

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrZIAGEN

abacavir tablets, 300 mg
(as abacavir sulfate)

abacavir oral solution, 20 mg/ml
(as abacavir sulfate)

Mfr. Standard

Antiretroviral Agent

ViiV Healthcare ULC
245, boulevard Armand-Frappier
Laval, Quebec
H7V 4A7

Date of Revision:
June 17, 2019

Submission Control No: 226227

© 2019 ViiV Healthcare group of companies or its licensor.
Trademarks are owned by or licensed to the ViiV Healthcare group of companies.

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.....	10
DRUG INTERACTIONS	15
DOSAGE AND ADMINISTRATION.....	16
OVERDOSAGE	18
ACTION AND CLINICAL PHARMACOLOGY	18
STORAGE AND STABILITY.....	19
SPECIAL HANDLING INSTRUCTIONS	20
DOSAGE FORMS, COMPOSITION AND PACKAGING	20
PART II: SCIENTIFIC INFORMATION	21
PHARMACEUTICAL INFORMATION.....	21
CLINICAL TRIALS.....	22
DETAILED PHARMACOLOGY	23
MICROBIOLOGY	26
TOXICOLOGY	27
REFERENCES	30
PART III: CONSUMER INFORMATION	33

PrZIAGEN

abacavir tablets

abacavir oral solution

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients^a
Oral	Tablet/ 300 mg abacavir (as abacavir sulfate)	None
	Oral Solution/ 20 mg/mL abacavir (as abacavir sulfate)	Propylene glycol, sorbitol

a: For a complete list see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

INDICATIONS AND CLINICAL USE

ZIAGEN (abacavir) is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection.

Pediatrics (> 3 months to < 18 years of age)

ZIAGEN is indicated in pediatric patients aged 3 months and older in combination with other antiretroviral agents.

Geriatrics (≥ 65 years of age)

Clinical studies of ZIAGEN did not include sufficient numbers of patients aged 65 and older 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.

CONTRAINDICATIONS

ZIAGEN tablets and oral solution are contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.
- Patients who are positive for the HLA-B*5701 allele and patients with a prior history of a hypersensitivity reaction to abacavir, or products containing abacavir, regardless of HLA-B*5701 status. Fatal hypersensitivity reactions have been associated with rechallenge of abacavir (see **WARNINGS AND PRECAUTIONS**).
- Patients 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**

All patients should be screened for the HLA-B*5701 allele prior to initiating or re-initiating treatment with ZIAGEN. Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir, a component of ZIAGEN although, hypersensitivity reactions have occurred in patients who do not carry the HLA-B*5701 allele. Serious and sometimes fatal hypersensitivity reactions have been associated with therapy with abacavir sulfate and other abacavir-containing products (see **WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions**).

General

ZIAGEN is a nucleoside analogue and should always be used in combination with other antiretroviral agents. ZIAGEN should not be administered concomitantly with other products containing abacavir, including KIVEXA, TRIZIVIR and TRIUMEQ.

ZIAGEN oral solution contains sorbitol which may cause abdominal pain and diarrhea. Sorbitol is metabolised to fructose and is therefore unsuitable for patients who have hereditary fructose intolerance.

Patients receiving ZIAGEN or any other antiretroviral therapy may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

Patients should be advised that current antiretroviral therapy, including ZIAGEN, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be taken.

ZIAGEN oral solution contains methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed).

Hypersensitivity Reactions

Abacavir is associated with a risk for hypersensitivity reactions (HSR) characterized by fever and/or rash with other symptoms indicating multi-organ involvement (see **WARNINGS AND PRECAUTIONS**, Clinical Description of Abacavir HSRs). HSR can be life-threatening, and in rare cases fatal, when not managed appropriately. The risk for abacavir HSR to occur is significantly increased for patients who test positive for the HLA-B*5701 allele. However, abacavir HSRs have been reported at a lower frequency in patients who do not carry this allele.

Clinical Management of Abacavir HSRs

All patients should be screened for the HLA-B*5701 allele prior to initiating or re-initiating treatment with ZIAGEN.

Do not use ZIAGEN in HLA-B*5701-positive patients or in patients with a negative HLA-B*5701 status who had a suspected abacavir HSR on a previous abacavir-containing regimen.

HLA-B*5701-negative patients may develop a hypersensitivity reaction to abacavir; however, this occurs significantly less frequently than in HLA-B*5701-positive patients.

Regardless of HLA-B*5701 status, 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, influenza; gastroenteritis; or reactions to other medications).

Restarting abacavir-containing products following a suspected abacavir HSR can result in a prompt return of symptoms within hours. This recurrence is usually more severe than on initial presentation, and may include life-threatening hypotension and death.

NEVER restart ZIAGEN or any other abacavir-containing product in patients who have stopped therapy with ZIAGEN or any other abacavir-containing product due to a hypersensitivity reaction.

When therapy with **ZIAGEN** has been discontinued for reasons other than symptoms of a hypersensitivity reaction, and if reinitiation of **ZIAGEN** is under consideration, carefully evaluate the reason for discontinuation of **ZIAGEN** to ensure that the patient did not have symptoms of a hypersensitivity reaction.

If hypersensitivity cannot be ruled out, **DO NOT** reintroduce **ZIAGEN** or any other abacavir-containing product.

If symptoms consistent with abacavir 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. Reintroduction should be attempted only if the potential benefit outweighs the risk and if medical care can be readily accessed by the patient or others in case an adverse reaction occurs.

Clinical Description of Abacavir HSRs

Abacavir HSR has been well characterised through clinical studies and during post marketing follow-up. Symptoms usually appeared within the first six weeks (median time to onset 11 days) of initiation of treatment with abacavir, **although these reactions may occur at any time during therapy.**

Almost all HSR to abacavir include fever and/or rash. Other signs and symptoms that have been observed as part of abacavir HSR may include respiratory and gastrointestinal symptoms, including but not limited to pharyngitis, dyspnea or cough), and gastrointestinal symptoms (including, but not limited to, nausea, vomiting, diarrhea or abdominal pain). Importantly, such symptoms **may lead to misdiagnosis of HSR as respiratory disease (pneumonia, bronchitis, pharyngitis), or gastroenteritis.** Other frequently observed signs or symptoms of HSR may include, but are not limited to, generalized malaise, fatigue or achiness (see **ADVERSE DRUG REACTIONS, Description of Abacavir Hypersensitivity Adverse Reactions**). The symptoms related to this HSR worsen with continued therapy and **can be life-threatening.** These symptoms usually resolve upon discontinuation of abacavir.

