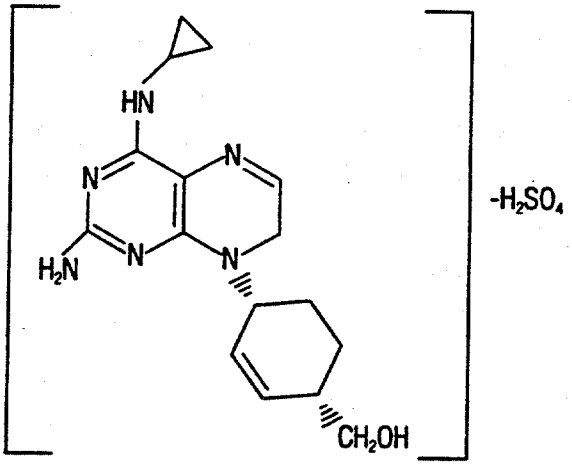
NEW ZIAGEN [abacavir sulfate] Tablets and Oral Solution

WARNING: FATAL HYPERSENSITIVITY REACTIONS HAVE BEEN ASSOCIATED WITH THERAPY WITH ZIAGEN. ZIAGEN SHOULD BE DISCONTINUED AS SOON AS A HYPERSENSITIVITY REACTION IS SUSPECTED. 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.

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).

ZIAGEN IN COMBINATION WITH OTHER ANTIRETROVIRAL AGENTS IS INDICATED FOR THE TREATMENT OF HIV-1 INFECTION. THIS INDICATION IS BASED ON ANALYSES OF SURROGATE MARKERS IN CONTROLLED STUDIES OF UP TO 24 WEEKS IN DURATION. AT PRESENT, THERE ARE NO RESULTS FROM CONTROLLED TRIALS EVALUATING LONG-TERM SUPPRESSION OF HIV-RNA OR DISEASE PROGRESSION WITH ZIAGEN.

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 (1*S,cis*)-4-[2-amino-6-(cyclopropylamino)-9H-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, a monocyte/macrophage tropic laboratory strain HIV-1 BaL and clinical isolates in lymphoblastic cell lines, primary monocytes/macrophages, and peripheral blood mononuclear cells, respectively. 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 eight 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*. Some of 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. Mutations M184V and L74V were most frequently observed in clinical isolates. Phenotypic analysis of HIV-1 isolates that harbor abacavir-associated mutations from 17 patients after 12 weeks of abacavir monotherapy exhibited a 3-fold decrease in susceptibility to abacavir *in vitro*. The clinical relevance of genotypic and phenotypic changes associated with abacavir therapy has not been established.

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.

Cross-resistance between abacavir and HIV protease inhibitors is unlikely because of the different enzyme targets involved. Cross-resistance between abacavir and non-nucleoside reverse transcriptase inhibitors is unlikely because of different binding sites on reverse transcriptase.

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 1200 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 $AUC_{(0\text{-}12\ hours)}$ was 6.02 ± 1.73 mcg•h/mL. Bioavailability of abacavir tablets was assessed in the fasting and fed states (standard meal: 967 kcal, 67 grams fat, 33 grams protein, 58 grams carbohydrate). 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 three subjects, the CSF $AUC_{(0\text{-}6\ h)}$ to plasma abacavir $AUC_{(0\text{-}6\ h)}$ 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: 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. In humans, abacavir is not significantly metabolized by cytochrome P450 enzymes.

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 per 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.

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 a day, steady-state $AUC_{0\text{-}12}$ and C_{max} were 9.8 ± 4.56 mcg•h/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, fifteen 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.

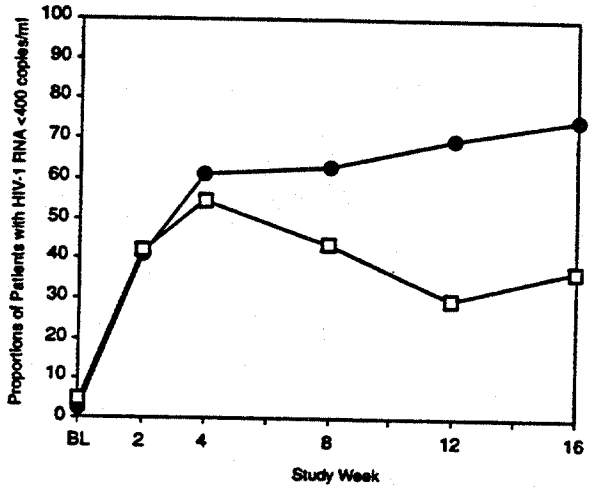
Due to their common metabolic pathways via alcohol dehydrogenase, the pharmacokinetic interaction between abacavir and ethanol was studied in 24 HIV-infected male patients. Each patient received the following treatments on separate occasions: a single 600-mg dose of abacavir, 0.7 g/kg ethanol (equivalent to five 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 $t_{1/2}$. These changes are not considered clinically significant. Abacavir had no effect on the pharmacokinetic properties of ethanol.

