

PRODUCT MONOGRAPH

PrZIAGEN[®]

abacavir sulfate

300 mg tablets and 20 mg/mL oral solution

Antiretroviral Agent

GlaxoSmithKline Inc.
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Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....	3
SUMMARY PRODUCT INFORMATION	3
INDICATIONS AND CLINICAL USE.....	3
CONTRAINDICATIONS	4
WARNINGS AND PRECAUTIONS.....	4
ADVERSE REACTIONS.....	11
DRUG INTERACTIONS	15
DOSAGE AND ADMINISTRATION	16
OVERDOSAGE	18
ACTION AND CLINICAL PHARMACOLOGY	18
STORAGE AND STABILITY.....	19
SPECIAL HANDLING INSTRUCTIONS	19
DOSAGE FORMS, COMPOSITION AND PACKAGING	20
PART II: SCIENTIFIC INFORMATION.....	21
PHARMACEUTICAL INFORMATION.....	21
CLINICAL TRIALS.....	22
DETAILED PHARMACOLOGY	23
MICROBIOLOGY	24
TOXICOLOGY	26
REFERENCES	30
PART III: CONSUMER INFORMATION.....	32

Pr ZIAGEN[®]

abacavir sulfate

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet/ 300 mg	colloidal silicon dioxide, hydroxypropyl methyl cellulose, magnesium stearate, microcrystalline cellulose, polysorbate 80, sodium starch glycolate, titanium dioxide, triacetin, and yellow iron oxide.
	Oral Solution/ 20 mg/mL	artificial strawberry and banana flavours, citric acid (anhydrous), hydrochloric acid, methylparaben, propylene glycol, propylparaben, saccharin sodium, sodium citrate (dihydrate), sodium hydroxide, and sorbitol solution.

INDICATIONS AND CLINICAL USE

ZIAGEN[®] (abacavir sulfate) is indicated in:

- antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection.

This indication is based on analyses of surrogate markers in controlled studies of up to 48 weeks in duration. The demonstration of the benefit of ZIAGEN[®] is mainly based on results of studies in treatment naïve patients on combination therapy conducted with lamivudine and zidovudine. In patients with high viral load (> 100,000 copies/mL) choice of therapy needs special consideration (see PART II SCIENTIFIC INFORMATION: CLINICAL TRIALS).

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 AND PRECAUTIONS, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

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.

CONTRAINDICATIONS

ZIAGEN[®] (abacavir sulfate) tablets and oral solution are contraindicated in patients:

- with previously demonstrated hypersensitivity to abacavir, or any of the other components of the product (see WARNINGS AND PRECAUTIONS, and DOSAGE FORMS, COMPOSITION AND PACKAGING sections).
- with moderate or severe hepatic impairment since the pharmacokinetics have not been studied in this patient group.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Fatal Hypersensitivity Reactions**

Fatal hypersensitivity reactions have been associated with therapy with ZIAGEN[®] (abacavir sulfate). Therapy ZIAGEN[®] should be discontinued in patients developing signs or symptoms of hypersensitivity 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, 5) respiratory (including pharyngitis, dyspnea, cough and abnormal chest x-ray findings, predominantly infiltrates, which can be localized). (see WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions to Abacavir). To 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 (acute onset of respiratory diseases, gastroenteritis or reactions to other medications).

The symptoms of a hypersensitivity reaction can occur at any time during treatment with abacavir, but usually occur within the first six weeks of therapy. **ZIAGEN[®] or any other medicinal product containing abacavir must never be restarted following a hypersensitivity reaction, as 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 ZIAGEN[®] re-introduction in patients who have no identified history or undiagnosed symptoms of hypersensitivity during their initial period of use of ZIAGEN[®].

- **Lactic Acidosis and 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 ZIAGEN[®] and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. 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) (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

General

ZIAGEN[®] (abacavir sulfate) should always be used in combination with other antiretroviral agents. When antiretroviral regimens are changed due to loss of virologic response, ZIAGEN[®] should not be added as a single agent.

Hypersensitivity Reactions

Fatal hypersensitivity reactions have been associated with therapy with ZIAGEN[®] (see Serious Warnings and Precautions Box).

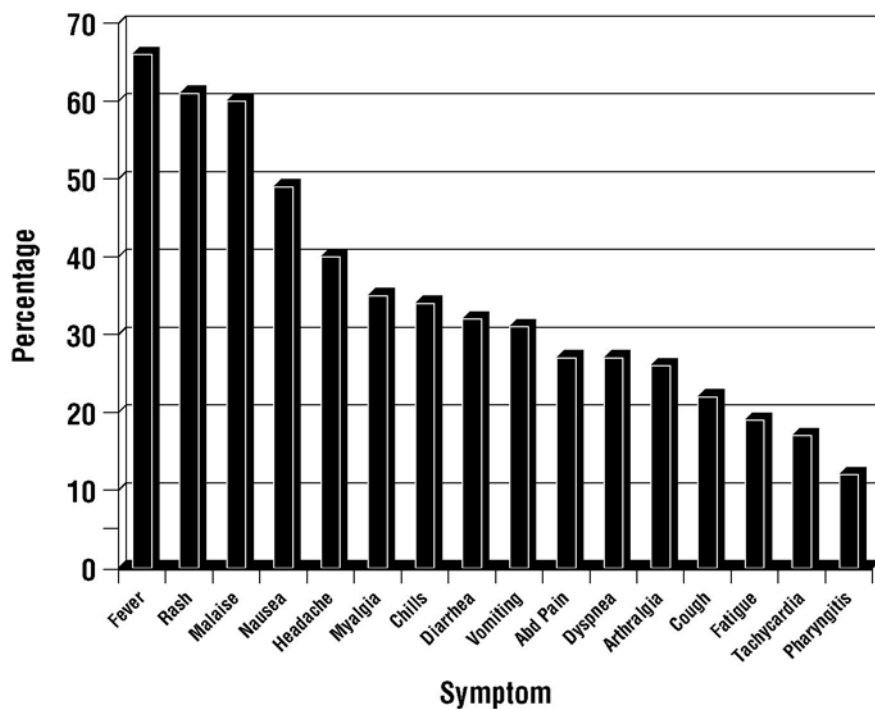
Discontinue ZIAGEN[®] as soon as a hypersensitivity reaction is suspected. To minimize the risk of a life-threatening hypersensitivity reaction, permanently discontinue ZIAGEN[®] if hypersensitivity cannot be ruled out, even when other diagnoses are possible (e.g., acute onset respiratory diseases such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

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.

If therapy with ZIAGEN[®] or any other medicinal product containing abacavir has been discontinued and restarting 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 a hypersensitivity reaction cannot be ruled out, ZIAGEN[®] or any other medicinal product containing abacavir should not be restarted.

Hypersensitivity to abacavir was reported in approximately 8% of 2670 patients (n = 206) in 9 clinical trials (range: 2% to 9%) with enrolment from November 1999 to February 2002. Data on time to onset and symptoms of suspected hypersensitivity in the nine studies were collected on a detailed data collection module. This reaction is characterized by the appearance of symptoms indicating multi-organ / body-system involvement. Symptoms can occur at any time during therapy; however they usually appear within the first 6 weeks (median time to onset 11 days) of initiation of treatment with ZIAGEN[®] (see WARNINGS AND PRECAUTIONS: ADVERSE REACTIONS).

Figure 1 Hypersensitivity Related Symptoms Reported with $\geq 10\%$ Frequency in Clinical Trials (n = 206 Patients)



In controlled study (CNA30021), more patients taking ZIAGEN[®] 600 mg once daily had severe hypersensitivity reactions than patients taking ZIAGEN[®] 300 mg twice daily (see DOSAGE AND ADMINISTRATION). In this 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.

A warning card with information for the patient about this hypersensitivity reaction is included in the ZIAGEN[®] pack (see PART III: CONSUMER INFORMATION: WARNING CARD).