A warning card with information for the patient about this hypersensitivity reaction is included in the **ZIAGEN** outer pack label (see a copy of this card on the last page).

Carcinogenesis and Mutagenesis

Carcinogenicity studies with abacavir in mice and rats showed an increase in malignant tumours 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 exposures equivalent to 24 to 33 times the expected systemic exposure in humans (see **TOXICOLOGY, Carcinogenicity**).

Abacavir was not mutagenic in a bacterial mutagenicity assay but induced chromosomal aberrations *in vitro* and was mutagenic in the absence of metabolic activation in an L5178Y mouse lymphoma assay. In an *in vivo* mouse bone marrow micronucleus assay,

abacavir was clastogenic in males at exposures ~9X higher than those in humans at the therapeutic dose (see **TOXICOLOGY, Mutagenicity**).

Cardiovascular

Several observational and epidemiological studies have reported an association with abacavir use and the risk of myocardial infarction. Meta-analyses of randomised controlled trials have observed no excess risk of myocardial infarction with abacavir use. To date, there is no established biological mechanism to explain a potential increase in risk. Overall, the available data from the observational studies and from controlled clinical trials show inconsistency and therefore the evidence for a causal relationship between abacavir treatment and the risk of myocardial infarction is inconclusive.

As a precaution, the underlying risk of coronary heart disease should be considered when prescribing antiretroviral therapies, including abacavir, and action taken to minimize all modifiable risk factors (e.g. hypertension, hyperlipidemia, diabetes mellitus and smoking).

Endocrine and Metabolism

Serum lipids and blood glucose

Serum lipid and blood glucose levels may increase during antiretroviral therapy. Disease control and life style changes may also be contributing factors. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders and blood glucose elevations should be managed as clinically appropriate.

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).

Female sex and obesity may be risk factors. Caution should be exercised when administering ZIAGEN or other nucleoside analogues, particularly to those 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 with or without hepatitis, which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations.

Hepatic Impairment

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 A) 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.

Immune

Immune Reconstitution Inflammatory Syndrome

During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as MAC, CMV, PCP and TB), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, autoimmune hepatitis and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution, however the time to onset is more variable, and can occur many months after initiation of treatment and sometimes can be an atypical presentation.

Renal Impairment

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 impairment.

Special Populations

Pregnant Women

ZIAGEN has not been studied in pregnant women. Therefore, ZIAGEN should not be used in pregnant women unless the potential benefits outweigh the potential risk to the fetus.

There have been reports of developmental delay, seizures and other neurological disease. However, a causal relationship between these events and NRTI exposure *in utero* or peripartum has not been established. Findings of developmental toxicity were also observed in animal toxicology studies (see **TOXICOLOGY**).

There have also 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.

Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant women exposed to ART (antiretroviral therapy), including ZIAGEN, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients:

<http://www.apregistry.com>

Telephone: (800) 258-4263

Fax: (800) 800-1052

To date, the Antiretroviral Pregnancy Registry has received reports of over 2,000 exposures to abacavir during pregnancy resulting in live birth. These consist of over 800 exposures during the first trimester, over 1,100 exposures during the second/third trimester and included 27 and 32 birth defects respectively. The prevalence (95% CI) of defects in the first trimester was 3.1% (2.0, 4.4%) and in the second/third trimester, 2.7% (1.9, 3.9%). Among pregnant women in the reference population, the background rate of birth defects is 2.7%. There appears to be no association between abacavir and overall birth defects observed in the abacavir pregnancy registry.

Nursing Women

HIV-1 infected mothers should not breast-feed their infants to avoid risking postnatal transmission of HIV. Abacavir is secreted in human breast milk at similar concentrations as plasma levels. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving ZIAGEN.**

Pediatrics (> 3 months to <18 years of age)

The safety and effectiveness of ZIAGEN have been established in pediatric patients aged 3 months and older. Use of ZIAGEN is supported by pharmacokinetic trials and evidence from adequate and well-controlled trials of ZIAGEN in adults and pediatric subjects (see **DOSAGE AND ADMINISTRATION – Recommended Dose and Dosage Adjustment, DETAILED PHARMACOLOGY, Special Populations and Conditions, Pediatric Patients and CLINICAL TRIALS – Treatment-Naive Pediatric Subjects).**

Geriatrics (≥ 65 years of age)

Clinical studies of ZIAGEN did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients. In general, caution should be exercised in the administration and monitoring of ZIAGEN in elderly patients, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The following adverse reactions are discussed in greater detail in other sections of the labelling:

- Serious and sometimes fatal hypersensitivity reaction (see **WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions**)
- Lactic acidosis and severe hepatomegaly (see **WARNINGS AND PRECAUTIONS, Lactic Acidosis and Severe Hepatomegaly with Steatosis**)
- Myocardial infarction (see **WARNINGS AND PRECAUTIONS, Cardiovascular**)
- Serum lipids and blood glucose (see **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism**)
- Immune reconstitution inflammatory syndrome (see **WARNINGS AND PRECAUTIONS, Immune**)

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.

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.

Therapy-Naive Adults

Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a greater than or equal to 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 1](#).

Table 1 Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2-4, $\geq 5\%$ Frequency) in Therapy-Naive Adults (CNA30024^a) 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% ^b
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%

^a This trial used double-blind ascertainment of suspected hypersensitivity reactions. During the blinded portion of the trial, suspected hypersensitivity to abacavir was reported by investigators in 9% of 324 subjects in the abacavir group and 3% of 325 subjects in the zidovudine group.

^b Ten (3%) cases of suspected drug hypersensitivity were reclassified as not being due to abacavir following unblinding.

Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a greater than or equal to 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 2](#).

Table 2 Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2-4, $\geq 5\%$ Frequency) in Therapy-Naive Adults (CNA3005) Through 48 Weeks of Treatment

Adverse Reaction	ZIAGEN plus Lamivudine/Zidovudine (n = 262)	Indinavir plus Lamivudine/Zidovudine (n = 264)
Nausea	19%	17%
Headache	13%	9%
Malaise and fatigue	12%	12%
Nausea and vomiting	10%	10%
Hypersensitivity reaction	8%	2%
Diarrhea	7%	5%
Fever and/or chills	6%	3%
Depressive disorders	6%	4%
Musculoskeletal pain	5%	7%
Skin rashes	5%	4%
Ear/nose/throat infections	5%	4%
Viral respiratory infections	5%	5%
Anxiety	5%	3%
Renal signs/symptoms	<1%	5%
Pain (non-site-specific)	<1%	5%

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 or ZIAGEN 300 mg twice daily, both in combination with lamivudine 300 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.

