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.

EPIVIR® Tablets (lamivudine tablets)
EPIVIR® Oral Solution (lamivudine oral solution)

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.

EPIVIR® Tablets (lamivudine tablets)
EPIVIR® Oral Solution (lamivudine oral solution)

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)

	24-Week Surrogate Endpoint Studies*		Clinical Endpoint Study*	
Test (Threshold Level)	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%
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. It is not known whether lamivudine can be removed by peritoneal dialysis or hemodialysis. 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

Insufficient data are available to recommend a dosage of EPIVIR in patients undergoing 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 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [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 in plastic bottles of 240 mL (NDC 0173-0471-00) with child-resistant closures. This product does not require reconstitution.

Store in tightly closed bottles at 25°C (77°F) [see USP Controlled Room Temperature].

EPIVIR® Tablets (lamivudine tablets)
EPIVIR® Oral Solution (lamivudine oral solution)

GlaxoSmithKline
Research Triangle Park, NC 27709

Manufactured under agreement from
Shire Pharmaceuticals Group plc
Basingstoke, UK

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September 2003 RL-2035

PRESCRIBING INFORMATION

ZIAGEN®

(abacavir sulfate)
Tablets

ZIAGEN®

(abacavir sulfate)
Oral Solution

WARNING

FATAL HYPERSENSITIVITY REACTIONS HAVE BEEN ASSOCIATED WITH THERAPY WITH ZIAGEN. PATIENTS DEVELOPING SIGNS OR SYMPTOMS OF HYPERSENSITIVITY (WHICH INCLUDE FEVER; SKIN RASH; FATIGUE; GASTROINTESTINAL SYMPTOMS SUCH AS NAUSEA, VOMITING, DIARRHEA, OR ABDOMINAL PAIN; AND RESPIRATORY SYMPTOMS SUCH AS PHARYNGITIS, DYSPNEA, OR COUGH) SHOULD DISCONTINUE ZIAGEN AS SOON AS A HYPERSENSITIVITY REACTION IS SUSPECTED. TO AVOID A DELAY IN DIAGNOSIS AND MINIMIZE THE RISK OF A LIFE-THREATENING HYPERSENSITIVITY REACTION, ZIAGEN SHOULD BE PERMANENTLY DISCONTINUED IF HYPERSENSITIVITY CANNOT BE RULED OUT, EVEN WHEN OTHER DIAGNOSES ARE POSSIBLE (E.G., ACUTE ONSET RESPIRATORY DISEASES, GASTROENTERITIS, OR REACTIONS TO OTHER MEDICATIONS).

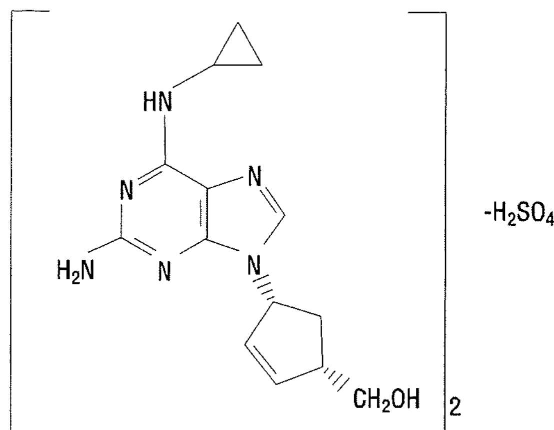
ZIAGEN SHOULD NOT BE RESTARTED FOLLOWING A HYPERSENSITIVITY REACTION BECAUSE MORE SEVERE SYMPTOMS WILL RECUR WITHIN HOURS AND MAY INCLUDE LIFE-THREATENING HYPOTENSION AND DEATH.

SEVERE OR FATAL HYPERSENSITIVITY REACTIONS CAN OCCUR WITHIN HOURS AFTER REINTRODUCTION OF ZIAGEN IN PATIENTS WHO HAVE NO IDENTIFIED HISTORY OR UNRECOGNIZED SYMPTOMS OF HYPERSENSITIVITY TO ABACAVIR THERAPY (SEE WARNINGS, PRECAUTIONS: INFORMATION FOR PATIENTS, AND ADVERSE REACTIONS).