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 analyses of surrogate markers in controlled studies up to 24 weeks in duration. At present there are no results from controlled trials evaluating long-term suppression of HIV-RNA or disease progression with therapy with ZIAGEN (see Description of Clinical Studies).

Description of Clinical Studies: ***Therapy-Naive Adults:*** CNAAB3003 is an ongoing, 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]



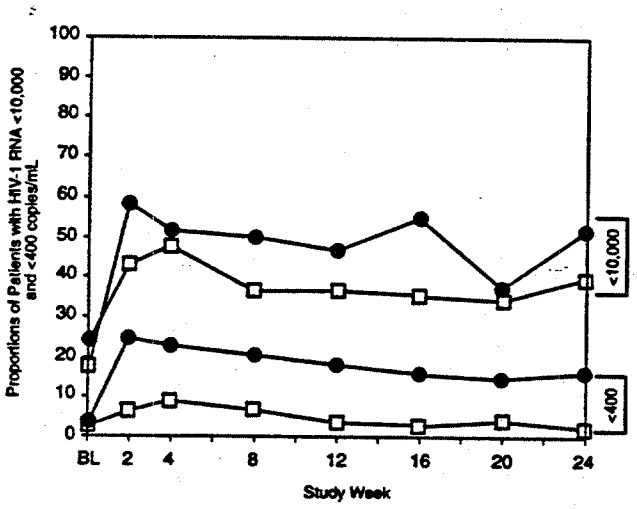
[1]Missing data were considered as HIV-RNA >400 copies/mL

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

Preliminary findings from a second controlled study in therapy-naive adults were supportive of the efficacy of abacavir.

Therapy-Experienced Pediatric Patients: CNAA3006 is an ongoing, randomized, double-blind study comparing ZIAGEN 8 mg/kg twice daily and lamivudine 4 mg/kg twice daily and zidovudine 180 mg/m² twice daily versus lamivudine 4 mg/kg twice daily and zidovudine 180 mg/m² 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 (minimum 12 weeks) with zidovudine and lamivudine, respectively, most often in combination. 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 2.

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



● ZIAGEN/Lamivudine/Zidovudine (n=102)

□ Lamivudine/Zidovudine (n=103)

[1]Missing data were considered as above the HIV-RNA threshold.

[2]No significant difference was observed at 24 weeks for the <10,000 copies/mL threshold

Through 16 weeks of therapy, the median CD4 changes from baseline were 69 cells/mm³ in the group receiving ZIAGEN and 9 cells/mm³ in the control group.

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

WARNINGS:

Hypersensitivity Reaction: Fatal hypersensitivity reactions have been associated with therapy with ZIAGEN. Patients developing signs or symptoms of hypersensitivity (which may include fever, skin rash, fatigue and gastrointestinal symptoms, such as nausea, vomiting, diarrhea, or abdominal pain) should discontinue treatment as soon as a hypersensitivity reaction is first suspected, and should 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 (see Information for Patients and ADVERSE REACTIONS).

In ongoing clinical trials, hypersensitivity reactions have been reported in 3-5% of 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).

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:

Therapy-Experienced Patients: In clinical trials, patients with uncontrolled viral replication following prolonged prior zidovudine and lamivudine exposure who had HIV-1 isolates that contained multiple mutations conferring resistance to nucleoside reverse transcriptase inhibitors showed minimal response to the addition of abacavir as a single new agent.

Information for Patients: Patients should be advised of the possibility of a hypersensitivity reaction to ZIAGEN. Patients developing signs or symptoms of hypersensitivity (which may include fever, skin rash, fatigue, and gastrointestinal symptoms, such as nausea, vomiting, diarrhea, or abdominal pain) should discontinue treatment with ZIAGEN and seek medical evaluation immediately. **ZIAGEN should not be restarted in patients who have developed a hypersensitivity reaction because more severe symptoms will recur within hours and may include life-threatening hypotension and death (see ADVERSE REACTIONS and WARNINGS).**

The Medication Guide provides written information for the patient, and should be dispensed with each new prescription and refill. The complete text of the Medication Guide is reprinted at the end of this document. A Warning Card summarizing the symptoms of the abacavir hypersensitivity reaction should be provided to the patient by the pharmacist with each prescription. Patients should be instructed to carry this card with them.

