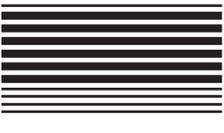




557-2016-11



Abacavir Tablets USP
2031588

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ABACAVIR TABLETS safely and effectively. See full prescribing information for ABACAVIR TABLETS.

ABACAVIR tablets USP, for oral use

Initial U.S. Approval: 1998

WARNING: HYPERSENSITIVITY REACTIONS, AND LACTIC ACIDOSIS, AND SEVERE HEPATOMEGALY
See full prescribing information for complete boxed warning.

Hypersensitivity Reactions

- Serious and sometimes fatal hypersensitivity reactions have occurred with abacavir tablets. (5.1)
- Hypersensitivity to abacavir is a multi-organ clinical syndrome. (5.1)
- Patients who carry the HLA-B*5701 allele are at a higher risk of experiencing a hypersensitivity reaction to abacavir. (5.1)
- Abacavir tablets are contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients. (4)
- Discontinue abacavir tablets as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B*5701 status, permanently discontinue abacavir tablets if hypersensitivity cannot be ruled out, even when other diagnoses are possible. (5.1)
- Following a hypersensitivity reaction to abacavir, NEVER restart abacavir tablet or any other abacavir-containing product. (5.1)

Lactic Acidosis and Severe Hepatomegaly with Steatosis

- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. (5.2)

RECENT MAJOR CHANGES

Boxed Warning	09/2015
Indications and Usage (1)	09/2015
Dosage and Administration, Screening for HLA-B*5701 Allele Prior to Starting Abacavir (2.1)	09/2015
Dosage and Administration, Recommended Dosage for Pediatric Patients (2.3)	03/2015
Contraindications (4)	09/2015
Warnings and Precautions, Hypersensitivity Reactions (5.1)	09/2015
Warnings and Precautions, Related Products that are Not Recommended (5.6)	03/2015

Abacavir tablet, USP a nucleoside analogue human immunodeficiency virus (HIV-1) reverse transcriptase inhibitor, is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. (1)

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: HYPERSENSITIVITY REACTIONS, AND LACTIC ACIDOSIS, AND SEVERE HEPATOMEGALY

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WARNING: HYPERSENSITIVITY REACTIONS, AND LACTIC ACIDOSIS, AND SEVERE HEPATOMEGALY
Hypersensitivity Reactions

Serious and sometimes fatal hypersensitivity reactions, with multiple organ involvement, have occurred with abacavir tablets.

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 **Warnings and Precautions (5.1)**).

Abacavir tablets are contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients (see **Contraindications (4)**, **Warnings and Precautions (5.1)**). All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with abacavir tablets or reinitiation of therapy with abacavir tablets, unless patients have a previously documented HLA-B*5701 allele assessment. Discontinue abacavir tablets immediately if a hypersensitivity reaction is suspected, regardless of HLA-B*5701 status and even when other diagnoses are possible (see **Contraindications (4)**, **Warnings and Precautions (5.1)**).

Following a hypersensitivity reaction to abacavir, NEVER restart abacavir tablet or any other abacavir-containing product because more severe symptoms, including death can occur within hours. Similar severe reactions have also occurred rarely following the reintroduction of abacavir-containing products in patients who have no history of abacavir hypersensitivity (see **Warnings and Precautions (5.1)**).

Lactic Acidosis and Severe Hepatomegaly with Steatosis
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues and other antiretrovirals. Discontinue abacavir if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur (see **Warnings and Precautions (5.2)**).

1 INDICATIONS AND USAGE

Abacavir tablets, USP in combination with other antiretroviral agents, are indicated for the treatment of human immunodeficiency virus (HIV-1) infection.

2 DOSAGE AND ADMINISTRATION

2.1 Screening for HLA-B*5701 Allele Prior to Starting Abacavir

Screen for the HLA-B*5701 allele prior to initiating therapy with abacavir (see **Boxed Warning**, **Warnings and Precautions (5.1)**).

2.2 Recommended Dosage for Adult Patients

The recommended dosage of abacavir tablets for adults is 600 mg daily, administered orally as either 300 mg twice daily or 600 mg once daily, in combination with other antiretroviral agents.

2.3 Recommended Dosage for Pediatric Patients

The recommended dosage of abacavir tablets in HIV-1-infected pediatric patients aged 3 months and older is 8 mg per kg orally twice daily (up to a maximum of 600 mg daily) in combination with other antiretroviral agents.