Risk Factors

Analyses of clinical risk factors for hypersensitivity to abacavir have consistently identified the risk for those of black race to be approximately half the risk of other racial groups combined. In addition, a genetic risk factor linked to the occurrence of abacavir hypersensitivity has been identified in retrospective, case-controlled, pharmacogenetic studies. HLA-B5701 was more common among patients who had a suspected hypersensitivity reaction to abacavir compared with those who did not:

Proportion of Patients with HLA-B5701 Allele

Patient reported race or ethnic group	Cases with suspected hypersensitivity	Controls without hypersensitivity
Caucasian	222/444 (50%)	11/486 (2%)
Black	4/50 (8%)	1/67 (2%)

This genetic association has not been assessed in prospective clinical studies. The clinical diagnosis of suspected hypersensitivity to abacavir remains the basis for clinical decision making. Therefore, it is important to permanently discontinue abacavir and not re-challenge with abacavir if hypersensitivity can not be ruled out, regardless of the presence or absence of the HLA-B5701 allele.

Carcinogenesis and Mutagenesis

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

Abacavir was not mutagenic in bacterial mutagenicity assays in the presence and absence of metabolic activation (see TOXICOLOGY: Mutagenicity).

Carcinogenicity studies with orally administered abacavir in mice and rats showed an increase in the incidence of malignant and non-malignant tumours. Malignant tumours occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver, urinary bladder, lymph nodes and subcutis of female rats. The majority of these tumours occurred at the highest abacavir dose in mice and rats, which corresponds to 24 - 32 times the expected systemic exposure in humans (see TOXICOLOGY: Carcinogenicity).

Endocrine and Metabolism

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.

Hepatic/Biliary/Pancreatic

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 either alone or in combination, including abacavir and other antiretrovirals. A majority of these cases have been in women.

Clinical features which may be indicative of the development of lactic acidosis include generalised weakness, anorexia and sudden unexplained weight loss, gastrointestinal symptoms and respiratory symptoms (dyspnea and tachypnea).

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).

Impaired Hepatic Function

Patients with impaired hepatic function

Abacavir is contraindicated in patients with moderate to severe hepatic impairment and dose reduction is required in patients with mild hepatic impairment.

Abacavir is metabolized primarily by the liver. The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh score 5-6) who had confirmed cirrhosis. The results showed that there was a mean increase of 1.89 fold in the abacavir AUC, and 1.58 fold in the half-life of abacavir. The AUCs of the metabolites were not modified by the liver disease. However, the rates of formation and elimination of these were decreased. The pharmacokinetics have not been studied in patients with moderate or severe hepatic impairment; therefore ZIAGEN[®] is contraindicated in these patient groups. Once-daily ZIAGEN[®] 600 mg dosing has not been studied in the patients with impaired hepatic function and is not recommended for use in this population (see DOSAGE AND ADMINISTRATION: Hepatic Impairment).

Immune

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).

In heavily pre-treated NRTI patients, the reduction in viral load with ZIAGEN[®] was very low. The degree of viral load reduction as part of a new combination regimen will depend on the nature and duration of prior therapy which may have selected for HIV-1 variants with cross-resistance to abacavir.

Immune Reconstitution Syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise and cause serious clinical conditions, or aggravations of symptoms. Typically, such reactions have been observed within the first few weeks or month of initiation of ART. Relevant examples are cytomegalovirus retinitis, generalized and/or focal mycobacterial infections and *Pneumocystis jirovecii* (*P.carinii*) pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary.

Renal

Preliminary data from a single-dose pharmacokinetic study of ZIAGEN[®] in 6 end-stage renal disease patients has demonstrated that abacavir concentrations were similar to those with normal renal function. The two major metabolites (5'-glucuronide and 5'-carboxylate metabolites) are likely to accumulate but are considered inactive. No dosing modification of ZIAGEN[®] is recommended in patients with renal dysfunction. However, ZIAGEN[®] should be avoided in patients with end-stage renal disease. Once-daily ZIAGEN[®] 600 mg dosing has not been studied in the patients with impaired renal function and is not recommended for use in this population.

Respiratory

Severe respiratory symptoms, some indicative of adult respiratory distress syndrome (ARDS), occur in a small proportion of hypersensitivity reaction cases. ARDS or respiratory failure appears more likely to occur in a rechallenge situation.

Special Populations

Pregnant Women

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.

There have been reports of mild, transient elevations in serum lactate levels, which may be due to mitochondrial dysfunction, in neonates and infants exposed *in utero* or peri-partum to nucleoside reverse transcriptase inhibitors (NRTIs). The clinical relevance of transient elevations in serum lactate is unknown. There have also been very rare reports on developmental delay, seizures and other neurological disease. However, a causal relationship between these events and NRTI exposure *in utero* or peri-partum has not been established. These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

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 1000 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 per day. The offspring of female rats treated with abacavir at 500 mg/kg (beginning at embryo implantation and ending at weaning) showed increased incidence of stillbirth and lower body weights throughout life. In the rabbit, there was no evidence of drug-related developmental toxicity and no increases in fetal malformations at doses up to 700 mg/kg (8.5 times the human exposure at the recommended dose, based on AUC).

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 GlaxoSmithKline's Drug Surveillance Department (1-800-387-7374).

Nursing Women

It is recommended that HIV infected women do not breastfeed their infants under any circumstances in order to avoid transmission of HIV. It is therefore recommended that mothers do not breastfeed their babies while receiving treatment with ZIAGEN[®].

Abacavir and its metabolites are secreted into the milk of lactating rats. It is expected that these will also be secreted into human milk, although this has not been confirmed. There is no data available on the safety of ZIAGEN[®] when administered to babies less than three months old.

Pediatrics

Abacavir is rapidly and well absorbed from the oral solution when administered to children. The overall pharmacokinetic parameters in children are comparable to adults, with greater variability in plasma concentrations (see DETAILED PHARMACOLOGY: Pediatric Patients). The recommended dose for children from 3 months to 12 years old is 8 mg/kg twice daily. This will provide slightly higher mean plasma concentrations in children, ensuring that the majority will achieve a therapeutic concentration equivalent to 300 mg twice daily in adults. There are insufficient safety data to recommend the use of ZIAGEN[®] in infants less than three months old.

Geriatrics

Clinical studies of ZIAGEN[®] did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Once-daily ZIAGEN[®] 600 mg dosing has not been studied in the elderly and is not recommended for use in this population.

Use of Once-Daily ZIAGEN[®] in Patients with CoMorbidity Conditions and in the Elderly:

A ZIAGEN[®] 600 mg OD regimen should not be used in patients over 65 years of age, or in patients with comorbid conditions such as hepatic or renal failure, as this dosing regimen has not been studied in this population.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Hypersensitivity Reactions

Fatal hypersensitivity reactions have been associated with therapy with ZIAGEN[®] (abacavir sulfate).

Therapy with ZIAGEN[®] or any other medicinal product containing abacavir **must 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 must 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 (respiratory diseases, flu-like illness, gastroenteritis or reactions to other medications). ZIAGEN[®] or any other medicinal product containing abacavir should not be restarted even if a recurrence of symptoms occurs following rechallenge with alternative medication(s).

Severe or fatal hypersensitivity reactions can occur within hours after ZIAGEN[®] reintroduction in patients who have no identified history or unrecognized symptoms of hypersensitivity during their initial period of use of ZIAGEN[®] (see WARNINGS AND PRECAUTIONS).

If therapy with ZIAGEN[®] or any other medicinal product containing abacavir has been discontinued and restarting 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 a hypersensitivity reaction cannot be ruled out, ZIAGEN[®] or any other medicinal product containing abacavir should not be restarted.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Hypersensitivity to abacavir was reported in approximately 8% of patients in 9 clinical trials (range: 2% to 9%). This reaction is characterized by the appearance of symptoms indicating multi-organ / body-system involvement. Symptoms can occur at any time during therapy; however they usually appear within the first six weeks (median time to onset 11 days) of initiation of treatment with abacavir.