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 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); this increase in exposure is not considered clinically relevant.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: 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 nine 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 per day, a dose expected to produce exposures approximately eight-fold higher than that in humans at the therapeutic dose based on body surface area comparisons.

Pregnancy: Pregnancy Category C. In the rat, developmental toxicity (depressed fetal body weight and reduced crown-rump length) and increased incidences of fetal anasarca and skeletal malformations were observed at 1000 mg/kg when rats were treated during organogenesis. This dose produced 35 times the human exposure, based on AUC. Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. 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 per day. The offspring of female rats treated with abacavir at 500 mg/kg (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 breast-feed their infants to avoid risking postnatal transmission of HIV infection.

Although it is not known if abacavir is excreted in human milk, abacavir is present in the milk of lactating rats dosed with abacavir. Because of both the potential for HIV transmission and any possible adverse effects of abacavir, **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: In clinical studies, 3% to 5% of patients receiving ZIAGEN developed a hypersensitivity reaction. This reaction is characterized by the appearance of symptoms indicating multi-organ/body system involvement. Symptoms usually appear within the first 6 weeks of treatment with ZIAGEN although these reactions may occur at any time during therapy. Frequently observed signs and symptoms include fever, skin rash, fatigue, and gastrointestinal symptoms, such as nausea, vomiting, diarrhea, or abdominal pain. Other signs and symptoms may include malaise, lethargy, myalgia, arthralgia, edema, shortness of breath, and paresthesia. Physical findings may include lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and rash. The rash usually appears maculopapular or urticarial but may be variable in appearance. Hypersensitivity reactions may occur without rash. Laboratory abnormalities include elevated liver function tests, increased creatine phosphokinase or creatinine, and lymphopenia. Anaphylaxis, liver failure, renal failure, hypotension, and death have occurred in association with hypersensitivity reactions. Symptoms worsen with continued therapy and usually resolve upon discontinuation of 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 (see WARNINGS, PRECAUTIONS, and Information for Patients).**

Risk factors that may predict the occurrence or severity of hypersensitivity to abacavir have not been identified.

Adults: Selected clinical adverse events with a ≥5% frequency during therapy with ZIAGEN 300 mg twice daily and lamivudine 150 mg twice daily and zidovudine 300 mg twice daily compared with lamivudine 150 mg twice daily and zidovudine 300 mg twice daily from CNAAB3003 are listed in Table 1.

Table 1: Selected Clinical Adverse Events (≥5% Frequency) in Therapy-Naive Adults (CNAAB3003) Through 16 Weeks of Treatment

	ZIAGEN/Lamivudine/ Zidovudine (n=83)		Lamivudine/Zidovudine (n=81)	
Adverse Event	All Events	Grade 3/4 Events	All Events	Grade 3/4 Events
Body as a whole				
Headache	31%	2%	20%	2%
Malaise and fatigue	34%	0%	25%	0%
Digestive				
Nausea	47%	2%	41%	2%
Diarrhea	12%	0%	11%	0%
Nausea and vomiting	16%	2%	11%	1%
Loss of appetite/anorexia	11%	0%	10%	0%
Nervous system				
Insomnia and other sleep disorders	7%	0%	5%	0%
Musculoskeletal				
Musculoskeletal pain	7%	0%	5%	0%

Laboratory abnormalities observed during therapy are listed in Table 2.

Table 2: Frequencies of Laboratory Abnormalities among Therapy-Naive Adults (CNAAB3003)

Test Abnormal Level	ZIAGEN/Lamivudine/ Zidovudine (n=83)	Lamivudine/Zidovudine (n=81)
Neutropenia (ANC<750 cells/mm³)	6%	4%
Creatine phosphokinase (>4.0 x ULN)	6%	5%
Triglycerides (>2.0 x ULN)	1%	0%
Hyperglycemia* (>250 mg/dL)	0%	0%

*Nonfasted.
ULN = Upper limit of normal.
ANC = Absolute neutrophil count.
n = Number of patients assesed.

In CNAB3001, ZIAGEN 600 mg twice daily was added to the background antiviral treatment of adults with AIDS-associated dementia. Selected clinical adverse events and laboratory abnormalities are listed in Tables 3 and 4.