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 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 and the inactive ingredients colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablets are coated with a film that is made of hydroxypropyl methylcellulose, polysorbate 80, synthetic yellow iron oxide, titanium dioxide, and triacetin.

ZIAGEN Oral Solution is for oral administration. One milliliter (1 mL) of ZIAGEN Oral Solution contains abacavir sulfate equivalent to 20 mg of abacavir (20 mg/mL) in an aqueous solution and the inactive ingredients artificial strawberry and banana flavors, citric acid (anhydrous), methylparaben and propylparaben (added as preservatives), propylene glycol, saccharin sodium, sodium citrate (dihydrate), and sorbitol solution.

In vivo, abacavir sulfate dissociates to its free base, abacavir. In this insert, all dosages for ZIAGEN are expressed in terms of abacavir.

MICROBIOLOGY

Mechanism of Action: Abacavir is a carbocyclic synthetic nucleoside analogue. Intracellularly, abacavir is converted by cellular enzymes to the active metabolite carbovir triphosphate. Carbovir triphosphate is an analogue of deoxyguanosine-5′-triphosphate (dGTP). Carbovir triphosphate 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 nucleoside analogue prevents the formation of the 5′ to 3′ phosphodiester linkage essential for DNA chain elongation, and therefore, the viral DNA growth is terminated.

Antiviral Activity In Vitro: The in vitro anti-HIV-1 activity of abacavir 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 inhibit viral replication by 50 percent (IC_{50}) ranged from 3.7 to 5.8 μM against HIV-1 IIIB, and was 0.26 ± 0.18 μM (1 μM = 0.28 mcg/mL) against 8 clinical isolates. The IC_{50} of abacavir against HIV-1 BaL varied from 0.07 to 1.0 μM. Abacavir had synergistic activity in combination with

amprenavir, nevirapine, and zidovudine, and additive activity in combination with didanosine, lamivudine, stavudine, and zalcitabine in vitro. These drug combinations have not been adequately studied in humans. The relationship between in vitro susceptibility of HIV to abacavir and the inhibition of HIV replication in humans has not been established.

Drug Resistance: HIV-1 isolates with reduced sensitivity to abacavir have been selected in vitro and were also obtained from patients treated with abacavir. Genetic analysis of isolates from abacavir-treated patients showed point mutations in the reverse transcriptase gene that resulted in amino acid substitutions at positions K65R, L74V, Y115F, and M184V. Phenotypic analysis of HIV-1 isolates that harbored abacavir-associated mutations from 17 patients after 12 weeks of abacavir monotherapy exhibited a 3-fold decrease in susceptibility to abacavir in vitro.

Genetic analysis of HIV-1 isolates from 21 previously antiretroviral therapy-naive patients with confirmed virologic failure (plasma HIV-1 RNA ≥400 copies/mL) after 16 to 48 weeks of abacavir/lamivudine/zidovudine therapy showed that 16/21 isolates had abacavir/lamivudine-associated mutation M184V, either alone (11/21), or in combination with Y115F (1/21) or zidovudine-associated (4/21) mutations at the last time point. Phenotypic data available on isolates from 10 patients showed that 7 of the 10 isolates had 25- to 86-fold decreases in susceptibility to lamivudine in vitro. Likewise, isolates from 2 of these 7 patients had 7- to 10-fold decreases in susceptibility to abacavir in vitro. The clinical relevance of genotypic and phenotypic changes associated with abacavir therapy has not been established, but is currently under evaluation.

Cross-Resistance: Recombinant laboratory strains of HIV-1 (HXB2) containing multiple reverse transcriptase mutations conferring abacavir resistance exhibited cross-resistance to lamivudine, didanosine, and zalcitabine in vitro. For clinical information in treatment-experienced patients, see INDICATIONS AND USAGE: Description of Clinical Studies and PRECAUTIONS.

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 $AUC_{(0-12\ hr)}$ was 6.02 ± 1.73 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 $AUC_{(0-6\ hr)}$ to plasma abacavir $AUC_{(0-6\ hr)}$ 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 $AUC_{(0-12\ hr)}$ 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: The pharmacokinetics of ZIAGEN with respect to gender have not been determined.

