

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

### Abacavir Tablets USP

Initial U.S. Approval: 1998

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

- Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate. (5.1)
- Hypersensitivity to abacavir is a multi-organ clinical syndrome. (5.1)
- Patients who carry the HLA-B\*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. (5.1)
- Discontinue abacavir sulfate as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B\*5701 status, permanently discontinue abacavir sulfate if hypersensitivity cannot be ruled out, even when other diagnoses are possible. (5.1)
- Following a hypersensitivity reaction to abacavir, NEVER restart abacavir sulfate or any other abacavir-containing product. (5.1)
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. (5.2)

### RECENT MAJOR CHANGES

Dosage and Administration (2) 05/2012  
Warnings and Precautions, Hypersensitivity reaction (5.1) 05/2012  
Warnings and Precautions, Immune Reconstitution syndrome (5.3) 11/2011

### INDICATIONS AND USAGE

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

### DOSE AND ADMINISTRATION

- A medication guide and warning card should be dispensed with each new prescription and refill. (2)
- Adults: 600 mg daily, administered as either 300 mg twice daily or 600 mg once daily. (2.1)

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### WARNING: RISK OF HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS, AND SEVERE HEPATOMEGALY

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

- 2.1 Adult Patients
- 2.2 Pediatric Patients
- 2.3 Patients with Hepatic Impairment

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

- 5.1 Hypersensitivity Reactions
- 5.2 Lactic Acidosis/Severe Hepatomegaly With Steatosis
- 5.3 Immune Reconstitution Syndrome
- 5.4 Fat Redistribution
- 5.5 Myocardial Infarction

#### 6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

#### 7 DRUG INTERACTIONS

#### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy

## FULL PRESCRIBING INFORMATION

**WARNING: RISK OF HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS, AND SEVERE HEPATOMEGALY**  
Hypersensitivity Reactions: Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate.

Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups: (1) fever, (2) rash, (3) gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain), (4) constitutional (including generalized malaise, fatigue, or achiness), and (5) respiratory (including dyspnea, cough, or pharyngitis). Discontinue abacavir sulfate as soon as a hypersensitivity reaction is suspected.

Patients who carry the HLA-B\*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, screening for the HLA-B\*5701 allele is recommended; this approach has been found to decrease the risk of hypersensitivity reaction. Screening is also recommended prior to reinitiation of abacavir in patients of unknown HLA-B\*5701 status who have previously tolerated abacavir. HLA-B\*5701-negative patients may develop a suspected 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 abacavir sulfate if hypersensitivity cannot be ruled out, even when other diagnoses are possible.

Following a hypersensitivity reaction to abacavir, NEVER restart abacavir sulfate or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.

Reintroduction of abacavir sulfate or any other abacavir-containing product, even in patients who have no identified history or unrecognized symptoms of hypersensitivity to abacavir therapy, can result in serious or fatal hypersensitivity reactions. Such reactions can occur within hours (see Warnings and Precautions (5.1)).

**Lactic Acidosis and Severe Hepatomegaly:** Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir sulfate and other antiretrovirals (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.

Additional important information on the use of abacavir tablet USP for treatment of HIV-1 infection:

- Abacavir tablet USP is one of multiple products containing abacavir. Before starting abacavir tablet USP, review medical history for prior exposure to any abacavir-containing product in order to avoid reintroduction in a patient with a history of hypersensitivity to abacavir. (see Warnings and Precautions (5.1), Adverse Reactions (6)).

#### 2 DOSAGE AND ADMINISTRATION

- A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill.
- Abacavir tablet may be taken with or without food.

##### 2.1 Adults Patients

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

##### 2.2 Pediatric Patients

Abacavir sulfate 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 tablets in Pediatric Patients**

Weight (Kg)	Dosage Regimen Using Scored Tablet		Total Daily Dose
	AM Dose	PM Dose	
14 to 21	½ tablet (150 mg)	½ tablet (150 mg)	300 mg
>21 to <30	½ tablet (150 mg)	1 tablet (300 mg)	450 mg
>30	1 tablet (300 mg)	1 tablet (300 mg)	600 mg

#### 2.3 Patients with Hepatic Impairment

The recommended dose of abacavir tablet in patients with mild hepatic impairment (Child-Pugh score 5 to 6) 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, capsule 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 with previously demonstrated hypersensitivity to abacavir or any other component of the products. NEVER restart abacavir tablet or any other abacavir-containing product following a hypersensitivity reaction to abacavir, regardless of HLA-B\*5701 status (see Warnings and Precautions (5.1), Adverse Reactions (6)).
- moderate or severe hepatic impairment (see Dosage and Administration (2.3)).