In 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 AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Almost all patients developing hypersensitivity reactions will have fever and/or rash (usually maculopapular or urticarial) as part of the syndrome; however reactions have occurred without rash or fever.

The signs and symptoms of this hypersensitivity reaction are listed below. Those reported **in at least 10% of patients** with a hypersensitivity reaction are in bold text.

Gastrointestinal tract:	Abdominal pain, diarrhea, mouth ulceration, nausea, vomiting
Haematological:	Lymphopenia
Liver/pancreas:	Elevated liver function tests, hepatic failure
Miscellaneous:	Anaphylaxis, conjunctivitis, edema, fatigue, fever, hypotension, lymphadenopathy, malaise

Musculoskeletal:	Arthralgia, elevated creatine phosphokinase, myalgia , rarely myolysis,
Neurological/Psychiatric:	Headache , paraesthesia
Respiratory tract:	Adult respiratory distress syndrome, cough , dyspnea , respiratory failure, sore throat
Skin:	Rash (usually maculopapular or urticarial)
Urology:	Elevated creatinine, renal failure

Some patients who experienced a hypersensitivity reaction were initially thought to have acute onset or worsening respiratory disease. The diagnosis of a 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, gastroenteritis or reactions to other medications are possible.

Symptoms worsen with continued therapy, and usually resolve upon discontinuation of ZIAGEN[®].

Restarting ZIAGEN[®] or any other medicinal product containing abacavir following a hypersensitivity reaction results in a prompt return of symptoms within hours. This recurrence of the hypersensitivity reaction may be more severe than on initial presentation, and may include life-threatening hypotension and death. Patients who develop this hypersensitivity reaction must discontinue ZIAGEN[®] and must never be rechallenged with ZIAGEN[®] or any other medicinal product containing abacavir (KIVEXA[®] or TRIZIVIR[®]).

For many of the other adverse events reported, it is unclear whether they are related to ZIAGEN[®], to the wide range of medicinal products used in the management of HIV disease or as a result of the disease process.

Many of the events listed (nausea, vomiting, diarrhea, fever, fatigue, rash) occur commonly as part of abacavir hypersensitivity. Therefore, patients with any of these symptoms should be carefully evaluated for the presence of this hypersensitivity reaction.

The majority of the events listed below have not been treatment-limiting. Care however, must be taken to eliminate the possibility of a hypersensitivity reaction if any of these symptoms occur.

The following convention has been used for classification: very common (> 1/10), common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100), rare (> 1/10,000, < 1/1,000) very rare (< 1/10,000).

Gastrointestinal:	Common: diarrhea, nausea, vomiting Rare: pancreatitis has been reported, but a causal relationship to ZIAGEN [®] treatment is uncertain
Metabolism and nutrition disorders:	Common: anorexia, hyperlactatemia Rare: lactic acidosis (see: WARNINGS AND PRECAUTIONS)
Nervous system disorders:	Common: headache
Other:	Common: fatigue, fever, lethargy
Skin and subcutaneous tissue disorders:	Common: rash (without systemic symptoms) Very rare: erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis

Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues.

In controlled clinical studies laboratory abnormalities related to ZIAGEN[®] treatment were uncommon, with no differences in incidence observed between ZIAGEN[®]-treated patients and the control arms.

ZIAGEN[®] Once Daily vs. ZIAGEN[®] Twice Daily (Study CNA30021)

Treatment-emergent clinical adverse reactions (rated by the investigator as at least moderate) with a $\geq 5\%$ frequency during therapy with ZIAGEN[®] 600 mg once daily and efavirenz 600 mg once daily from Study 30021 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.

Post-Market Adverse Drug Reactions

In addition to adverse events 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 WARNINGS AND PRECAUTIONS: Fat Redistribution).

Hepatic: Lactic acidosis and hepatic steatosis (see WARNINGS AND PRECAUTIONS: Lactic Acidosis/Severe Hepatomegaly with Steatosis).

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 the clinical signs and symptoms between hypersensitivity to abacavir, 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 been reports of erythema multiforme with abacavir use.

Other Warnings

A patient with a diagnosis of AIDS dementia and a history of seizure disorder experienced a seizure 3 days after stopping ZIAGEN[®] therapy. In the absence of an autopsy, a definitive diagnosis could not be adequately made, and a possible relationship to abacavir therefore could not be ruled out.

DRUG INTERACTIONS

Overview

Based on the results of *in vitro* experiments and the known major metabolic pathways of abacavir sulfate, the potential for drug interactions involving abacavir sulfate is low. Abacavir sulfate shows low potential to inhibit metabolism mediated by the cytochrome P₄₅₀ 3A4 enzyme. It has also been shown *in vitro* not to interact with drugs that are metabolized by CYP3A4, CYP2C9 or CYP2D6 enzymes. Induction of hepatic metabolism has not been observed in clinical studies. Therefore, there is little potential for drug interactions with antiretroviral protease inhibitors and other drugs metabolized by major P₄₅₀ enzymes. Clinical studies have shown that there are no clinically significant interactions between abacavir sulfate, zidovudine, and lamivudine.

Drug-Drug Interactions

The drugs listed in the table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e. those identified as contraindicated).

Table 1 Established or Potential Drug-Drug Interactions

Proper name	Effect	Clinical comment
Ethanol	In men, the metabolism of abacavir sulfate is altered.	In men, the metabolism of abacavir sulfate is altered by concomitant ethanol resulting in an increase in AUC of abacavir of about 41%. The clinical significance of this is unknown. In men, abacavir sulfate has no effect on the metabolism of ethanol. This interaction has not been studied in women.
Methadone	Changes in abacavir pharmacokinetics.	In a pharmacokinetic study, coadministration of 600 mg abacavir twice daily and methadone showed a 35% reduction in abacavir C _{max} and a 1 hour delay, but AUC was unchanged. The changes in abacavir pharmacokinetics are not considered clinically relevant. In this study abacavir increased methadone systemic clearance by 22%. This change is not considered clinically relevant for the majority of patients; however occasionally methadone retitration may be required.
Retinoids	Interaction with elimination is possible.	Retinoid compounds such as isotretinoin, are eliminated via alcohol dehydrogenase. Interaction with abacavir is possible but has not been studied.

DOSAGE AND ADMINISTRATION

ZIAGEN[®] (abacavir sulfate) is available as an oral solution for use in children and for those patients for whom tablets are inappropriate.

Dosing Considerations

A Consumer Information Leaflet and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill.

ZIAGEN[®] can be taken with or without food.

Recommended Dose and Dosage Adjustment

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. The use of 600 mg once daily may be associated with a higher incidence of severe hypersensitivity reactions.

The use of once daily ZIAGEN[®] 600 mg has not been studied in patients less than 18 years of age.

The use of once daily ZIAGEN[®] 600 mg has not been studied in elderly patients or patients with comorbid conditions.

Adolescents over 12 years of age: The recommended dose of ZIAGEN[®] is 300 mg (one tablet or 15 mL of oral solution) twice daily in combination with other antiretroviral agents.

Adolescent and Pediatric patients (over three months of age to age 12): The recommended oral dose of ZIAGEN[®] for adolescent and pediatric patients 3 months up to 12 years of age is 8 mg/kg twice daily (up to a maximum of 300 mg twice daily) in combination with other antiretroviral agents.

Children less than three months of age: There are insufficient data to recommend the use of ZIAGEN[®] in infants less than three months old (see WARNINGS AND PRECAUTIONS: Pediatrics).

Change in Regimen: Patients changing to the once daily regimen should take 300 mg twice a day and switch to 600 mg once a day the following morning. Where an evening once daily regimen is preferred, 300 mg of ZIAGEN[®] should be taken on the first morning only, followed by 600 mg in the evening. When changing back to a twice daily regimen, patients should complete the day's treatment and start 300 mg twice a day the following morning.

Patients, guardians and caregivers of pediatric patients must be made aware of the potential signs and symptoms of a hypersensitivity reaction to abacavir and that abacavir must be stopped and never restarted following a possible hypersensitivity reaction (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections).