Abacavir tablet 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 abacavir tablets, children should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow abacavir tablets, the oral solution formulation should be prescribed. The recommended oral dosage of abacavir tablets for HIV-1-infected pediatric patients is presented in Table 1.

Table 1. Dosing Recommendations for Abacavir Scored Tablets in Pediatric Patients

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

Additional pediatric use information for patients aged 3 months and above is approved for ViiV Healthcare Company's ZIGEN® (abacavir sulfate) tablets and oral solution. However, due to ViiV Healthcare Company's marketing exclusivity rights, this drug product is not labeled with that pediatric information.

2.3 Recommended Dosage for Patients with Hepatic Impairment

The recommended dose of abacavir tablet in patients with mild hepatic impairment (Child-Pugh Class A) is 200 mg twice daily. To enable dose reduction, abacavir oral solution (10 mL twice daily) should be used for the treatment of these patients. The safety, efficacy, and pharmacokinetic properties of abacavir have not been established in patients with moderate to severe hepatic impairment; therefore, abacavir tablet is contraindicated in these patients.

3 DOSAGE FORMS AND STRENGTHS

Abacavir tablets, USP containing abacavir sulfate, USP equivalent to 300 mg abacavir, are yellow colored, biconvex shaped, film coated tablets debossed with 'H' on one side and '139' on other side separating 13.9 with score line.

4 CONTRAINDICATIONS

Abacavir tablet is contraindicated in patients:

- who have the HLA-B*5701 allele (see **Warnings and Precautions (5.1)**).
- with prior hypersensitivity reaction to abacavir (see **Warnings and Precautions (5.1)**).
- with moderate or severe hepatic impairment (see **Use in Specific Populations (8.6)**).

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Serious and sometimes fatal hypersensitivity reactions have occurred with abacavir. These hypersensitivity reactions have included multi-organ failures and anaphylaxis and typically occurred within the first 7 weeks of treatment with abacavir (median time to onset was 9 days); although abacavir hypersensitivity reactions have occurred any time during treatment (see **Adverse Reactions (6.1)**). Patients who carry the HLA-B*5701 allele are at a higher risk of abacavir hypersensitivity reactions; although, patients who do not carry the HLA-B*5701 allele have developed hypersensitivity reactions. Hypersensitivity to abacavir was reported in approximately 206 (8%) of 2,670 patients in 9 clinical trials with abacavir-containing products where HLA-B*5701 screening was not performed. The incidence of suspected abacavir hypersensitivity reactions in clinical trials was 1% when subjects carrying the HLA-B*5701 allele were excluded. In any patient treated with abacavir, the clinical diagnosis of hypersensitivity reaction must remain the basis of clinical decision making.

Due to the potential for severe, serious, and possibly fatal hypersensitivity reactions with abacavir:

- All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with abacavir or reinitiation of therapy with abacavir, unless patients have a previously documented HLA-B*5701 allele assessment.
- Abacavir tablets are contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients.
- Before starting abacavir tablets, review medical history for prior exposure to any abacavir-containing product. NEVER restart abacavir tablets or any other abacavir-containing product following a hypersensitivity reaction to abacavir, regardless of HLA-B*5701 status.
- To reduce the risk of a life-threatening hypersensitivity reaction, regardless of HLA-B*5701 status, discontinue abacavir immediately if a hypersensitivity reaction is suspected, even when other diagnoses are possible (e.g., acute onset respiratory diseases such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions to other medications).

6 ADVERSE REACTIONS

- Before initiating abacavir, screen for the HLA-B*5701 allele. (2.1)
- Adults: 600 mg daily, administered as either 300 mg twice daily or 600 mg once daily. (2.2)
- Pediatric Patients Aged 3 Months and Older: Administered twice daily. Dose should be calculated on body weight (kg) and should not exceed 600 mg daily. (2.3)
- Patients with Hepatic Impairment: Mild hepatic impairment – 200 mg twice daily. (2.4)

7 DOSAGE FORMS AND STRENGTHS

- Tablets: 300 mg scored (3)

8 CONTRAINDICATIONS

- Presence of HLA-B*5701 allele. (4)
- Prior hypersensitivity reaction to abacavir. (4)
- Moderate or severe hepatic impairment. (4)

