

PRESCRIBING INFORMATION

ZIAGEN[®]
(abacavir sulfate)
Tablets

ZIAGEN[®]
(abacavir sulfate)
Oral Solution

WARNING

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

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

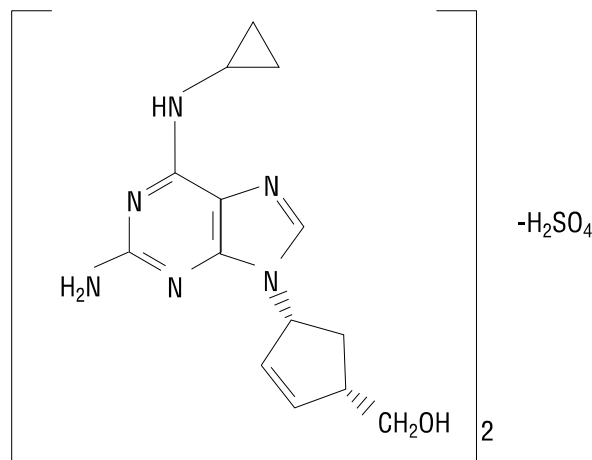
SEVERE OR FATAL HYPERSENSITIVITY REACTIONS CAN OCCUR WITHIN HOURS AFTER REINTRODUCTION OF ZIAGEN IN PATIENTS WHO HAVE NO IDENTIFIED HISTORY OR UNRECOGNIZED SYMPTOMS OF HYPERSENSITIVITY TO ABACAVIR THERAPY (SEE WARNINGS, PRECAUTIONS: INFORMATION FOR PATIENTS, AND ADVERSE REACTIONS).

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

DESCRIPTION

ZIAGEN is the brand name for abacavir sulfate, a synthetic carbocyclic nucleoside analogue with inhibitory activity against HIV. The chemical name of abacavir sulfate is (1*S*,*cis*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1). Abacavir sulfate is the enantiomer with 1*S*, 4*R* 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 hypromellose, 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, 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. Abacavir 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_{IIB} in lymphoblastic cell lines, a monocyte/macrophage tropic laboratory strain HIV-1_{BaL} in primary monocytes/macrophages, and clinical isolates in peripheral blood mononuclear

cells. The concentration of drug necessary to inhibit viral replication by 50 percent (IC_{50}) ranged from 3.7 to 5.8 μM against HIV-1_{IIIB}, and was $0.26 \pm 0.18 \mu\text{M}$ ($1 \mu\text{M} = 0.28 \text{ mcg/mL}$) against 8 clinical isolates. The IC_{50} value of abacavir against HIV-1_{BaL} varied from 0.07 to 1.0 μM . Abacavir had synergistic activity in vitro in combination with amprenavir, nevirapine, and zidovudine, and additive activity in combination with didanosine, lamivudine, stavudine, and zalcitabine.

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 K65R, L74V, Y115F, and M184V amino acid substitutions. HIV-1 isolates from virologic failure antiretroviral-naive patients treated with abacavir alone ($n = 67$) contained the M184V mutation ($n = 27$), often in combination with the L74V mutation ($n = 18$). In some patients, the M184V mutation was also detected in combination with K65R and/or Y115F. Genetic analysis of isolates from virologic failure antiretroviral-naive patients treated with abacavir in combination with other antiretrovirals ($n = 55$) also showed that many isolates contained the M184V mutation ($n = 26$) alone, and, sometimes in combination with L74V ($n = 2$). In a clinical study of treatment-naive patients (CNA30024, $n = 649$) comparing ZIAGEN to zidovudine both in combination with efavirenz and lamivudine, 34 patients experienced virologic failure (plasma HIV-1 RNA >50 copies/mL, see CLINICAL STUDIES). Four patients in each treatment arm had viral isolates containing resistance-associated mutations including M184V and non-nucleoside reverse transcriptase inhibitor (NNRTI) mutations.

Cross-Resistance: Cross-resistance has been observed among nucleoside reverse transcriptase inhibitors. Recombinant laboratory strains of HIV-1_{HXB2} containing multiple abacavir resistance-associated mutations, namely, K65R, L74V, M184V, and Y115F, exhibited cross-resistance to didanosine, emtricitabine, lamivudine, tenofovir, and zalcitabine in vitro. The K65R mutation may also confer resistance to stavudine. 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 $3.0 \pm 0.89 \text{ mcg/mL}$ (mean \pm SD) and $AUC_{(0-12 \text{ hr})}$ was $6.02 \pm 1.73 \text{ mcg}\cdot\text{hr/mL}$. Bioavailability of abacavir tablets was assessed in the fasting and fed states. There was no significant difference in systemic exposure (AUC_{∞}) in the fed and fasting states; therefore, ZIAGEN Tablets may be administered with or without food. Systemic exposure to abacavir was comparable after administration of ZIAGEN Oral Solution and ZIAGEN Tablets. Therefore, these products may be used interchangeably.