Renal impairment: No dosage adjustment of ZIAGEN[®] is necessary in patients with renal dysfunction. However, ZIAGEN[®] should be avoided in patients with end-stage renal disease. The use of ZIAGEN[®] 600 mg once daily has not been studied in patients with renal impairment and is not recommended for use in this population (see WARNINGS AND PRECAUTIONS: Renal).

Hepatic impairment: Abacavir is primarily metabolized by the liver. The recommended dose of ZIAGEN[®] in patients with mild hepatic impairment (Child-Pugh score 5-6) who have confirmed cirrhosis is 200 mg twice a day. To enable dose reduction ZIAGEN[®] oral solution should be used for the treatment of these patients. ZIAGEN[®] is contraindicated in patients with moderate or severe hepatic impairment, as the pharmacokinetics have not been studied in these patient groups. (See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS: Impaired Hepatic Function).

Missed Dose

If the patient forgets to take their medicine, they should take it as soon as they remember. Then continue as before. Patients should not take a double dose to make up for forgotten individual doses. If a patient stops therapy with ZIAGEN[®] because of side effects or illness, they must check with their doctor before restarting therapy to make sure that symptoms of a hypersensitivity reaction have not been missed.

OVERDOSAGE

There is no known antidote for ZIAGEN[®] (abacavir sulfate).

If overdosage occurs, the patient should be monitored, and standard supportive treatment applied as required. Although no data is available, administration of activated charcoal may be used to aid in the removal of unabsorbed drug. It is not known whether abacavir sulfate can be removed by peritoneal dialysis or hemodialysis.

Limited data are available on the consequences of ingestion of acute overdoses in humans. Single doses up to 1200 mg and daily doses up to 1800 mg of abacavir sulfate have been administered to patients in clinical studies. No unexpected adverse reactions were reported. The effects of higher doses are not known. No specific signs or symptoms have been identified following such overdose.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Abacavir is a nucleoside analogue reverse transcriptase inhibitor. Abacavir is metabolized intracellularly to the active moiety, carbovir 5'-triphosphate (TP), a potent, selective inhibitor of HIV-1 and HIV-2, including HIV-1 isolates with reduced susceptibility to zidovudine, lamivudine, zalcitabine, didanosine and nevirapine. *In vitro* studies have demonstrated that its mechanism of action in relation to HIV is inhibition of the HIV reverse transcriptase enzyme, an event which results in chain termination and interruption of the viral replication cycle. Abacavir shows synergy *in vitro* in combination with nevirapine or zidovudine. It has been shown to be additive in combination with didanosine, zalcitabine, lamivudine and stavudine.

Pharmacokinetics

Abacavir sulfate is rapidly and well absorbed following oral administration. The absolute bioavailability of oral abacavir sulfate in adults is about 83%. Following oral administration, the mean time (t_{\max}) to maximal serum concentrations of abacavir is about 1.5 hours for the tablet formulation and about 1.0 hour for the solution formulation.

There are no differences observed between the AUC for the tablet or solution. At 300 mg twice daily, the steady state C_{\max} of abacavir sulfate tablets is approximately 3 $\mu\text{g/mL}$, and the AUC over a dosing interval of 12 hours is approximately 6 $\mu\text{g}\cdot\text{h/mL}$. The C_{\max} value for the oral solution is slightly higher than the tablet.

Food delayed absorption and decreased C_{\max} but did not affect overall plasma concentrations (AUC). Therefore, ZIAGEN[®] can be taken with or without food.

In a study of 20 HIV-infected patients receiving abacavir 300 mg twice daily, with only one 300 mg dose taken prior to the 24 h sampling period, the geometric mean terminal carbovir-TP intracellular half-life at steady-state was 20.6 h, compared to the geometric mean abacavir plasma half-life in this study of 2.6 h. The steady state pharmacokinetic properties of abacavir 600 mg once daily was compared to abacavir 300 mg twice daily in a crossover study in 27 HIV-infected patients. Intracellular carbovir triphosphate exposures in peripheral blood mononuclear cells were higher for abacavir 600 mg once daily with respect to $\text{AUC}_{24,ss}$ (32 %, higher), $C_{\max 24,ss}$ (99% higher) and trough values (18% higher), compared to the 300 mg twice daily regimen. These data support the use of abacavir 600 mg once daily for the treatment of HIV-infected patients. Additionally, the efficacy and safety of this combination given once daily has been demonstrated in a pivotal clinical study (see CLINICAL TRIALS).

STORAGE AND STABILITY

Tablets

ZIAGEN[®] tablets should be stored between 15° and 30°C.

Oral solution

ZIAGEN[®] oral solution should be stored between 15° and 25°C.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms and Packaging

Tablets

ZIAGEN[®] (abacavir sulfate) tablets, containing abacavir sulfate equivalent to 300 mg abacavir, are yellow, biconvex, capsule-shaped, film-coated tablets imprinted with "GX 623" on one side with no marking on the reverse side. They are available in bottles of 60.

Oral Solution

ZIAGEN[®] oral solution, a clear to opalescent, yellowish, strawberry-banana flavoured liquid, contains abacavir sulfate equivalent to 20 mg of abacavir in each 1 mL. Available in bottles of 240 mL.

Composition

Tablets

Each ZIAGEN[®] 300 mg tablet contains 300 mg of abacavir as abacavir sulfate and the non-medicinal ingredients colloidal silicon dioxide, hydroxypropyl methyl cellulose, magnesium stearate, microcrystalline cellulose, polysorbate 80, sodium starch glycolate, titanium dioxide, triacetin and yellow iron oxide.

Oral Solution

Each millilitre of ZIAGEN[®] 20 mg/mL oral solution contains 20 mg of abacavir as abacavir sulfate and the non-medicinal ingredients artificial strawberry and banana flavours, citric acid (anhydrous), hydrochloric acid, methylparaben, propylene glycol, propylparaben, saccharin sodium, sodium citrate (dihydrate), sodium hydroxide and sorbitol solution.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

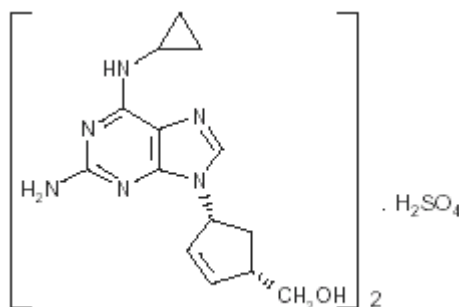
Drug Substance

Proper name: abacavir sulfate

Chemical name: (1S,cis)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1)

Molecular formula and molecular mass: $(C_{14}H_{18}N_6O)_2 \cdot H_2SO_4$, 670.76

Structural formula:



Physicochemical properties:

Description: Abacavir sulfate is a white to off-white powder with a melting point around 219 ° C followed by decomposition.

The aqueous solubility and pH of abacavir sulfate was determined at 25 ° C as follows:

Solvent	Solubility (mg/mL)	pH
Distilled water	77	3.1
0.1 M HCL	110	1.6
0.1 M NaOH	22	12.2

PKa: The pK_a for abacavir have been determined by UV spectroscopy at 25 ° C as follows:

pK₁ = 0.4, pK₂ = 5.06.

CLINICAL TRIALS

CNAAB3005 is a multi-centre, double-blind study in which 562 HIV-1 infected, therapy-naive adults were randomized to receive either ZIAGEN[®] (300 mg twice daily) and COMBIVIR[®] (lamivudine, 150 mg and zidovudine, 300 mg twice daily) or indinavir (800 mg three times daily) and COMBIVIR[®] (twice daily) for 48 weeks. All subjects were required to adhere to the TID regimen and food/water restrictions. Study participants were predominantly male (87%) and Caucasian (73%). The median age was 35.7 years, the median pretreatment CD4 cell count was 360 cells/mm³, and median plasma HIV-1 RNA was 4.83 log₁₀ copies/mL.

Over 48 weeks, treatment of naive adult patients, with the combination of abacavir, lamivudine and zidovudine showed a similar antiviral effect to the combination with indinavir, lamivudine and zidovudine when 400 copies/mL was the threshold used.