9 WARNINGS AND PRECAUTIONS

- Immune reconstitution syndrome and redistribution/accumulation of body fat have been reported in patients treated with combination antiretroviral therapy. (5.3, 5.4)
- Administration of abacavir with other products containing abacavir is not recommended. (5.6)

10 ADVERSE REACTIONS

- The most commonly reported adverse reactions of at least moderate intensity (incidence greater than or equal to 10%) in adult HIV-1 clinical trials were nausea, headache, malaise and fatigue, nausea and vomiting, and dreams/sleep disorders. (6.1)
- The most commonly reported adverse reactions of at least moderate intensity (incidence greater than or equal to 5%) in pediatric HIV-1 clinical trials were fever and/or chills, nausea and vomiting, skin rashes, and ear/nose/throat infections. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Hetero Labs Limited at 1-866-495-1995 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

11 DRUG INTERACTIONS

- Methadone: An increased methadone dose may be required in a small number of patients. (7.1)

12 USE IN SPECIFIC POPULATIONS

- Lactation: Breastfeeding not recommended. (8.2)

13 FULL PATIENT COUNSELING INFORMATION and Medication Guide.

See additional pediatric use information for patients aged 3 months and above is approved for ViiV Healthcare Company's ZIGEN® (abacavir sulfate) tablets and oral solution. However, due to ViiV Healthcare Company's marketing exclusivity rights, this drug product is not labeled with that pediatric information.

Revised: 11/2015

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- *Sections or subsections omitted from the full prescribing information are not listed

- If a hypersensitivity reaction cannot be ruled out, do not restart abacavir tablets or any other abacavir-containing products because more severe symptoms which may include life-threatening hypotension and death can occur within hours.
- If a hypersensitivity reaction is ruled out, patients may restart abacavir. Rarely, patients who have stopped abacavir for reasons other than symptoms of hypersensitivity have also experienced life-threatening reactions within hours of reinitiating abacavir therapy. Therefore, reintroduction of abacavir or any other abacavir-containing product is recommended only if medical care can be readily accessed.
- A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill.

5.2 Lactic Acidosis and Severe Hepatomegaly with Steatosis

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

5.3 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including abacavir. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré 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.

5.4 Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

5.5 Myocardial Infarction

In a published prospective, observational, epidemiological trial designed to investigate the rate of myocardial infarction (MI) in patients on combination antiretroviral therapy, the use of abacavir within the previous 6 months was correlated with an increased risk of MI. In a sponsor-conducted pooled analysis of clinical trials, no excess risk of MI was observed in abacavir-treated subjects as compared with control subjects. In totality, the available data from the observational cohort and from clinical trials are 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, smoking).

5.6 Related Products that are Not Recommended

Abacavir is one of multiple abacavir-containing products. Concomitant administration of abacavir with other products containing abacavir is not recommended.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Serious and sometimes fatal hypersensitivity reactions (see **Boxed Warning**, **Warnings and Precautions (5.1)**).
- Lactic acidosis and severe hepatomegaly with steatosis (see **Boxed Warning**, **Warnings and Precautions (5.2)**).
- Immune reconstitution syndrome (see **Warnings and Precautions (5.3)**).
- Fat redistribution (see **Warnings and Precautions (5.4)**).
- Myocardial infarction (see **Warnings and Precautions (5.5)**).

6.1 Clinical Trials Experience in Adult Subjects

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Serious and Fatal Abacavir-associated Hypersensitivity Reactions
In clinical trials, serious and sometimes fatal hypersensitivity reactions have occurred with abacavir (see **Boxed Warning**, **Warnings and Precautions (5.1)**). These reactions have been characterized by 2 or more of the following signs or symptoms: (1) fever; (2) rash; (3) gastrointestinal symptoms (including nausea, vomiting, diarrhea, or abdominal pain); (4) constitutional symptoms (including generalized malaise, fatigue, or achiness); (5) respiratory symptoms (including dyspnea, cough, or pharyngitis). Almost all abacavir hypersensitivity reactions include fever and/or rash as part of the syndrome.

Other signs and symptoms have included lethargy, headache, myalgia, edema, arthralgia, and paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure, myolysis, and death have occurred in association with these hypersensitivity reactions. Physical findings have included lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and maculopapular or urticarial rash (although some patients had other types of rashes and others did not have a rash). There were reports of erythema multiforme with laboratory abnormalities included elevated liver chemistries, elevated creatine phosphokinase, elevated creatinine, and lymphopenia, and abnormal chest x-ray findings (predominantly infiltrates, which were localized).