Race: The pharmacokinetics of ZIAGEN with respect to race have not been determined.

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 their common metabolic pathways via glucuronyl transferase with zidovudine, 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.

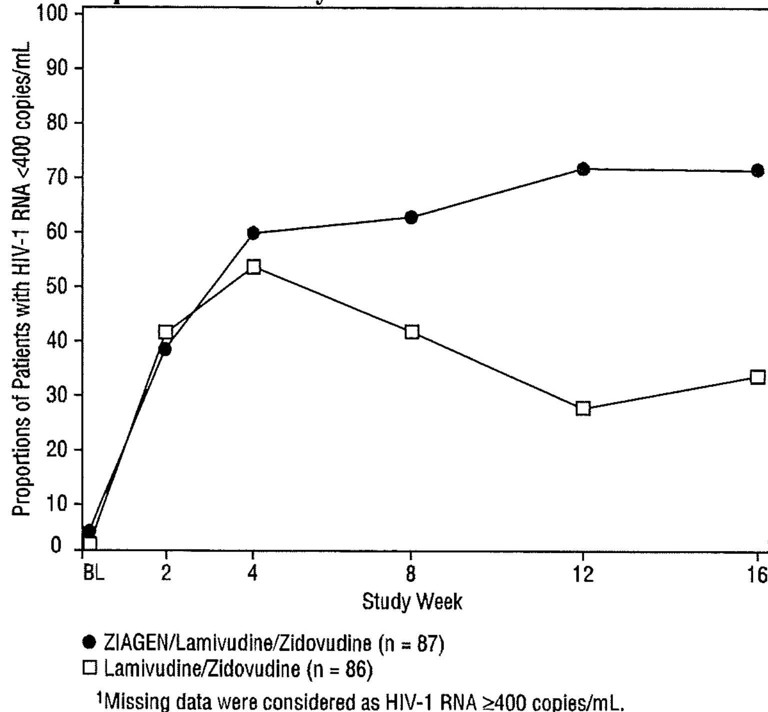
Methadone: In a study of 11 HIV-infected subjects receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of ZIAGEN twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI 6% to 42%). This alteration will not result in a methadone dose modification 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. This indication is based on 2 controlled trials of 16 and 48 weeks' duration that evaluated suppression of HIV RNA and changes in CD4 cell count. At present, there are no results from controlled trials evaluating the effect of ZIAGEN on clinical progression of HIV (see Description of Clinical Studies).

Description of Clinical Studies: ***Therapy-Naive Adults:*** CNAAB3003 is a multicenter, double-blind, placebo-controlled study in which 173 HIV-infected, therapy-naive adults were randomized to receive either ZIAGEN (300 mg twice daily), lamivudine (150 mg twice daily), and zidovudine (300 mg twice daily) or lamivudine (150 mg twice daily) and zidovudine (300 mg twice daily). The duration of double-blind treatment was 16 weeks. Study participants were: male (76%), Caucasian (54%), African-American (28%), and Hispanic (16%). The median age was 34 years, the median pretreatment CD4 cell count was 450 cells/mm^3, and median plasma HIV-1 RNA was 4.5 log_{10} copies/mL. Proportions of patients with plasma HIV-1 RNA <400 copies/mL (using Roche Amplicor HIV-1 MONITOR® Test) through 16 weeks of treatment are summarized in Figure 1.

