CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-977 / S-014
20-978 / S-016

Trade Name: Ziagen

Generic Name: (abacavir sulfate)

Sponsor: GlaxoSmithKline

Approval Date: August 11, 2006

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-977 / S-014
20-978 / S-016

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-977 / S-014
20-978 / S-016

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-977/S-014
NDA 20-978/S-016

GlaxoSmithKline
Attention: Martha Anne A. Moore, R.Ph.
Antiviral/Antibacterial US Regulatory Affairs
PO Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Dear Ms. Moore:

Please refer to your supplemental new drug applications NDA 20-977 and 20-978 dated January 10, 2006, received January 11, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ziagen® (abacavir sulfate) tablets and oral solution.

We also acknowledge receipt of your submissions dated April 26, 2006 received April 27, 2006 amending the January 20, 2006 submission.

These supplements (CBE) provide updates to the CLINICAL PHARMACOLOGY and PRECAUTION sections as requested by the Division. Also included are updates to the MICROBIOLOGY section to incorporate the updated lamivudine and zidovudine information approved in the Trizivir® tablets prescribing information approved on May 13, 2005. The information regarding Study CNA2005 has also been updated to agree with the approved Trizivir® prescribing information. The Medication Guide has been revised to advise patients to tell their doctor before they take Ziagen® if they have liver problems. Also added is information regarding immune reconstitution to the Medication Guide.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please contact Tanima Sinha, M.S., Regulatory Project Manager, at (301) 796-0812.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial

Enclosure: Final Approval Label

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jeffrey Murray
8/11/2006 03:56:24 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-977 / S-014
20-978 / S-016

LABELING

PRESCRIBING INFORMATION

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.

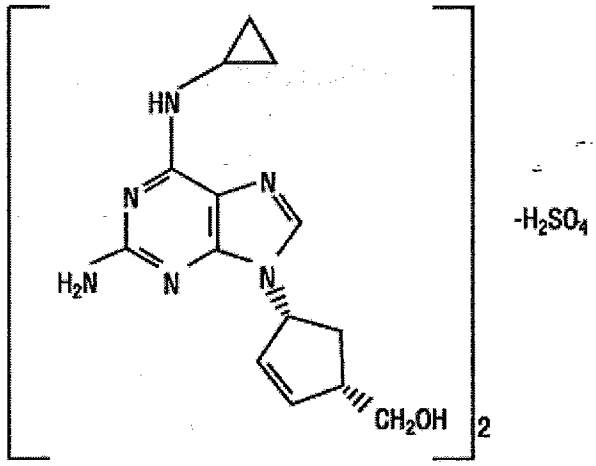
Following a hypersensitivity reaction to abacavir, NEVER restart ZIAGEN or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.

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 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 (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

IC_{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 vitro 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 in vitro anti–HIV-1 activity of abacavir.

Resistance: HIV-1 isolates with reduced susceptibility to abacavir have been selected in vitro and were also obtained from patients treated with abacavir. Genotypic analysis of isolates selected in vitro 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 vitro 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/mm^3, 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/mm^3 in the group receiving ZIAGEN and 155 cells/mm^3 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/mm^3, 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.

