APO-ABACAVIRPRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr APO-ABACAVIR
Abacavir Tablets USP

300 mg abacavir
(as abacavir sulfate)

Antiretroviral Agent

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RECENT MAJOR LABEL CHANGES

SERIOUS WARNINGS AND PRECAUTIONS BOX (3)	12/2021
DOSAGE AND ADMINISTRATION, Dosing Considerations (4.1)	12/2021
WARNINGS AND PRECAUTIONS, General (7)	12/2021
WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions (7)	12/2021

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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

1.1 Pediatrics

Pediatrics (≥ 3 months to < 18 years of age):
APO-ABACAVIR is indicated in pediatric patients aged 3 months and older in combination with other antiretroviral agents. The safety and efficacy of abacavir in pediatric patients less than 3 months of age have not been established; therefore, Health Canada has not authorized an indication for pediatric use in patients less than 3 months of age.

1.2 Geriatrics

Geriatrics (≥ 65 years of age):
Clinical studies of abacavir 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.

2 CONTRAINDICATIONS

APO-ABACAVIR tablets 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 **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING** section of the product monograph.
- 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 **7 WARNINGS AND PRECAUTIONS**).
- with moderate or severe hepatic impairment since the pharmacokinetics have not been studied in this patient group.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Fatal Hypersensitivity Reactions**

Serious and sometimes fatal hypersensitivity reactions, with multiple organ involvement, have occurred with abacavir and abacavir-containing products.

Patients who carry the HLA B*5701 allele are at a higher risk of a hypersensitivity reaction to abacavir; although, hypersensitivity reactions have occurred in patients who do not carry the HLA-B*5701 allele (see 7 WARNINGS AND PRECAUTIONS).

APO-ABACAVIR is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS).

All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with APO-ABACAVIR or reinitiation of therapy with APO-ABACAVIR, unless patients have a previously documented HLA-B*5701 allele assessment. Discontinue APO-ABACAVIR immediately if a hypersensitivity reaction is suspected, regardless of HLA-B*5701 status and even when other diagnoses are possible (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS).

Following a hypersensitivity reaction to APO-ABACAVIR, NEVER restart APO-ABACAVIR or any other abacavir-containing product because more severe symptoms, including death can occur within hours. Similar severe reactions have also occurred rarely death can occur within hours. Similar severe reactions have also occurred rarely following the reintroduction of abacvir-containing products in patients who have no history of abacvir hypersensitivity (see 7 WARNINGS AND PRECAUTIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Screening for HLA-B*5701 Allele Prior to Initiating or Re-initiating Therapy with APO-ABACAVIR

All patients should be screened for the HLA-B*5701 allele prior to initiating or re-initiating treatment with APO-ABACAVIR, unless patients have a previously documented HLA-B*5701

allele assessment (see **2 CONTRAINDICATIONS** and **3 SERIOUS WARNINGS AND PRECAUTIONS BOX)**.

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

APO-ABACAVIR can be taken with or without food.

4.2 Recommended Dose and Dosage Adjustment

Adults weighing at least 25 kg
The recommended oral dose of APO-ABACAVIR 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 APO-ABACAVIR can be administered as 300 mg (1 tablet) twice daily.

Pediatrics (≥ three months of age) and weighing less than 25 kg:
The recommended dose of APO-ABACAVIR is 8 mg/kg twice daily (up to a maximum of 300 mg twice daily).

Scored Tablets
APO-ABACAVIR 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 APO-ABACAVIR tablets, children should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow APO-ABACAVIR tablets, the oral solution formulation should be prescribed.

The recommended oral dosage of APO-ABACAVIR tablets for HIV-1-infected pediatric patients is presented in Table 1.

Table 1 Dosing Recommendations for APO-ABACAVIR Tablets in Pediatric Patients

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

[a]Data regarding the efficacy of once-daily dosing is limited to subjects who transitioned from twice-daily dosing to once-daily dosing after 36 weeks of treatment (see **14 CLINICAL TRIALS**).

Pediatrics (< three months of age):

The safety and efficacy of abacavir in pediatric patients less than 3 months of age have not been established; therefore, Health Canada has not authorized an indication for pediatric use in patients less than 3 months of age.

