY

Mechanism of Action: Abacavir is a carbocyclic synthetic nucleoside analogue. Abacavir is converted by cellular enzymes to the active metabolite, carbovir triphosphate (CBV-TP), an analogue of deoxyguanosine-5′-triphosphate (dGTP). CBV-TP inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation into viral DNA. The lack of a 3′-OH group in the incorporated nucleotide analogue prevents the formation of the 5′ to 3′ phosphodiester linkage essential for DNA chain elongation, and therefore, the viral DNA growth is terminated. CBV-TP is a weak inhibitor of cellular DNA polymerases α, β, and γ.

Antiviral Activity: The antiviral activity of abacavir against HIV-1 was evaluated against a T-cell tropic laboratory strain HIV-1_{IIIB} in lymphoblastic cell lines, a monocyte/macrophage tropic laboratory strain HIV-1_{BaL} in primary monocytes/macrophages, and clinical isolates in peripheral blood mononuclear cells. The concentration of drug necessary to effect viral replication by 50 percent (EC_{50}) ranged from 3.7 to 5.8 μM (1 μM = 0.28 mcg/mL) and 0.07 to 1.0 μM against HIV-1_{IIIB} and HIV-1_{BaL}, respectively, and was 0.26 ± 0.18 μM against 8 clinical isolates. The EC_{50} values of abacavir against different HIV-1 clades (A-G) ranged from 0.0015 to 1.05 μM, and against HIV-2 isolates, from 0.024 to 0.49 μM. Abacavir had synergistic activity in cell culture in combination with the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, and the protease inhibitor (PI) amprenavir; and additive activity in combination with the NRTIs didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine. Ribavirin (50 μM) had no effect on the anti–HIV-1 activity of abacavir in cell culture.

Resistance: HIV-1 isolates with reduced susceptibility to abacavir have been selected in cell culture and were also obtained from patients treated with abacavir. Genotypic analysis of isolates selected in cell culture and recovered from abacavir-treated patients demonstrated that amino acid substitutions K65R, L74V, Y115F, and M184V/I in RT contributed to abacavir resistance. In a study of therapy-naive adults receiving ZIAGEN 600 mg once daily (n = 384) or 300 mg twice daily (n = 386), in a background regimen of lamivudine 300 mg once daily and efavirenz 600 mg once daily (Study CNA30021), the incidence of virologic failure at 48 weeks was similar between the 2 groups (11% in both arms). Genotypic (n = 38) and phenotypic analyses (n = 35) of virologic failure isolates from this study showed that the RT mutations that emerged during abacavir once-daily and twice-daily therapy were K65R, L74V, Y115F, and M184V/I. The mutation M184V/I was the most commonly observed mutation in virologic failure isolates from patients receiving abacavir once daily (56%, 10/18) and twice daily (40%, 8/20).

Thirty-nine percent (7/18) of the isolates from patients who experienced virologic failure in the abacavir once-daily arm had a >2.5-fold decrease in abacavir susceptibility with a median-fold decrease of 1.3 (range 0.5 to 11) compared with 29% (5/17) of the failure isolates in the twice-daily arm with a median-fold decrease of 0.92 (range 0.7 to 13).

Cross-Resistance: Cross-resistance has been observed among NRTIs. Isolates containing abacavir resistance-associated mutations, namely, K65R, L74V, Y115F, and M184V, exhibited cross-resistance to didanosine, emtricitabine, lamivudine, tenofovir, and zalcitabine in cell culture and in patients. The K65R mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine; the L74V mutation can confer resistance to abacavir, didanosine, and zalcitabine; and the M184V mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, and zalcitabine. An increasing number of thymidine analogue mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219E/R/H/Q/N) is associated with a progressive reduction in abacavir susceptibility.

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults: The pharmacokinetic properties of abacavir have been studied in asymptomatic, HIV-infected adult patients after administration of a single intravenous (IV) dose of 150 mg and after single and multiple oral doses. The pharmacokinetic properties of abacavir were independent of dose over the range of 300 to 1,200 mg/day.

Absorption and Bioavailability: Abacavir was rapidly and extensively absorbed after oral administration. The geometric mean absolute bioavailability of the tablet was 83%. After oral administration of 300 mg twice daily in 20 patients, the steady-state peak serum abacavir concentration (C_{max}) was 3.0 ± 0.89 mcg/mL (mean ± SD) and $AUC_{(0\text{-}12\ hr)}$ was 6.02 ± 1.73 mcg•hr/mL. After oral administration of a single dose of 600 mg of abacavir in 20 patients, C_{max} was 4.26 ± 1.19 mcg/mL (mean ± SD) and AUC∞ was 11.95 ± 2.51 mcg•hr/mL. Bioavailability of abacavir tablets was assessed in the fasting and fed states. There was no significant difference in systemic exposure (AUC∞) in the fed and fasting states; therefore, ZIAGEN Tablets may be administered with or without food. Systemic exposure to abacavir was comparable after administration of ZIAGEN Oral Solution and ZIAGEN Tablets. Therefore, these products may be used interchangeably.

Distribution: The apparent volume of distribution after IV administration of abacavir was 0.86 ± 0.15 L/kg, suggesting that abacavir distributes into extravascular space. In 3 subjects, the CSF $AUC_{(0\text{-}6\ hr)}$ to plasma abacavir $AUC_{(0\text{-}6\ hr)}$ ratio ranged from 27% to 33%.

Binding of abacavir to human plasma proteins is approximately 50%. Binding of abacavir to plasma proteins was independent of concentration. Total blood and plasma drug-related radioactivity concentrations are identical, demonstrating that abacavir readily distributes into erythrocytes.

Metabolism: In humans, abacavir is not significantly metabolized by cytochrome P450 enzymes. The primary routes of elimination of abacavir are metabolism by alcohol dehydrogenase (to form the 5′-carboxylic acid) and glucuronyl transferase (to form the 5′-glucuronide). The metabolites do not have antiviral activity. In vitro experiments reveal that abacavir does not inhibit human CYP3A4, CYP2D6, or CYP2C9 activity at clinically relevant concentrations.