In a secondary analysis of patients with baseline plasma HIV-1-RNA levels above 100,000 copies/mL and when the ultrasensitive assay was used to determine the proportion of patients with less than 50 copies/mL, patients receiving the combination containing indinavir had a superior response.

In a multi-centre, double-blind controlled study (CNA30021), 770 HIV-infected adults were randomized to receive either abacavir 600 mg once daily or 300 mg twice daily, both in combination with lamivudine 300 mg once daily and efavirenz 600 mg once daily. Patients were stratified at baseline based on plasma HIV-RNA ≤ 100 000 copies/mL or > 100 000 copies/mL. The duration of double-blind treatment was at least 48 weeks. The results are summarized in Table 2 below.

Table 2 Virological Response Based in Plasma HIV-1 RNA < 50 copies/mL at Week 48 ITT-Exposed Population

Populations	abacavir once/day +3TC[®]+EFV (N=384)	abacavir twice/day +3TC[®]+EFV (N=386)
Sub-group by baseline RNA		
≤ 100,000 copies/mL	141/217 (65%)	145/217 (67%)
> 100,000 copies/mL	112/167 (67%)	116/169 (69%)
Total population	253/384 (66%)	261/386 (68%)

The abacavir once-daily arm was demonstrated to be non-inferior when compared to the twice daily group in the overall and baseline viral load sub-groups.

In a study comparing the unblinded NRTI combinations (with or without blinded nelfinavir) in children, a greater proportion treated with abacavir and lamivudine (71%) or abacavir and zidovudine (60%) had HIV-1 RNA ≤ 400 copies/mL at 48 weeks, compared with those treated with lamivudine and zidovudine (47%) [p=0.09, intention to treat analysis]. Similarly, greater proportions of children treated with the abacavir-containing combinations had HIV-1 RNA ≤ 50 copies/mL at 48 weeks (53%, 42% and 28% respectively, p=0.07).

DETAILED PHARMACOLOGY

Clinical Pharmacology

Pharmacokinetics in Adults

The pharmacokinetic properties of abacavir sulfate 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 sulfate were independent of dose over the range of 300 to 1200 mg/day.

Absorption and Bioavailability

Abacavir sulfate was rapidly and extensively absorbed after oral administration. Absolute bioavailability of the tablet was $86\% \pm 25\%$ (mean \pm SD). After oral administration of 300 mg twice daily in 20 patients, the steady-state peak serum abacavir concentration (C_{\max}) was $3.0 \pm 0.89 \mu\text{g/mL}$ (mean \pm SD) and $\text{AUC}_{(0-12 \text{ hours})}$ was $6.02 \pm 1.73 \mu\text{g}\cdot\text{h/mL}$. After oral administration of a single dose of 600 mg of abacavir in 20 patients, C_{\max} was $4.26 \pm 1.19 \mu\text{g/mL}$ (mean \pm SD) and AUC_{∞} was $11.95 \pm 2.51 \mu\text{g}\cdot\text{h/mL}$. Bioavailability of abacavir sulfate tablets was assessed in the fasting and fed states (standard meal; 967 kcal, 67 grams fat, 33 grams protein, 58 grams carbohydrate). Food decreased C_{\max} by 35% and delayed T_{\max} by 0.5 hours to 1.5 hours. However, there was no significant difference in systemic exposure (AUC_{∞}) in the fed and fasted states; therefore, ZIAGEN[®] (abacavir sulfate) tablets may be administered with or without food. ZIAGEN[®] oral solution and ZIAGEN[®] tablets are bioequivalent with respect to AUC and the products may be used interchangeably.

Distribution

Following intravenous administration, the apparent volume of distribution was about 0.8 L/ kg, indicating that abacavir penetrates freely into body tissues.

Studies in HIV-infected patients have shown good penetration of abacavir into the cerebrospinal fluid (CSF), with a CSF to plasma AUC ratio of between 30 to 44%. In a Phase I pharmacokinetic study, the penetration of abacavir into the CSF was investigated following administration of abacavir 300 mg twice a day.

The mean concentration of abacavir achieved in the CSF 1.5 hours post dose was 0.14 $\mu\text{g/mL}$. In a further pharmacokinetic study of 600 mg twice a day, the CSF concentration of abacavir increased over time, from approximately 0.13 $\mu\text{g/mL}$ at 0.5 to 1 hour after dosing, to approximately 0.74 $\mu\text{g/mL}$ after 3 to 4 hours. While peak concentrations may not have been attained by 4 hours, the observed values are 9-fold greater than the IC_{50} of abacavir of 0.08 $\mu\text{g/mL}$ or 0.26 μM . However, no effect on neuropsychological performance was seen when administered to patients with AIDS Dementia Complex.

Plasma protein binding studies *in vitro* indicate that abacavir binds only low to moderately (~ 49%) to human plasma proteins at therapeutic concentrations. This indicates a low likelihood for drug interactions through plasma protein binding displacement.

Metabolism

The primary routes of elimination of abacavir are metabolism by alcohol dehydrogenase (to form the 5'-carboxylic acid) and glucuronyl transferase (to form the 5'-glucuronide). The metabolites do not have antiviral activity. *In vitro* experiments reveal that abacavir had weak inhibition of human CYP3A4, CYP2D6, or CYP2C9 activity at clinically relevant concentrations. In humans, abacavir is not significantly metabolized by cytochrome P₄₅₀ enzymes.

Abacavir is metabolized intracellularly to the active moiety, carbovir triphosphate.

Elimination

Elimination of abacavir was quantified in a mass balance study following administration of a 600 mg dose of ¹⁴C-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 the unidentified minor metabolite 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. Total clearance was 0.84 ± 0.24 L/hr per kg (mean \pm SD).

Pediatric Patients

The pharmacokinetics of abacavir has been studied after either single or repeat doses of ZIAGEN[®] in 68 pediatric patients. Following multiple-dose administration of ZIAGEN[®] 8 mg/kg twice a day, steady-state AUC_∞ and C_{max} were 9.94 ± 4.50 µg•h/mL and 3.71 ± 1.36 µg/mL (mean \pm SD), respectively.

MICROBIOLOGY

Antiviral Activity In Vitro

The *in vitro* anti-HIV-1 activity of abacavir was evaluated against a T-cell tropic laboratory strain HIV-1 IIIB in lymphoblastic cell lines, a monocyte/macrophage tropic laboratory strain HIV-1 BaL in primary monocytes/macrophages, and clinical isolates in peripheral blood mononuclear cells. The concentration of drug necessary to inhibit viral replication by 50 percent (IC₅₀) ranged from 3.7 to 5.8 µM against HIV-1 IIIB, and was 0.26 ± 0.18 µM (1µM = 0.28 µg/mL) against eight clinical isolates. The IC₅₀ of abacavir against HIV-1 BaL varied from 0.07 to 1.0µM. Abacavir had synergistic activity in combination with amprenavir, nevirapine, or zidovudine, and additive activity in combination with didanosine, lamivudine, stavudine, or zalcitabine *in vitro*. These drug combinations have not been adequately studied in humans. The relationship between *in vitro* susceptibility of HIV to abacavir and the inhibition of HIV replication in humans has not been established.

Drug Resistance

Abacavir-resistant isolates of HIV-1 have been selected *in vitro* and are associated with specific genotypic changes in the reverse transcriptase (RT) coding region (codons K65R, L74V, Y115F, and M184V). *In vitro* selection for resistance to abacavir occurs relatively slowly and requires multiple mutations. The mutations selected by *in vitro* passage have also been observed among isolates obtained from patients participating in clinical trials, with L74V and M184V being the most common. Combination therapy with ZIAGEN[®] (abacavir sulfate) and zidovudine delays the emergence of mutations associated with resistance to ZIAGEN[®] compared with monotherapy with ZIAGEN[®].