Clinical Trials Experience in Pediatric Subjects

Once-Daily Dosing (COL105677): No additional safety issues were identified in pediatrics subjects (n = 669) receiving either once- or twice- daily dosing compared to adults.

Abnormal Hematologic and Clinical Chemistry Findings

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 3](#).

Table 3 Laboratory Abnormalities (Grades 3-4) in Therapy-Naive Adults (CNA30024) Through 48 Weeks of Treatment

Grade 3/4 Laboratory Abnormalities	ZIAGEN plus Lamivudine plus Efavirenz (n = 324)	Zidovudine plus Lamivudine plus Efavirenz (n = 325)
Elevated CPK (>4 X ULN)	8%	8%
Elevated ALT (>5 X ULN)	6%	6%
Elevated AST (>5 X ULN)	6%	5%
Hypertriglyceridemia (>750 mg/dL)	6%	5%
Hyperamylasemia (>2 X ULN)	4%	5%
Neutropenia (ANC <750/mm ³)	2%	4%
Anemia (Hgb ≤6.9 gm/dL)	<1%	2%
Thrombocytopenia (Platelets <50,000/mm ³)	1%	<1%
Leukopenia (WBC ≤1,500/mm ³)	<1%	2%

ULN = Upper limit of normal.

n = Number of subjects assessed.

Other Adverse Events

Other adverse reactions observed in clinical studies include neutropenia, anemia, thrombocytopenia, anorexia, hyperlactatemia, lactic acidosis, pancreatitis, erythema multiforme, upper abdominal pain, transient rise in liver enzymes (AST, ALT, GGT), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN).

Post-Market Adverse Drug Reactions

In addition to adverse events included from clinical trial data, the following adverse events listed below have been identified during post-approval use of abacavir.

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. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Digestive: pancreatitis

Hepatic: lactic acidosis (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**), hepatic steatosis, hyperlactatemia.

Immune System: Immune Reconstitution Inflammatory Syndrome (see **WARNINGS AND PRECAUTIONS, Immune**)

Skin: rash (without systemic symptoms), **erythema multiforme**,

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (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.

Description of Abacavir Hypersensitivity Adverse Reactions

Hypersensitivity

The signs and symptoms of abacavir hypersensitivity reaction are listed below. These have been identified either from clinical studies or post marketing surveillance. Those reported in at least 10% of patients with a hypersensitivity reaction are in **bold** text.

As described in Warnings and Precautions, 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. Other key symptoms include gastrointestinal, respiratory or constitutional symptoms such as lethargy and malaise.

Skin:	Rash (usually maculopapular or urticarial)
Gastrointestinal tract:	Nausea, vomiting, diarrhoea, abdominal pain , mouth ulceration
Respiratory tract:	Dyspnoea, cough , sore throat, adult respiratory distress syndrome, respiratory failure
Miscellaneous:	Fever, fatigue, malaise , oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis
Neurological/Psychiatry:	Headache , paraesthesia
Haematological:	Lymphopenia
Liver/pancreas:	Elevated liver function tests , hepatic failure
Musculoskeletal:	Myalgia , rarely myolysis, arthralgia, elevated creatine phosphokinase
Urology:	Elevated creatinine, renal failure

Restarting abacavir following an abacavir HSR results in a prompt return of symptoms within hours. This recurrence of the HSR is usually more severe than on initial presentation, and may include life-threatening hypotension and death. Reactions have also occurred infrequently after restarting abacavir in patients who had only one of the key symptoms of hypersensitivity (see above) prior to stopping abacavir; and on very rare occasions have also been seen in patients who have restarted therapy with no preceding symptoms of a HSR (i.e., patients previously considered to be abacavir tolerant).

For details of clinical management in the event of a suspected abacavir HSR (see **WARNINGS AND PRECAUTIONS, Clinical Management of Abacavir HSRs**).

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.

Effect of Abacavir on the Pharmacokinetics of Other Agents

In vitro, abacavir demonstrates no or weak inhibition of the drug transporters organic anion transporter 1B1 (OATP1B1), OATP1B3, breast cancer resistance protein (BCRP) or P-glycoprotein (Pgp) and minimal inhibition of organic cation transporter 1 (OCT1), OCT2 and multidrug and toxin extrusion protein 2-K (MATE2-K). Abacavir is therefore not expected to affect the plasma concentrations of drugs that are substrates of these drug transporters.

Abacavir is an inhibitor of MATE1 *in vitro*, however abacavir has low potential to affect the plasma concentrations of MATE1 substrates at therapeutic drug exposures (up to 600 mg).

Effect of Other Agents on the Pharmacokinetics of Abacavir

In vitro, abacavir is not a substrate of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, MATE1, MATE2-K, Multidrug resistance-associated protein 2 (MRP2) or MRP4, therefore drugs that modulate these transporters are not expected to affect abacavir plasma concentrations.

Although abacavir is a substrate of BCRP and Pgp *in vitro*, clinical studies demonstrate no clinically significant changes in abacavir pharmacokinetics when co-administered with lopinavir/ritonavir (Pgp and BCRP inhibitors).

Drug-Drug Interactions

No drug interaction studies have been conducted with ZIAGEN. The drugs listed in the following 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 4 **Established or Potential Drug-Drug Interactions**

Proper name	Effect	Clinical comment
Ethanol	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	In a pharmacokinetic study, coadministration of 600 mg abacavir twice daily with methadone showed a 35% reduction in abacavir C _{max} and a one hour delay in t _{max} , but AUC was unchanged	The changes in abacavir pharmacokinetics are not considered clinically relevant. In this study, abacavir increased the mean methadone systemic clearance by 22%. This change is not considered clinically relevant for the majority of patients; however occasionally methadone dose retitration may be required.
Retinoids		Retinoid compounds, such as isotretinoin, are eliminated via alcohol dehydrogenase. Interaction with abacavir is possible but has not been studied.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbs have not been established.

Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

ZIAGEN is available as an oral solution for use in children and for those patients for whom tablets are inappropriate.

Dosing Considerations

ZIAGEN can be taken with or without food.

Recommended Dose and Dosage Adjustment

Adults weighing at least 25 kg

The recommended oral dose of ZIAGEN for adults is 600 mg daily administered as either 300 mg twice daily or 600 mg once daily.

Adolescents and children weighing at least 25 kg

The recommended dose of ZIAGEN is 300 mg (one tablet or 15 mL of oral solution) twice daily or 600 mg once daily (two tablets or 30 mL of oral solution).