Elimination: Elimination of abacavir was quantified in a mass balance study following administration of a 600-mg dose of ^{14}C-abacavir: 99% of the radioactivity was recovered, 1.2% was excreted in the urine as abacavir, 30% as the 5′-carboxylic acid metabolite, 36% as the 5′-glucuronide metabolite, and 15% as unidentified minor metabolites in the urine. Fecal elimination accounted for 16% of the dose.

In single-dose studies, the observed elimination half-life ($t_{1/2}$) was 1.54 ± 0.63 hours. After intravenous administration, total clearance was 0.80 ± 0.24 L/hr/kg (mean ± SD).

Special Populations: ***Adults With Impaired Renal Function:*** The pharmacokinetic properties of ZIAGEN have not been determined in patients with impaired renal function. Renal excretion of unchanged abacavir is a minor route of elimination in humans.

Adults With Impaired Hepatic Function: The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh score 5 to 6). Results showed that there was a mean increase of 89% in the abacavir AUC, and an increase of 58% in the half-life of abacavir after a single dose of 600 mg of abacavir. The AUCs of the metabolites were not modified by mild liver disease; however, the rates of formation and elimination of the metabolites were decreased. A dose of 200 mg (provided by 10 mL of ZIAGEN Oral Solution) administered twice daily is recommended for patients with mild liver disease. The safety, efficacy, and pharmacokinetics of abacavir have not been studied in patients with moderate or severe hepatic impairment, therefore ZIAGEN is contraindicated in these patients.

Pediatric Patients: The pharmacokinetics of abacavir have been studied after either single or repeat doses of ZIAGEN in 68 pediatric patients. Following multiple-dose administration of ZIAGEN 8 mg/kg twice daily, steady-state $AUC_{(0\text{-}12\ hr)}$ and C_{max} were 9.8 ± 4.56 mcg•hr/mL and 3.71 ± 1.36 mcg/mL (mean ± SD), respectively (see PRECAUTIONS: Pediatric Use).

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

Gender: A population pharmacokinetic analysis in HIV-infected male (n = 304) and female (n = 67) patients showed no gender differences in abacavir AUC normalized for lean body weight.

Race: There are no significant differences between blacks and Caucasians in abacavir pharmacokinetics.

Drug Interactions: In human liver microsomes, abacavir did not inhibit cytochrome P450 isoforms (2C9, 2D6, 3A4). Based on these data, it is unlikely that clinically significant drug interactions will occur between abacavir and drugs metabolized through these pathways.

Due to the common metabolic pathways of abacavir and zidovudine via glucuronyl transferase, 15 HIV-infected patients were enrolled in a crossover study evaluating single doses of abacavir (600 mg), lamivudine (150 mg), and zidovudine (300 mg) alone or in combination. Analysis showed no clinically relevant changes in the pharmacokinetics of abacavir with the addition of lamivudine or zidovudine or the combination of lamivudine and zidovudine. Lamivudine exposure (AUC decreased 15%) and zidovudine exposure (AUC increased 10%) did not show clinically relevant changes with concurrent abacavir.

Due to their common metabolic pathways via alcohol dehydrogenase, the pharmacokinetic interaction between abacavir and ethanol was studied in 24 HIV-infected male patients. Each patient received the following treatments on separate occasions: a single 600-mg dose of abacavir, 0.7 g/kg ethanol (equivalent to 5 alcoholic drinks), and abacavir 600 mg plus 0.7 g/kg ethanol. Coadministration of ethanol and abacavir resulted in a 41% increase in abacavir AUC∞ and a 26% increase in abacavir $t_{1/2}$. In males, abacavir had no effect on the pharmacokinetic properties of ethanol, so no clinically significant interaction is expected in men. This interaction has not been studied in females.

Methadone: In a study of 11 HIV-infected patients receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of ZIAGEN twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI 6% to 42%). This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients.

INDICATIONS AND USAGE

ZIAGEN Tablets and Oral Solution, in combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection.

Additional important information on the use of ZIAGEN for treatment of HIV-1 infection:

- ZIAGEN is one of multiple products containing abacavir. Before starting ZIAGEN, review medical history for prior exposure to any abacavir-containing product in order to avoid reintroduction in a patient with a history of hypersensitivity to abacavir.
- In one controlled study (CNA30021), more patients taking ZIAGEN 600 mg once daily had severe hypersensitivity reactions than patients taking ZIAGEN 300 mg twice daily.

See WARNINGS, ADVERSE REACTIONS, and Description of Clinical Studies.

Description of Clinical Studies: ***Therapy-Naive Adults:*** **CNA30024** was a multicenter, double-blind, controlled study in which 649 HIV-infected, therapy-naive adults were randomized and received either ZIAGEN (300 mg twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once daily) or zidovudine (300 mg twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once daily). The duration of double-blind treatment was at least 48 weeks. Study participants were: male (81%), Caucasian (51%), black (21%), and Hispanic (26%). The median age was 35 years, the median pretreatment CD4+ cell count was 264 cells/mm³, and median plasma HIV-1 RNA was 4.79 log_{10} copies/mL. The outcomes of randomized treatment are provided in Table 1.

Table 1. Outcomes of Randomized Treatment Through Week 48 (CNA30024)

Outcome	ZIAGEN plus Lamivudine plus Efavirenz (n = 324)	Zidovudine plus Lamivudine plus Efavirenz (n = 325)
Responder*	69% (73%)	69% (71%)
Virologic failures†	6%	4%
Discontinued due to adverse reactions	14%	16%
Discontinued due to other reasons‡	10%	11%

*Patients achieved and maintained confirmed HIV-1 RNA ≤50 copies/mL (<400 copies/mL) through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR® standard test 1.0 PCR).

† Includes viral rebound, insufficient viral response according to the investigator, and failure to achieve confirmed ≤50 copies/mL by Week 48.

‡ Includes consent withdrawn, lost to follow up, protocol violations, those with missing data, clinical progression, and other.

After 48 weeks of therapy, the median CD4+ cell count increases from baseline were 209 cells/mm³ in the group receiving ZIAGEN and 155 cells/mm³ in the zidovudine group. Through Week 48, 8 subjects (2%) in the group receiving ZIAGEN (5 CDC classification C events and 3 deaths) and 5 subjects (2%) on the zidovudine arm (3 CDC classification C events and 2 deaths) experienced clinical disease progression.