Additional Adverse Reactions with Use of Abacavir
Therapy-naïve 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 are listed in Table 2.

Table 2. Treatment-emergent (All Causally) Adverse Reactions of at Least Moderate Intensity (Grades 2 to 4, Greater than or Equal to 5% Frequency) in Therapy-naïve Adults (CNA30024) 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%
Drug hypersensitivity	0%	<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 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 lamivudine 150 mg twice daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily from CNA3005 are listed in Table 3.

Table 3. Treatment-emergent (All Causally) Adverse Reactions of at Least Moderate Intensity (Grades 2 to 4, Greater than or Equal to 5% Frequency) in Therapy-naïve Adults (CNA3005) through 48 Weeks of Treatment

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

Five subjects receiving abacavir in CNA3005 experienced worsening of pre-existing depression compared with none in the indinavir arm. The background rates of pre-existing depression were similar in the 2 treatment arms.

Abacavir Once Daily Versus Abacavir Twice Daily (CNA30021): Treatment-emergent clinical adverse reactions (rated by the investigator as at least moderate) with a greater than or equal to 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 CNA30021, were similar. For hypersensitivity reactions, subjects receiving abacavir once daily showed a rate of 4% in comparison with a rate of 7% for subjects receiving abacavir twice daily. However, subjects receiving abacavir 600 mg once daily experienced a significantly higher incidence of severe drug hypersensitivity reactions and severe diarrhea compared with subjects who received abacavir 300 mg twice daily. Five percent (5%) of subjects receiving abacavir 600 mg once daily had severe drug hypersensitivity reactions compared with 2% of subjects receiving abacavir 300 mg twice daily. Two percent (2%) of subjects receiving abacavir 600 mg once daily had severe diarrhea while none of the subjects receiving abacavir 300 mg twice daily had this event.

Laboratory Abnormalities: Laboratory abnormalities (Grades 3 to 4) in therapy-naïve 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 4.

Table 4. Laboratory Abnormalities (Grades 3 to 4) in Therapy-naïve 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%
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%



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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity
Abacavir was administered orally at 3 dosage levels to separate groups of mice and rats in 2-year carcinogenicity studies. Results showed an increase in the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the citral gland of females of both species, and in the liver of female rats. In addition, non-malignant tumors also occurred in the liver and thyroid gland of female rats. These observations were made at systemic exposures in the range of 6 to 32 times the human exposure at the recommended dose of 600 mg.

Mutagenicity
Abacavir induced chromosomal aberrations both in the presence and absence of metabolic activation in an *in vitro* cytogenetic study in human lymphocytes. Abacavir was mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence of metabolic activation in an L5178Y mouse lymphoma assay. Abacavir was clastogenic in males and not clastogenic in females in an *in vivo* mouse bone marrow micronucleus assay.

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

Impairment of Fertility

Abacavir did not affect male or female fertility in rats at a dose associated with exposures approximately 8 times higher than the exposure in humans at the dose of 600 mg.

13.2 Animal Toxicology and/or Pharmacology

Myocardial degeneration was found in mice and rats following administration of abacavir for 2 years. The systemic exposures were equivalent to 7 to 24 times the expected systemic exposure in humans at a dose of 600 mg. The clinical relevance of this finding has not been determined.

14 CLINICAL STUDIES

14.1 Adult Trials

Therapy-naïve Adults

CNA3024 was a multicenter, double-blind, controlled trial in which 649 HIV-1-infected, therapy-naïve adults were randomized and received either abacavir (300 mg twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once daily); or zidovudine (300 mg twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once daily). The duration of double-blind treatment was at least 48 weeks. Trial participants were: male (81%), white (51%), black (21%), and Hispanic (28%). The median age was 35 years; the median pretreatment CD4+ cell count was 264 cells per mm³, and median plasma HIV-1 RNA was 4.79 log₁₀ copies per mL. The outcomes of randomized treatment are provided in Table 7.

Table 7. Outcomes of Randomized Treatment through Week 48 (CNA30024)

Outcome	Abacavir plus Lamivudine plus Efavirenz (n = 324)	Zidovudine plus Lamivudine plus Efavirenz (n = 325)
Responder ^a	69% (73%)	69% (71%)
Virologic failure ^b	6%	4%
Discontinued due to adverse reactions	14%	16%
Discontinued due to other reasons ^c	10%	11%

^a subjects achieved and maintained confirmed HIV-1 RNA less than or equal to 50 copies per mL (less than 400 copies per mL) through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR[®] standard test PCR).