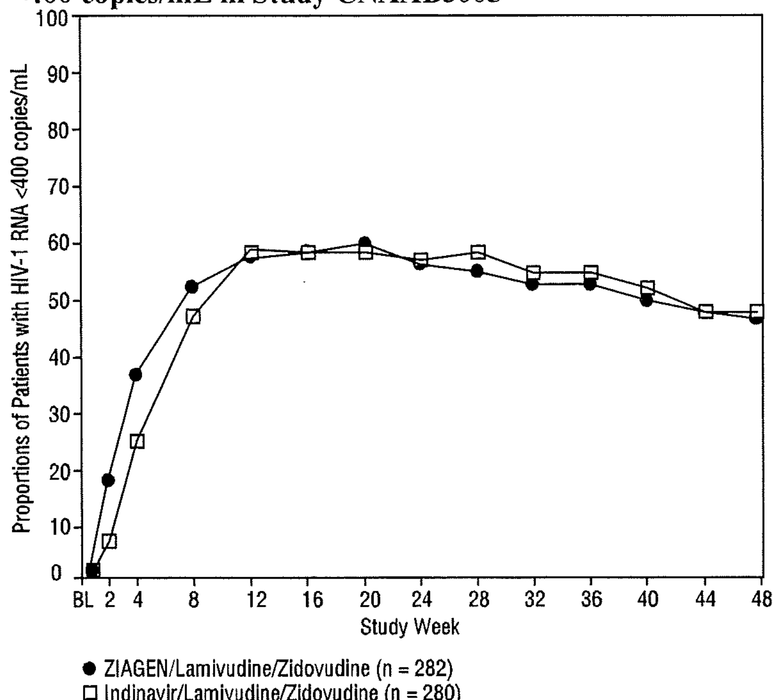
Figure 1. Proportions of Patients with HIV-1 RNA <400 copies/mL in Study CNAAB3003[1]



After 16 weeks of therapy, the median CD4 increases from baseline were 47 cells/mm^3 in the group receiving ZIAGEN and 112 cells/mm^3 in the placebo group.

CNAAB3005 was a multicenter, double-blind, controlled study in which 562 HIV-infected, therapy-naive adults with a pre-entry plasma HIV-1 RNA >10,000 copies/mL 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. Study participants were male (87%), Caucasian (73%), African-American (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 Figure 2.

Figure 2. Proportions of Patients with HIV-1 RNA <400 copies/mL in Study CNAAB3005[1]



[1]Discontinuations of randomized therapy or missing data were considered as HIV-1 RNA ≥400 copies/mL.

Through Week 48, an overall mean increase in CD4 cells of about 150 cells/mm^3 was observed in both treatment arms.

Table 1. Outcomes of Randomized Treatment Through Week 48 (CNAAB3005)

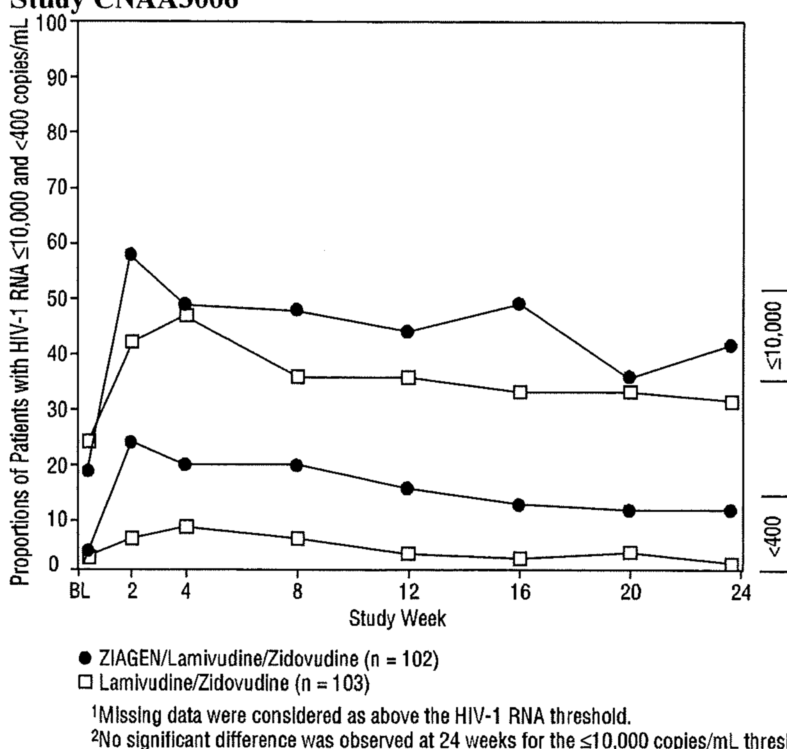
Outcome	ZIAGEN/Lamivudine/ Zidovudine (n = 282)	Indinavir/ Lamivudine/Zidovudine (n = 280)
HIV RNA <400 copies/mL	46%	47%
HIV RNA ≥400 copies/mL*	29%	28%
CDC Class C event	2%	<1%
Discontinued due to adverse reactions	9%	11%
Discontinued due to other reasons†	6%	6%
Randomized but never initiated treatment	7%	5%

*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, and other.