- Pediatric Patients Aged 3 Months and Older: Dose should be calculated on body weight (kg) and should not exceed 300 mg twice daily. (2.2)
- Patients With Hepatic Impairment: Mild hepatic impairment <200 mg twice daily; moderate/severe hepatic impairment – contraindicated. (2.3)

### DOSAGE FORMS AND STRENGTHS

Tablets: 300 mg, scored.

### CONTRAINDICATIONS

- Previously demonstrated hypersensitivity to abacavir. (4, 5.1)
- Moderate or severe hepatic impairment. (4)

### WARNINGS AND PRECAUTIONS

- Hypersensitivity: Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate and other abacavir-containing products. Read full prescribing information section 5.1 before prescribing abacavir sulfate. (5.1)
- Lactic acidosis and severe hepatomegaly with steatosis have been reported with the use of nucleoside analogues. (5.2)
- Immune reconstitution syndrome (5.3) and redistribution/accumulation of body fat have been reported in patients treated with combination antiretroviral therapy. (5.4)

### ADVERSE REACTIONS

- The most commonly reported adverse reactions of at least moderate intensity (incidence ≥10%) in adult HIV-1 clinical studies 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 ≥5%) in pediatric HIV-1 clinical studies were fever and/or chills, nausea and vomiting, skin rashes, and ear/nose/throat infections. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Hetero Labs Limited at 866-495-1995 (or) FDA at 1-800-FDA-1988 or www.fda.gov/medwatch.

### DRUG INTERACTIONS

- Ethanol: Decreases elimination of abacavir. (7.1)
- Methadone: An increased methadone dose may be required in a small number of patients. (7.2)

See 17 for PATIENT COUNSELING INFORMATION AND MEDICATION GUIDE.

Revised: 12/2012

- 8.3 Nursing Mothers
  - 8.4 Pediatric Use
  - 8.5 Geriatric Use
- #### 10 OVERDOSAGE
- #### 11 DESCRIPTION
- #### 12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
  - 12.3 Pharmacokinetics
  - 12.4 Microbiology
- #### 13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
  - 13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

- 14.1 Adults
- 14.2 Pediatric Trials

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

- 17.1 Information About Therapy With Abacavir Sulfate

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

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hypersensitivity Reaction

Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate and other abacavir-containing products. Patients who carry the HLA-B\*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, screening for the HLA-B\*5701 allele is recommended; this approach has been found to decrease the risk of a hypersensitivity reaction. Screening is also recommended prior to reinitiation of abacavir in patients of unknown HLA-B\*5701 status who have previously tolerated abacavir. For HLA-B\*5701-positive patients, treatment with an abacavir-containing regimen is not recommended and should be discontinued with close medical supervision and under exceptional circumstances when the potential benefit outweighs the risk.

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 abacavir sulfate if hypersensitivity cannot be ruled out, even when other diagnoses are possible.

Important information on signs and symptoms of hypersensitivity, as well as clinical management, is presented below.

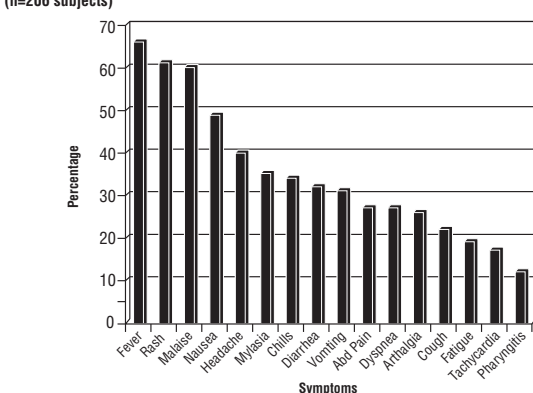
Signs and Symptoms of Hypersensitivity: Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups.

- Group 1: Fever
- Group 2: Rash
- Group 3: Gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain)
- Group 4: Constitutional (including generalized malaise, fatigue, or achiness)
- Group 5: Respiratory (including dyspnea, cough, or pharyngitis).

Hypersensitivity to abacavir following the presentation of a single sign or symptom has been reported infrequently.

Hypersensitivity to abacavir was reported in approximately 8% of 2,670 subjects (n = 206) in 9 clinical trials (range: 2% to 9%) with enrollment from November 1999 to February 2002. Data on time to onset and symptoms of suspected hypersensitivity were collected on a detailed data collection module. The frequencies of symptoms are shown in Figure 1. Symptoms usually appeared within the first 6 weeks of treatment with abacavir, although the reaction may occur at any time during therapy. Median time to onset was 3 days; 89% appeared within the first 6 weeks; 95% of patients reported symptoms from 2 or more of the 5 groups listed above.

**Figure 1. Hypersensitivity-Related Symptoms Reported With ≥10% Frequency in Clinical in Clinical Trials (n=206 subjects)**



Other less common signs and symptoms of hypersensitivity include lethargy, myolysis, edema, abnormal chest x-ray findings (predominantly infiltrates, which can be localized), and paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure, and death have occurred in association with hypersensitivity reactions. In one trial, 4 subjects (11% receiving abacavir sulfate 600 mg once daily experienced hypotension with a hypersensitivity reaction compared with 0 subjects receiving abacavir sulfate 300 mg twice daily.