Adolescents and children (over three months of age) weighing less than 25 kg

The recommended oral dose of ZIAGEN for adolescents and children over 3 months of age is 8 mg/kg twice daily (up to a maximum of 300 mg twice daily) or 16 mg/kg once daily (up to a maximum of 600 mg once daily).

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 **DETAILED PHARMACOLOGY – Special Populations and Conditions – Pediatric Patients**).

Scored Tablets

ZIAGEN is also available as a scored tablet for HIV-1-infected pediatric patients weighing greater than or equal to 14 kg for whom a solid dosage form is appropriate. Before prescribing ZIAGEN tablets, children should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow ZIAGEN tablets, the oral solution formulation should be prescribed. The recommended oral dosage of ZIAGEN tablets for HIV-1-infected pediatric patients is presented in [Table 5](#).

Table 5 Dosing Recommendations for ZIAGEN Tablets in Pediatric Patients

Weight (kg)	Once-Daily Dosing Regimen	Twice-Daily Dosing		Total Daily Dose
		AM Dose	PM Dose	
14 to <20	1 tablet (300 mg)	½ tablet (150 mg)	½ tablet (150 mg)	300 mg
≥20 to <25	1 ½ tablets (450 mg)	½ tablet (150 mg)	1 tablet (300 mg)	450 mg
≥25	2 tablets (600 mg)	1 tablet (300 mg)	1 tablet (300 mg)	600 mg

Special Populations**Renal impairment**

No dosage adjustment of ZIAGEN is necessary in patients with renal dysfunction. The use of ZIAGEN 600 mg once daily has not been studied in patients with renal impairment (see **WARNINGS AND PRECAUTIONS, Renal Impairment**).

Hepatic impairment

Abacavir is primarily metabolized by the liver. The recommended dose of ZIAGEN in patients with mild hepatic impairment (Child-Pugh Score A) 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, Hepatic Impairment**). Pharmacokinetic and safety data on the use of

abacavir in patients with moderate and severe hepatic impairment are not available. Therefore the use of ZIAGEN is contraindicated in patients with moderate or severe hepatic impairment. Once daily ZIAGEN 600 mg dosing has not been studied in the patients with 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

For management of a suspected drug overdose, please contact your regional Poison Control Centre.

If overdosage occurs, the patient should be monitored, and standard supportive treatment applied as required.

Administration of activated charcoal may also be used to aid in the removal of unabsorbed active substance. General supportive measures are recommended.

It is not known whether abacavir can be removed by peritoneal dialysis or hemodialysis.

Limited data are available on the consequences of ingestion of acute overdoses in humans. No fatalities occurred, and the patients recovered.

Single doses up to 1,200 mg and daily doses up to 1,800 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 carbocyclic synthetic nucleoside analogue of deoxyguanosine-5'-triphosphate. Abacavir is metabolized by intracellular kinases to its triphosphate (TP), which is the active moiety carbovir triphosphate (CBV-TP). CBV-TP is a substrate for and competitive inhibitor of HIV reverse transcriptase (RT). Inhibition of RT is via viral DNA chain termination after nucleoside analogue incorporation. CBV-TP shows significantly less affinity for host cell DNA polymerases and is a weak inhibitor of mammalian α , β and γ -DNA polymerases. Abacavir is a nucleoside reverse transcriptase inhibitor (NRTI), and is 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. The antiviral activity of abacavir in cell culture was not antagonized when combined with the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine or zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, or the protease inhibitor (PI) amprenavir.

Pharmacokinetics

Abacavir sulfate is rapidly and well absorbed following oral administration. The absolute bioavailability of oral abacavir sulfate in adults is about 83%. Plasma abacavir AUC was similar following administration of the oral solution or tablets. 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 $\mu\text{g}/\text{ml}$, and the AUC over a dosing interval of 12 hours is approximately 6 $\mu\text{g}\cdot\text{h}/\text{ml}$. 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 $AUC_{24,ss}$ (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 tablets, containing abacavir sulfate equivalent to 300 mg abacavir, are yellow, biconvex, capsule-shaped, and film-coated. The tablets are scored and embossed "GX 623" on both sides. They are available in bottles of 60.

Oral Solution

ZIAGEN oral solution is a clear to opalescent, yellowish, strawberry-banana-flavoured liquid, which may turn brown over time. Each mL of the solution contains abacavir sulfate equivalent to 20 mg of abacavir. It is packaged in plastic bottles of 240 mL with child-resistant closure.

Composition

Tablets

Each ZIAGEN 300 mg tablet contains 300 mg of abacavir (as 351 mg 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, purified water, saccharin sodium, sodium citrate (dihydrate), sodium hydroxide and sorbitol solution.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

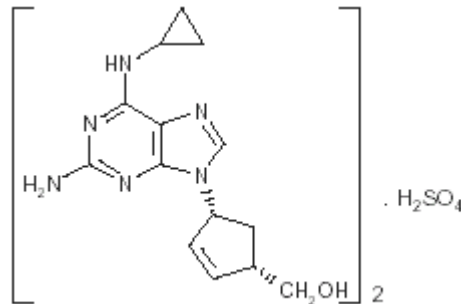
Drug Substance

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: $(C_{14}H_{18}N_6O)_2 \cdot H_2SO_4$, 670.74

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

Therapy-naive adults

CNA3005 was 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 White (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 subjects with baseline viral load greater than 100,000 copies/mL, percentages of subjects with HIV-1 RNA levels less than 50 copies/mL were 31% in the group receiving abacavir versus 45% in the group receiving indinavir.

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 \leq 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 6](#) below.

Table 6 **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		
\leq 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.

Treatment-Naive Pediatric Patients

ARROW (COL105677) was a 5-year randomized, multicenter trial which compared a regimen of once-daily dosing with twice-daily dosing of ZIAGEN/ lamivudine in HIV-1-infected pediatric patients. There were 1,206 patients enrolled aged 3 months to 17 years. Patients were dosed according to the weight-band based dosing recommended by the World Health Organization treatment guidelines. After 36 weeks on treatment, 669 patients receiving ZIAGEN/ lamivudine twice daily were randomized to either twice-daily or once-daily dosing through an additional 96 weeks. The proportions of subjects

with viral loads of <80 copies/mL remained similar through 96 weeks (Table 7) following randomization for the 2 groups.