Therapy-Experienced Pediatric Patients: CNAA3006 is a randomized, double-blind study comparing ZIAGEN 8 mg/kg twice daily, lamivudine 4 mg/kg twice daily, and zidovudine 180 mg/m^2 twice daily versus lamivudine 4 mg/kg twice daily and zidovudine 180 mg/m^2 twice daily. Two hundred and five pediatric patients were enrolled: female (56%), Caucasian (17%),

African-American (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. Proportions of patients with plasma HIV-1 RNA levels ≤10,000 and <400 copies/mL, respectively, through 24 weeks of treatment are summarized in Figure 3.

Figure 3. Proportions of Patients with Plasma HIV-1 RNA ≤10,000 copies/mL or <400 copies/mL Through Week 24 in Study CNAA3006[1,2]



After 16 weeks of therapy, the median CD4 increases from baseline were 69 cells/mm^3 in the group receiving ZIAGEN and 9 cells/mm^3 in the control group.

CONTRAINDICATIONS

Abacavir sulfate has been associated with fatal hypersensitivity reactions. ZIAGEN SHOULD NOT BE RESTARTED FOLLOWING A HYPERSENSITIVITY REACTION TO ABACAVIR (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS).

ZIAGEN Tablets and Oral Solution are contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the products (see WARNINGS).

ZIAGEN Tablets and Oral Solution are contraindicated in patients with moderate or severe hepatic impairment.

WARNINGS

Hypersensitivity Reaction: Fatal hypersensitivity reactions have been associated with therapy with ZIAGEN. Patients developing signs or symptoms of hypersensitivity (which include fever; skin rash; fatigue; gastrointestinal symptoms such as nausea, vomiting, diarrhea, or abdominal pain; and respiratory symptoms such as pharyngitis, dyspnea, or cough) should discontinue ZIAGEN as soon as a hypersensitivity reaction is first suspected, and should seek medical evaluation immediately. To avoid a delay in diagnosis and minimize the risk of a life-threatening hypersensitivity reaction, ZIAGEN should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (e.g., acute onset respiratory diseases, gastroenteritis, or reactions to other medications).

ZIAGEN SHOULD NOT be restarted following a hypersensitivity reaction because more severe symptoms will recur within hours and may include life-threatening hypotension and death.

Severe or fatal hypersensitivity reactions can occur within hours after reintroduction of ZIAGEN in patients who have no identified history or unrecognized symptoms of hypersensitivity to abacavir therapy.

When therapy with ZIAGEN has been discontinued for reasons other than symptoms of a hypersensitivity reaction, and if reinitiation of therapy is under consideration, the reason for discontinuation should be evaluated to ensure that the patient did not have symptoms of a hypersensitivity reaction. If hypersensitivity cannot be ruled out, abacavir should **NOT** be reintroduced. If symptoms consistent with hypersensitivity are not identified, reintroduction can be undertaken with continued monitoring for symptoms of a hypersensitivity reaction. Patients should be made aware that a hypersensitivity reaction can occur with reintroduction of abacavir, and that abacavir reintroduction should be undertaken only if medical care can be readily accessed by the patient or others (see ADVERSE REACTIONS).

In clinical trials, hypersensitivity reactions have been reported in approximately 5% of adult and pediatric patients receiving abacavir. Symptoms usually appear within the first 6 weeks of treatment with ZIAGEN although these reactions may occur at any time during therapy (see PRECAUTIONS: Information for Patients and ADVERSE REACTIONS).

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 nucleoside reverse transcriptase inhibitor (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).

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: PATIENTS SHOULD BE ADVISED THAT A MEDICATION GUIDE AND WARNING CARD SUMMARIZING THE SYMPTOMS OF ABACAVIR HYPERSENSITIVITY REACTIONS SHOULD BE DISPENSED BY THE PHARMACIST WITH EACH NEW PRESCRIPTION AND REFILL OF ZIAGEN. THE COMPLETE TEXT OF THE MEDICATION GUIDE IS REPRINTED AT THE END OF THIS DOCUMENT. PATIENTS SHOULD BE INSTRUCTED TO CARRY THE WARNING CARD WITH THEM.