Physical findings associated with hypersensitivity to abacavir in some patients include lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and rash. The rash usually appears maculopapular or urticarial, but may be variable in appearance. There have been reports of erythema multiforme. Hypersensitivity reactions have occurred without rash.

Laboratory abnormalities associated with hypersensitivity to abacavir in some patients include elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, and lymphopenia.

**Clinical Management of Hypersensitivity:** Discontinue abacavir sulfate as soon as a hypersensitivity reaction is suspected. To minimize the risk of a life-threatening hypersensitivity reaction, permanently discontinue abacavir sulfate if hypersensitivity cannot be ruled out, even when other diagnoses are possible (e.g., acute onset respiratory distresses such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions to other medications).

Following a hypersensitivity reaction to abacavir, NEVER restart abacavir sulfate or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.

When therapy with abacavir sulfate has been discontinued for reasons other than symptoms of a hypersensitivity reaction, and if reinitiation of abacavir sulfate or any other abacavir-containing product is under consideration, carefully evaluate the reason for discontinuation of abacavir sulfate to ensure that the patient did not have symptoms of a hypersensitivity reaction. If the patient is of unknown HLA-B\*5701 status, screening for the allele is recommended prior to reinitiation of abacavir sulfate.

If hypersensitivity cannot be ruled out, DO NOT reintroduce abacavir sulfate or any other abacavir-containing product. Even in the absence of the HLA-B\*5701 allele, it is important to permanently discontinue abacavir and not rechallenge with abacavir if a hypersensitivity reaction cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

If symptoms consistent with hypersensitivity are not identified, reintroduction can be undertaken with continued monitoring for symptoms of a hypersensitivity reaction. Make patients aware that a hypersensitivity reaction can occur with reintroduction of abacavir sulfate or any other abacavir-containing product and that reintroduction of abacavir sulfate or any other abacavir-containing product needs to be undertaken only if medical care can be readily accessed by the patient or others.

**Risk Factor: HLA-B\*5701 Allele:** Trials have shown that carriage of the HLA-B\*5701 allele is associated with a significantly increased risk of a hypersensitivity reaction to abacavir.

CNA106030 (PREDICT-1), a randomized, double-blind trial evaluated the clinical utility of prospective HLA-B\*5701 screening on the incidence of abacavir hypersensitivity reaction in abacavir-naïve HIV-1-infected adults (n = 1,650). In this trial, use of pre-therapy screening for the HLA-B\*5701 allele and exclusion of subjects with this allele reduced the incidence of clinically suspected abacavir hypersensitivity reactions from 7.8% (66/847) to 3.4% (27/803). Based on this trial, it is estimated that 61% of patients with the HLA-B\*5701 allele will develop a clinically suspected hypersensitivity reaction during the course of abacavir treatment compared with 4% of patients who do not have the HLA-B\*5701 allele.

Screening for carriage of the HLA-B\*5701 allele is recommended prior to initiating treatment with abacavir. Screening is also recommended prior to reinitiation of abacavir in patients of unknown HLA-B\*5701 status who have previously tolerated abacavir. For HLA-B\*5701-positive patients, initiating or reinitiating treatment with an abacavir-containing regimen is not recommended and should be considered only with close medical supervision and under exceptional circumstances where potential benefit outweighs the risk.

Skin patch testing is used as a research tool and should not be used to aid in the clinical diagnosis of abacavir hypersensitivity.

In any patient treated with abacavir, the clinical diagnosis of hypersensitivity reaction must remain the basis of clinical decision-making. Even in the absence of the HLA-B\*5701 allele, it is important to permanently discontinue abacavir and not rechallenge with abacavir if a hypersensitivity reaction cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

### 5.2 Lactic Acidosis/Severe Hepatomegaly With Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering abacavir sulfate 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 sulfate 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 sulfate. 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), or to disseminated *Mycobacterium* infections.

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 in patients on combination antiretroviral therapy, the use of abacavir within the previous 6 months was correlated with an increased risk of myocardial infarction (MI).<sup>1</sup> In a sponsor-conducted pooled analysis of clinical trials, no excess risk of myocardial infarction 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 therapy, and action taken to minimize all modifiable risk factors (e.g., hypertension, hyperlipidemia, diabetes mellitus, and smoking).

## 6 ADVERSE REACTIONS

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

- Serious and sometimes fatal hypersensitivity reaction. In one trial, once-daily dosing of abacavir was associated with more severe hypersensitivity reactions (see **Boxed Warning, Warnings and Precautions (5.1)**).
- Lactic acidosis and severe hepatomegaly (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

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 practice.