CNA3005 was a multicenter, double-blind, controlled study in which 562 HIV-infected, therapy-naive adults were randomized to receive either ZIAGEN (300 mg twice daily) plus COMBIVIR (lamivudine 150 mg/zidovudine 300 mg twice daily), or indinavir (800 mg 3 times a day) plus COMBIVIR twice daily. The study was stratified at randomization by pre-entry plasma HIV-1 RNA 10,000 to 100,000 copies/mL and plasma HIV-1 RNA >100,000 copies/mL. Study participants were male (87%), Caucasian (73%), black (15%), and Hispanic (9%). At baseline the median age was 36 years, the median baseline CD4+ cell count was 360 cells/mm³, and median baseline plasma HIV-1 RNA was 4.8 log_{10} copies/mL. Proportions of patients with plasma HIV-1 RNA <400 copies/mL (using Roche AMPLICOR HIV-1 MONITOR Test) through 48 weeks of treatment are summarized in Table 2.

Table 2. Outcomes of Randomized Treatment Through Week 48 (CNA3005)

Outcome	ZIAGEN plus Lamivudine/Zidovudine (n = 262)	Indinavir plus Lamivudine/Zidovudine (n = 265)
Responder*	49%	50%
Virologic failure†	31%	28%
Discontinued due to adverse reactions	10%	12%
Discontinued due to other reasons‡	11%	10%

* Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL.

† Includes viral rebound and failure to achieve confirmed <400 copies/mL by Week 48.

‡ Includes consent withdrawn, lost to follow up, protocol violations, those with missing data, clinical progression, and other.

Treatment response by plasma HIV-1 RNA strata is shown in Table 3.

Table 3. Proportions of Responders Through Week 48 By Screening Plasma HIV-1 RNA Levels (CNA3005)

Screening HIV-1 RNA (copies/mL)	ZIAGEN plus Lamivudine/Zidovudine (n = 262)		Indinavir plus Lamivudine/Zidovudine (n = 265)	
	<400 copies/mL	N	<400 copies/mL	n
≥10,000 - ≤100,000	50%	166	48%	165
>100,000	48%	96	52%	100

In subjects with baseline viral load >100,000 copies/mL, percentages of patients with HIV-1 RNA levels <50 copies/mL were 31% in the group receiving abacavir vs. 45% in the group receiving indinavir.

Through Week 48, an overall mean increase in CD4+ cell count of about 150 cells/mm^3 was observed in both treatment arms. Through Week 48, 9 subjects (3.4%) in the group receiving abacavir sulfate (6 CDC classification C events and 3 deaths) and 3 subjects (1.5%) in the group receiving indinavir (2 CDC classification C events and 1 death) experienced clinical disease progression.

CNA30021 was an international, multicenter, double-blind, controlled study in which 770 HIV-infected, therapy-naive adults were randomized and received either abacavir 600 mg once daily or abacavir 300 mg twice daily, both in combination with lamivudine 300 mg once daily and efavirenz 600 mg once daily. The double-blind treatment duration was at least 48 weeks. Study participants had a mean age of 37 years, were: male (81%), Caucasian (54%), black (27%), and American Hispanic (15%). The median baseline CD4+ cell count was 262 cells/mm^3 (range 21 to 918 cells/mm^3) and the median baseline plasma HIV-1 RNA was 4.89 $\log_{10}$ copies/mL (range: 2.60 to 6.99 $\log_{10}$ copies/mL).

The outcomes of randomized treatment are provided in Table 4.

Table 4. Outcomes of Randomized Treatment Through Week 48 (CNA30021)

Outcome	ZIAGEN 600 mg q.d. plus EPIVIR plus Efavirenz (n = 384)	ZIAGEN 300 mg b.i.d. plus EPIVIR plus Efavirenz (n = 386)
Responder*	64% (71%)	65% (72%)
Virologic failure†	11% (5%)	11% (5%)
Discontinued due to adverse reactions	13%	11%
Discontinued due to other reasons‡	11%	13%

* Patients achieved and maintained confirmed HIV-1 RNA <50 copies/mL (<400 copies/mL) through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR standard test version 1.0).

† Includes viral rebound, failure to achieve confirmed <50 copies/mL (<400 copies/mL) by Week 48, and insufficient viral load response.

‡ Includes consent withdrawn, lost to follow up, protocol violations, clinical progression, and other.

After 48 weeks of therapy, the median CD4+ cell count increases from baseline were 188 cells/mm^3 in the group receiving abacavir 600 mg once daily and 200 cells/mm^3 in the group receiving abacavir 300 mg twice daily. Through Week 48, 6 subjects (2%) in the group receiving ZIAGEN 600 mg once daily (4 CDC classification C events and 2 deaths) and 10 subjects (3%) in the group receiving ZIAGEN 300 mg twice daily (7 CDC classification C events and 3 deaths) experienced clinical disease progression. None of the deaths were attributed to study medications.

CONTRAINDICATIONS

ZIAGEN Tablets and Oral Solution are contraindicated in patients with previously demonstrated hypersensitivity to abacavir or any other component of the products (see WARNINGS). Following a hypersensitivity reaction to abacavir, NEVER restart ZIAGEN or any other abacavir-containing product. Fatal rechallenge reactions have been associated with readministration of abacavir to patients with a prior history of a hypersensitivity reaction to abacavir (see WARNINGS and PRECAUTIONS).

ZIAGEN Tablets and Oral Solution are contraindicated in patients with moderate or severe hepatic impairment.

WARNINGS

Hypersensitivity Reaction: Serious and sometimes fatal hypersensitivity reactions have been associated with ZIAGEN and other abacavir-containing products. To minimize the risk of a life-threatening hypersensitivity reaction, permanently discontinue ZIAGEN if hypersensitivity cannot be ruled out, even when other diagnoses are possible. Important information on signs and symptoms of hypersensitivity, as well as clinical management, is presented below.

Signs and Symptoms of Hypersensitivity: Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups.