Renal Impairment
No dosage adjustment of APO-ABACAVIR is necessary in patients with renal dysfunction. The use of abacavir 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 APO-ABACAVIR in patients with mild hepatic impairment (Child-Pugh Score A) who have confirmed cirrhosis is 200 mg twice a day. To enable dose reduction abacavir oral solution should be used for the treatment of these patients. Abacavir is contraindicated in patients with moderate or severe hepatic impairment, as the pharmacokinetics have not been studied in these patient groups. (See **2 CONTRAINDICATIONS and 7 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 APO-ABACAVIR is contraindicated in patients with moderate or severe hepatic impairment. Once daily abacavir 600 mg dosing has not been studied in the patients with impaired hepatic function.

4.3 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 APO-ABACAVIR 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.

5 OVERDOSAGE

For management of a suspected drug overdose, 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablet/ 300 mg abacavir (as abacavir sulfate)	colloidal silicon dioxide, croscarmellose sodium, hydroxy propylmethyl cellulose, iron oxide yellow, magnesium stearate, microcrystalline cellulose, polyethylene glycol and titanium dioxide.

Dosage Forms

APO-ABACAVIR tablets are yellow colored, modified capsule-shaped, scored, biconvex film coated tablets with engraved "APO" on one side and “AB” bisect “300” on the other side contains abacavir sulfate equivalent to 300 mg abacavir.

Packaging

Supplied in bottles of 60 tablets.

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General

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

Patients receiving APO-ABACAVIR 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.

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

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 7 **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 abacavir unless patients have a previously documented HLA-B*5701 allele assessment.

Do not use APO-ABACAVIR 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 APO-ABACAVIR 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 APO-ABACAVIR or any other abacavir-containing product in patients who have stopped therapy with APO-ABACAVIR or any other abacavir-containing product due to a hypersensitivity reaction.

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

If hypersensitivity cannot be ruled out, **DO NOT** reintroduce **APO-ABACAVIR** 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 **APO-ABACAVIR** 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 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 **8 ADVERSE 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 APO-ABACAVIR 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 **16 NON-CLINICAL 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 **16 NON-CLINICAL TOXICOLOGY**, **Mutagencity**).

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 APO-ABACAVIR 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 APO-ABACAVIR 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 abacavir 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 abacavir 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 abacavir is recommended in patients with renal impairment.

7.1 Special Populations

7.1.1 Pregnant Women

Abacavir has not been studied in pregnant women. Therefore, APO-ABACAVIR 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 peri-partum has not been established. Findings of developmental toxicity were also observed in animal toxicology studies (see **16 NON-CLINICAL 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 APO-ABACAVIR, 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.

7.1.2 Breast-feeding

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 APO-ABACAVIR**.

7.1.3 Pediatrics

Pediatrics (< 3 months)
The safety and effectiveness of abacavir have not been established in pediatric patients aged less than 3 months of age. Health Canada has not authorized an indication for use in pediatric patients less than 3 months of age.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age):
Clinical studies of abacavir 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 APO-ABACAVIR in elderly patients, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following adverse reactions are discussed in the **7 WARNINGS AND PRECAUTIONS** section:

- Serious and sometimes fatal hypersensitivity reaction (see **Hypersensitivity Reaction**)

- Lactic acidosis and severe hepatomegaly (see **Lactic Acidosis and Severe Hepatomegaly with Steatosis**)
- Myocardial infarction (see **Cardiovascular**)
- Serum lipids and blood glucose (see **Endocrine and Metabolism**)
- Immune reconstitution inflammatory syndrome (see **Immune**)

8.2 Clinical Trial Adverse 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 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 abacavir 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg daily compared with zidovudine 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg daily from CNA30024 are listed in Table 3.

Table 3 Treatment Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2-4, ≥5% Frequency) in Therapy Naive Adults (CNA30024[a]) Through 48 Weeks of Treatment

Adverse Reaction	Abacavir 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%

Adverse Reaction	Abacavir plus Lamivudine plus Efavirenz (n = 324)	Zidovudine plus Lamivudine plus Efavirenz (n = 325)
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 abacavir 300 mg twice daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily compared with indinavir 800 mg 3 times daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily from CNA3005 are listed in Table 4.