**Adults: 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 sulfate 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 2.

**Table 2. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2 to 4, ≥5% Frequency) in Therapy-Naïve Adults (CNA30024) Through 48 Weeks of Treatment**

Adverse Reaction	Abacavir sulfate plus Lamivudine plus Efavirenz (n = 324)	Zidovudine plus Lamivudine plus Efavirenz (n = 325)
	Dreams/sleep disorders	10%
Drug hypersensitivity	9%	<1%*
Headaches/migraine	7%	11%
Nausea	7%	11%
Fatigue/malaise	7%	10%
Diarrhea	7%	6%
Rashes	6%	12%
Abdominal pain/gastritis/gastrointestinal signs and symptoms	6%	8%
Depressive disorders	6%	6%
Dizziness	6%	6%
Musculoskeletal pain	6%	5%
Bronchitis	4%	5%
Vomiting	2%	9%

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 sulfate 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 3.

**Table 3. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2 to 4, ≥5% Frequency) in Therapy-Naïve Adults (CNA3005) Through 48 Weeks of Treatment**

Adverse Reaction	Abacavir sulfate plus Lamivudine/Zidovudine (n = 262)	Indinavir plus Lamivudine/Zidovudine (n = 264)
	Nausea	19%
Headache	12%	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	6%	7%
Skin rashes	5%	4%
Ear/nose/throat infections	5%	4%
Respiratory infections	5%	5%
Anxiety	5%	3%
Renal signs/symptoms	<1%	3%
Pain (non-site-specific)	<1%	5%

Five subjects receiving abacavir sulfate 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 Sulfate Once Daily Versus Abacavir Sulfate 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 sulfate 600 mg once daily and efavirenz 600 mg once 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 sulfate once daily showed a rate of 9% compared with a rate of 7% for subjects receiving abacavir sulfate twice daily. However, subjects receiving abacavir sulfate 600 mg once daily, experienced a significantly higher incidence of severe drug hypersensitivity reactions and severe diarrhea compared with subjects who received abacavir sulfate 300 mg twice daily. Five percent (5%) of subjects receiving abacavir sulfate 600 mg once daily had severe drug hypersensitivity reactions compared with 2% of subjects receiving abacavir sulfate 300 mg twice daily. Two percent (2%) of subjects receiving abacavir sulfate 600 mg once daily had severe diarrhea while none of the subjects receiving abacavir sulfate 300 mg twice daily had this event.

**Laboratory Abnormalities:** Laboratory abnormalities (Grades 3 to 4) in therapy-naïve adults during therapy with abacavir sulfate 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 sulfate plus Efavirenz (n = 324)	Zidovudine 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 <sup>3</sup> )	2%	4%
Anemia (Hgb ≤6.9 gm/dL)	<1%	2%
Thrombocytopenia (Platelets <50,0		

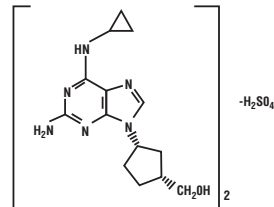


## 10 OVERDOSSAGE

There is no known antidote for abacavir sulfate. It is not known whether abacavir can be removed by peritoneal dialysis or hemodialysis.

## 11 DESCRIPTION

Abacavir sulfate USP is a synthetic carbocyclic nucleoside analogue with inhibitory activity against HIV-1. The chemical name of abacavir sulfate USP is (1S,2S)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1). Abacavir sulfate USP is the enantiomer with 1S, 4R absolute configuration on the cyclopentene ring. It has a molecular formula of  $(C_{10}H_{14}N_6O)_2 \cdot H_2SO_4$  and a molecular weight of 670.76 daltons. It has the following structural formula:



Abacavir sulfate USP is a white to off-white solid with a solubility of approximately 77 mg/mL in distilled water at 25°C. It has an octanol/water (pH 7.1 to 7.3) partition coefficient ( $\log P$ ) of approximately 1.20 at 25°C.

Abacavir tablets USP are for oral administration. Each tablet contains abacavir sulfate USP equivalent to 300 mg of abacavir as active ingredient and the following inactive ingredients: microcrystalline cellulose, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate. The tablets are coated with opadry yellow which contains hypromellose, titanium dioxide, triacetin, iron oxide yellow, polyisobutyl 80.

*In vivo*, abacavir sulfate USP dissociates to its free base, abacavir. All dosages for abacavir sulfate USP are expressed in terms of abacavir.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Abacavir is an antiviral agent. [See *Clinical Pharmacology* (12.4)].

### 12.3 Pharmacokinetics

**Pharmacokinetics in Adults:** The pharmacokinetic properties of abacavir have been studied in asymptomatic, HIV-1-infected adult subjects after administration of a single intravenous (IV) dose of 150 mg and after single and multiple oral doses. The pharmacokinetic properties of abacavir were independent of dose over the range of 300 to 1,200 mg/day.