Group 1: Fever

Group 2: Rash

Group 3: Gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain)

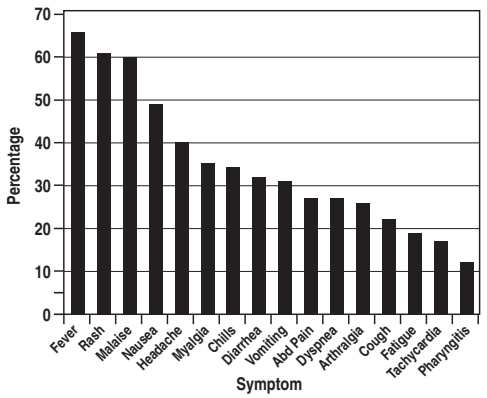
Group 4: Constitutional (including generalized malaise, fatigue, or achiness)

Group 5: Respiratory (including dyspnea, cough, or pharyngitis).

Hypersensitivity to abacavir following the presentation of a single sign or symptom has been reported infrequently.

Hypersensitivity to abacavir was reported in approximately 8% of 2,670 patients (n = 206) in 9 clinical trials (range: 2% to 9%) with enrollment from November 1999 to February 2002. Data on time to onset and symptoms of suspected hypersensitivity were collected on a detailed data collection module. The frequencies of symptoms are shown in Figure 1. Symptoms usually appeared within the first 6 weeks of treatment with abacavir, although the reaction may occur at any time during therapy. Median time to onset was 9 days; 89% appeared within the first 6 weeks; 95% of patients reported symptoms from 2 or more of the 5 groups listed above.

Figure 1: Hypersensitivity-Related Symptoms Reported with ≥10% Frequency in Clinical Trials (n = 206 Patients)



Other less common signs and symptoms of hypersensitivity include lethargy, myolysis, edema, abnormal chest x-ray findings (predominantly infiltrates, which can be localized), and paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure, and death have occurred in association with hypersensitivity reactions. In one study, 4 patients (11%) receiving ZIAGEN 600 mg once daily experienced hypotension with a hypersensitivity reaction compared with 0 patients receiving ZIAGEN 300 mg twice daily.

Physical findings associated with hypersensitivity to abacavir in some patients include lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and rash. The rash usually appears maculopapular or urticarial, but may be variable in appearance. There have been reports of erythema multiforme. Hypersensitivity reactions have occurred without rash.

Laboratory abnormalities associated with hypersensitivity to abacavir in some patients include elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, and lymphopenia.

Clinical Management of Hypersensitivity: **Discontinue ZIAGEN as soon as a hypersensitivity reaction is suspected. To minimize the risk of a life-threatening hypersensitivity reaction, permanently discontinue ZIAGEN if hypersensitivity cannot be ruled out, even when other diagnoses are possible (e.g., acute onset respiratory diseases such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions to other medications).**

Following a hypersensitivity reaction to abacavir, NEVER restart ZIAGEN or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.

When therapy with ZIAGEN has been discontinued for reasons other than symptoms of a hypersensitivity reaction, and if reinitiation of ZIAGEN or any other abacavir-containing product is under consideration, carefully evaluate the reason for discontinuation of ZIAGEN to ensure that the patient did not have symptoms of a hypersensitivity reaction. If hypersensitivity cannot be ruled out, DO NOT reintroduce ZIAGEN or any other abacavir-containing product. If symptoms consistent with hypersensitivity are not identified, reintroduction can be undertaken with continued monitoring for symptoms of a hypersensitivity reaction. Make patients aware that a hypersensitivity reaction can occur with reintroduction of ZIAGEN or any other abacavir-containing product and that reintroduction of ZIAGEN or any other abacavir-containing product needs to be undertaken only if medical care can be readily accessed by the patient or others.

Abacavir Hypersensitivity Reaction Registry: To facilitate reporting of hypersensitivity reactions and collection of information on each case, an Abacavir Hypersensitivity Registry has been established. **Physicians should register patients by calling 1-800-270-0425**.

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 abacavir 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 ZIAGEN 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 ZIAGEN 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).

PRECAUTIONS

General: Abacavir should always be used in combination with other antiretroviral agents. Abacavir should not be added as a single agent when antiretroviral regimens are changed due to loss of virologic response.

Therapy-Experienced Patients: In clinical trials, patients with prolonged prior NRTI exposure or who had HIV-1 isolates that contained multiple mutations conferring resistance to NRTIs had limited response to abacavir. The potential for cross-resistance between abacavir and other NRTIs should be considered when choosing new therapeutic regimens in therapy-experienced patients (see MICROBIOLOGY: Cross-Resistance).

Immune Reconstitution Syndrome: Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including ZIAGEN. 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.

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.

Information for Patients: ***Hypersensitivity Reaction:*** Inform patients:

- **that a Medication Guide and Warning Card summarizing the symptoms of the abacavir hypersensitivity reaction and other product information will be dispensed by the pharmacist with each new prescription and refill of ZIAGEN, and encourage the patient to read the Medication Guide and Warning Card every time to obtain any new information that may be present about ZIAGEN. (The complete text of the Medication Guide is reprinted at the end of this document.)**
- **to carry the Warning Card with them.**
- how to identify a hypersensitivity reaction (see WARNINGS and MEDICATION GUIDE).
- that if they develop symptoms consistent with a hypersensitivity reaction to discontinue treatment with ZIAGEN and seek medical evaluation immediately.
- that a hypersensitivity reaction can worsen and lead to hospitalization or death if ZIAGEN is not immediately discontinued.
- that in one study, more severe hypersensitivity reactions were seen when ZIAGEN was dosed 600 mg once daily.
- **to not restart ZIAGEN or any other abacavir-containing product following a hypersensitivity reaction because more severe symptoms can occur within hours and may include life-threatening hypotension and death.**
- that a hypersensitivity reaction is usually reversible if it is detected promptly and ZIAGEN is stopped right away.
- that if they have interrupted ZIAGEN for reasons other than symptoms of hypersensitivity (for example, those who have an interruption in drug supply), a serious or fatal hypersensitivity reaction may occur with reintroduction of abacavir.
- to not restart ZIAGEN or any other abacavir-containing product without medical consultation and that restarting abacavir needs to be undertaken only if medical care can be readily accessed by the patient or others.
- ZIAGEN should not be coadministered with EPZICOM™ or TRIZIVIR®.