Distribution: The apparent volume of distribution after IV administration of abacavir was 0.86 ± 0.15 L/kg, suggesting that abacavir distributes into extravascular space. In 3 subjects, the CSF $AUC_{(0-6 \text{ hr})}$ to plasma abacavir $AUC_{(0-6 \text{ hr})}$ 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 \pm SD).

Special Populations: Adults With Impaired Renal Function: The pharmacokinetic properties of ZIAGEN have not been determined in patients with impaired renal function. Renal excretion of unchanged abacavir is a minor route of elimination in humans.

Adults with Impaired Hepatic Function: The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh score 5 to 6). Results showed that there was a mean increase of 89% in the abacavir AUC, and an increase of 58% in the half-life of abacavir after a single dose of 600 mg of abacavir. The AUCs of the metabolites were not modified by mild liver disease; however, the rates of formation and elimination of the metabolites were decreased. A dose of 200 mg (provided by 10 mL of ZIAGEN Oral Solution) administered twice daily is recommended for patients with mild liver disease. The safety, efficacy, and pharmacokinetics of abacavir have not been studied in patients with moderate or severe hepatic impairment, therefore ZIAGEN is contraindicated in these patients.

Pediatric Patients: The pharmacokinetics of abacavir have been studied after either single or repeat doses of ZIAGEN in 68 pediatric patients. Following multiple-dose administration of ZIAGEN 8 mg/kg twice daily, steady-state $AUC_{(0-12 \text{ hr})}$ and C_{max} were 9.8 ± 4.56 mcg•hr/mL and 3.71 ± 1.36 mcg/mL (mean \pm SD), respectively (see PRECAUTIONS: Pediatric Use).

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

Gender: The pharmacokinetics of ZIAGEN with respect to gender have not been determined.

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

Drug Interactions: In human liver microsomes, abacavir did not inhibit cytochrome P450 isoforms (2C9, 2D6, 3A4). Based on these data, it is unlikely that clinically significant drug interactions will occur between abacavir and drugs metabolized through these pathways.

Due to their common metabolic pathways via glucuronyl transferase with zidovudine, 15 HIV-infected patients were enrolled in a crossover study evaluating single doses of abacavir (600 mg), lamivudine (150 mg), and zidovudine (300 mg) alone or in combination. Analysis showed no clinically relevant changes in the pharmacokinetics of abacavir with the addition of lamivudine or zidovudine or the combination of lamivudine and zidovudine. Lamivudine exposure (AUC decreased 15%) and zidovudine exposure (AUC increased 10%) did not show clinically relevant changes with concurrent abacavir.

Due to their common metabolic pathways via alcohol dehydrogenase, the pharmacokinetic interaction between abacavir and ethanol was studied in 24 HIV-infected male patients. Each patient received the following treatments on separate occasions: a single 600-mg dose of abacavir, 0.7 g/kg ethanol (equivalent to 5 alcoholic drinks), and abacavir 600 mg plus 0.7 g/kg ethanol. Coadministration of ethanol and abacavir resulted in a 41% increase in abacavir AUC_{∞} and a 26% increase in abacavir $t_{1/2}$. In males, abacavir had no effect on the pharmacokinetic properties of ethanol, so no clinically significant interaction is expected in men. This interaction has not been studied in females.

Methadone: In a study of 11 HIV-infected 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.

Description of Clinical Studies: Therapy-Naive Adults: CNA30024 was a multicenter, double-blind, controlled study in which 649 HIV-infected, therapy-naive adults were randomized and received either ZIAGEN (300 mg twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once daily) or zidovudine (300 mg twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once daily). The duration of double-blind treatment was at least 48 weeks. Study participants were: male (81%), Caucasian (51%), black (21%), and Hispanic (26%). The median age was 35 years, the median pretreatment CD4+ cell count was 264 cells/mm³, and median plasma HIV-1 RNA was 4.79 log₁₀ copies/mL. The outcomes of randomized treatment are provided in Table 1.