**Absorption and Bioavailability:** Abacavir was rapidly and extensively absorbed after oral administration. The geometric mean absolute bioavailability of the tablet was 83%. After oral administration of 300 mg twice daily in 20 subjects, the steady-state peak serum abacavir concentration ( $C_{max}$ ) was  $3.0 \pm 0.89$  mcg/mL (mean  $\pm$  SD) and AUC<sub>0-12h</sub> was  $6.02 \pm 1.73$  mcg•hr/mL. After oral administration of a single dose of 600 mg of abacavir in 20 patients,  $C_{max}$  was  $4.26 \pm 1.19$  mcg/mL (mean  $\pm$  SD) and AUC<sub>0-6h</sub> was  $11.95 \pm 2.51$  mcg•hr/mL.

**Distribution:** The apparent volume of distribution after IV administration of abacavir was  $0.86 \pm 0.15$  L/kg, suggesting that abacavir distributes into extravascular space. In 3 subjects, the CSF AUC (0 to 6 hr) to plasma abacavir AUC (0 to 6 hr) ratio ranged from 27% to 33%.

Binding of abacavir to human plasma proteins is approximately 50%. Binding of abacavir to plasma proteins was independent of concentration. Total blood and plasma drug-related radioactivity concentrations are identical, demonstrating that abacavir readily distributes into erythrocytes.

**Metabolism:** In humans, abacavir is not significantly metabolized by cytochrome P450 enzymes. The primary routes of elimination of abacavir are metabolic and non-metabolic. Abacavir is metabolized to form the 5-carboxylic acid and glucuronide transferase (to form the 5-glucuronide). The metabolites do not have antiviral activity. *In vitro* experiments reveal that abacavir does not inhibit human CYP3A4, CYP2D6, or CYP2C9 activity at clinically relevant concentrations.

**Elimination:** Elimination of abacavir was quantified in a mass balance trial following administration of a 600-mg dose of <sup>14</sup>C-abacavir. 89% of the radioactivity was recovered, 12% was excreted in the urine as abacavir, 30% as the 5-carboxylic acid metabolite, 36% as the 5-glucuronide metabolite, and 15% as unidentified minor metabolites in the urine. Fecal elimination accounted for 16% of the dose.

In single-dose trials, the observed elimination half-life ( $t_{1/2}$ ) was  $1.54 \pm 0.63$  hours. After intravenous administration, total clearance was  $0.80 \pm 0.24$  L/hr/kg (mean  $\pm$  SD).

**Effects of Food on Oral Absorption:** Bioavailability of abacavir tablets was assessed in the fasting and fed states. There was no significant difference in systemic exposure (AUC) in the fed and fasting states; therefore, abacavir tablets may be administered with or without food. Systemic exposure to abacavir was comparable after administration of abacavir sulfate oral solution and abacavir tablets. Therefore, these products may be used interchangeably.

**Special Populations: Renal Impairment:** The pharmacokinetic properties of abacavir sulfate have not been determined in patients with impaired renal function. Renal excretion of unchanged abacavir is a minor route of elimination in humans.

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

**Pediatric Patients:** The pharmacokinetics of abacavir have been studied after either single or repeat doses of abacavir sulfate in 68 pediatric patients. Following multiple-dose administration of abacavir sulfate 8 mg/kg twice daily, steady-state AUC<sub>0-12h</sub> and  $C_{max}$  were  $9.8 \pm 4.56$  mcg•hr/mL and  $3.71 \pm 1.36$  mcg/mL (mean  $\pm$  SD), respectively [see *Use in Specific Populations* (8.4)]. In addition, to support dosing of abacavir sulfate scored tablet (300 mg) for pediatric patients 14 to greater than 30 kg, analysis of actual and simulated pharmacokinetic data indicates that comparable exposures are expected following administration of 300 mg scored tablet and the 8 mg/kg dosing regimen using oral solution.

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

**Gender:** A population pharmacokinetic analysis in HIV-1-infected male (n = 304) and female (n = 67) patients showed no gender differences in abacavir AUC normalized for lean body weight.

**Race:** There are no significant differences between blacks and Caucasians in abacavir pharmacokinetics.

**Drug Interactions:** In human liver microsomes, abacavir did not inhibit cytochrome P450 isoforms (C2C, 2D6, 3A4). Based on these data, it is unlikely that clinically significant drug interactions will occur between abacavir and drugs metabolized through these pathways.