^b includes viral rebound, insufficient viral response according to the investigator, and failure to achieve confirmed less than or equal to 50 copies per mL by Week 48.

^c includes consent withdrawn, lost to follow up, protocol violations, those with missing data, clinical progression, and other.

After 48 weeks of therapy, the median CD4+ cell count increases from baseline were 209 cells per mm³ in the group receiving abacavir and 155 cells per mm³ in the zidovudine group. Through Week 48, 8 subjects (2%) in the group receiving abacavir (5 CDC classification C events and 3 deaths) and 5 subjects (2%) in the zidovudine arm (3 CDC classification C events and 2 deaths) experienced clinical disease progression. CNA3005 was a multicenter, double-blind, controlled trial in which 562 HIV-1-infected, therapy-naïve adults were randomized to receive either abacavir (300 mg twice daily) plus COMBIVIR[®] (lamivudine 150 mg/zidovudine 300 mg twice daily), or indinavir (800 mg 3 times a day) plus COMBIVIR twice daily. The trial was stratified at randomization by pre-entry plasma HIV-1 RNA 10,000 to 100,000 copies per mL and plasma HIV-1 RNA greater than 100,000 copies per mL. Trial participants were male (87%), white (73%), black (15%), and Hispanic (9%). At baseline the median age was 36 years; the median baseline CD4+ cell count was 360 cells per mm³, and median baseline plasma HIV-1 RNA was 4.8 log₁₀ copies per mL. Proportions of subjects with plasma HIV-1 RNA less than 400 copies per mL (using Roche AMPLICOR HIV-1 MONITOR Test) through 48 weeks of treatment are summarized in Table 8.

Table 8. Outcomes of Randomized Treatment through Week 48 (CNA3005)

Outcome	Abacavir plus Lamivudine/Zidovudine (n = 282)	Indinavir plus Lamivudine/Zidovudine (n = 285)
Responder ^a	49%	50%
Virologic failure ^b	31%	28%
Discontinued due to adverse reactions	10%	12%
Discontinued due to other reasons ^c	11%	10%

^a Subjects achieved and maintained confirmed HIV-1 RNA less than 400 copies per mL.

^b Includes viral rebound and failure to achieve confirmed less than 400 copies per mL by Week 48.

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

Treatment response by plasma HIV-1 RNA strata is shown in Table 9.

Table 9. Proportions of Responders through Week 48 By Screening Plasma HIV-1 RNA Levels (CNA3005)

Screening HIV-1 RNA (copies/mL)	Abacavir plus Lamivudine/Zidovudine (n = 282)		Indinavir plus Lamivudine/Zidovudine (n = 285)	
	<400 copies/mL	n	<400 copies/mL	n
≥10,000 - <100,000	50%	166	48%	165
>100,000	48%	96	52%	100

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

Through Week 48, an overall mean increase in CD4+ cell count of about 150 cells per mm³ was observed in both treatment arms. Through Week 48, 9 subjects (3.4%) in the group receiving abacavir (6 CDC classification C events and 3 deaths) and 3 subjects (1.5%) in the group receiving indinavir (6 CDC classification C events and 1 death) experienced clinical disease progression.

CNA30021 was an international, multicenter, double-blind, controlled trial in which 770 HIV-1-infected, therapy-naïve adults were randomized and received either abacavir 600 mg once daily or abacavir 300 mg twice daily, both in combination with lamivudine 300 mg once daily and efavirenz 600 mg once daily. The double-blind treatment duration was at least 48 weeks. Trial participants had a mean age of 37 years; were male (81%), white (54%), black (27%), and American Hispanic (15%). The median baseline CD4+ cell count was 262 cells per mm³ (range 21 to 918 cells per mm³) and the median baseline plasma HIV-1 RNA was 4.89 log₁₀ copies per mL (range: 2.60 to 6.99 log₁₀ copies per mL).

The outcomes of randomized treatment are provided in Table 10.

Table 10. Outcomes of Randomized Treatment through Week 48 (CNA30021)

Outcome	Abacavir 600 mg q.d. plus EPIVIR [®] plus Efavirenz (n = 384)	Abacavir 300 mg b.i.d. plus EPIVIR plus Efavirenz (n = 386)
	Responder ^a	64% (71%)
Virologic failure ^b	11% (5%)	11% (5%)
Discontinued due to adverse reactions	13%	11%
Discontinued due to other reasons ^c	11%	13%

^a subjects achieved and maintained confirmed HIV-1 RNA less than 50 copies per mL (less than 400 copies per mL) through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR standard test version 1).