Table 1. Outcomes of Randomized Treatment Through Week 48 (CNA30024)

Outcome	ZIAGEN plus Lamivudine plus Efavirenz (n = 324)	Zidovudine plus Lamivudine plus Efavirenz (n = 325)
Responder*	69% (73%)	69% (71%)
Virologic failures [†]	6%	4%
Discontinued due to adverse reactions	14%	16%
Discontinued due to other reasons [‡]	10%	11%

*Patients achieved and maintained confirmed HIV-1 RNA ≤ 50 copies/mL (< 400 copies/mL) through Week 48 (Roche[®] AMPLICOR Ultrasensitive HIV-1 MONITOR standard test 1.0 PCR).

[†]Includes viral rebound, insufficient viral response according to the investigator, and failure to achieve confirmed ≤ 50 copies/mL by Week 48.

[‡]Includes consent withdrawn, lost to follow up, protocol violations, those with missing data, clinical progression, and other.

After 48 weeks of therapy, the median CD4+ cell count increases from baseline were 209 cells/mm³ in the group receiving ZIAGEN and 155 cells/mm³ in the zidovudine group.

Through Week 48, 8 subjects (2%) in the group receiving ZIAGEN (5 CDC classification C events and 3 deaths) and 5 subjects (2%) on the zidovudine arm (3 CDC classification C events and 2 deaths) experienced clinical disease progression.

CNA3005 was a multicenter, double-blind, controlled study in which 562 HIV-infected, therapy-naive adults with a pre-entry plasma HIV-1 RNA $> 10,000$ copies/mL were randomized to receive either ZIAGEN (300 mg twice daily) plus COMBIVIR (lamivudine 150 mg/zidovudine 300 mg twice daily), or indinavir (800 mg 3 times a day) plus COMBIVIR twice daily. Study participants were male (87%), Caucasian (73%), black (15%), and Hispanic (9%). At baseline the median age was 36 years, the median pretreatment CD4+ cell count was 360 cells/mm³, and median plasma HIV-1 RNA was 4.8 log₁₀ 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 = 282)	Indinavir plus Lamivudine/Zidovudine (n = 280)
HIV-1 RNA <400 copies/mL	46%	47%
HIV-1 RNA ≥400 copies/mL*	29%	28%
Discontinued due to adverse reactions	10%	13%
Discontinued due to other reasons†	8%	8%
Randomized but never initiated treatment	7%	5%

* Includes viral rebound and failure to achieve confirmed <400 copies/mL by Week 48.

† Includes consent withdrawn, lost to follow up, protocol violations, those with missing data, clinical progression, and other.

Through Week 48, an overall mean increase in CD4+ cell count of about 150 cells/mm³ was observed in both treatment arms.

CONTRAINDICATIONS

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

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

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

WARNINGS

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

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

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

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

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

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

Lactic Acidosis/Severe Hepatomegaly with Steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering ZIAGEN to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with ZIAGEN should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

PRECAUTIONS

General: Abacavir should always be used in combination with other antiretroviral agents. Abacavir should not be added as a single agent when antiretroviral regimens are changed due to loss of virologic response.

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

Fat Redistribution: Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and “cushingoid appearance” have been observed in patients receiving antiretroviral therapy. The

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

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

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

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

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

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 (60 females and 60 males per group) and rats (56 females and 56 males in each group) in carcinogenicity studies. Single doses were 55, 110, and 330 mg/kg/day in mice and 30, 120, and 600 mg/kg/day in rats. Results showed an increase in the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver of female rats. In addition, non-malignant tumors also occurred in the liver and thyroid gland of female rats. These observations were made at systemic exposures in the range of 6 to 32 times the human exposure at the recommended dose (300 mg twice daily). It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Abacavir induced chromosomal aberrations both in the presence and absence of metabolic activation in an in vitro cytogenetic study in human lymphocytes. Abacavir was mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence of metabolic activation in an L5178Y mouse lymphoma assay. At systemic exposures approximately 9 times higher than that in humans at the therapeutic dose, abacavir was clastogenic in males and not clastogenic in females in an in vivo mouse bone marrow micronucleus assay.

Abacavir was not mutagenic in bacterial mutagenicity assays in the presence and absence of metabolic activation.

Abacavir had no adverse effects on the mating performance or fertility of male and female rats at doses of up to 500 mg/kg/day, a dose expected to produce exposures approximately 8-fold higher than that in humans at the therapeutic dose based on body surface area comparisons.