**Lamivudine and/or Zidovudine:** Due to the common metabolic pathways of abacavir and zidovudine via glucuronyl transferase, 15 HIV-1-infected subjects were enrolled in a crossover trial evaluating single doses of abacavir (600 mg), lamivudine (150 mg), and zidovudine (300 mg) alone or in combination. Analysis showed no clinically relevant changes in the pharmacokinetics of abacavir with the addition of lamivudine or zidovudine or the combination of lamivudine and zidovudine. Lamivudine exposure (AUC decreased 15%) and zidovudine exposure (AUC increased 10%) did not show clinically relevant changes with concurrent abacavir.

**Ethanol:** Due to their common metabolic pathways via alcohol dehydrogenase, the pharmacokinetic interaction between abacavir and ethanol was studied in 24 HIV-1-infected male subjects. Each subject received the following treatments on separate occasions: a single 600-mg dose of abacavir, 0.7 g/kg ethanol (equivalent to 5 alcoholic drinks), and abacavir 600 mg plus 0.7 g/kg ethanol. Coadministration of ethanol and abacavir resulted in a 41% increase in abacavir AUC 8 and a 28% increase in abacavir  $t_{1/2}$ . In males, abacavir had no effect on the pharmacokinetic properties of ethanol, so no clinically significant interaction is expected in men. This interaction has not been studied in females.

**Methadone:** In a trial of 11 HIV-1-infected subjects receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of abacavir sulfate twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI 0% to 42%). This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients. The addition of methadone had no clinically significant effect on the pharmacokinetic properties of abacavir.

## 12.4 Microbiology

Abacavir is a carbocyclic synthetic nucleoside analogue. Abacavir is converted by cellular enzymes to the active metabolite, carbonyl triphosphate (CBV-TP), an analogue of deoxyguanosine 5'-triphosphate (dGTP). CBV-TP inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation into viral DNA. The lack of a 3'-OH group in the incorporated nucleotide analogue prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation, and therefore, the viral DNA growth is terminated. CBV-TP is a weak inhibitor of cellular DNA polymerases  $\alpha$ ,  $\beta$ , and  $\gamma$ .

**Antiviral Activity:** The antiviral activity of abacavir against HIV-1 was evaluated against a T-cell tropic laboratory strain HIV-1<sub>IIIB</sub> in lymphoblastic cell lines, a monocyte/macrophage tropic laboratory strain HIV-1<sub>MAC</sub>, in primary macrocytes/macrophages, and clinical isolates in peripheral blood mononuclear cells. The concentration of drug necessary to effect viral replication by 50 percent ( $EC_{50}$ ) ranged from 3.7 to 5.8  $\mu$ M (1  $\mu$ M = 0.28 mcg/mL) and 0.07 to 1.0  $\mu$ M against HIV-1<sub>IIIB</sub> and HIV-1<sub>MAC</sub>, respectively, and was  $0.26 \pm 0.18$   $\mu$ M against 8 clinical isolates. The  $EC_{50}$  values of abacavir against different HIV-1 clades (A-G) ranged from 0.0015 to 1.05  $\mu$ M, and against HIV-2 isolates, from 0.24 to 0.49  $\mu$ M. Abacavir had synergistic activity in cell culture in combination with the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, and the protease inhibitor (PI) amprenavir; and additive activity in combination with the NRTIs didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine. Ribavirin (50  $\mu$ M) had no effect on the anti-HIV-1 activity of abacavir in cell culture.

**Resistance:** HIV-1 isolates with reduced susceptibility to abacavir have been selected in cell culture and were also observed in clinical subjects treated with abacavir. Genotypic analysis of isolates selected in cell culture and recovered from abacavir-treated subjects demonstrated that amino acid substitutions K65R, L74V, Y115F, and M184V/I in RT contributed to abacavir resistance. In a trial of therapy-naïve adults receiving abacavir sulfate 600 mg once daily (n = 384) or 300 mg twice daily (n = 386), in a background regimen of lamivudine 300 mg once daily and zidovudine 600 mg once daily (CNA3021), the incidence of virologic failure at 48 weeks was similar between the 2 groups (11% in both arms). Genotypic (n = 38)

and phenotypic analyses (n = 35) of virologic failure isolates from this trial showed that the RT substitutions that emerged during abacavir once-daily and twice-daily therapy were K65R, L74V, Y115F, and M184V/I. The substitution M184V/I was the most commonly observed substitution in virologic failure isolates from subjects receiving abacavir once daily (56%, 10/18) and twice daily (40%, 8/20).

Thirty-nine percent (7/18) of the isolates from subjects who experienced virologic failure in the abacavir once-daily arm had a greater than 2.5-fold decrease in abacavir susceptibility with a median-fold decrease of 1.3 (range 0.5 to 11) compared with 29% (5/17) of the failure isolates in the twice-daily arm with a median-fold decrease of 0.92 (range 0.7 to 13).