Phenotypic analysis of HIV-1 isolates that harbour abacavir-associated mutations from 17 patients after 12 weeks of abacavir monotherapy exhibited a 3-fold decrease in susceptibility to abacavir *in vitro*. The clinical relevance of genotypic and phenotypic changes associated with abacavir therapy has not been established.

A once-daily regimen of abacavir was investigated in a multi-centre, double-blind, controlled study, (CNA30021) of 770 HIV-infected, therapy-naive adults. They were randomized to receive either abacavir 600 mg once daily or 300 mg twice daily, both in combination with lamivudine 300 mg once daily and efavirenz 600 mg once daily. Patients were stratified at baseline based on plasma HIV-1 RNA \leq 100 000 copies/mL or $>$ 100,000 copies/mL. The duration of the double-blind treatment was at least 48 weeks.

There was a low overall incidence of virologic failure (confirmed HIV RNA $>$ 50 copies/mL) in both the once-and twice-daily treatment groups (10% and 8% respectively). Additionally for technical reasons, genotyping was restricted to samples with plasma HIV-RNA $>$ 500 copies/mL. This resulted in a small sample size. Therefore no firm conclusions could be drawn regarding differences in treatment-emergent mutations between the two treatment groups. Reverse transcriptase amino acid residue 184 was consistently the most frequent position for NRTI resistance-associated mutations (M184V or M184I). The second most frequent mutation was L74V. Mutations Y115F and K65R were uncommon.

Cross-resistance

In vitro, isolates selected for resistance to abacavir may also be resistant to lamivudine, zalcitabine, and/or didanosine, but remain sensitive to zidovudine and stavudine.

The likelihood of a response to abacavir sulfate in an individual patient who has received prior treatment with other nucleoside analogues cannot be predicted. However, limited data seems to suggest patients with viral isolates carrying only the M184V mutation experienced comparable decreases in plasma HIV-1 RNA as patients with wild-type virus.

TOXICOLOGY

Acute Toxicity

Single oral or intravenous dose acute toxicity studies in the mouse and rat revealed no significant effects. The maximum non-lethal oral dose of abacavir in the mouse and rat was at least 100- and 115-fold greater, respectively, than the maximum intended therapeutic dose in humans of 300 mg BID (12 mg (base)/kg/day for a 50 kg person).

The results are summarized in Table 3.

Table 3 Median Lethal Doses of Abacavir in Mice and Rats Following Oral and Intravenous Administration

Species (strain)	Route of Administration	Sex	Median Lethal Dose (mg/kg)		Multiple of Therapeutic Dose*
			Succinate	Base	
Mouse (CD-1)	Oral	Male	1731.68	1226	102
		Female	> 1900	1345	112
	Intravenous	Male	> 260	> 184	> 15
		Female	> 260	> 184	> 15
Rat (CD)	Oral	Male	> 2000	> 1416	118
		Female	> 2000	> 1416	118
	Intravenous	Male	> 260	> 184	> 15
		Female	> 260	> 184	> 15

Key:

* = Median lethal dose/ therapeutic dose (300 mg (base) b.i.d., equivalent to 12 mg(base)/kg/day based on a 50 kg person).

Long-term toxicity

Repeated oral administration of abacavir succinate to mice at 330 mg/kg/day for up to 6 months, and to monkeys at 300 mg/kg/day for up to 52 weeks, or abacavir sulfate to rats at 530 mg/kg/day for up to 3 months, resulted in few changes which were mostly reversible.

The only consistent findings in rodents and monkeys were changes in the liver. Increases in liver weights seemed to be dose-related in the monkey. Microscopically, slight centrilobular hepatocellular hypertrophy was seen in these animal species. Occasional individual cell necrosis, pigment deposits in centrilobular hepatocyte and Kupffer cells were seen in mice and rats. In high-dose monkeys, slightly swollen mitochondria, a decrease in the amount of rough endoplasmic reticulum and increase number of lysosomes was observed using electron microscopy.

The results are summarized in Table 4.

Table 4 Findings in Mice, Rats and Monkeys Following Long-Term Oral Administration of Abacavir

Species (Strain) Report No. [Salt used]	Study Duration	Number of Animals/Group		Dosage (mg/kg/day)		Toxic Effects Observed
		Males	Females	Salt	Base	
Mouse (CD1) RD 1996/00245/00 [Abacavir succinate]	6 months	30 30 40	30 30 40	55 110 330	39 78 234	Very slight increase in serum cholesterol in males at 110 mg and both sexes at 330 mg. Increased liver weight and hepatocellular hypertrophy seen at 330 mg. Dose-related and reversible increases in endogenous pigment deposition in Kupffer cells and centrilobular hepatocytes. Very slight increase in caecal crypt epithelial cell apoptosis associated with submucosal inflammation at 330 mg.
Rats (Han Wistar) RD 1997/03595/00 [Abacavir hemisulfate]	3 months	5 5 5	5 5 5	35 135 530	25 96 375	Slight decreases in serum albumin and total protein and a slight increase in serum cholesterol at 530 mg. Very slight decrease in serum albumin in females at 135 mg. Slight increase in liver weight, centrilobular hepatocellular hypertrophy and accumulation of brown pigment in Kupffer cells at 530 mg. Similar liver changes also observed in males at 135 mg. Trace hypertrophy of thyroid follicular epithelium and germ cell loss in testes at 530 mg.
Monkey (Cynomolgus) RD 1996/00310/01 [Abacavir succinate]	12 months	7 7 9	7 7 9	50 140 300 †	35 99 212	Emesis at 420 mg decreased when dosage reduced to 300 mg. Hunched posture, hypoactivity, decreased appetite and/or abnormal or reduced fecal output seen at 420 mg, but not at 300 mg. Reduced body weight gain at 420/300 mg during first 5-6 weeks of treatment. Transient reductions in erythrocyte count (females only), hemoglobin concentration and hematocrit and an increase in reticulocyte count at 420 mg, but these changes not seen at 300 mg. Increased liver weight and hepatocellular hypertrophy seen at 300 mg, with some evidence of an effect at lower dosages. Ultrastructural liver changes included slightly swollen mitochondria, decreased rough endoplasmic reticulum, and an increase in lysosomes at 300 mg. Slight increases in serum alanine aminotransferase and triglycerides probably related to the liver changes.

Key:

† = Initially 420 mg/kg/day, but reduced to 300 mg/kg/day on day 36 due to unacceptable toxicity

Carcinogenicity

Carcinogenicity studies with orally administered abacavir in mice and rats showed an increase in the incidence of malignant and non-malignant tumours. Malignant tumours occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver, urinary bladder, lymph nodes and the subcutis of female rats.

The majority of these tumours occurred at the highest abacavir dose of 330 mg/kg/day in mice and 600 mg/kg/day in rats. These dose levels were equivalent to 24 to 32 times the expected systemic exposure in humans. The exception was the preputial gland tumour which occurred at a dose of 110 mg/kg. This is equivalent to six times the expected human systemic exposure. There is no structural counterpart for this gland in humans.

Reductions in survival and body weight in rats at 600 mg/kg/day resulted in the early discontinuation of dosing in Weeks 84 (males) and 100 (females). Survival in mice was also reduced at 330 mg/kg/day, resulting in the early discontinuation of dosing of males in Week 98.

While the carcinogenic potential in humans is unknown, these data suggest that a carcinogenic risk to humans is outweighed by the potential clinical benefit.

Mild myocardial degeneration in the heart of mice and rats was observed following administration of abacavir for two 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.

Mutagenicity

In an *in vitro* cytogenetic study performed in human lymphocytes, abacavir induced chromosomal aberrations following exposure at 2800 and 3200 µg/mL for 3 hours in the presence of metabolic activation and after exposure at 100 and 125 µg/mL for 50.3 hours in the absence of metabolic activation. The abacavir concentrations at which evidence of genotoxicity was seen *in vitro* were at least 33 times higher than the expected maximum human blood level.