Patients should be advised of the possibility of a hypersensitivity reaction to ZIAGEN that may result in death. Patients developing signs or symptoms of hypersensitivity (which include fever; skin rash; fatigue; gastrointestinal symptoms such as nausea, vomiting, diarrhea, or abdominal pain; and respiratory symptoms such as sore throat, shortness of breath, or cough) should discontinue treatment with ZIAGEN and seek medical evaluation immediately. **ZIAGEN SHOULD NOT be restarted following a hypersensitivity reaction because more severe symptoms will recur within hours and may include life-threatening hypotension and death.** Patients who have interrupted ZIAGEN for reasons other than symptoms of hypersensitivity (for example, those who have an interruption in drug supply) should be made aware that a severe or fatal hypersensitivity reaction can occur with reintroduction of abacavir. Patients should be instructed not to reintroduce abacavir without medical consultation and that reintroduction of abacavir should be undertaken only if medical care can be readily accessed by the patient or others (see ADVERSE REACTIONS and WARNINGS).

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. Patients should be advised 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.

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

Patients should be advised that the long-term effects of ZIAGEN are unknown 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 subjects 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 (60 females and 60 males per group) and rats (56 females and 56 males in each group) in carcinogenicity studies. Single doses were 55, 110, and 330 mg/kg/day in mice and 30, 120, and 600 mg/kg/day in rats. 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 (300 mg twice daily). 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. At systemic exposures approximately 9 times higher than that in humans at the therapeutic dose, 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 doses of up to 500 mg/kg/day, a dose expected to produce exposures approximately 8-fold higher than that in humans at the therapeutic 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. Developmental toxicity (depressed fetal body weight and reduced crown-rump length) and increased incidences of fetal anasarca and skeletal malformations were observed when rats were treated with abacavir at doses of 1,000 mg/kg during organogenesis. This dose produced 35 times the human exposure, based on AUC. In a fertility study, evidence of toxicity to the developing embryo and fetuses (increased resorptions, decreased fetal body weights) occurred only at 500 mg/kg/day. The offspring of female rats treated with abacavir at 500 mg/kg/day (beginning at embryo implantation and ending at weaning) showed increased incidence of stillbirth and lower body weights throughout life. In the rabbit, there was no evidence of drug-related developmental toxicity and no increases in fetal malformations at doses up to 700 mg/kg (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 aged 3 months to 13 years. 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, INDICATIONS AND USAGE: Description of Clinical Studies, WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION).

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: Fatal hypersensitivity reactions have been associated with therapy with ZIAGEN. Therapy with ZIAGEN SHOULD NOT be restarted following a hypersensitivity reaction because more severe symptoms will recur within hours and may include life-threatening hypotension and death. Patients developing signs or symptoms of hypersensitivity should discontinue treatment as soon as a hypersensitivity reaction is first suspected, and should seek medical evaluation immediately. To avoid a delay in diagnosis and minimize the risk of a life-threatening hypersensitivity reaction, ZIAGEN should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (e.g., acute onset respiratory diseases, gastroenteritis, or reactions to other medications).

Severe or fatal hypersensitivity reactions can occur within hours after reintroduction of ZIAGEN in patients who have no identified history or unrecognized symptoms of hypersensitivity to abacavir therapy (see WARNINGS and PRECAUTIONS: Information for Patients).

When therapy with ZIAGEN has been discontinued for reasons other than symptoms of a hypersensitivity reaction, and if reinitiation of therapy is under consideration, the reason for discontinuation should be evaluated to ensure that the patient did not have symptoms of a hypersensitivity reaction. If hypersensitivity cannot be ruled out, abacavir should **NOT** be reintroduced. If symptoms consistent with hypersensitivity are not identified, reintroduction can be undertaken with continued monitoring for symptoms of hypersensitivity reaction. Patients should be made aware that a hypersensitivity reaction can occur with reintroduction of abacavir, and that abacavir reintroduction should be undertaken only if medical care can be readily accessed by the patient or others (see WARNINGS).