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

Adverse Reaction	Abacavir plus Lamivudine/Zidovudine (n = 262)	Indinavir plus Lamivudine/Zidovudine (n = 264)
Nausea	19%	17%
Headache	13%	9%[b]
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%

Abacavir Once Daily vs. Abacavir Twice Daily (Study CNA30021)
Treatment emergent clinical adverse reactions (rated by the investigator as at least moderate) with a ≥ 5% frequency during therapy with abacavir 600 mg once daily or abacavir 300 mg twice daily, both in combination with lamivudine 300 mg once daily and efavirenz 600 mg once daily from Study 30021, were similar. For hypersensitivity reactions, patients receiving abacavir once daily showed a rate of 9% in comparison to a rate of 7% for patients receiving abacavir twice daily. However, patients receiving abacavir 600 mg once daily, experienced a significantly higher incidence of severe drug hypersensitivity reactions and severe diarrhea compared to patients who received abacavir 300 mg twice daily. Five percent (5%) of patients receiving abacavir 600 mg once daily had severe drug hypersensitivity reactions compared to 2% of patients receiving abacavir 300 mg twice daily. Two percent (2%) of patients receiving abacavir 600 mg once daily had severe diarrhea while none of the patients receiving abacavir 300 mg twice daily had this event.

8.2.1 Clinical Trials Adverse Reactions - Pediatrics

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.

8.3 Less common clinical trial adverse reactions

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).

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Laboratory abnormalities (Grades 3-4) in therapy-naive adults during therapy with abacavir 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg daily compared with zidovudine 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg daily from CNA30024 are listed in Table 5.

Table 5 - Laboratory Abnormalities (Grades 3-4) in Therapy-Naive Adults (CNA30024) Through 48 Weeks of Treatment

Grade 3/4 Laboratory Abnormalities	Abacavir 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%

Grade 3/4 Laboratory Abnormalities	Abacavir plus Lamivudine plus Efavirenz (n = 324)	Zidovudine plus Lamivudine plus Efavirenz (n = 325)
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.

8.5 Post-Market Adverse 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 **7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**), hepatic steatosis, hyperlactatemia.

Immune System: Immune Reconstitution Inflammatory Syndrome (see **7 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.

8.6 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 **7 WARNINGS AND PRECAUTIONS, Clinical Management of Abacavir HSRs**).

9 DRUG INTERACTIONS

9.1 Overview

In vitro studies have shown that abacavir inhibits cytochrome P450 1A1 (CYP1A1) and shows limited potential to inhibit metabolism mediated by the CYP3A4 enzyme. It has also been shown *in vitro* not to interact with drugs that are metabolized by CYP2C9 or CYP2D6 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 has been shown to inhibit CYP1A1, and to a limited degree CYP3A4. When coadministered with abacavir or abacavir-containing fixed dose combination drugs, exposures to drugs that are substrates of CYP1A1 could increase.

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).

9.2 Drug-Drug Interactions

No drug interaction studies have been conducted with abacavir. 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 6 - 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.
Riociguat	*In vitro*, abacavir inhibits CYP1A1. Coadministration of a single dose of riociguat (0.5 mg) to HIV-1–infected subjects receiving TRIUMEQ (abacavir/dolutegravir/lamivudine 600mg/50mg/300mg once daily) resulted in approximately 3-fold higher riociguat AUC(0-∞) compared with historical riociguat AUC(0-∞) reported in healthy subjects.	APO-ABACAVIR and ADEMPAS (riociguat) should be co-administered with caution. Riociguat dose may need to be reduced, consult the riociguat product labeling for dosing recommendations.

9.3 Drug-Food Interactions

Abacavir can be taken with or without food (see **10 CLINICAL PHARMACOLOGY**).

9.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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.

10.2 Pharmacokinetics

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.

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. There are no differences observed between the AUC for the tablet. At 300 mg twice daily, the steady state C_{max} of abacavir sulfate tablets is approximately 3 mcg/ml, and the AUC over a dosing interval of 12 hours is approximately 6 mcg.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, abacavir 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**).

Absorption and Bioavailability
Abacavir sulfate was rapidly and extensively absorbed after oral administration. Absolute bioavailability of the tablet was 86% ± 25% (mean ± SD). After oral administration of 300 mg twice daily in 20 patients, the steady-state peak serum abacavir concentration (C_{max}) was 3.0 ± 0.89 mcg/mL (mean ± SD) and AUC ($_{0\text{-}12\ hours}$) was 6.02 ± 1.73 mcg•h/mL. After oral administration of a single dose of 600 mg of abacavir in 20 patients, C_{max} was 4.26 ± 1.19 mcg/mL(mean ± SD) and AUC_{∞} was 11.95 ± 2.51 mcg•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, abacavir tablets may be administered with or without food.