In an *in vitro* mouse bone marrow micronucleus test, there was a small (2.3-fold) increase in the number of micronucleated polychromatic erythrocytes in males at 1000 mg/kg. No significant increase was seen in bone marrow harvested from females. Findings in the micronucleus test were seen at systemic exposures (in terms of AUC) approximately nine times higher than exposure in humans at the therapeutic dose, and C_{max} values approximately 14 times higher than the maximum concentration in humans at the therapeutic dose.

No evidence of mutagenicity (with or without metabolic activation) was observed in bacterial mutagenicity assays at concentrations up to approximately 5000 µg/plate. In a mutagenicity assay conducted in L5178Y mouse lymphoma cells, abacavir was weakly mutagenic following exposure at 250 µg/mL for 24 hours in the absence of metabolic activation. Abacavir was not mutagenic to L5178Y mouse lymphoma cells in a 3-hour exposure in the presence or absence of metabolic activation.

Reproduction and Teratology

Abacavir had no adverse effects on the mating performance or fertility of male and female rats at doses of up to 500 mg/kg per day.

Reproduction studies were performed in rats and rabbits at orally administered doses up to 1000 mg/kg per day and 700 mg/kg per day, respectively. These doses in rats and rabbits achieved approximately 35 and 8.5 times, respectively, the exposure associated with the recommended human dose. In the rat, development toxicity (depressed fetal body weight and reduced crown-rump length) and increased incidences of fetal anasarca and skeletal malformations were observed at the highest dose assessed. Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. In a fertility study, evidence of toxicity to the developing embryo and fetuses (increased resorptions, decreased fetal body weights) occurred only at 500 mg/kg per day, a dose that was toxic to the parental generation. This dose in rats achieved approximately 33 times the exposure with the usual human dose. In the rabbit, there was no evidence of drug-related developmental toxicity and no increases in fetal malformations.

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PART III: CONSUMER INFORMATION

Pr **ZIAGEN[®]**
abacavir sulfate

This leaflet is part III of a three-part "Product Monograph" published when ZIAGEN[®] (abacavir sulfate) was approved for sale in Canada and is designed specifically for Consumers. This leaflet contains important information about your treatment with ZIAGEN[®]. Please read this leaflet carefully before you start your medicine. This leaflet is a summary and will not tell you everything about ZIAGEN[®]. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

The name of your medicine is ZIAGEN[®]. ZIAGEN[®] is an antiretroviral medication used in combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection. It is used in combination with other antiretrovirals to reduce the HIV in your blood. ZIAGEN[®] can be obtained with a prescription from your doctor.

What it does:

The Human Immunodeficiency Virus (HIV) is a retrovirus. Infection with HIV damages the immune system and can lead to Acquired Immune Deficiency Syndrome (AIDS) and other related illnesses.

ZIAGEN[®] is an antiretroviral medication. ZIAGEN[®] in combination with other antiretrovirals reduces the HIV in your blood. However, ZIAGEN[®] does not have this effect in all patients. Your doctor will be monitoring the effectiveness of your treatment. ZIAGEN[®] does not cure AIDS or kill the HIV virus, but may help to prevent further damage to the immune system by slowing down the production of new viruses. At this time, there is no evidence that ZIAGEN[®] will help you live longer or have fewer of the medical problems that are associated with HIV infection or AIDS. Because of this, you must be sure to be seen regularly by your health care provider.

When it should not be used:

Do not take ZIAGEN[®] if:

- you are allergic (hypersensitive) to the active substance abacavir, which is also included in a medicine called KIVEXA[®] and TRIZIVIR[®].
- you are allergic to any non-medicinal ingredient in ZIAGEN[®].
- you have moderate or severe liver disease.

If you are not sure whether you should be taking ZIAGEN[®], please discuss with your doctor before taking this medicine.

What the medicinal ingredient is:**Tablets**

Each ZIAGEN[®] 300 mg tablet contains 300 mg of abacavir as abacavir sulfate.

Oral Solution

Each millilitre of ZIAGEN[®] 20 mg/mL oral solution contains 20 mg of abacavir as abacavir sulfate.

What the important nonmedicinal ingredients are:**Tablets**

ZIAGEN[®] tablets also contain colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, polysorbate 80, microcrystalline cellulose, sodium starch glycolate, titanium dioxide, triacetin, and yellow iron oxide.

Oral Solution

ZIAGEN[®] oral solution also contains artificial strawberry and banana flavours, citric acid (anhydrous), hydrochloric acid, methylparaben, propylene glycol, propylparaben, saccharin sodium, sodium citrate (dihydrate), sodium hydroxide, and sorbitol solution.

What dosage forms it comes in:

ZIAGEN[®] is available in a 300 mg tablet and 20 mg/mL oral solution.

WARNINGS AND PRECAUTIONS**Serious Warnings and Precautions
Hypersensitivity Reaction**

Patients taking ZIAGEN[®] may develop a hypersensitivity reaction (serious allergic reaction) which **can be life threatening** if you continue to take ZIAGEN[®].

If you have two or more of the following sets of symptoms, you may be having this kind of reaction:

- **Rash**
- **Fever**
- **Nausea, vomiting, diarrhea, or abdominal pain**
- **Severe tiredness, achiness or generally ill feeling**
- **Sore throat, shortness of breath, or cough**

A written list of these symptoms is on the Warning Card provided by your pharmacist. You should carry this Warning Card with you. **If you notice these symptoms while taking ZIAGEN[®], stop taking ZIAGEN[®] and call your doctor immediately.**

If you have had this reaction to **ZIAGEN[®]**, **never take ZIAGEN[®] or any other medicine containing abacavir (such as KIVEXA[®] or TRIZIVIR[®]) again as within hours you may experience a life-threatening lowering of your blood pressure or death.**

It is important if you have stopped taking ZIAGEN[®] either on medical advice or because you think you are having side effects or due to other illness, that you **contact your doctor for advice** before restarting ZIAGEN[®]. Your doctor will check whether any symptoms you had before stopping may be related to this hypersensitivity reaction. If your doctor has any doubt about this, you will be advised to **never to take ZIAGEN[®] or any other medicine containing abacavir such as KIVEXA[®] or TRIZIVIR[®] again.**

You should return all of your unused ZIAGEN[®] to the doctor or pharmacist for proper disposal.

Lactic acidosis and swollen and fatty liver (hepatomegaly with steatosis), including fatal cases have been reported in patients using nucleoside analogues, including ZIAGEN[®] and other antiretrovirals (See Side Effects).

About 8 in every 100 patients, who are treated with ZIAGEN[®], develop a hypersensitivity reaction to the active ingredient abacavir. The symptoms usually include fever and a skin rash. Other frequently observed signs and symptoms include nausea, vomiting, diarrhea, abdominal pain, shortness of breath, cough, headache, and severe tiredness. Other symptoms may include sore throat, joint or muscle pain, and swelling of the neck. Occasionally inflammation of the eye (conjunctivitis), ulcers in the mouth or low blood pressure may occur. The symptoms of this allergic reaction usually occur in the first six weeks of treatment with ZIAGEN[®], but may occur at any time, and get worse with continued treatment.

Other Special Warnings

The class of medicines to which ZIAGEN[®] belongs (nucleoside reverse transcriptase inhibitor) (NRTIs) can cause a condition called lactic acidosis (high levels of lactic acid in the blood), together with an enlarged liver. Symptoms of lactic acidosis include feeling of weakness, loss of appetite, sudden unexplained weight loss, upset stomach and difficulty breathing or rapid breathing. This rare, but serious side effect occurs more often in women. If you have liver disease you may also be more at risk of getting this condition. While you are being treated with ZIAGEN[®] your doctor will monitor you closely for any signs that you may be developing lactic acidosis.

ZIAGEN[®] helps to control your condition but is not a cure for HIV infection. You will need to take it every day. Unless you suspect that you are having an allergic reaction with

ZIAGEN[®], do not stop taking your medicine without first talking to your doctor.

Treatment with ZIAGEN[®] has not been shown to reduce the risk of passing HIV infection on to others by sexual contact or by blood transfer. You should continue to use appropriate precautions to prevent this.