Table 3: Selected Clinical Adverse Events (≥5% Frequency in Adults With AIDS-Associated Dementia (CNAB3001)

	ZIAGEN/Lamivudine/Zidovudine (n=49)		Lamivudine/Zidovudine (n=50)	
Adverse Event	All Events	Grade 3/4 Events	All Events	Grade 3/4 Events
Body as a whole				
Headache	16%	4%	30%	8%
Malaise and fatigue	24%	4%	16%	6%
Fever or chills	10%	2%	4%	2%
Sweating	4%	2%	8%	4%
Digestive				
Nausea	47%	14%	32%	8%
Diarrhea	29%	2%	26%	4%
Nausea and vomiting	12%	0%	10%	4%
Loss of appetite/anorexia	12%	4%	10%	0%
Dyspeptic symptoms	6%	0%	4%	0%
Abdominal discomfort & pain	4%	0%	14%	4%
Nervous system				
Dizziness	6%	0%	8%	0%
Insomnia and other sleep disorders	12%	0%	16%	4%
Neuropathy	16%	2%	12%	2%
Anxiety	4%	0%	6%	2%
Depressive disorders	6%	0%	4%	0%
Musculoskeletal				
Musculoskeletal pain	10%	0%	6%	0%
Muscle cramps and spasms	6%	0%	6%	2%
Respiratory				
Cough	6%	0%	8%	0%
Skin				
Skin rashes	8%	2%	12%	0%
Non-site Specific				
Weight problems	6%	2%	4%	0%
Disorders of lipid metabolism	12%	10%	8%	2%

Table 4 : Frequencies of Laboratory Abnormalities Among Adult Patients with AIDS-Associated Dementia (CNAB3001)

Test Abnormal Level	ZIAGEN/Lamivudine/ Zidovudine (n=49)	Lamivudine/Zidovudine (n=50)
Neutropenia (ANC<750 cells/mm³)	10%	6%
Anemia (Hgb <6.9 g/dL)	0%	2%
Amylase (>2.0 x ULN)	4%	6%
Total bilirubin (>2.5 x ULN)	0%	2%
ALT (>5.0 x ULN)	0%	6%
AST (>5.0 x ULN)	2%	10%
Alkaline phosphatase (>5.0 x ULN)	0%	2%
Hypoglycemia* (<39 mg/dL)	0%	0%
Hyperglycemia* (>250 mg/dL)	8%	2%
Creatinine (>3.0 x ULN)	0%	0%
CPK (>4.0 x ULN)	2%	4%
Triglycerides (>750 mg/dL)	8%	8%
Platelets (<50,000 cells/mm³)	0%	2%
WBC (≤1500 cells/mm³)	6%	4%

*Nonfasted.
ULN = Upper limit of normal.
ANC = Absolute neutrophil count.
n = Number of patients assesed.

Pediatric Patients: Selected clinical adverse events with a ≥5% frequency during therapy with ZIAGEN 8 mg/kg twice daily and lamivudine 4 mg/kg twice daily and zidovudine 180 mg/m² twice daily compared with lamivudine 4 mg/kg twice daily and zidovudine 180 mg/m² twice daily from CNAA3006 are listed in Table 5.

Table 5: Selected Clinical Adverse Events (≥5% Frequency) in Therapy-Experienced Pediatric Patients (CNAA3006) Through 24 Weeks of Treatment

	ZIAGEN/Lamivudine/Zidovudine (n=102)		Lamivudine/Zidovudine (n=103)	
Adverse Event	All Events	Grade 3/4 Events	All Events	Grade 3/4 Events
Body as a whole				
Headache	16%	0%	12%	0%
Fever	19%	1%	12%	2%
Digestive				
Diarrhea	16%	0%	15%	0%
Nausea and vomiting	38%	2%	18%	0%
Loss of appetite/anorexia	9%	0%	2%	0%
Skin				
Skin rashes	11%	0%	8%	0%

Laboratory abnormalities observed during therapy are listed in Table 6.

Table 6: Frequencies of Laboratory Abnormalities Among Therapy-Experienced Pediatric Patients (CNAA3006)

Test Abnormal Levels	ZIAGEN/Lamivudine/Zidovudine (n=102)	Lamivudine/Zidovudine (n=103)
Neutropenia (ANC<400 cells/mm³)	1%	5%
Anemia (Hgb <7.0 g/dL)	1%	2%
ALT (>1.1 x ULN)	15%	13%
ALT (>5.0 x ULN)	2%	2%
ALT (>10 x ULN)	2%	1%
AST (>1.1 x ULN)	27%	19%
AST (>5.0 x ULN)	2%	1%
AST (>10 x ULN)	2%	1%
Bilirubin (>3.0 x ULN)	2%	0%
Hyperglycemia* (>250 mg/dL)	0%	0%

*Nonfasted.
ULN=Upper limit of normal.
ANC=Absolute neutrophil count.
n=Number of patients assessed.