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 mcg/ mL. In a further pharmacokinetic study of 600 mg twice a day, the CSF concentration of abacavir increased over time, from approximately 0.13 mcg/mL at 0.5 to 1 hour after dosing, to approximately 0.74 mcg/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 mcg/mL or 0.26 mcM. 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 P_{450} 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

Pediatrics:
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. The recommended dose for children over 3 months of age is 8 mg/kg twice daily. There are insufficient safety data to recommend the use of abacavir 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.

11 STORAGE, STABILITY AND DISPOSAL

Store at 15ºC and 30ºC.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

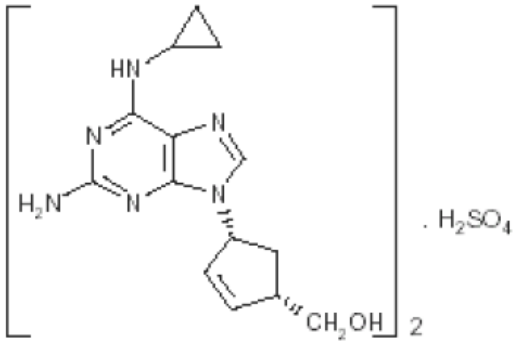
Drug Substance

Proper name: abacavir sulfate USP

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 weight: $(C_{14}H_{18}N_6O)_2 . H_2SO_4$, 670.76 g/mol

Structural formula:



Physicochemical properties:

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

The aqueous solubility and pH of abacavir sulfate was determined at 37º C as follows:

Solvent	Solvent Solubility (mg/mL)	pH
Water	30.459	pH 7.0
0.1N HCl	93.744	pH1.01
Simulated gastric fluid (SGF)	163.017	
Simulated intestinal fluid (SIF)	146.838	
Phosphate buffer	125.697	pH 2.5
Phosphate buffer	126.376	pH 3.0
Acetate buffer	168.753	pH 4.5
Phosphate buffer	136.816	pH 4.5
Phosphate buffer	166.426	pH 5.0
Phosphate buffer	108.492	pH 5.5
Phosphate buffer	145.995	pH 6.0
Phosphate buffer	150.467	pH 6.8
Phosphate buffer	149.571	pH 7.0
Phosphate buffer	159.219	pH 7.5

Solvent	Solvent Solubility (mg/mL)	pH
Phosphate buffer	177.146	pH 8.0

PKa: The pK_a for abacavir have been determined by UV spectroscopy at 25 º C as follows: $pK_1 = 0.46$, $pK_2 = 5.06$.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

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 abacavir (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/mm^3, and median plasma HIV-1 RNA was 4.83 log_{10} copies/mL.

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 7 below.

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 abacavir/ 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 abacavir / 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 8) following randomization for the 2 groups.

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].

14.2 Study Results

Therapy-naive adults

CNA3005

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.

CNA30021

Table 7 - 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.

Treatment-Naive Pediatric Patients - ARROW

Table 8 - Proportions of Responders by HIV-1 RNA Copies Through 96 Weeks (From Randomization to Once-Daily or Twice-Daily Dosing - Snapshot Analysis)

	Abacavir/ lamivudine Twice Daily Dosing n = 333 N (%)	Abacavir/ 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 Abacavir/ 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
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).

14.3 Comparative Bioavailability Studies

A randomized, single dose, double-blinded, 2-way crossover comparative bioavailability study conducted under fasting conditions was performed on 16 healthy male volunteers. The rate and extent of absorption of abacavir were measured and compared following a single oral dose of Apo-Abacavir (Abacavir sulfate) 300 mg tablets (Apotex Inc.) or Ziagen® (Abacavir sulfate) 300 mg tablets (GlaxoSmithKline Inc.). The results from measured data are summarized in the following table.