Table 7 Proportions of Responders by HIV-1 RNA Copies Through 96 Weeks (From Randomization to Once-Daily or Twice-Daily Dosing - Snapshot Analysis)

	ZIAGEN/ lamivudine Twice Daily Dosing n = 333 N (%)	ZIAGEN/ lamivudine Once Daily Dosing n= 336 N (%)
Week 0 (After ≥36 Weeks on Treatment)		
Virological Response (<80 copies/mL)	250 (75)	237 (71)
Risk difference	-4.5% (95% CI -11.3% to +2.2%)	
Week 48		
Virological Response (<80 copies/mL)	242 (73)	233 (69)
Risk difference	-3.3% (95% CI -10.2% to + 3.5%)	
Week 96		
Virological Response (<80 copies/mL)	232 (70)	226 (67)
Risk difference	-2.4% (95% CI -9.4% to +4.6%)	

The ZIAGEN/ lamivudine once daily dosing group was demonstrated to be non-inferior to the twice daily group according to the pre-specified non-inferiority margin of -12% at Week 48 and Week 96 (<200c/mL, <400c/mL, <1000c/mL). Virologic outcomes between treatment arms were comparable across baseline characteristics (gender, age, or viral load at randomization).

Treatment-Experienced Pediatric Patients

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 1,200 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 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

Abacavir is primarily metabolized by the liver with less than 2% of the administered dose being renally excreted as unchanged compound. The primary pathways of metabolism in humans are by alcohol dehydrogenase and by glucuronidation to produce the 5'-

carboxylic acid and 5'-glucuronide which account for about 66% of the administered dose. These metabolites are excreted in the urine. 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.

Elimination

The mean half life of abacavir is about 1.5 hours. Following multiple oral doses of abacavir 300 mg twice a day, there is no significant accumulation of abacavir. Elimination of abacavir is via hepatic metabolism with subsequent excretion of metabolites primarily in the urine. The metabolites and unchanged abacavir account for about 83% of the administered abacavir dose in the urine. The remainder is eliminated in the feces.

Special Populations and Conditions

Pediatric Patients

Abacavir is rapidly and well absorbed from oral solution and tablet formulations when administered to children. Plasma abacavir exposure has been shown to be the same for both formulations when administered at the same dose. Children receiving abacavir oral solution according to the recommended dosage regimen achieve plasma abacavir exposure similar to adults. Children receiving abacavir oral tablets according to the recommended dosage regimen achieve higher plasma abacavir exposure than children receiving oral solution because higher mg/kg doses are administered with the tablet formulation (see **DETAILED PHARMACOLOGY, Special Populations and Conditions, Pediatric Patients**). Pediatric pharmacokinetic studies have demonstrated that once daily dosing provides equivalent AUC₀₋₂₄ to twice daily dosing of the same total daily dose for both oral solution and tablet formulations. The recommended dose for children over 3 months of age is 8 mg/kg twice daily or 16 mg/kg once daily. There are insufficient safety data to recommend the use of ZIAGEN in infants less than three months old.

Patients with Impaired Hepatic Function

Abacavir is metabolised primarily by the liver. The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh Score A) 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. Dosage reduction of abacavir is required in patients with mild hepatic impairment. The pharmacokinetics of abacavir have not been studied in patients with moderate or severe hepatic impairment.

Patients with Impaired Renal Function

Abacavir is primarily metabolized by the liver, with approximately 2% of abacavir

excreted unchanged in the urine. The pharmacokinetics of abacavir in patients with end stage renal disease is similar to patients with normal renal function. Therefore no dosage reduction is required in patients with renal impairment.

MICROBIOLOGY

In Vitro Activity

The *in vitro* anti-HIV-1 activity of abacavir was evaluated against a T-cell tropic laboratory strain HIV-1 IIIB in lymphoblastic cell lines, a monocyte/macrophage tropic laboratory strain HIV-1 BaL in primary monocytes/macrophages, and clinical isolates in peripheral blood mononuclear cells. The concentration of drug necessary to inhibit viral replication by 50 percent (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. The antiviral activity of abacavir in cell culture was not antagonized when combined with the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine or zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, or the protease inhibitor (PI) amprenavir. Ribavirin (50µM) had no effect on the anti-HIV 1 activity of abacavir in cell culture.

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) codon region (codons M184V, K65R, L74V, and Y115F). Viral resistance to abacavir develops relatively slowly *in vitro* and *in vivo*, requiring multiple mutations to reach an eight fold increase in IC₅₀ over wild type virus, which may be a clinically relevant level. 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 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.

Cross-resistance

Reduced susceptibility to abacavir has been demonstrated in clinical isolates of patients with uncontrolled viral replication, who have been pre-treated with and are resistant to other nucleoside inhibitors (except lamivudine and emtricitabine). Cross resistance conferred by the M184V RT is limited within the nucleoside inhibitor class of antiretroviral agents. Zidovudine, stavudine, abacavir and tenofovir maintain their antiretroviral activities against lamivudine-resistant HIV-1 harbouring only the M184V mutation. Clinical isolates with three or more mutations associated with NRTIs are unlikely to be susceptible to abacavir.

In vitro, isolates resistant to abacavir might also show reduced sensitivity to lamivudine, zalcitabine, tenofovir, emtricitabine and/or didanosine, but remain sensitive to zidovudine and stavudine.

Observed During Clinical Trial:

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.

Genotypic analysis was attempted for all subjects with virologic failure (confirmed HIV RNA $>$ 50 copies/mL). There was a low overall incidence of virologic failure 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. These factors 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.

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 b.i.d. (12 mg (base)/kg/day for 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. Slight increases in serum alanine aminotransferase and triglycerides were also observed in monkeys. Microscopically, slight centrilobular hepatocellular hypertrophy was seen in these animal species. In high dose monkeys, slightly swollen mitochondria, a decrease in the amount of rough endoplasmic reticulum and an increase in the number of lysosomes were observed using electron microscopy. Occasional individual cell necrosis, pigment deposits in centrilobular hepatocyte and Kupffer cells were seen in mice and rats. Additional changes observed in toxicity studies included slight alterations in cholesterol, albumin and/or total protein in mice and/or rats and transient reductions in hematology

parameters in monkeys. Clinical observations of toxicity (including emesis, hunched posture, hypoactivity, decreased appetite, and abnormal feces) occurred in monkeys administered high doses of abacavir daily for 12 months.

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 2,800 and 3,200 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 1,000 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 5,000 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 1,000 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, at doses up to 700 mg/kg (8.5 times the human exposure at the recommended dose, based on AUC). 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.