You may continue to develop other infections and other illnesses associated with HIV disease. You should therefore keep in regular contact with your doctor while taking ZIAGEN[®].

Use Of This Medicine During Pregnancy And Breastfeeding: If you are pregnant, or planning to become pregnant soon, or if you are breastfeeding, please inform your doctor before taking any medicines. The safe use of ZIAGEN[®] in human pregnancy has not been established. Your doctor will advise whether you should continue to take ZIAGEN[®].

Babies and infants exposed to Nucleoside Reverse Transcriptase Inhibitors (NRTIs) during labour, show minor temporary increases in blood levels of lactate. The clinical importance of these temporary increases is unknown.

There have been very rare reports of diseases that affect the nervous system such as delayed development and seizures.

These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent transmission of HIV to their babies.

The active substance abacavir in this medicine is likely to be found in human breast milk. There are no safety data available following treatment with ZIAGEN[®] in babies under three months of age. You are therefore recommended not to breastfeed your baby while taking ZIAGEN[®]. It is recommended that HIV infected women do not breastfeed their infants under any circumstances in order to avoid transmission of HIV from mother to child.

INTERACTIONS WITH THIS MEDICATION

ZIAGEN[®] is unlikely to interact with other medicines you are being treated with; however, it is important that you tell your doctor about all the medicines you are taking, including those you have bought yourself. In men, alcohol does increase the amount of abacavir in your blood. However, the meaning of this is unknown. This interaction has not been studied in women.

PROPER USE OF THIS MEDICATION**Usual dose:**

Take ZIAGEN[®] as your doctor has advised you. If you are unsure about how to take it, ask your doctor or pharmacist.

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. The use of 600 mg once daily may be associated with a higher incidence of severe hypersensitivity reactions.

The use of once daily ZIAGEN[®] 600 mg has not been studied in patients less than 18 years of age.

The use of once daily ZIAGEN[®] 600 mg has not been studied in elderly patients or patients with co-morbid conditions.

Adolescents over 12 years: The recommended dose of ZIAGEN[®] is 300 mg (one tablet or 15 mL of oral solution) twice daily in combination with other antiretroviral agents.

Adolescent and Pediatric patients (Over three months of age to age 12): The recommended oral dose of ZIAGEN[®] for adolescent and pediatric patients 3 months up to 12 years of age is 8 mg/kg twice daily (up to a maximum of 300 mg twice daily) in combination with other antiretroviral agents.

Children less than three months of age: There are insufficient data to recommend the use of ZIAGEN[®] in infants less than three months old.

Change in Regimen:

Patients changing to the once daily regimen should take 300 mg twice a day and switch to 600 mg once a day the following morning. Where an evening once daily regimen is preferred, 300 mg of ZIAGEN[®] should be taken on the first morning only, followed by 600 mg in the evening. When changing back to a twice daily regimen, patients should complete the day's treatment and start 300 mg twice a day the following morning.

The daily dose of ZIAGEN[®] may need to be reduced in some patients with liver disease.

An oral solution (20 mg abacavir/mL) is available for the treatment of children and adult patients unable to take tablets.

ZIAGEN[®] can be taken with food or on an empty stomach.

Overdose:

If you accidentally take too much of your medicine you should **immediately** contact either your doctor, your hospital emergency department, or the nearest poison control centre.

Missed Dose:

If you forgot to take your medicine, take it as soon as you remember. Then continue as before. Do not take a double dose to make up for forgotten individual doses. If you stop your therapy with ZIAGEN[®] because of side effects or illness, check with your doctor before restarting therapy to make sure that symptoms of a hypersensitivity reaction have not been missed.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

All medicines may cause some side effects. When treating HIV infection it is not always possible to tell whether any side effects that occur are caused by ZIAGEN[®], by other medicines you are taking at the same time, or by the HIV disease.

The side effects listed for ZIAGEN[®] are shown below:

The most common (could affect at least 1 in 10 in every 100 people) are nausea (feeling of sickness), vomiting, lethargy (unusual lack of energy), fatigue, anorexia (loss of appetite), fever (high temperature), headache, diarrhea, hyperlactatemia (high blood lactate level) and skin rash (without any other illness).

Rare (could affect < 1 in 1000 people) – lactic acidosis (excess of lactic acid in your blood) and inflammation of the pancreas (pancreatitis). This may result in increasing pain and discomfort in the upper abdomen and may be accompanied by nausea and vomiting. However, it is not known whether this is caused by ZIAGEN[®], other medicines you may be taking or by your HIV infection.

Very rare (could affect less < 1 in 10,000 people) – serious skin reactions which include erythema multiforme (a skin condition characterized by a red rash), Stevens-Johnson syndrome (a severe and sometimes fatal skin rash) and toxic epidermal necrolysis (a life threatening skin disorder characterized by blistering and peeling of the skin).

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"), breasts, and around the trunk. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health affects of these conditions are not known at this time.

Within the first few weeks of treatment with anti-HIV medicines, some may develop inflammatory reactions (e.g. pain, redness, swelling, high temperature) which may resemble an infection and may be severe. It is thought that these reactions are caused by a recovery in the body's ability to fight infections, previously suppressed by HIV.

The use of ZIAGEN® 600 mg once daily may be associated with a higher incidence of severe hypersensitivity reaction (HSR). If you suffer from these symptoms, please discuss with your doctor.

Always tell your doctor or pharmacist about any new symptoms, even those not mentioned in this leaflet. If you feel ill in any other way that you do not understand, tell your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

A hypersensitivity reaction (serious allergic reaction) has been reported in about 8 in every 100 patients who have been treated with ZIAGEN®. This is described in the section on Hypersensitivity Reaction (under WARNINGS AND PRECAUTIONS) in the beginning of this leaflet.

It is important that you read and understand the information about this serious reaction.

This is not a complete list of side effects. For any unexpected effects while taking ZIAGEN®, contact your doctor or pharmacist.

HOW TO STORE IT

Tablets

Store ZIAGEN® tablets between 15° and 30°C.

Oral Solution

Store ZIAGEN® oral solution between 15° and 25°C.

As with all medicines, keep ZIAGEN® out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmpp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

Serious Side Effect /Symptoms (2 or more of the following)		Talk with your doctor or pharmacist	Stop taking drug and call your doctor or pharmacist immediately
		In all cases	
Common: Fatal Hypersensitivity	Fever, skin rash, fatigue, Gastrointestinal symptoms (nausea, vomiting, diarrhea or abdominal pain), Respiratory symptoms, pharyngitis, (inflammation of the throat, causing sore throat, fever, earache, and swollen glands), dyspnea (difficulty breathing) and cough.	X	X
Rare: Lactic acidosis (high level of acid in the blood)	Weight loss, fatigue, malaise, abdominal pain, shortness of breath.	X	X
Rare: Severe hepatomegaly (swollen and fatty liver)	Nausea, vomiting, abdominal pain, weakness and diarrhea.	X	X

MORE INFORMATION

Remember: This medicine is for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

You may need to read this leaflet again. Please do not throw it away until you have finished treatment with ZIAGEN®.

This document plus the full product monograph, prepared for health professionals can be found at:

<http://www.gsk.ca>

or by contacting the sponsor, GlaxoSmithKline Inc.

7333 Mississauga Road

Mississauga, Ontario

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

Patients taking ZIAGEN[®] (abacavir sulfate) may develop a hypersensitivity reaction (a serious allergic reaction) which can be life-threatening if you continue to take ZIAGEN[®]. **If you have two or more of the following sets of symptoms while taking ZIAGEN[®], stop taking it and call your doctor immediately.**

	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

If you have had this reaction to ZIAGEN[®], **never** take ZIAGEN[®] or any other medicine containing abacavir (such as KIVEXA[®] or TRIZIVIR[®]) again as **within hours** you may experience a **life-threatening lowering of your blood pressure or death.**

Carry this card with you at all times.

You should return all of your unused ZIAGEN[®] to your doctor or pharmacist for proper disposal.