^b includes viral rebound, failure to achieve confirmed less than 50 copies per mL (less than 400 copies per mL) by Week 48, and insufficient viral load response.

^c includes consent withdrawn, lost to follow up, protocol violations, clinical progression, and other.

After 48 weeks of therapy, the median CD4+ cell count increases from baseline were 188 cells per mm³ in the group receiving abacavir 600 mg once daily and 200 cells per mm³ in the group receiving abacavir 300 mg twice daily. Through Week 48, 9 subjects (2%) in the group receiving abacavir 600 mg once daily (4 CDC classification C events and 2 deaths) and 10 subjects (3%) in the group receiving abacavir 300 mg twice daily (7 CDC classification C events and 3 deaths) experienced clinical disease progression. None of the deaths were attributed to trial medications.

14.2 Pediatric Trials

Therapy-experienced Pediatric Subjects

CNA3006 was a randomized, double-blind trial comparing abacavir 8 mg per kg twice daily plus lamivudine 4 mg per kg twice daily plus zidovudine 180 mg per m² twice daily versus lamivudine 4 mg per kg twice daily plus zidovudine 180 mg per m² twice daily. Two hundred and five therapy-experienced pediatric subjects were enrolled: female (56%), white (17%), black (50%), Hispanic (30%), median age of 5.4 years, baseline CD4+ cell percent greater than 15% (median = 27%), and median baseline plasma HIV-1 RNA of 4.6 log₁₀ copies per mL. Eighty percent and 55% of subjects had prior therapy with zidovudine and lamivudine, respectively, most often in combination. The median duration of prior nucleoside analogue therapy was 2 years. At 16 weeks the proportion of subjects responding based on plasma HIV-1 RNA less than or equal to 400 copies per mL was significantly higher in subjects receiving abacavir plus lamivudine plus zidovudine compared with subjects receiving lamivudine plus zidovudine, 15% versus 2%, respectively. Median plasma HIV-1 RNA changes from baseline were -0.53 log₁₀ copies per mL in the group receiving abacavir plus lamivudine plus zidovudine compared with -0.21 log₁₀ copies per mL in the group receiving lamivudine plus zidovudine. Median CD4+ cell count increases from baseline were 69 cells per mm³ in the group receiving abacavir plus lamivudine plus zidovudine and 9 cells per mm³ in the group receiving lamivudine plus zidovudine.

Additional pediatric use information for patients aged 3 months and above is approved for HIV Healthcare Company's ZIAGEN[®] (abacavir sulfate) tablets and oral solution. However, due to HIV Healthcare Company's marketing exclusivity rights, this drug product is not labeled with that pediatric information.

16 HOW SUPPLIED/STORAGE AND HANDLING

Abacavir tablets, USP containing abacavir sulfate, USP equivalent to 300 mg abacavir are yellow colored, biconvex, capsule shaped, film coated tablets debossed with 'H' on one side and '139' on other side separating 13 & 9 with score line. They are packaged as follows:
Bottles of 60 tablets (31722-557-60)

Store at 20° to 25°C (68° to 77°F) (see USP Controlled Room Temperature).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide)

Hypersensitivity Reactions

Inform patients:

- that a Medication Guide and Warning Card summarizing the symptoms of the abacavir hypersensitivity reaction and other product information will be dispensed by the pharmacist with each new prescription and refill of abacavir tablets, and instruct the patient to read the Medication Guide and Warning Card every time to obtain any new information that may be present about abacavir tablets. The complete text of the Medication Guide is reprinted at the end of this document.
- to carry the Warning Card with them.
- how to identify a hypersensitivity reaction [see Warnings and Precautions (5.1), Medication Guide].
- that if they develop symptoms consistent with a hypersensitivity reaction they should call their healthcare provider right away to determine if they should stop taking abacavir tablets.
- that a hypersensitivity reaction can worsen and lead to hospitalization or death if abacavir tablet is not immediately discontinued.
- to not restart abacavir tablet or any other abacavir-containing product following a hypersensitivity reaction because more severe symptoms can occur within hours and may include life-threatening hypotension and death.
- that a hypersensitivity reaction is usually reversible if it is detected promptly and abacavir tablet is stopped right away.
- that if they have interrupted abacavir tablets for reasons other than symptoms of hypersensitivity (for example, those who have an interruption in drug supply), a serious or fatal hypersensitivity reaction may occur with reintroduction of abacavir.