REFERENCES

1. Chittick GE, Gillotin C, McDowell JA, Lou Y, Edwards KD, Prince WT, Stein DS. Abacavir: absolute bioavailability, bioequivalence of three oral formulations, and effect of food. *Pharmacotherapy* 1999 Aug; 19(8): 932-42.
2. Clay PG, Rathbun RC, Slater LN. Management protocol for abacavir-related hypersensitivity reaction. *Ann Pharmacother* 2000 Feb; 34(2): 247-249.
3. Cutrell AG, Hernandez JE, Fleming JW, Edwards MT, Moore MA, Brothers CH, et al. Updated clinical risk factor analysis of suspected hypersensitivity reactions to abacavir. *Ann Pharmacother* 2004 Dec; 38(12): 2171-2172.
4. Daluge SM, Good SS, Faletto MB, Miller WH, St Clair MH, Boone LR et al. 1592U89, a novel carbocyclic nucleoside analog with potent, selective anti-human immunodeficiency virus activity. *Antimicrob Agents Chemother* 1997; 41(5):1082-1093.
5. Deeks SG, Hellmann NS, Grant RM, Parkin NT, Petropoulos CJ, Becker M, et al. Novel four-drug salvage treatment regimens after failure of a human immunodeficiency virus Type I protease inhibitor-containing regimen: antiviral activity and correlation of baseline phenotypic drug susceptibility with virologic outcome. *J. Infect Dis.* 1999; 179(6): 1375-81.
6. Faletto MB, Miller WH, Garvey EP, St Clair MH, Daluge SM, Good SS. Unique intracellular activation of the potent anti-human immunodeficiency virus agent 1592U89. *Antimicrob Agents Chemother* 1997; 41(5):1099-1107.
7. Harris M, Back D, Kewn S, Jutha S, Marina R, Montaner J. Intracellular carbovir triphosphate levels in patients taking abacavir once a day. *AIDS* 2002; 16(8):1196-1197.
8. Hetherington S, McGuirk S, Powell G, Cutrell A, Naderer O, Spreen B, et al. Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir. *Clin Ther* 2001 Oct; 23(10): 1603-1614.
9. Hetherington S, Hughes AR, Mosteller M, Shortino D, Baker KL, Spreen W, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. *Lancet* 2002 Mar 30; 359(9312): 1121-1122.
10. Hewitt RG. Abacavir hypersensitivity reaction. *Clin Infect Dis* 2002 Apr 15; 34(8): 1137-1142.

11. Hughs W, McDowell JA, Shenep J, Flynn P, Kline MW, Yogev R, Symonds W, Lou Y, Hetherington S. Safety and single-dose pharmacokinetics of Abacavir (1592U89) in human immunodeficiency virus Type I-infected children. *Antimicrob Agents and Chemother* 1999 Mar; 43(3): 609-15.
12. Hughes AR, Mosteller M, Bansal AT, Davies K, Haneline SA, Lai EH, et al. Association of genetic variations in HLA-B region with hypersensitivity to abacavir in some, but not all, populations. *Pharmacogenomics* 2004 Mar; 5(2): 203-211.
13. Hughes AR, Warren LL, Mosteller M, Lai EH, Haneline AD, Spreen WR, et al. Pharmacogenetic investigation of drug-associated adverse events: Hypersensitivity to Abacavir. *Drug Metabolism Reviews* 2006 Feb; 38(1): 2-3.
14. Hughes S, Hughes A, Brothers C, Spreen W, Thorborn D. PREDICT-1 (CNA106030): the first powered, prospective trial of pharmacogenetic screening to reduce drug adverse events. *Pharm Stat* 2007 May 29.
15. Hughes AR, Spreen WR, Mosteller M, Warren LL, et al. Pharmacogenetics of hypersensitivity to abacavir: from PGx hypothesis to confirmation to clinical utility. *Pharmacogenomics J*. 2008 Dec; 8(6):365-74.
16. Keiser P, Nassar N, Skiest D, Andrews C, Yazdani B, White A, et al. Comparison of symptoms of influenza A with abacavir-associated hypersensitivity reaction. *Int J STD AIDS* 2003 Jul; 14(7): 478-481.
17. Kline MW, Blanchard S, Fletcher CV, Shenep JL, McKinney Jr. RE, Brundage RC, Culnane M, Dyke RBV, Dankner WM, Kovacs A, McDowell JA, Hetherington S. A phase I study of Abacavir (1592U89) alone and in combination with other antiretroviral agents in infants and children with human immunodeficiency virus infection. *Pediatrics* 1999; 103: e47.
18. Kumar PN, Sweet DE, McDowell JA, Symonds W, Lou Y, Hetherington S, Lafon S. Safety and pharmacokinetics of Abacavir (1592U89) following oral administration of escalating single doses in human immunodeficiency virus Type I-infected adults. *Antimicrob Agents and Chemother* 1999 Mar; 43(3):603-8.
19. Lucas A, Nolan D, Mallal S. HLA-B*5701 screening for susceptibility to abacavir hypersensitivity. *J Antimicrob Chemother* 2007 Apr; 59(4): 591-593.
20. Mallal S, Phillips E, Carosi G, Molina JM, Workman C, et al. PREDICT-1 Study Team. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. 2008 Feb; 358(6):568-79.

21. Martin AM, Nolan D, Gaudieri S, Almeida CA, Nolan R, James I, et al. Predisposition to abacavir hypersensitivity conferred by HLA-B*5701 and a haplotypic Hsp70-Hom variant. *Proc Natl Acad Sci U S A* 2004 Mar 23; 101(12): 4180-4185.
22. Moyle G, Boffito M, Fletcher C, Higgs C, Hay PE, et al. Steady-state pharmacokinetics of abacavir in plasma and intracellular carbovir triphosphate following administration of abacavir at 600 milligrams once daily and 300 milligrams twice daily in human immunodeficiency virus-infected subjects. *Antimicrob Agents Chemother*. 2009 Apr; 53(4):1532-8.
23. Moyle G, DeJesus E, Cahn P, Castillo S, Zhao H, Gordon D, Craig C, and Scott T. ZIAGEN once-daily in Antiretroviral Combination Therapy (CNA30021) Study Team. Abacavir once or twice daily combined with once-daily lamivudine and Efavirenz for the Treatment of Antiretroviral Naïve HIV-infected Adults. Results of the Ziagen once daily in antiretroviral combination study. *J AIDS* 2005; 38(4): 417-425.
24. PENTA (Paediatric European Network for Treatment of AIDS). Comparison of dual nucleoside – analogue reverse transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomized trial. *Lancet* 2002; 359:733-740.
25. Phillips EJ, Wong GA, Kaul R, Shahabi K, Nolan DA, Knowles SR, et al. Clinical and immunogenetic correlates of abacavir hypersensitivity. *AIDS* 2005 Jun 10; 19(9): 979-981.
26. Symonds W, Cutrell A, Edwards M, Steel H, Spreen B, Powell G, et al. Risk factor analysis of hypersensitivity reactions to abacavir. *Clin Ther* 2002 Apr; 24(4): 565-573.
27. Tisdale M, Alnadaf T, Cousens D. Combination of mutations in human immunodeficiency virus type 1 reverse transcriptase required for resistance to the carbocyclic nucleoside 1592U89. *Antimicrob Agents Chemother* 1997; 41(5):1094-1098.
28. Zucman D, Truchis P, Majerholc C, Stegman S, Caillat-Zucman S. Prospective screening for human leukocyte antigen-B*5701 avoids abacavir hypersensitivity reaction in the ethnically mixed French HIV population. *J Acquir Immune Defic Syndr* 2007 May 1; 45(1): 1-3.