General: Inform patients that some HIV medicines, including ZIAGEN, can cause a rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly).

ZIAGEN is not a cure for HIV infection and patients may continue to experience illnesses associated with HIV infection, including opportunistic infections. Patients should remain under the care of a physician when using ZIAGEN. Advise patients that the use of ZIAGEN has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Inform patients 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.

ZIAGEN Tablets and Oral Solution are for oral ingestion only.

Patients should be advised of the importance of taking ZIAGEN exactly as it is prescribed.

Drug Interactions: Pharmacokinetic properties of abacavir were not altered by the addition of either lamivudine or zidovudine or the combination of lamivudine and zidovudine. No clinically significant changes to lamivudine or zidovudine pharmacokinetics were observed following concomitant administration of abacavir.

Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol decreases the elimination of abacavir causing an increase in overall exposure (see CLINICAL PHARMACOLOGY: Drug Interactions).

The addition of methadone has no clinically significant effect on the pharmacokinetic properties of abacavir. In a study of 11 HIV-infected patients receiving methadone-maintenance therapy (40 mg and 90 mg daily) with 600 mg of ZIAGEN twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI 6% to 42%) This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Abacavir was administered orally at 3 dosage levels to separate groups of mice and rats in 2-year carcinogenicity studies. Results showed an increase in the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver of female rats. In addition, non-malignant tumors also occurred in the liver and thyroid gland of female rats. These observations were made at systemic exposures in the range of 6 to 32 times the human exposure at the recommended dose. It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Abacavir induced chromosomal aberrations both in the presence and absence of metabolic activation in an in vitro cytogenetic study in human lymphocytes. Abacavir was mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence of metabolic activation in an L5178Y mouse lymphoma assay. Abacavir was clastogenic in males and not clastogenic in females in an in vivo mouse bone marrow micronucleus assay.

Abacavir was not mutagenic in bacterial mutagenicity assays in the presence and absence of metabolic activation.

Abacavir had no adverse effects on the mating performance or fertility of male and female rats at a dose approximately 8 times the human exposure at the recommended dose based on body surface area comparisons.

Pregnancy: Pregnancy Category C. Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. Fetal malformations (increased incidences of fetal anasarca and skeletal malformations) and developmental toxicity (depressed fetal body weight and reduced crown-rump length) were observed in rats at a dose which produced 35 times the human exposure, based on AUC. Embryonic and fetal toxicities (increased resorptions, decreased fetal body weights) and toxicities to the offspring (increased incidence of stillbirth and lower body weights) occurred at half of the above-mentioned dose in separate fertility studies conducted in rats. In the rabbit, no developmental toxicity and no increases in fetal malformations occurred at doses that produced 8.5 times the human exposure at the recommended dose based on AUC.

There are no adequate and well-controlled studies in pregnant women. ZIAGEN should be used during pregnancy only if the potential benefits outweigh the risk.

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

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV infection.

Although it is not known if abacavir is excreted in human milk, abacavir is secreted into the milk of lactating rats. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving ZIAGEN.**

Pediatric Use: The safety and effectiveness of ZIAGEN have been established in pediatric patients 3 months to 13 years of age. Use of ZIAGEN in these age groups is supported by pharmacokinetic studies and evidence from adequate and well-controlled studies of ZIAGEN in adults and pediatric patients (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Special Populations: Pediatric Patients, WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION).

CNA3006 was a randomized, double-blind study comparing ZIAGEN 8 mg/kg twice daily plus lamivudine 4 mg/kg twice daily plus zidovudine 180 mg/m^2 twice daily versus lamivudine 4 mg/kg twice daily plus zidovudine 180 mg/m^2 twice daily. Two hundred and five therapy-experienced pediatric patients were enrolled: female (56%), Caucasian (17%), black (50%), Hispanic (30%), median age of 5.4 years, baseline CD4+ cell percent >15% (median = 27%), and median baseline plasma HIV-1 RNA of 4.6 $\log_{10}$ copies/mL. Eighty percent and 55% of patients had prior therapy with zidovudine and lamivudine, respectively, most

often in combination. The median duration of prior nucleoside analogue therapy was 2 years. At 16 weeks the proportion of patients responding based on plasma HIV-1 RNA ≤400 copies/mL was significantly higher in patients receiving ZIAGEN plus lamivudine plus zidovudine compared with patients receiving lamivudine plus zidovudine, 13% versus 2%, respectively. Median plasma HIV-1 RNA changes from baseline were -0.53 $\log_{10}$ copies/mL in the group receiving ZIAGEN plus lamivudine plus zidovudine compared with -0.21 $\log_{10}$ copies/mL in the group receiving lamivudine plus zidovudine. Median CD4+ cell count increases from baseline were 69 cells/mm^3 in the group receiving ZIAGEN plus lamivudine plus zidovudine and 9 cells/mm^3 in the group receiving lamivudine plus zidovudine.

Geriatric Use: Clinical studies of ZIAGEN did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Hypersensitivity Reaction: Serious and sometimes fatal hypersensitivity reactions have been associated with ZIAGEN (abacavir sulfate). In one study, once-daily dosing of ZIAGEN was associated with more severe hypersensitivity reactions (see WARNINGS and PRECAUTIONS: Information for Patients).

Therapy-Naive Adults: Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a ≥5% frequency during therapy with ZIAGEN 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg daily compared with zidovudine 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg daily from CNA30024 are listed in Table 5.

Table 5. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2–4, ≥5% Frequency) in Therapy-Naive Adults (CNA30024*) Through 48 Weeks of Treatment

Adverse Reaction	ZIAGEN plus Lamivudine plus Efavirenz (n = 324)	Zidovudine plus Lamivudine plus Efavirenz (n = 325)
Dreams/sleep disorders	10%	10%
Drug hypersensitivity	9%	<1%†
Headaches/migraine	7%	11%
Nausea	7%	11%
Fatigue/malaise	7%	10%
Diarrhea	7%	6%
Rashes	6%	12%
Abdominal pain/gastritis/ gastrointestinal signs and symptoms	6%	8%
Depressive disorders	6%	6%
Dizziness	6%	6%
Musculoskeletal pain	6%	5%
Bronchitis	4%	5%
Vomiting	2%	9%

* This study used double-blind ascertainment of suspected hypersensitivity reactions. During the blinded portion of the study, suspected hypersensitivity to abacavir was reported by investigators in 9% of 324 patients in the abacavir group and 3% of 325 patients in the zidovudine group.