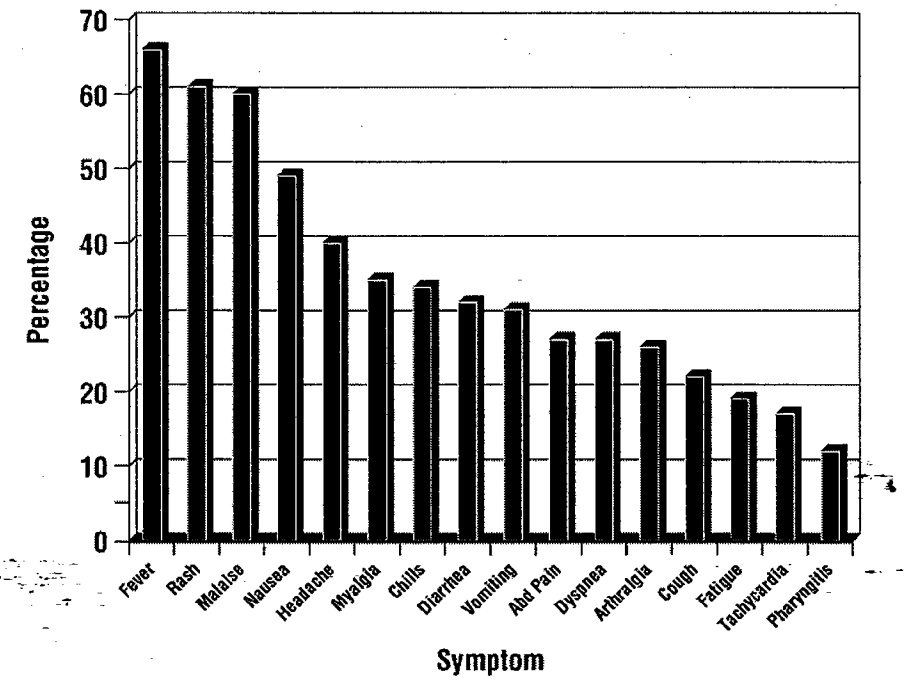
Group 1: Fever
Group 2: Rash

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 signs/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 gm/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).

Skin: 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.

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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.

GlaxoSmithKline
Research Triangle Park, NC 27709

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March 2006 MG-037

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

(Front of card)

WARNING CARD
ZIAGEN® (abacavir sulfate) Tablets and Oral Solution

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, or abdominal (stomach area) pain
Group 4	Generally ill feeling, extreme tiredness, or achiness
Group 5	Shortness of breath, cough, or sore throat

Always carry this Warning Card with you to help recognize symptoms of this allergic reaction.

(Back of Card)

WARNING CARD

ZIAGEN® (abacavir sulfate) Tablets and Oral Solution

If you must stop treatment with Ziagen because you have had an allergic reaction to abacavir, **NEVER** take Ziagen or another abacavir-containing medicine (Epzicom™ and Trizivir®) again. If you take Ziagen or another 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**.

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

Please read the Medication Guide for additional information on Ziagen.

March 2006 RL-

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-977 / S-014
20-978 / S-016

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

Division of Antiviral Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: 20-977 (SLR-014)
20-978 (SLR-016)

Name of Drug: Ziagen® (abacavir sulfate) tablets and oral solution

Applicant: GlaxoSmithKline

Material Reviewed:

Submission Dates: January 9, 2006
April 26, 2006

Receipt Dates: January 10, 2006
April 27, 2006

BACKGROUND AND SUMMARY

This supplement (CBE) provides updates to the CLINICAL PHARMACOLOGY and PRECAUTION sections as requested by the Division. Also included are updates to the MICROBIOLOGY section to incorporate the updated lamivudine and zidovudine information approved in the Trizivir tablets prescribing information approved on May 13, 2005. The information regarding Study CNA2005 has also been updated to agree with the approved Trizivir prescribing information. The Medication Guide has been revised to advise patients to tell their doctor before they take Ziagen if they have liver problems. Also added is information regarding immune reconstitution to the Medication Guide.

REVIEW

The label provided in NDA 20-977 (SLR 014) and NDA 20-978 (SLR 016) was compared to the latest approved label (August 2004) and the changes can be seen below in the attached annotated version.

Minor edits were also made and can be seen in the attached annotated label below.

WITHHOLD 27 PAGE(S)

Draft labeling

CONCLUSIONS

It should be conveyed to the applicant that the changes provided in NDA 20-977 SLR CBE 014 and NDA 20-978 SLR CBE 016 are as requested and a letter should be sent.

Tanima Sinha
Regulatory Health Project Manager

Supervisory Comment/Concurrence:

Virginia L. Behr
Chief, Project Management Staff

Drafted: TS/8-11-06
Revised/Initialed:
Finalized:
Filename: V:\DAVDP\CSO\SINHA\NDA\20-977-78\Labeling Supplements\SLR 014\Ziagen CSO Review (SLR 014/016)

CSO LABELING REVIEW

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Tanima Sinha
8/11/2006 03:39:19 PM
CSO
Hard copy signed off, Ziagen CBE/SLRs
Please sign off by COB 8-11-06

Virginia Behr
8/16/2006 02:35:42 PM
CSO