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

Abacavir sulfate and Lamivudine Tablets

WARNINGS: RISK OF HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, AND EXACERBATIONS OF HEPATITIS
See full prescribing information for complete boxed warning.
- **Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir-containing products (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 and lamivudine as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B*5701 status, permanently discontinue abacavir sulfate and lamivudine if hypersensitivity cannot be ruled out, even when other diagnoses are possible. (5.1)**
- **Following a hypersensitivity reaction to abacavir, NEVER restart abacavir sulfate and lamivudine 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)**
- **Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine, a component of abacavir sulfate and lamivudine. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.3)**

---------- INDICATIONS AND USAGE----------
Abacavir sulfate and lamivudine, a combination of abacavir and lamivudine, both nucleoside analogue HIV-1 reverse transcriptase inhibitors, are indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. (1)

----------DOSAGE AND ADMINISTRATION----------
- A medication guide and warning card should be dispensed with each new prescription and refill. (2)
- Pediatric patients 3 months and Older: Dosage should be based on body weight (2.2)
- Do not prescribe for patients requiring a dosage adjustment or patients with hepatic impairment. (2.2)

---------- DOSAGE FORMS AND STRENGTHS----------
Tablets contain 60 mg of abacavir and 30 mg of lamivudine. (3)

---------- CONTRAINDICATIONS ----------
- Previously demonstrated hypersensitivity to abacavir or any other component of the product. (4, 5.1)
- Hepatic impairment. (4)

---------- WARNINGS AND PRECAUTIONS----------
- See boxed warning for information about the following: hypersensitivity reactions, lactic acidosis and severe hepatomegaly, and severe acute exacerbations of hepatitis B. (5.1, 5.2, 5.3)
- Hepatic decompensation, some fatal, has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy and interferon alfa with or without ribavirin. Discontinue abacavir sulfate and lamivudine as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.4)
- Immune reconstitution syndrome (5.5) and redistribution/accumulation of body fat have been reported in patients treated with combination antiretroviral therapy. (5.6)
- Abacavir sulfate and lamivudine should not be administered with other lamivudine- or zidovudine-containing products or emtricitabine-containing products. (5.8)
- Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue treatment as clinically appropriate. (5.9)

---------- ADVERSE REACTIONS ----------
- The most commonly reported adverse reactions of at least moderate intensity (incidence >5%) in an adult HIV-1 clinical study were drug hypersensitivity, insomnia, depression/depressed mood, headache/migraine, fatigue/malaise, dizziness/vertigo, nausea, and diarrhea. (6.1)
- Abacavir: 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)
- Lamivudine: The most commonly reported adverse reactions (incidence ≥15%) in pediatric patients were fever and cough (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Mylan Laboratories. at 1-877-446-3679 or FDA at 1-800-FDA-1088 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. (7.3)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE.

Revised: January 2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNINGS: RISK OF HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, AND EXACERBATIONS OF HEPATITIS B

HYPERSENSITIVITY REACTIONS: SERIOUS AND SOMETIMES FATAL HYPERSENSITIVITY REACTIONS HAVE BEEN ASSOCIATED WITH ABACAVIR SULFATE, A COMPONENT OF ABACAVIR SULFATE AND LAMIVUDINE TABLETS. 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 AND LAMIVUDINE 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 AND LAMIVUDINE IF HYPERSENSITIVITY CANNOT BE RULED OUT, EVEN WHEN OTHER DIAGNOSES ARE POSSIBLE.

FOLLOWING A HYPERSENSITIVITY REACTION TO ABACAVIR, NEVER RESTART ABACAVIR AND LAMIVUDINE 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 AND LAMIVUDINE 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, LAMIVUDINE, AND OTHER ANTIRETROVIRALS [SEE WARNINGS AND PRECAUTIONS (5.2)].

EXACERBATIONS OF HEPATITIS B: SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED WITH HEPATITIS B VIRUS (HBV) AND HUMAN IMMUNODEFICIENCY VIRUS (HIV-1) AND HAVE DISCONTINUED LAMIVUDINE, WHICH IS ONE COMPONENT OF ABACAVIR AND LAMIVUDINE. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE ABACAVIR AND LAMIVUDINE AND ARE CO-INFECTED WITH HIV-1 AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED [SEE WARNINGS AND PRECAUTIONS (5.3)].

1 INDICATIONS AND USAGE

Abacavir sulfate and Lamivudine Tablets, in combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection.