- to not restart abacavir tablet or any other abacavir-containing product without medical consultation and only if medical care can be readily accessed by the patient or others.

Related Products that are Not Recommended

Inform patients that they should not take abacavir with EPZICOM[®], TRIUMEQ[®], or TRIZIVIR[®].

Lactic Acidosis/Hepatomegaly

Inform patients that some HIV medicines, including abacavir tablets, can cause a rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly) [see Boxed Warning, Warnings and Precautions (5.2)].

Immune Reconstitution Syndrome

In some patients with advanced HIV infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. Advise patients to inform their healthcare provider immediately of any symptoms of infection [see Warnings and Precautions (5.3)].

Redistribution/Accumulation of Body Fat

Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time. [see Warnings and Precautions (5.4)].

Information About HIV-1 Infection

Inform patients that abacavir tablet is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients must remain on continuous HIV therapy to control HIV-1 infection and decrease HIV-related illness. Inform patients that sustained decreases in plasma HIV-1 RNA have been associated with a reduced risk of progression to AIDS and death.

Advise patients to remain under the care of a physician when using abacavir.

Advise patients to take all HIV medications exactly as prescribed. Instruct patients that if they miss a dose, they should take it as soon as they remember. If they do not remember until it is time for the next dose, they should be instructed to skip the missed dose and go back to the regular schedule. Patients should not double their next dose or take more than the prescribed dose.

Advise patients to avoid doing things that can spread HIV-1 infection to others.

Advise patients not to re-use or share needles or other injection equipment.

Advise patients not to share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.

Advise patients to always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

Female patients should be advised not to breastfeed. Mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

Instruct patients to read the Medication Guide before starting abacavir and to reread it each time the prescription is renewed. Instruct patients to inform their physician or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.

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Manufactured for:
Camber Pharmaceuticals, Inc.
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By: **HETERO™**
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MEDICATION GUIDE

Abacavir Tablets, USP
(ah-BAH-kah-veer)

What is the most important information I should know about abacavir tablets?

Abacavir can cause serious side effects, including:

- Serious allergic reaction (hypersensitivity reaction) that can cause death have happened with abacavir tablets and other abacavir-containing products. Your risk of this allergic reaction is much higher if you have a gene variation called HLA-B*57:01. Your healthcare provider can determine with a blood test if you have this gene variation.

If you get a symptom from 2 or more of the following groups while taking abacavir tablets, call your healthcare provider right away to find out if you should stop taking abacavir tablets.

Group	Symptom(s)
Group 1	Fever
Group 2	Rash
Group 3	Nausea, vomiting, diarrhea, abdominal (stomach area) pain
Group 4	Generally ill feeling, extreme tiredness, or achiness
Group 5	Shortness of breath, cough, sore throat

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

If you stop abacavir tablets because of an allergic reaction, never take abacavir or any other abacavir-containing medicine (EPZICOM[®], TRIUMEQ[®], or TRIZIVIR[®]) again.

If you take abacavir tablets or any other abacavir-containing medicine again after you have had an allergic reaction, within hours you may get life-threatening symptoms that may include very low blood pressure or death.

If you stop abacavir tablets for any other reason, even for a few days, and you are not allergic to abacavir, talk to your healthcare provider before taking it again. Taking abacavir tablets again can 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 abacavir tablets again, start taking it when you are around medical help or people who can call a healthcare provider if you need one.

Build-up of acid in your blood (lactic acidosis). Lactic acidosis can happen in some people who take abacavir tablets. Lactic acidosis is a serious medical emergency that can cause death. Call your healthcare provider right away if you get any of the following symptoms that could be signs of lactic acidosis:

- feel very weak or tired
- feel cold, especially in your arms and legs
- unusual (not normal) muscle pain
- feel dizzy or light-headed
- trouble breathing
- have a fast or irregular heartbeat
- stomach pain with nausea and vomiting

Serious liver problems can happen in people who take abacavir. In some cases, these serious liver problems can lead to death. Your liver may become large (hepatomegaly) and you may develop fat in your liver (steatosis) when you take abacavir tablets. Call your healthcare provider right away if you have any of the following signs of liver problems:

- your skin or the white part of your eyes turns yellow (jaundice)
- loss of appetite for several days or longer
- dark or "tea-colored" urine
- nausea
- light-colored stools (bowel movements)
- pain, aching, or tenderness on the right side of your stomach area

You may be more likely to get lactic acidosis or serious liver problems if you are female, very overweight (obese), or have been taking nucleoside analogue medicines for a long time.