† Ten (3%) cases of suspected drug hypersensitivity were reclassified as not being due to abacavir following unblinding.

Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a ≥5% frequency during therapy with ZIAGEN 300 mg twice daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily compared with indinavir 800 mg 3 times daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily from CNA3005 are listed in Table 6.

Table 6. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Naive Adults (CNA3005) Through 48 Weeks of Treatment

Adverse Reaction	ZIAGEN plus Lamivudine/Zidovudine (n = 262)	Indinavir plus Lamivudine/Zidovudine (n = 264)
Nausea	19%	17%
Headache	13%	9%
Malaise and fatigue	12%	12%
Nausea and vomiting	10%	10%
Hypersensitivity reaction	8%	2%
Diarrhea	7%	5%
Fever and/or chills	6%	3%
Depressive disorders	6%	4%
Musculoskeletal pain	5%	7%
Skin rashes	5%	4%
Ear/nose/throat infections	5%	4%
Viral respiratory infections	5%	5%
Anxiety	5%	3%
Renal sign/symptoms	<1%	5%
Pain (non-site-specific)	<1%	5%

Five patients receiving ZIAGEN in Study CNA3005 experienced worsening of pre-existing depression compared to none in the indinavir arm. The background rates of pre-existing depression were similar in the 2 treatment arms.

ZIAGEN Once Daily versus ZIAGEN Twice Daily (Study CNA30021): Treatment-emergent clinical adverse reactions (rated by the investigator as at least moderate) with a ≥5% frequency during therapy with ZIAGEN 600 mg once daily or ZIAGEN 300 mg twice daily both in combination with lamivudine 300 mg once daily and efavirenz 600 mg once daily from Study CNA30021 were similar. (For hypersensitivity reactions, patients receiving ZIAGEN once daily showed a rate of 9% in comparison to a rate of 7% for patients receiving ZIAGEN twice daily.) However, patients receiving ZIAGEN 600 mg once daily, experienced a significantly higher incidence of severe drug hypersensitivity reactions and severe diarrhea compared to patients who received ZIAGEN 300 mg twice daily. Five percent (5%) of patients receiving ZIAGEN 600 mg once daily had severe drug hypersensitivity reactions compared to 2% of patients receiving ZIAGEN 300 mg twice daily. Two percent (2%) of patients receiving ZIAGEN 600 mg once daily had severe diarrhea while none of the patients receiving ZIAGEN 300 mg twice daily had this event.

Therapy-Experienced Pediatric Patients: Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a ≥5% frequency during therapy with ZIAGEN 8 mg/kg twice daily, lamivudine 4 mg/kg twice daily, and zidovudine 180 mg/m^2 twice daily compared with lamivudine 4 mg/kg twice daily and zidovudine 180 mg/m^2 twice daily from CNA3006 are listed in Table 7.

Table 7. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Experienced Pediatric Patients (CNA3006) Through 16 Weeks of Treatment

Adverse Reaction	ZIAGEN plus Lamivudine plus Zidovudine (n = 102)	Lamivudine plus Zidovudine (n = 103)
Fever and/or chills	9%	7%
Nausea and vomiting	9%	2%
Skin rashes	7%	1%
Ear/nose/throat infections	5%	1%
Pneumonia	4%	5%
Headache	1%	5%

Laboratory Abnormalities: Laboratory abnormalities (Grades 3-4) in therapy-naive adults during therapy with ZIAGEN 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg daily compared with zidovudine 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg daily from CNA30024 are listed in Table 8.

Table 8. Laboratory Abnormalities (Grades 3-4) in Therapy-Naive Adults (CNA30024) Through 48 Weeks of Treatment

Grade 3/4 Laboratory Abnormalities	ZIAGEN plus Lamivudine plus Efavirenz (n = 324)	Zidovudine plus Lamivudine plus Efavirenz (n = 325)
Elevated CPK (>4 X ULN)	8%	8%
Elevated ALT (>5 X ULN)	6%	6%
Elevated AST (>5 X ULN)	6%	5%
Hypertriglyceridemia (>750 mg/dL)	6%	5%
Hyperamylasemia (>2 X ULN)	4%	5%
Neutropenia (ANC <750/mm^3)	2%	4%
Anemia (Hgb ≤6.9 g/dL)	<1%	2%
Thrombocytopenia (Platelets <50,000/mm^3)	1%	<1%
Leukopenia (WBC≤1,500/mm^3)	<1%	2%

ULN = Upper limit of normal.
n = Number of patients assessed.
Laboratory abnormalities in study CNA3005 are listed in Table 9.

Table 9. Treatment-Emergent Laboratory Abnormalities (Grades 3-4) in Study CNA3005

Grade 3/4 Laboratory Abnormalities	Number of Subjects by Treatment Group	
	ZIAGEN plus Lamivudine/Zidovudine (n = 262)	Indinavir plus Lamivudine/Zidovudine (n = 264)
Elevated CPK (>4 X ULN)	18 (7%)	18 (7%)
ALT (>5.0 X ULN)	16 (6%)	16 (6%)
Neutropenia (<750/mm^3)	13 (5%)	13 (5%)
Hypertriglyceridemia (>750 mg/dL)	5 (2%)	3 (1%)
Hyperamylasemia (>2.0 X ULN)	5 (2%)	1 (<1%)
Hyperglycemia (>13.9 mmol/L)	2 (<1%)	2 (<1%)
Anemia (Hgb ≤6.9 g/dL)	0 (0%)	3 (1%)

ULN = Upper limit of normal.
n = Number of patients assessed.

In a study of therapy-experienced pediatric patients (CNA3006), laboratory abnormalities (anemia, neutropenia, liver function test abnormalities, and CPK elevations) were observed with similar frequencies as in a study of therapy-naive adults (CNA30024). Mild elevations of blood glucose were more frequent in pediatric patients receiving ZIAGEN (CNA3006) as compared to adult patients (CNA30024).