Pregnancy: Pregnancy Category C. Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. Developmental toxicity (depressed fetal body weight and reduced crown-rump length) and increased incidences of fetal anasarca and skeletal malformations were observed when rats were treated with abacavir at doses of 1,000 mg/kg during organogenesis. This dose produced 35 times the human exposure, based on AUC. In a fertility study, evidence of toxicity to the developing embryo and fetuses (increased resorptions, decreased fetal body weights) occurred only at 500 mg/kg/day. The offspring of female rats treated with abacavir at 500 mg/kg/day (beginning at embryo implantation and ending at weaning) showed increased incidence of stillbirth and lower body weights throughout life. In the rabbit, there was no evidence of drug-related developmental toxicity and no increases in fetal malformations at doses up to 700 mg/kg (8.5 times the human exposure at the recommended dose, based on AUC).

There are no adequate and well-controlled studies in pregnant women. ZIAGEN should be used during pregnancy only if the potential benefits outweigh the risk.

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

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

Although it is not known if abacavir is excreted in human milk, abacavir is secreted into the milk of lactating rats. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving ZIAGEN.**

Pediatric Use: The safety and effectiveness of ZIAGEN have been established in pediatric patients aged 3 months to 13 years. Use of ZIAGEN in these age groups is supported by pharmacokinetic studies and evidence from adequate and well-controlled studies of ZIAGEN in adults and pediatric patients (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Special Populations: Pediatric Patients, INDICATIONS AND USAGE: Description of Clinical Studies, WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION).

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/m² twice daily versus lamivudine 4 mg/kg twice daily plus zidovudine 180 mg/m² 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 log₁₀ 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 log₁₀ copies/mL in the group receiving ZIAGEN plus lamivudine plus zidovudine compared with -0.21 log₁₀ copies/mL in the group receiving lamivudine plus zidovudine. Median CD4+ cell count increases from baseline were 69 cells/mm³ in the group receiving ZIAGEN plus lamivudine plus zidovudine and 9 cells/mm³ 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: Fatal hypersensitivity reactions have been associated with therapy with ZIAGEN. Therapy with ZIAGEN SHOULD NOT be restarted following a hypersensitivity reaction because more severe symptoms will recur within hours and may include life-threatening hypotension and death. Patients developing signs or symptoms of hypersensitivity should discontinue treatment as soon as a hypersensitivity reaction is first suspected, and should seek medical evaluation immediately. To avoid a delay in diagnosis and minimize the risk of a life-threatening hypersensitivity reaction, ZIAGEN should be permanently discontinued if

hypersensitivity cannot be ruled out, even when other diagnoses are possible (e.g., acute onset respiratory diseases, gastroenteritis, or reactions to other medications).

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

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

In clinical studies, approximately 5% of adult and pediatric 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 include malaise, lethargy, myalgia, myolysis, arthralgia, edema, pharyngitis, cough, abnormal chest x-ray findings (predominantly infiltrates, which can be localized), dyspnea, headache, and paresthesia. Some patients who experienced a hypersensitivity reaction were initially thought to have acute onset or worsening respiratory disease. The diagnosis of hypersensitivity reaction should be carefully considered for patients presenting with symptoms of acute onset respiratory diseases, even if alternative respiratory diagnoses (pneumonia, bronchitis, pharyngitis, or flu-like illness) are possible.

Physical findings 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 include elevated liver function tests, increased creatine phosphokinase or creatinine, and lymphopenia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure, and death have occurred in association with hypersensitivity reactions. Symptoms worsen with continued therapy but often resolve upon discontinuation of ZIAGEN.

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

Therapy-Naive Adults: Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a $\geq 5\%$ 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 3.

Table 3. 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%

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 4.

Table 4. 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%
Diarrhea	7%	5%
Fever and/or chills	6%	3%
Depressive disorders	6%	4%
Musculoskeletal pain	5%	7%
Skin rashes	5%	4%
Ear/nose/throat infections	5%	4%
Viral respiratory infections	5%	5%
Anxiety	5%	3%
Renal sign/symptoms	<1%	5%
Pain (non-site-specific)	<1%	5%

Five patients receiving ZIAGEN in Study CNA3005 experienced worsening of pre-existing depression compared to none in the indinavir arm. The background rates of pre-existing depression were similar in the 2 treatment arms.

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/m² twice daily compared with lamivudine 4 mg/kg twice daily and zidovudine 180 mg/m² twice daily from CNA3006 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-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 6.

Table 6. 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 (P1t <50,000/mm ³)	1%	<1%
Leukopenia (WBC ≤1,500/mm ³)	<1%	2%

In another study of therapy-naive adults (CNA3005), hyperglycemia and disorders of lipid metabolism occurred with similar frequency in patients treated with ZIAGEN and patients treated with indinavir.