PART III: CONSUMER INFORMATION

**PrZIAGEN
abacavir tablets
abacavir oral solution**

This leaflet is part III of a three-part "Product Monograph" published when ZIAGEN was approved for sale in Canada and is designed specifically for Consumers. Please read this leaflet carefully before you start to take your medicine. You may need to read this leaflet again during your treatment. 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 Human Immunodeficiency Virus (HIV) is a retrovirus (a type of virus). Infection with HIV damages the immune system and can lead to Acquired Immune Deficiency Syndrome (AIDS) and other related illnesses.

ZIAGEN belongs to a group of antiretroviral medicines called nucleoside analogue reverse transcriptase inhibitors (NRTIs), and is used in combination with other antiretrovirals to treat HIV infection.

What it does:

ZIAGEN does not cure HIV, but helps to prevent further damage to the immune system by slowing down production of new viruses. You must be sure to be seen regularly by your health care provider.

ZIAGEN also increases the CD4 cell count in your blood. CD4 cells are a type of white blood cells that are important in helping your body fight infection.

When it should not be used:

ZIAGEN should not be taken if you:

- previously had an allergic reaction (hypersensitivity) to the active ingredient abacavir, which is also included in medicines called KIVEXA, TRIZIVIR, or to any of the other ingredients found in ZIAGEN (see **What the important nonmedicinal ingredients are**).
- have the HLA-B* 5701 gene variation.
- have moderate or severe liver disease.

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**

Each ZIAGEN tablet contains the following nonmedicinal ingredients: 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 contains the following nonmedicinal ingredients: artificial strawberry and banana flavours, citric acid (anhydrous), hydrochloric acid, methylparaben, propylene glycol, propylparaben, purified water, saccharin sodium, sodium citrate (dihydrate), sodium hydroxide, and sorbitol solution.

What dosage forms it comes in:

ZIAGEN 300 mg tablets are yellow, biconvex, capsule-shaped, film-coated, scored tablets, embossed with "GX 623" on both sides. Available in bottles of 60.

ZIAGEN 20 mg/mL oral solution is a clear to opalescent, yellowish, strawberry-banana-flavoured liquid, which may turn into a brown colour over time. Available in bottles of 240 mL.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reaction

You should be screened for the HLA-B*5701 gene variation prior to starting or re-starting treatment with ZIAGEN. Patients who have the HLA-B*5701 gene variation have a high risk of developing a hypersensitivity reaction (serious allergic reaction) to abacavir, which is in the drug ZIAGEN. This hypersensitivity reaction **can be life threatening** if you continue to take ZIAGEN (see **Important Information on Hypersensitivity Reactions**).

Important Information on Hypersensitivity Reactions

If you get two or more of the following groups of symptoms while taking ZIAGEN contact your doctor immediately to find out if you should stop taking ZIAGEN:

	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

A list of these symptoms is on the Warning Card provided by your pharmacist. You should carry this Warning Card with you at all times. **If you notice these symptoms while taking ZIAGEN, call your doctor immediately. Your doctor may advise you to stop taking ZIAGEN.**

If you stop ZIAGEN because of a serious allergic reaction, never take ZIAGEN or any other medicine containing abacavir (such as KIVEXA, TRIZIVIR or TRIUMEQ) again, regardless of whether you have the HLA-B*5701 gene variation or not. Within hours you may experience a life threatening lowering of your blood pressure or death.

If you stop ZIAGEN for any other reason, even for a few days, and you are not allergic to ZIAGEN, talk with your doctor before taking it again. Taking ZIAGEN again may cause a serious allergic or life-threatening reaction, even if you never had an allergic reaction to it before.

If your healthcare provider tells you that you can take ZIAGEN, again, start taking it when you are around medical help or people who can call a doctor if you need one.

Occasionally, reactions have developed in people who start taking abacavir again, and had only one symptom on the Warning Card before they stopped taking it.

If you are hypersensitive to ZIAGEN, return all your unused ZIAGEN tablets for safe disposal. Ask your doctor or pharmacist for advice.

Before you use ZIAGEN, talk to your doctor or pharmacist:

- about all your medicines and medical conditions
- if you have liver disease
- if you have been tested and know whether or not you have a gene variation called HLA-B*5701
- if you are pregnant, or planning to become pregnant, breastfeeding or planning to breastfeed
- about all the medicines you are taking including vitamins, herbal supplements and nonprescription drugs

Other Special Warnings

Your blood sugar levels (glucose) or level of fats (lipids) in your blood may increase with HIV treatment. Your doctor may order blood tests for you.

The class of medicines to which ZIAGEN belongs (NRTIs) can cause a condition called lactic acidosis (excess of lactic acid in your 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.

Some HIV medicines including abacavir may increase your risk of heart attack. If you have heart problems, smoke or suffer from diseases that increase your risk of heart disease such as high blood pressure and diabetes, tell your doctor. Do not stop taking your medication unless you are advised to do so by your doctor.

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.

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.

ZIAGEN oral solution contains sorbitol which may cause stomach (abdominal) pain and diarrhea. Sorbitol changes to fructose in the body and not recommended for patients who cannot tolerate fructose.

Use of this medicine during pregnancy and breastfeeding:

If you are pregnant, or planning to become pregnant soon, you must inform your doctor before taking any medicine. The safe use of ZIAGEN in pregnancy has not been established. Your doctor will decide whether you should continue to be treated with ZIAGEN if you are pregnant. If you take ZIAGEN while you are pregnant, talk to your doctor about how you can be included in the Antiretroviral Pregnancy Registry.