The frequencies of treatment-emergent laboratory abnormalities were comparable between treatment groups in Study CNA30021.

Other Adverse Events: In addition to adverse reactions in Tables 5, 6, 7, 8, and 9, other adverse events observed in the expanded access program were pancreatitis and increased GGT.

Observed During Clinical Practice: In addition to adverse reactions reported from clinical trials, the following events have been identified during use of abacavir in clinical practice. 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 either their seriousness, frequency of reporting, potential causal connection to abacavir, or a combination of these factors.

Body as a Whole: Redistribution/accumulation of body fat (see PRECAUTIONS: Fat Redistribution).

Hepatic: Lactic acidosis and hepatic steatosis (see WARNINGS and PRECAUTIONS).

Skins: Suspected Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients receiving abacavir primarily in combination with medications known to be associated with SJS and TEN, respectively. Because of the overlap of clinical signs and symptoms between hypersensitivity to abacavir and SJS and TEN, and the possibility of multiple drug sensitivities in some patients, abacavir should be discontinued and not restarted in such cases.

There have also been reports of erythema multiforme with abacavir use.

OVERDOSAGE

There is no known antidote for ZIAGEN. It is not known whether abacavir can be removed by peritoneal dialysis or hemodialysis.

DOSAGE AND ADMINISTRATION

A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill. To facilitate reporting of hypersensitivity reactions and collection of information on each case, an Abacavir Hypersensitivity Registry has been established. **Physicians should register patients by calling 1-800-270-0425.**

ZIAGEN may be taken with or without food.

Adults: The recommended oral dose of ZIAGEN for adults is 600 mg daily, administered as either 300 mg twice daily or 600 mg once daily, in combination with other antiretroviral agents.

Adolescents and Pediatric Patients: The recommended oral dose of ZIAGEN for adolescents and pediatric patients 3 months to up to 16 years of age is 8 mg/kg twice daily (up to a maximum of 300 mg twice daily) in combination with other antiretroviral agents.

Dose Adjustment in Hepatic Impairment: The recommended dose of ZIAGEN in patients with mild hepatic impairment (Child-Pugh score 5 to 6) is 200 mg twice daily. To enable dose reduction, ZIAGEN Oral Solution (10 mL twice daily) should be used for the treatment of these patients. The safety, efficacy, and pharmacokinetic properties of abacavir have not been established in patients with moderate to severe hepatic impairment, therefore ZIAGEN is contraindicated in these patients.

HOW SUPPLIED

ZIAGEN is available as tablets and oral solution.

ZIAGEN Tablets: Each tablet contains abacavir sulfate equivalent to 300 mg abacavir. The tablets are yellow, biconvex, capsule-shaped, film-coated, and imprinted with "GX 623" on one side with no marking on the reverse side. They are packaged as follows:

Bottles of 60 tablets (NDC 0173-0661-01).

Unit dose blister packs of 60 tablets (NDC 0173-0661-00). Each pack contains 6 blister cards of 10 tablets each.

Store at controlled room temperature of 20° to 25°C (68° to 77°F) (see USP).

ZIAGEN Oral Solution: It is a clear to opalescent, yellowish, strawberry-banana-flavored liquid. Each mL of the solution contains abacavir sulfate equivalent to 20 mg of abacavir. It is packaged in plastic bottles as follows:

Bottles of 240 mL (NDC 0173-0664-00) with child-resistant closure. This product does not require reconstitution.

Store at controlled room temperature of 20° to 25°C (68° to 77°F) (see USP). DO NOT FREEZE. May be refrigerated.

ANIMAL TOXICOLOGY

Myocardial degeneration was found in mice and rats following administration of abacavir for 2 years. The systemic exposures were equivalent to 7 to 24 times the expected systemic exposure in humans. The clinical relevance of this finding has not been determined.

MEDICATION GUIDE

ZIAGEN® (ZY-uh-jen) Tablets
ZIAGEN® Oral Solution

Generic name: abacavir (uh-BACK-ah-veer) sulfate tablets and oral solution

Read the Medication Guide that comes with Ziagen before you start taking it and each time you get a refill because there may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment. Be sure to carry your Ziagen Warning Card with you at all times.

What is the most important information I should know about Ziagen?

- **Serious Allergic Reaction to Abacavir.** Ziagen contains abacavir (also contained in Epzicom™ and Trizivir®). Patients taking Ziagen may have a serious allergic reaction (hypersensitivity reaction) that can cause death. **If you get a symptom from 2 or more of the following groups while taking Ziagen, stop taking Ziagen and call your doctor right away.**

	Symptom(s)
Group 1	**Fever**
Group 2	**Rash**
Group 3	**Nausea, vomiting, diarrhea, abdominal (stomach area) pain**
Group 4	**Generally ill feeling, extreme tiredness, or achiness**
Group 5	**Shortness of breath, cough, sore throat**

A list of these symptoms is on the Warning Card your pharmacist gives you. Carry this Warning Card with you.

If you stop Ziagen because of an allergic reaction, NEVER take Ziagen (abacavir sulfate) or any other abacavir-containing medicine (Epzicom and Trizivir) again. If you take Ziagen or any other abacavir-containing medicine again after you have had an allergic reaction, **WITHIN HOURS you may get life-threatening symptoms that may include very low blood pressure** or **death**.

If you stop Ziagen for any other reason, even for a few days and you are not allergic to Ziagen, talk with your doctor before taking it again. Taking Ziagen again can cause a serious allergic or life-threatening reaction, even if you never had an allergic reaction to it before. If your doctor tells you that you can take Ziagen again, **start taking it when you are around medical help or people who can call a doctor if you need one**.

- **Lactic Acidosis. Some HIV medicines, including Ziagen, can cause a rare but serious condition called lactic acidosis with liver enlargement (hepatomegaly).** Nausea and tiredness that don't get better may be symptoms of lactic acidosis. In some cases this condition can cause death. Women, overweight people, and people who have taken HIV medicines like Ziagen for a long time have a higher chance of getting lactic acidosis and liver enlargement. Lactic acidosis is a medical emergency and must be treated in the hospital.