**Cross-Resistance:** Cross-resistance has been observed among NRTIs. Isolates containing abacavir resistance-associated substitutions, namely, K65R, L74V, Y115F, and M184V, exhibited cross-resistance to didanosine, emtricitabine, lamivudine, tenofovir, and zalcitabine in cell culture and in subjects. The K65R substitution can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine; the L74V substitution can confer resistance to abacavir, didanosine, and zalcitabine; and the M184V substitution can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, and zalcitabine. An increasing number of thymidine analogue mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219E/R/H/Q/W) is associated with a progressive reduction in abacavir susceptibility.

## 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 clitoral gland of females of both species, and in the liver of female rats. In addition, non-malignant tumors also occurred in the liver and thyroid gland of female rats. These observations were made at systemic exposures in the range of 6 to 32 times the human exposure at the recommended dose. It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

**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 had no adverse effects on the mating performance or fertility of male and female rats at a dose approximately 8 times the human exposure at the recommended dose based on body surface area comparisons.

### 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. The clinical relevance of this finding has not been determined.

## 14 CLINICAL STUDIES

### 14.1 Adults

**Therapy-Naïve Adults:** CNA30024 was a multicenter, double-blind, controlled trial in which 649 HIV-1-infected, therapy-naïve adults were randomized and received either abacavir sulfate (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%), Caucasian (51%), black (21%), and Hispanic (26%). The median age was 35 years, the median pretreatment CD4+ cell count was 294 cells/mm<sup>3</sup>, and median plasma HIV-1 RNA was 4.79 log<sub>10</sub> copies/mL. The outcomes of randomized treatment are provided in Table 7.

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

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

<sup>a</sup> Subjects achieved and maintained confirmed HIV-1 RNA  $\leq 50$  copies/mL (<400 copies/mL) through Week 48 (Roche AMPLICOR UltraSensitive HIV-1 MONITOR standard test 1.0 PCR).

<sup>b</sup> Includes viral rebound, insufficient viral response according to the investigator, and failure to achieve confirmed  $\leq 50$  copies/mL by Week 48.

<sup>c</sup> 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/mm<sup>3</sup> in the group receiving abacavir sulfate and 155 cells/mm<sup>3</sup> in the zidovudine group. Through Week 48, 5 subjects (2%) in the group receiving abacavir sulfate (4 CDC classification C events and 3 deaths) and 5 subjects (2%) on the zidovudine arm (3 CDC classification C events and 2 deaths) experienced clinical disease progression.

CNA3005 was a multicenter, double-blind, controlled trial in which 562 HIV-1-infected, therapy-naïve adults were randomized to receive either abacavir sulfate (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/mL and plasma HIV-1 RNA greater than 100,000 copies/mL. Trial participants were male (87%), Caucasian (73%), black (15%), and Hispanic (9%). At baseline the median age was 36 years, the median baseline CD4+ cell count was 360 cells/mm<sup>3</sup> and median baseline plasma HIV-1 RNA was 4.8 log<sub>10</sub> copies/mL. Proportions of subjects with plasma HIV-1 RNA less than 400 copies/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 sulfate plus Lamivudine/Zidovudine (n = 262)	Indinavir plus Lamivudine/Zidovudine (n = 265)
Responder <sup>a</sup>	49%	50%
Virologic failure <sup>b</sup>	31%	28%
Discontinued due to adverse reactions <sup>c</sup>	10%	12%
Discontinued due to other reasons <sup>d</sup>	11%	10%

<sup>a</sup> Subjects achieved and maintained confirmed HIV-1 RNA <400 copies/mL.

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

<sup>c</sup> 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 sulfate plus Lamivudine/Zidovudine (n = 262)	Indinavir plus Lamivudine/Zidovudine (n = 265)		
>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/mL, percentages of subjects with HIV-1 RNA levels less than 50 copies/mL were 31% in the group receiving abacavir sulfate and 45% in the group receiving indinavir.

Through Week 48, an overall mean increase in CD4+ cell count of about 150 cells/mm<sup>3</sup> was observed in both treatment arms. Through Week 48, 9 subjects (3.4%) in the group receiving abacavir sulfate (6 CDC classification C events and 3 deaths) and 3 subjects (1.5%) in the group receiving indinavir (2 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 and efavirenz 600 mg once daily twice daily, both in combination with lamivudine 300 mg once daily and zidovudine 300 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%), Caucasian (54%), black (27%), and American Hispanic (15%). The median baseline CD4+ cell count was 262 cells/mm<sup>3</sup> (range 21 to 918 cells/mm<sup>3</sup>) and the median baseline plasma HIV-1 RNA was 4.89 log<sub>10</sub> copies/mL (range: 2.60 to 6.99 log<sub>10</sub> copies/mL).

The outcomes of randomized treatment are provided in Table 10.