Additional important information on the use of abacavir sulfate and lamivudine for treatment of HIV-1 infection:

- Abacavir sulfate and lamivudine are one of multiple products containing abacavir. Before starting abacavir sulfate and lamivudine, 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)].
- As part of a triple-drug regimen, Abacavir sulfate and Lamivudine Tablets are recommended for use with antiretroviral agents from different pharmacological classes and not with other nucleoside/nucleotide reverse transcriptase inhibitors.

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 sulfate and Lamivudine Tablets can be taken with or without food.

2.1 Pediatric Patients

The recommended oral dosage of abacavir sulfate and lamivudine in HIV-1-infected pediatric patients 3 months and older is abacavir 8 mg/kg twice daily (up to a maximum of 300 mg twice daily) and lamivudine 4 mg/kg twice daily (up to a maximum of 150 mg twice daily) in combination with other antiretroviral agents. Dosing recommendations for the tablets are provided in Table 1.

Table 1. Dosing Recommendations for Abacavir Sulfate and Lamivudine Tablets Pediatric Patients

Weight (kg)	Dosage Regimen Using Scored Abacavir sulfate and Lamivudine Tablets, 60 mg/30 mg		Total Daily Dose (mg)
	AM Dose (mg)	PM Dose (mg)	
5	½ tablet (30 mg A/15 mg L)	1 tablet (60 mg A/30 mg L)	90A/45L
6 - < 9	1 tablet (60 mg A/30 mg L)	1 tablet (60 mg A/30 mg L)	120A/60L
9 - < 12	1.5 tablets (90 mg A/45 mg L)	1.5 tablets (90 mg A/45 mg L)	180A/90L
12 - < 17	2 tablets (120 mg A/60 mg L)	2 tablets (120 mg A/60 mg L)	240A/120L
17 - < 20	2.5 tablets (150 mg A/75 mg L)	2.5 tablets (150 mg A/75 mg L)	300A/150L
20 - < 25	3 tablets (180 mg A/90 mg L)	3 tablets (180 mg A/90 mg L)	360A/180L
25 - < 29	3.5 tablets (210 mg A/105 mg L)	3.5 tablets (210 mg A/105 mg L)	420A/210L
29 - < 35	4 tablets (240 mg A/120 mg L)	4 tablets (240 mg A/120 mg L)	480A/240L
≥ 35	5 tablets (300 mg A/150 mg L)	5 tablets (300 mg A/150 mg L)	600A/300L

A= abacavir sulfate; L= lamivudine

Method of Preparation

For children unable to swallow tablets, the following procedure can be used:

1. Place the tablet(s) in a container and add two teaspoonfuls (10 mL) of drinking water per tablet.
2. Swirl the container until the tablet(s) breaks up into pieces small enough for the child to swallow. A spoon can be used to crush the pieces, if needed.
3. Drink the mixture within 1 hour.
4. Rinse the container with an additional small amount of water and drink the contents to assure that the entire dosage is taken.

DO NOT MIX THE ABACAVIR SULFATE AND LAMIVUDINE TABLETS WITH ANY LIQUID OTHER THAN WATER.

2.2 Dose Adjustment

Because Abacavir sulfate and Lamivudine Tablets are a fixed-dose combination, it should not be prescribed for:

- patients requiring dosage adjustment such as those with creatinine clearance <50 mL/min
- patients with hepatic impairment.

3 DOSAGE FORMS AND STRENGTHS

Each tablet of abacavir sulfate and lamivudine contain 60 mg of abacavir as abacavir sulfate and 30 mg of lamivudine.

4 CONTRAINDICATIONS

Abacavir sulfate and Lamivudine Tablets are contraindicated in patients with:

- previously demonstrated hypersensitivity to abacavir or to any other component of the product. **Never restart abacavir and lamivudine 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)].**
- hepatic impairment [see Use in Specific Populations (8.7)].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reaction

Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir and lamivudine 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 considered only 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 and lamivudine 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 two or more of the following groups:

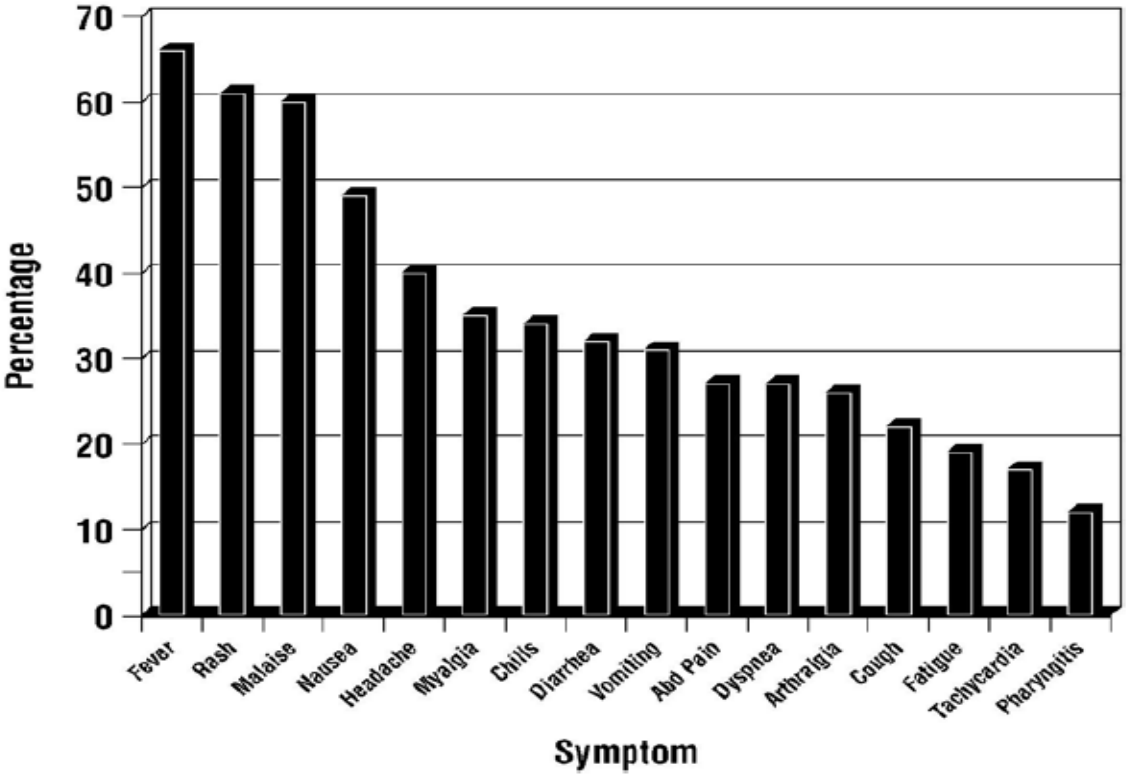
Group 1: Fever
Group 2: Rash
Group 3: Gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain)
Group 4: Constitutional (including generalized malaise, fatigue, or achiness)

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 patients (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 9 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 Trials (n = 206 Patients)



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 study, 4 patients (11%) receiving abacavir 600 mg once daily experienced hypotension with a hypersensitivity reaction compared with 0 patients receiving abacavir 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 and lamivudine as soon as a hypersensitivity reaction is suspected. To minimize the risk of a life-threatening hypersensitivity reaction, permanently discontinue abacavir and lamivudine if hypersensitivity cannot be ruled out, even when other diagnoses are possible (e.g. acute onset respiratory diseases such as pneumonia, bronchitis, pharynxgitis, or influenza; gastroenteritis; or reactions to other medications).

Following a hypersensitivity reaction to abacavir, NEVER restart Abacavir and lamivudine 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 and lamivudine has been discontinued for reasons other than symptoms of a hypersensitivity reaction, and if reinitiation of abacavir and lamivudine or any other abacavir-containing product is under consideration, carefully evaluate the reason for discontinuation of abacavir and lamivudine 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 and lamivudine.

If hypersensitivity cannot be ruled out, DO NOT reintroduce abacavir and lamivudine 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 and lamivudine or any other abacavir-containing product and that reintroduction of abacavir and lamivudine or introduction of 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: Studies 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 study, evaluated the clinical utility of prospective HLA-B*5701 screening on the incidence of abacavir hypersensitivity reaction in abacavir-naive HIV-1-infected adults (n = 1,650). In this

study, 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 study, 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 sulfate and lamivudine 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 and lamivudine 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 and lamivudine 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 Patients With HIV-1 and Hepatitis B Virus Co-Infection

Post-treatment Exacerbations of Hepatitis: In clinical trials in non-HIV-1-infected patients treated with lamivudine for chronic HBV, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence of HBV DNA. Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from post-marketing experience after changes from lamivudine-containing HIV-1 treatment

regimens to non-lamivudine-containing regimens in patients infected with both HIV-1 and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters the course of posttreatment exacerbations of hepatitis.