Ziagen can have other serious side effects. Be sure to read the section below entitled "What are the possible side effects of Ziagen?"

What is Ziagen?

Ziagen is a prescription medicine used to treat HIV infection. Ziagen is taken by mouth as a tablet or a strawberry-banana-flavored liquid. Ziagen is a medicine called a nucleoside analogue reverse transcriptase inhibitor (NRTI). Ziagen is always used with other anti-HIV medicines. When used in combination with these other medicines, Ziagen helps lower the amount of HIV found in your blood. This helps to keep your immune system as healthy as possible so that it can help fight infection.

Different combinations of medicines are used to treat HIV infection. You and your doctor should discuss which combination of medicines is best for you.

- **Ziagen does not cure HIV infection or AIDS.** We do not know if Ziagen will help you live longer or have fewer of the medical problems that people get with HIV or AIDS. It is very important that you see your doctor regularly while you are taking Ziagen.
- **Ziagen does not lower the risk of passing HIV to other people through sexual contact, sharing needles, or being exposed to your blood.** For your health and the health of others, it is important to always practice safe sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood. Never use or share dirty needles.

Ziagen has not been studied in children under 3 months of age or in adults over 65 years of age.

Who should not take Ziagen?

Do not take Ziagen if you:

- **have ever had a serious allergic reaction (a hypersensitivity reaction) to Ziagen or any other medicine that has abacavir as one of its ingredients (Epzicom and Trizivir).** See the end of this Medication Guide for a complete list of ingredients in Ziagen. If you have had such a reaction, return all of your unused Ziagen to your doctor or pharmacist.
- **have a liver that does not function properly.**

Before starting Ziagen, tell your doctor about all your medical conditions, including if you:

- **are pregnant or planning to become pregnant.** We do not know if Ziagen will harm your unborn child. You and your doctor will need to decide if Ziagen is right for you. If you use Ziagen while you are pregnant, talk to your doctor about how you can be on the Antiviral Pregnancy Registry for Ziagen.
- **are breastfeeding.** We do not know if Ziagen can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV should not breastfeed because HIV can be passed to the baby in the breast milk.
- **have liver problems.**

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Especially tell your doctor if you take:

- **methadone**
- **Epzicom (abacavir sulfate and lamivudine) and Trizivir (abacavir sulfate, lamivudine, and zidovudine).**

How should I take Ziagen?

- **Take Ziagen by mouth exactly as your doctor prescribes it.** Your doctor will tell you the right dose to take. The usual doses are 1 tablet twice a day or 2 tablets once a day. Do not skip doses.
- **You can take Ziagen with or without food.**
- **If you miss a dose of Ziagen, take the missed dose right away. Then, take the next dose at the usual time.**
- **Do not let your Ziagen run out.**
- **Starting Ziagen again can cause a serious allergic or life-threatening reaction, even if you never had an allergic reaction to it before.** If you run out of Ziagen even for a few days, you must ask your doctor if you can start Ziagen again. If your doctor tells you that you can take Ziagen again, start taking it when you are around medical help or people who can call a doctor if you need one.
- If you stop your anti-HIV drugs, even for a short time, the amount of virus in your blood may increase and the virus may become harder to treat.
- **If you take too much Ziagen, call your doctor or poison control center right away.**

What should I avoid while taking Ziagen?

- Do not take Epzicom **(abacavir sulfate and lamivudine)** or Trizivir **(abacavir sulfate, lamivudine, and zidovudine)** while taking Ziagen. Some of these medicines are already in Ziagen.

Avoid doing things that can spread HIV infection, as Ziagen does not stop you from passing the HIV infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** We do not know if Ziagen can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV should not breastfeed because HIV can be passed to the baby in the breast milk.

What are the possible side effects of Ziagen?

Ziagen can cause the following serious side effects:

- **Serious allergic reaction that can cause death.** (See "What is the most important information I should know about Ziagen?" at the beginning of this Medication Guide.)
- **Lactic acidosis with liver enlargement (hepatomegaly) that can cause death.** (See "What is the most important information I should know about Ziagen?" at the beginning of this Medication Guide.)
- **Changes in immune system.** When you start taking HIV medicines, your immune system may get stronger and could begin to fight infections that have been hidden in your body, such as pneumonia, herpes virus, or tuberculosis. If you have new symptoms after starting your HIV medicines, be sure to tell your doctor.
- **Changes in body fat.** These changes have happened in patients taking antiretroviral medicines like Ziagen. The changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the back, chest, and stomach area. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known.

The most common side effects of Ziagen include nausea, vomiting, tiredness, headache, diarrhea, trouble sleeping, fever and chills, and loss of appetite. Most of these side effects did not cause people to stop taking Ziagen.

This list of side effects is not complete. Ask your doctor or pharmacist for more information.

How should I store Ziagen?

- Store Ziagen at room temperature, between 68° to 77°F (20° to 25°C). Do not freeze Ziagen.
- Return your unused Ziagen to your doctor or pharmacist for proper disposal.
- **Keep Ziagen and all medicines out of the reach of children.**

General information for safe and effective use of Ziagen

Medicines are sometimes prescribed for conditions that are not mentioned in Medication Guides. Do not use Ziagen for a condition for which it was not prescribed. Do not give Ziagen to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Ziagen. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for the information that is written for healthcare professionals or call 1-888-825-5249.

What are the ingredients in Ziagen?

Tablets: Each tablet contains abacavir sulfate equivalent to 300 mg of abacavir as active ingredient and the following inactive ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The film-coating is made of hypromellose, polysorbate 80, synthetic yellow iron oxide, titanium dioxide, and triacetin.

Oral Solution: Each milliliter (1 mL) of Ziagen Oral Solution contains abacavir sulfate equivalent to 20 mg of abacavir (i.e., 20 mg/mL) as active ingredient and the following inactive ingredients: artificial strawberry and banana flavors, citric acid (anhydrous), methylparaben and propylparaben (added as preservatives), propylene glycol, saccharin sodium, sodium citrate (dihydrate), sorbitol solution, and water.

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This Medication Guide has been approved by the US Food and Drug Administration.

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