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

Outcome	Abacavir sulfate 600 mg q.d. plus Lamivudine plus Efavirenz (n = 384)	Abacavir sulfate 300 mg b.i.d. plus Lamivudine plus Efavirenz (n = 386)
Responder <sup>a</sup>	64% (71%)	65% (72%)
Virologic failure <sup>b</sup>	11% (5%)	11% (5%)
Discontinued due to adverse reactions <sup>c</sup>	13%	13%
Discontinued due to other reasons <sup>d</sup>	11%	13%

<sup>a</sup> Subjects achieved and maintained confirmed HIV-1 RNA  $\leq 50$  copies/mL (<400 copies/mL) through Week 48 (Roche AMPLICOR UltraSensitive HIV-1 MONITOR standard test version 1.0).

<sup>b</sup> Includes viral rebound, failure to achieve confirmed  $\leq 50$  copies/mL (<400 copies/mL) by Week 48, and insufficient viral load response.

<sup>c</sup> 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/mm<sup>3</sup> in the group receiving abacavir 600 mg once daily and 200 cells/mm<sup>3</sup> in the group receiving abacavir 300 mg once daily. Through Week 48, 6 subjects (2%) in the group receiving abacavir sulfate 600 mg once daily (4 CDC classification C events and 2 deaths) and 10 subjects (3%) in the group receiving abacavir sulfate 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 sulfate 8 mg/kg twice daily plus lamivudine 4 mg/kg twice daily plus zidovudine 180 mg/m<sup>2</sup> twice daily versus lamivudine 4 mg/kg twice daily plus zidovudine 180 mg/m<sup>2</sup> twice daily. Two hundred and five

therapy-experienced pediatric subjects were enrolled: female (56%), Caucasian (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 log<sub>10</sub> copies/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/mL was significantly higher in subjects receiving abacavir sulfate plus lamivudine plus zidovudine compared with subjects receiving lamivudine plus zidovudine, 13% versus 2%, respectively. Median plasma HIV-1 RNA changes from baseline were -0.53 log<sub>10</sub> copies/mL in the group receiving abacavir sulfate plus lamivudine plus zidovudine compared with -0.21 log<sub>10</sub> copies/mL in the group receiving lamivudine plus zidovudine. Median CD4+ cell count increases from baseline were 69 cells/mm<sup>3</sup> in the group receiving abacavir sulfate plus lamivudine plus zidovudine and 9 cells/mm<sup>3</sup> in the group receiving lamivudine plus zidovudine.

## 15 REFERENCES

1. Data Collection on Adverse Events of Anti-HIV Drugs (D: A: D) Study Group. *Lancet* 2008; 371(9622):1417-1426.

## 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 "1" on one side and "139" on other side separating 13 & 9 with score line. They are packaged as follows:

NDC 31722-557-60 bottles of 60

## Stored at Room Temperature

Repack 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature.]

## 17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

## 17.1 Information About Therapy With Abacavir Sulfate

**Hypersensitivity Reaction:** 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 sulfate, and encourage the patient to read the Medication Guide and Warning Card every time to obtain any new information that may be present about abacavir sulfate. (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 *Medication Guide* (17.2)].
- that if they develop symptoms consistent with a hypersensitivity reaction they should call their doctor right away to determine if they should stop taking abacavir sulfate.
- that a hypersensitivity reaction can worsen and lead to hospitalization or death if abacavir sulfate is not immediately discontinued.
- that in one trial, more severe hypersensitivity reactions were seen when abacavir sulfate was dosed 600 mg once daily.
- to not restart abacavir sulfate 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 sulfate is stopped right away.
- that if they have interrupted abacavir sulfate 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 sulfate or any other abacavir-containing product without medical consultation and that restarting abacavir sulfate may be undertaken only if medical care can be readily accessed by the patient or others.

Abacavir sulfate should not be coadministered with EPZICOM® (abacavir sulfate and lamivudine) Tablets or TRIZIVIR® (abacavir sulfate, lamivudine, and zidovudine) Tablets.

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

**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:** Abacavir Sulfate is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using abacavir sulfate.

Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

- Do not share 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 safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

- Do not breastfeed.** We do not know if abacavir sulfate can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

Patients should be informed to take all HIV medications exactly as prescribed.

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Manufactured for: Camber Pharmaceuticals, Inc. Piscataway, NJ 08854

By: HETERO™ Hetero Labs Limited Jeedimetla, Hyderabad - 500 055, India

Revised: 12/2012

## MEICATION GUIDE Abacavir Tablets USP

Read this Medication Guide before you start taking abacavir sulfate and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment. Be sure to carry your abacavir sulfate Warning Card with you at all times.

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

1. **Serious allergic reaction (hypersensitivity reaction).** Abacavir Sulfate contains abacavir (also contained in EPZICOM® and TRIZIVIR®). Patients taking abacavir sulfate may have a serious allergic reaction (hypersensitivity reaction) that can cause death. 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 sulfate, call your healthcare provider right away to find out if you should stop taking Abacavir Sulfate.