Other Adverse Events: In addition to adverse events in Tables 1-6, other adverse events observed in the expanded access program were pancreatitis and increased GGT.

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 unit of use.

ZIAGEN may be taken with or without food.

Adults: The recommended oral dose of ZIAGEN for adults is 300 mg twice 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: Insufficient data are available to recommend a dosage of ZIAGEN in patients with hepatic impairment.

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).

Bottles of 180 tablets (NDC 0173-0661-XX).

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.

GlaxoWellcome
Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

MEDICATION GUIDE

ZIAGEN™ (abacavir sulfate) Tablets and Oral Solution

Brand name: Ziagen™ (z-EYE-uh-jen) Tablets and Oral Solution

Established name: abacavir (uh-BACK-ah-veer) sulfate tablets and oral solution

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

About 3% of patients (3 in 100) who take Ziagen have a hypersensitivity reaction (a serious allergic reaction). If you have two or more of the following sets of symptoms, you may be having this kind of reaction:

- fever
- nausea, vomiting, diarrhea, or abdominal pain
- severe tiredness, run-down feeling, achiness, or generally ill feeling
- skin rash (redness and /or itching)

A written list of these symptoms is on the Warning Card provided by your pharmacist. You should carry this Warning Card with you. **IF YOU NOTICE THESE SYMPTOMS WHILE TAKING ZIAGEN, STOP TAKING ZIAGEN AND CALL YOUR DOCTOR IMMEDIATELY.**

If you must stop treatment with Ziagen because you have had this serious reaction, **NEVER** take Ziagen again. If you take Ziagen again after you have had this serious reaction, WITHIN HOURS you may experience a life-threatening lowering of your blood pressure or death.

You should return all of your unused Ziagen to your doctor or pharmacist for proper disposal.

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

What is Ziagen?

Ziagen is an oral medication used to treat HIV infection. Ziagen is taken orally as a tablet or a strawberry-banana flavored oral solution. It belongs to a class of anti-HIV medicines called nucleoside analogue reverse transcriptase inhibitors (NRTIs). Ziagen is only proven to work when taken in combination with other anti-HIV medications. When used in combination with these other medications, Ziagen helps lower the amount of HIV found in your blood and keep your immune system as healthy as possible so that it can help fight infection. However, Ziagen does not have these effects in all patients.

Ziagen does not cure HIV infection or AIDS. At this time, there is no evidence that Ziagen will help you live longer or have fewer of the medical problems that are associated with HIV infection or AIDS. Because of this, you must be sure to be seen regularly by your health care provider.

Who should not take Ziagen?

Do not take Ziagen if you have ever had a hypersensitivity reaction (a serious allergic reaction) to Ziagen.

How should I take Ziagen?

Take Ziagen exactly as your doctor prescribes it.

The usual dosage for adults (at least 16 years of age) is one 300-mg tablet twice a day.

Adolescents and children from 3 months to 16 years of age can also take Ziagen. Your doctor will tell you if the oral solution or tablet is best for your child. Also, your child's doctor will decide the right dose based on your child's weight and age. Ziagen has not been studied in children under 3 months of age.

Ziagen can be taken with food or on an empty stomach.

To help make sure that your anti-HIV therapy is as effective as it can be, be very careful to take all of your medication exactly as your doctor prescribed it and do not skip any doses.

If you miss a dose of Ziagen, take the missed dose immediately. Then, take the next dose at the regularly scheduled time.

When your supply of Ziagen and other anti-HIV drugs starts to run low, get more from your doctor or pharmacy. It is very important that you take anti-HIV drugs as prescribed by your doctor because the amount of virus in your blood may increase if one or more of the drugs is stopped, even for a short time.

What should I avoid while taking Ziagen?

Ziagen has not been shown to reduce the risk of passing HIV to others through sexual contact or blood contamination. Continue to practice safe sex while using Ziagen. Do not use or share dirty needles.

Talk to your doctor if you are pregnant or if you become pregnant while taking Ziagen. Ziagen has not been studied in pregnant women and the risk to the unborn child is not known.

Mothers with HIV should not breastfeed their infants because HIV in the breast milk can be passed to the infant.

Tell your doctor if you have kidney or liver problems.

FEW ZIAGEN [abacavir sulfate]

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