Summary Table of the Comparative Bioavailability Data

Summary Table of the Comparative Bioavailability Data
Abacavir
(A single 300 mg dose: 1 x 300 mg tablet)
From Measured Data/Fasting Conditions
Geometric Mean
Arithmetic Mean (CV%)

Parameter	Test*	Reference†	Ratio of Geometric Means (%)	90% Confidence Interval (%)
AUC_t (ng•h/mL)	7473.7 7790.3 (26)	7528.9 7835.2 (25)	99.3	92.8 – 106.2
AUC_{inf} (ng•h/mL)	7599.2 7919.7 (26)	7650.0 7960.0 (25)	99.3	92.9 – 106.2
C_{max} (ng/mL)	3875.0 4306.8 (47)	3940.6 4156.6 (33)	98.3	82.2 – 117.7
T_{max}€ (h)	0.50 (0.17 – 1.25)	0.46 (0.25 – 2.00)		
$T_{1/2}$§ (h)	1.93 (14)	1.90 (24)		

* Apo– Abacavir (Abacavir sulfate) 300 mg tablets (Apotex Inc.)

† Ziagen® (Abacavir sulfate) 300 mg tablets (GlaxoSmithKline Inc. currently manufactured by ViiV Healthcare ULC) were purchased in Canada.

€ Expressed as the Median (range) only

§ Expressed as arithmetic mean (CV %) only.

15 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 (IC_{50}) ranged from 3.7 to 5.8 mcM against HIV-1 IIIB, and was 0.26 ± 0.18 mcM (1 mcM = 0.28 mcg/mL) against eight clinical isolates. The IC_{50} of abacavir against HIV-1 BaL varied from 0.07 to 1.0 mcM. 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 (50 mcM) 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 IC_{50} 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 abacavir and zidovudine delays the emergence of mutations associated with resistance to abacavir compared with monotherapy with abacavir.

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 ≤ 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.

16 NON-CLINICAL 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 mcg/mL for 3 hours in the presence of metabolic activation and after exposure at 100 and 125 mcg/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 mcg/plate. In a mutagenicity assay conducted in L5178Y mouse lymphoma cells, abacavir was weakly mutagenic following exposure at 250 mcg/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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. Pr ZIAGEN® (Abacavir Tablets, 300 mg), submission control 243476, Product Monograph, ViiV Healthcare ULC. January 20, 2021

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

Pr APO-ABACAVIR
Abacavir Tablets USP

Read this carefully before you start taking **APO-ABACAVIR** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **APO-ABACAVIR**.

Serious Warnings and Precautions
Hypersensitivity Reaction
Serious and sometimes fatal hypersensitivity reactions (serious allergic reactions) have happened in people taking abacavir and other medicines containing abacavir. You should be screened for the HLA-B*5701 gene variation prior to starting or re-starting treatment with APO-ABACAVIR, unless you have been screened previously and this is documented. Patients who have the HLA-B*5701 gene variation have a high risk of developing a hypersensitivity reaction to abacavir, which is the medicinal ingredient in APO-ABACAVIR. This hypersensitivity reaction **can be life threatening** if you continue to take APO-ABACAVIR. Do **not** take APO-ABACAVIR if you have the HLA-B*5701 gene variation or have had a reaction in the past to APO-ABACAVIR or any other medicine containing abacavir (such as TRIZIVIR (no longer marketed in Canada), KIVEXA or TRIUMEQ).

If you stop APO-ABACAVIR because of a hypersensitivity reaction, never take APO-ABACAVIR or any other medicine containing abacavir again, regardless of whether you have the HLA-B*5701 gene variation or not. If you restart APO-ABACAVIR or any other medicine containing abacavir, within hours you may experience a life threatening lowering of your blood pressure or death.

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

Important Information on Hypersensitivity Reactions
If you get two or more of the following groups of symptoms while taking APO-ABACAVIR contact your doctor immediately to find out if you should stop taking APO-ABACAVIR:

	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 APO-ABACAVIR, call your doctor immediately. Your doctor may advise you to stop taking APO-ABACAVIR.**

If your healthcare professional tells you that you can take APO-ABACAVIR, 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 (allergic) to APO-ABACAVIR, return all your unused APO-ABACAVIR tablets for safe disposal. Ask your doctor or pharmacist for advice.

What is APO-ABACAVIR used for?
APO-ABACAVIR is a medicine used with other antiretrovirals to treat Human Immunodeficiency Virus (HIV) infection.