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

These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent transmission of HIV to their babies. There have been very rare reports of disease that affect the neonatal (babies) nervous system such as delayed development and seizures. The long term effects of ZIAGEN are not known.

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. The active substance in ZIAGEN (abacavir) is likely to be found in breast milk.

You are recommended **not** to breastfeed your baby while taking ZIAGEN.

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.

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 or pharmacist about all the medicines listed below or any that you are taking or have recently taken, including those you have bought yourself:

- Methadone
- Retinoids

If you are taking methadone, your doctor may need to adjust your methadone dose, as abacavir increases the rate at which methadone leaves your body. This is unlikely to affect most methadone users.

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 tablets **exactly as your doctor has advised you, and try not to miss any doses.** If you are unsure about how to take it, ask your doctor or pharmacist.

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

Adults weighing at least 25 kg: The recommended oral dose of ZIAGEN for adults is 600 mg daily administered as either

300 mg twice daily or 600 mg once daily, in combination with other antiretroviral agents.

Adolescents and children weighing at least 25 kg: The recommended dose of ZIAGEN is 300 mg (one tablet or 15 mL of oral solution) twice daily or 600 mg once daily (two tablets or 30 mL of oral solution) in combination with other antiretroviral agents.

Adolescents and children (over three months of age) weighing less than 25 kg:

Tablets:

For children able to swallow tablets as determined by the doctor/parent:

Children weighing 14 to less than 20 kg: one-half of a scored abacavir tablet twice daily or one tablet taken once daily.

Children weighing more than 20 kg and less than 25 kg : one-half of a scored abacavir tablet taken in the morning and one whole tablet taken in the evening or one and a half tablets taken once daily.

Oral Solution:

The recommended oral dose of ZIAGEN for adolescents and children over 3 months of age is 8 mg/kg twice daily (up to a maximum of 300 mg twice daily) or 16 mg/kg once daily (up to a maximum of 600 mg once 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.

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

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

Overdose:

If you are concerned that you may have taken too much ZIAGEN, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

It is important to take this medicine as prescribed to ensure you get maximum benefit. If you forget to take a dose, take it as soon as you remember, and then continue as before. Do not take a double dose to make up for forgotten individual doses.

If you stopped taking ZIAGEN:

If you stop taking ZIAGEN because of side effects or illness, you must contact your doctor before restarting to make sure that symptoms of a hypersensitivity reaction have not been missed. In some cases your doctor will ask you to restart ZIAGEN under direct medical supervision or in a place where you will be able to get ready access to medical care if needed.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, ZIAGEN can have side effects. When treating HIV infection, it is not always possible to tell whether some of the undesirable effects that occur are caused by ZIAGEN, by other medicines you are taking at the same time or by the HIV infection. For this reason it is very important that you inform your doctor about any changes in your health.

A hypersensitivity reaction (serious allergic reaction) has been reported in 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.

The most common side effects (could affect at least 1 in 10 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). **If these symptoms persist or become bothersome, contact your doctor.**

Other side effects include:

Rare (could affect < 1 in 1,000 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 to your immune system (Immune Reconstitution Inflammatory Syndrome) can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time.

Autoimmune disorders (when the immune system attacks healthy body tissue), may also occur after you start taking medicines for HIV infection. Examples of this include: Grave's disease (which affects the thyroid gland), Guillain-Barré syndrome (which affects the nervous system), polymyositis (which affects the muscles), or autoimmune hepatitis (which affects the liver). Autoimmune disorders may occur many months after the start of treatment. Look for any other symptoms such as:

- high temperature (fever), redness, rash or swelling
- fatigue
- joint or muscle pain
- numbness or weakness beginning in the hands and feet and moving up towards the trunk of the body
- palpitations (chest pain) or rapid heart rate
- yellowing of the eyes and skin

If you notice these or any symptoms of inflammation or infection, tell your doctor immediately.

Always tell your doctor or pharmacist if any of the side effects mentioned becomes severe or troublesome, or if you notice any other side effects not listed in this leaflet.

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist immediately
		Only if severe	In all cases	
Common	<u>Hypersensitivity to abacavir</u> : Serious allergic reaction and 2 or more of the following symptoms: fever, skin rash, nausea, vomiting, diarrhea, abdominal pain, severe tiredness, achiness, general ill-feeling, sore throat, shortness of breath.		X	

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

Rare	<u>Lactic acidosis (high level of acid in the blood)</u> : Weight loss, fatigue, malaise, abdominal pain, shortness of breath, severe hepatomegaly (swollen and enlarged liver) with symptoms of liver problems such as nausea, vomiting, abdominal pain, weakness and diarrhea.		X	
------	--	--	---	--

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 the reach and sight of children.

Do not take your medicine after the expiry date shown on the bottle and/or the carton.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 1908C
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

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

www.viivhealthcare.com
or by contacting the sponsor, ViiV Healthcare ULC at:
245, boulevard Armand-Frappier
Laval, Quebec
H7V 4A7
1-877-393-8448

This leaflet was prepared by ViiV Healthcare ULC.

Last revised: June 17, 2019

© 2019 ViiV Healthcare group of companies or its licensor. Trademarks are owned by or licensed to the ViiV Healthcare group of companies.

INFORMATION FOR PRESCRIBERS:

A copy of the warning card included with the ZIAGEN carton is shown below.

WARNING CARD	
ZIAGEN abacavir tablets and oral solution	
<p>Patients taking ZIAGEN may develop a hypersensitivity reaction (a serious allergic reaction) which can be life-threatening if you continue to take ZIAGEN. If you notice two or more of the following sets of symptoms while taking ZIAGEN, contact your doctor immediately to find out if you should stop taking ZIAGEN.</p>	
	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
<p>If you have already had this reaction to ZIAGEN, never take any medicine containing abacavir, such as KIVEXA (abacavir/lamivudine), TRIZIVIR (abacavir/lamivudine/zidovudine) or TRIUMEQ (dolutegravir/abacavir/lamivudine) again. If you take any medicine containing abacavir, such as ZIAGEN, KIVEXA, TRIZIVIR or TRIUMEQ again, within hours you may experience a life-threatening lowering of your blood pressure or death.</p>	
<p>Carry this card with you at all times.</p>	
<p>You should return all of your unused ZIAGEN to your doctor or pharmacist for proper disposal.</p>	
<p>Questions or concerns? ViiV Healthcare ULC Laval, Quebec H7V 4A7 www.viivhealthcare.ca</p>	