What is abacavir tablets?

Abacavir tablet is a prescription HIV-1 (Human Immunodeficiency Virus type 1) medicine used with other antiretroviral medicines to treat HIV-1 infection. HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

The safety and effectiveness of abacavir has not been established in children under 3 months of age.

When used with other antiretroviral medicines to treat HIV-1 infection, abacavir tablet may help:

- reduce the amount of HIV-1 in your blood. This is called "viral load".
- increase the number of CD4+ (T) cells in your blood, that help fight off other infections.

Reducing the amount of HIV-1 and increasing the CD4+ (T) cells in your blood may help improve your immune system. This may reduce your risk of death or getting infections that can happen when your immune system is weak (opportunistic infections).

Abacavir tablets does not cure HIV-1 infection or AIDS. You must keep taking HIV-1 medicines to control HIV-1 infection and decrease HIV-related illnesses.

Avoid doing things that can spread HIV-1 infection to others.

- Do not share or re-use needles or other injection equipment.
- Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.
- Do not have any kind of sex without protection. Always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood.

Ask your healthcare provider if you have any questions about how to prevent passing HIV to other people.

Who should not take abacavir tablets?

Do not take abacavir tablets if you:

- have a certain type of gene variation called the HLA-B*57:01 allele. Your healthcare provider will test you for this before prescribing treatment with abacavir.
- are allergic to abacavir or any of the ingredients in abacavir tablets. See the end of this Medication Guide for a complete list of ingredients in abacavir tablets.
- have liver problems.

What should I tell my healthcare provider before taking abacavir tablets?

Before you take abacavir tablets, tell your healthcare provider if you:

- have been tested and know whether or not you have a particular gene variation called HLA-B*57:01.
- have or have had liver problems, including hepatitis B or C virus infection.
- have heart problems, smoke, or have diseases that increase your risk of heart disease such as high blood pressure, high cholesterol, or diabetes.
- drink alcohol or take medicines that contain alcohol.
- are pregnant or plan to become pregnant. Taking abacavir tablets during pregnancy has not been associated with an increased risk of birth defects. Talk to your healthcare provider if you are pregnant or plan to become pregnant.

Pregnancy Registry. There is a pregnancy registry for women who take antiretroviral medicines during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.

- are breastfeeding or plan to breastfeed. **Do not breastfeed if you take abacavir tablets.**
 - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some medicines interact with abacavir. **Keep a list of your medicines to show your healthcare provider and pharmacist.** You can ask your healthcare provider or pharmacist for a list of medicines that interact with abacavir. **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take abacavir with other medicines.

You should not take abacavir tablets if you also take:

- abacavir (EPZICOM, TRIUMEQ, or TRIZIVIR)

Tell your healthcare provider if you take:

- any other medicine to treat HIV-1
- methadone

How should I take abacavir tablet?

- Take abacavir tablet exactly as your healthcare provider tells you.**
- Do not change your dose or stop taking abacavir tablets without talking with your healthcare provider. If you miss a dose of abacavir tablets, take it as soon as you remember. Do not take 2 doses at the same time. If you are not sure about your dosing, call your healthcare provider.
- Stay under the care of a healthcare provider while taking abacavir tablets.
- Abacavir tablet may be taken with or without food.
- For children aged 3 months and older, your healthcare provider will prescribe a dose of abacavir based on your child's body weight.
- Tell your healthcare provider if you or your child has trouble swallowing tablets. Abacavir comes as a tablet or as a liquid (oral solution).
- Do not run out of abacavir tablets. The virus in your blood may increase and the virus may become harder to treat. When your supply starts to run out, get more from your healthcare provider or pharmacy.
- If you take too much abacavir, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of abacavir tablets?

Abacavir can cause serious side effects including:

See "What is the most important information I should know about abacavir tablets?"

Changes in your immune system (Immune Reconstitution Syndrome) can happen when your 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. Tell your healthcare provider right away if you start having new symptoms after you start taking abacavir tablets.

Changes in body fat can happen in people who take HIV-1 medicines. These