How does APO-ABACAVIR work?
APO-ABACAVIR contains the medicinal ingredient abacavir sulfate. This belongs to a group of antiretroviral medicines called nucleoside analogue reverse transcriptase inhibitors (NRTIs), which are used to treat HIV infection.

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.

APO-ABACAVIR **does not cure HIV infection; it reduces the amount of virus in your body, and keeps it at a low level. It 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 to fight infection.**

What are the ingredients in APO-ABACAVIR?
Medicinal ingredients: abacavir (as abacavir sulfate).

Non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxy propylmethyl cellulose, iron oxide yellow, magnesium stearate, microcrystalline cellulose, polyethylene glycol and titanium dioxide.

APO-ABACAVIR comes in the following dosage forms:
300 mg tablets

Do not use APO-ABACAVIR if you:
- previously had an allergic reaction (hypersensitivity) to the medicinal ingredient abacavir, which is also included in medicines called KIVEXA, TRIUMEQ and TRIZIVIR (no longer marketed in Canada), or to any of the other ingredients found in APO-ABACAVIR.
- have the HLA-B* 5701 gene variation.
- have moderate or severe liver disease.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-ABACAVIR. Talk about any health conditions or problems you may have, including if you:
- have liver problems
- have been tested and know whether or not you have a gene variation called HLA-B*5701
- are already taking a medicine that contains abacavir, including KIVEXA or TRIUMEQ.
- or the person your are caring for is less than 3 months of age or 65 years of age or older"

Other warnings you should know about:

APO-ABACAVIR can cause serious side effects, including:
Lactic Acidosis and Severe Liver Problems: The class of medicines to which APO-ABACAVIR 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 problems you may also be more at risk of getting this condition.

Heart Attack: 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 healthcare professional.

Risk of Infections: You may continue to develop other infections and other illnesses associated with HIV while you are taking APO-ABACAVIR. You should therefore keep in regular contact with your healthcare professional.

Immune Reconstitution Inflammatory Syndrome: Changes to your immune system 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 happen when the immune system attacks healthy body tissue. This may happen 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.

See the Serious side effects and what to do about them table, below, for more information on these and other serious side effects.

Blood Tests: Your blood sugar levels (glucose) or level of fats (lipids) in your blood may increase with HIV treatment. Your healthcare professional will decide when to do blood tests, to check for these and other side effects, and will interpret the results.

Pregnancy and Newborns: If you are pregnant, or planning to become pregnant, talk to your healthcare professional before taking APO-ABACAVIR. It is not known if APO-ABACAVIR is safe to use during pregnancy. Your healthcare professional will decide whether you should continue to take APO-ABACAVIR if you are pregnant. If you are pregnant and taking APO-ABACAVIR to prevent passing HIV to your unborn baby continue to follow your healthcare professionals recommendations. If you have questions about the risks to your baby talk to your healthcare professional. If you take APO-ABACAVIR while you are pregnant, talk to your healthcare professional about how you can be included in the Antiretroviral Pregnancy Registry.

Babies born to mothers who have taken Nucleoside Reverse Transcriptase Inhibitors (NRTIs) like APO-ABACAVIR during pregnancy or labour have had increased levels of lactate in their blood. The increases are usually temporary. There have also been very rare reports of problems that affect the babies nervous system such as delayed development and seizures. The long term effects of APO-ABACAVIR are not known.

Breastfeeding: Do not breastfeed while taking APO-ABACAVIR. There is a risk of passing HIV-1 to your baby if you breastfeed. Abacavir can also be passed through breast milk and could harm your baby. If you are breastfeeding or planning to breastfeed, talk with your healthcare professional about the best way to feed your baby.

Infecting Others with HIV: APO-ABACAVIR will not stop you from passing HIV to others, although this risk is lower if you take your HIV medicine as instructed by your healthcare professional. You should take steps to avoid infecting others by:

- Using condoms when you have oral or penetrative sex.
- Not reusing or sharing needles, syringes, or other injection equipment.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with APO-ABACAVIR:

- Methadone, to treat pain and drug addiction
- Retinoids, to treat skin conditions
- Riociguat, to treat high blood pressure
- Alcohol

Talk to your healthcare professional for further advice if you are taking any of these medicines. For some of these medicines, your healthcare professional may need to adjust the dose of one of your medicines in order for it to work properly.