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).

Other Adverse Events: In addition to adverse reactions in Tables 3, 4, 5, and 6, 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).

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 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: 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[®] (z-EYE-uh-jen) (abacavir sulfate) Tablets and Oral Solution

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

Read the Medication Guide you get each time you fill your prescription for Ziagen. There may be new information since you filled your last prescription.

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

About 1 in 20 patients (5%) who take Ziagen will have a **serious allergic reaction** (hypersensitivity reaction) **that may cause death if the drug is not stopped right away.**

You may be having this reaction if:

(1) you get a skin rash, or

(2) you get 1 or more symptoms from at least 2 of the following groups:

- **Fever**
- **Nausea, vomiting, diarrhea, abdominal (stomach area) pain**
- **Extreme tiredness, achiness, generally ill feeling**
- **Sore throat, shortness of breath, cough**

If you think you may be having a reaction, **STOP taking Ziagen and call your doctor right away.**

If you stop treatment with Ziagen because of this serious reaction, **NEVER take Ziagen (abacavir) again.** If you take Ziagen again after you have had this serious reaction, **you could die within hours.**

Some patients who have stopped taking Ziagen (abacavir) and who have then started taking Ziagen (abacavir) again have had serious or life-threatening allergic (hypersensitivity) reactions. If you must stop treatment with Ziagen for reasons other than symptoms of hypersensitivity, do not begin taking it again without talking to your health care provider. If your health care provider decides that you may begin taking Ziagen again, you should do so only in a setting with other people to get access to a doctor if needed.

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

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 medication 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 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. This helps to keep your immune system as healthy as possible so that it can help fight infection.

Ziagen does not cure HIV infection or AIDS. Ziagen has not been studied long enough to know if it will help you live longer or have fewer of the medical problems that are associated with HIV infection or AIDS. Therefore, you must see your health care provider regularly.

Who should not take Ziagen?

Do not take Ziagen if you have ever had a serious allergic reaction (a hypersensitivity reaction) to abacavir (as Ziagen or Trizivir[®] [abacavir, lamivudine, and zidovudine] Tablets). If you have had such a reaction, return all of your unused Ziagen to your doctor or pharmacist.

Talk to your doctor if you have liver problems, as some patients with liver disease should not take Ziagen.

How should I take Ziagen?

To help make sure that your anti-HIV therapy is as effective as possible, take your Ziagen exactly as your doctor prescribes it. Do not skip any doses.

The usual dosage for adults (at least 16 years of age) is one 300-mg tablet twice a day. You can take Ziagen with food or on an empty stomach.

Adolescents and children 3 months and older 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.

If you miss a dose of Ziagen, take the missed dose right away. Then, take the next dose at the usual scheduled time. Do not let your Ziagen run out. The amount of virus in your blood may increase if your anti-HIV drugs are stopped, even for a short time. Also, the virus in your body may become harder to treat.

What should I avoid while taking Ziagen?

Practice safe sex while using Ziagen. Do not use or share dirty needles. Ziagen does not reduce the risk of passing HIV to others through sexual contact or blood contamination.

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

Mothers with HIV should not breastfeed their babies because HIV is passed to the baby in breast milk. Also Ziagen can be passed to babies in breast milk and could cause the child to have side effects.

What are the possible side effects of Ziagen?

Life-threatening allergic reaction. Ziagen has caused some people to have a life-threatening reaction (hypersensitivity reaction) that can cause death. How to recognize a possible reaction, and what to do are discussed in "What is the most important information I should know about Ziagen?" at the beginning of this Medication Guide.

Lactic Acidosis and severe liver problems. Ziagen can cause a serious condition called lactic acidosis and, in some cases, this condition can cause death. Nausea and tiredness that don't get better may be symptoms of lactic acidosis. Women are more likely than men to get this rare but serious side effect.

Ziagen can cause other side effects. In studies, the most common side effects with Ziagen were nausea, vomiting, malaise or fatigue, headache, diarrhea, and loss of appetite. Most of these side effects did not cause people to stop taking Ziagen.

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

This listing of side effects is not complete. Your doctor or pharmacist can discuss with you a more complete list of side effects with Ziagen.

Ask a health care professional about any concerns about Ziagen. If you want more information, ask your doctor or pharmacist for the labeling for Ziagen that was written for health care professionals.

Do not use Ziagen for a condition for which it was not prescribed. Do not give Ziagen to other persons.



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