How to take APO-ABACAVIR:

- Take APO-ABACAVIR exactly as directed by your healthcare professional. If you are unsure about how to take it, ask your doctor or pharmacist.
- You can take APO-ABACAVIR with or without food.
- APO-ABACAVIR is always prescribed with other antiretroviral agents.
- If you have liver problems your healthcare professional may have to adjust your dose.
- APO-ABACAVIR tablets can be given to children and adults able to swallow tablets.

Usual dose:

Adults, Adolescents and Children (weighing at least 25 kg): 600 mg daily.

- **Tablets:** 1 tablet (300 mg) twice daily or 2 tablets (600 mg) once daily

Adolescents and children (≥ 3 months of age and weighing less than 25 kg): The dose of APO-ABACAVIR tablets will be decided by your healthcare professional based on your child's weight.

Overdose:

If you think you, or a person you are caring for, have taken too much APO-ABACAVIR, contact a healthcare professional, 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 APO-ABACAVIR:
If you stop taking APO-ABACAVIR because of side effects or illness, you must contact your healthcare professional before restarting to make sure that symptoms of a hypersensitivity reaction have not been missed. In some cases your healthcare professional will ask you to restart APO-ABACAVIR under direct medical supervision or in a place where you will be able to get ready access to medical care if needed.

What are possible side effects from using APO-ABACAVIR?

These are not all the possible side effects you may feel when taking APO-ABACAVIR. If you experience any side effects not listed here, contact your healthcare professional.

Like all medicines, APO-ABACAVIR can have side effects. When treating HIV infection, it is not always possible to tell whether some of the side effects that occur are caused by APO-ABACAVIR, 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 healthcare professional about any changes in your health.

Side effects may include:

- nausea (feeling sick), vomiting
- diarrhea
- loss of appetite
- lack of energy, fatigue
- fever
- headache
- rash

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Hypersensitivity Reaction/Serious Allergic Reaction, which can present as skin rash and/or symptoms from at least 2 of the following groups: – fever – shortness of breath, sore throat or cough – nausea or vomiting, diarrhea, or stomach pain – severe tiredness or achiness, or generally feeling ill.		√	
RARE			
Lactic Acidosis (high level of acid in the blood) and Liver Problems: weight loss, fatigue, malaise, abdominal pain, shortness of breath, swollen and enlarged liver with symptoms of liver problems such as nausea, vomiting, abdominal pain, weakness and diarrhea		√	
Pancreatitis (inflammation of the pancreas): abdominal pain that lasts and gets worse when you lie down, nausea, vomiting		√	
VERY RARE			
Serious Skin Reactions [erythema multiforme, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)]: severe rash, itching, fever, swollen lymph nodes, flu-like feeling, blisters and peeling of skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body			√
FREQUENCY NOT KNOWN			
Immune Reconstitution Inflammatory Syndrome and Autoimmune Disorders:		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
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			
Heart Attack: chest pain or discomfort, pain in the jaw, neck or back or pain radiating down the left arm, shortness of breath, nausea, dizziness		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store APO-ABACAVIR tablets between 15°C and 30°C.

Keep out of reach and sight of children.

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

If you want more information about APO-ABACAVIR:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html). Find the Patient Medication Information on the manufacturer's website http://www.apotex.ca/products, or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

Last revised: December 13, 2021

INFORMATION FOR PRESCRIBERS:

A copy of the warning card included with the APO-ABACAVIR carton is shown below.

WARNING CARD

APO-ABACAVIR (Abacavir Tablets USP)

Patients taking APO-ABACAVIR (Abacavir Tablets USP) may develop a hypersensitivity reaction (a serious allergic reaction) which can be life-threatening if you continue to take APO-ABACAVIR. **If you notice two or more of the following sets of symptoms while taking APO-ABACAVIR, contact your doctor immediately to find out if you should stop taking APO-ABACAVIR.**

	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 already had this reaction to **APO-ABACAVIR, never take any medicine containing abacavir**, **such as KIVEXA®** (abacavir/lamivudine), **TRIUMEQ®** (dolutegravir/ abacavir/lamivudine) or **ZIAGEN** (abacavir) **again**. **If you take any medicine containing abacavir, such as APO-ABACAVIR, KIVEXA®, TRIUMEQ® or ZIAGEN again, 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 APO-ABACAVIR to your doctor or pharmacist for proper disposal.