Emergence of Lamivudine-Resistant HBV: Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients dually infected with HIV-1 and HBV. In non-HIV-1-infected patients treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected and has been associated with diminished treatment response [see full prescribing information for EPIVIR-HBV (lamivudine)] for additional information). Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-1-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

5.4 Use With Interferon- and Ribavirin-Based Regimens

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine, a component of abacavir sulfate and lamivudine tablets. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-l/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-l/HCV co-infected subjects [see Clinical Pharmacology (12.3)], hepatic decompensation (some fatal) has occurred in HIV-l/HCV co-infected subjects receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and abacavir and lamivudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of abacavir and lamivudine should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Childs Pugh >6) (See the complete prescribing-information for interferon and ribavirin).

5.5 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including abacavir and lamivudine. During the initial phase of combination antiretroviral treatment, patients whose immune system responds 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-Barre syndrome) have 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.

5.6 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**.**

5.7 Myocardial Infarction
In a published prospective, observational, epidemiological study 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).[1] 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 therapies, including abacavir, and action taken to minimize all modifiable risk factors (e.g., hypertension, hyperlipidemia, diabetes mellitus, and smoking).

5.8 Use With Other Abacavir-, Lamivudine-, and/or Emtricitabine-Containing Products
Abacavir sulfate and Lamivudine Tablets contain fixed doses of 2 nucleoside analogues, abacavir and lamivudine, and should not be administered concomitantly with other abacavir-containing and/or lamivudine-containing products including ZIAGEN® (abacavir sulfate), EPIVIR® and EPIVIR®-HBV (lamivudine), COMBIVIR® (lamivudine and zidovudine], EPZICOM®(abacavir sulfate and lamivudine), TRIZIVIR® [abacavir sulfate, lamivudine, and zidovudine]; or emtricitabine-containing products, including ATRIPLA® (efavirenz, emtricitabine, and tenofovir disoproxil fumarate), EMTRIVA® (emtricitabine), or TRUVADA® (emtricitabine and tenofovir disoproxil fumarate), or COMPLERA® (rilpivirine/emtricitabine/tenofovir).

5.9 Pancreatitis
In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, lamivudine should be used with caution. Treatment with lamivudine, one component of abacavir sulfate and lamivudine, should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur [see Adverse Reactions (6.1)].

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 study, 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)].
- Acute exacerbations of hepatitis B [see Boxed Warning, Warnings and Precautions (5.3)].
- Hepatic decompensation in patients co-infected with HIV-1 and Hepatitis C [see Warnings and Precautions (5.4)].
- Immune reconstitution syndrome [see Warnings and Precautions (5.5].
- Fat redistribution [see Warnings and Precautions (5.6].
- Myocardial infarction [see Warnings and Precautions (5.7)].
- Pancreatitis [see Warnings and Precautions (5.9)].

6.1 Clinical Trials Experience

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

Abacavir and lamivudine

Adults: *Therapy-Naive Adults:* Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a ≥5% frequency during therapy with abacavir 600 mg once daily or abacavir 300 mg twice daily, both in combination with lamivudine 300 mg once daily and efavirenz 600 mg once daily are listed in Table 2.

Table 2. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Naive Adults (CNA30021) Through 48 Weeks of Treatment

Adverse Event	Abacavir 600 mg q.d. plus Lamivudine plus Efavirenz (n = 384)	Abacavir 300 mg b.i.d. plus Lamivudine plus Efavirenz (n = 386)
Drug hypersensitivity[a,b]	9%	7%
Insomnia	7%	9%
Depression/Depressed mood	7%	7%
Headache/Migraine	7%	6%
Fatigue/Malaise	6%	8%
Dizziness/Vertigo	6%	6%
Nausea	5%	6%
Diarrhea[a]	5%	6%
Rash	5%	5%
Pyrexia	5%	3%
Abdominal pain/gastritis	4%	5%
Abnormal dreams	4%	5%
Anxiety	3%	5%

[a] 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.

[b] Study CNA30024 was a multi-center, double-blind, controlled study in which 649 HIV-1-infected, therapy-naive 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). CNA30024 used double-blind ascertainment of suspected hypersensitivity reactions. During the blinded portion of the study, 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.

Laboratory Abnormalities: Laboratory abnormalities observed in clinical studies of abacavir sulfate were anemia, neutropenia, liver function test abnormalities, and elevations of CPK, blood glucose, and triglycerides. Additional laboratory abnormalities observed in clinical studies of lamivudine were thrombocytopenia and elevated levels of bilirubin, amylase, and lipase.

The frequencies of treatment-emergent laboratory abnormalities were comparable between treatment groups in Study CNA30021.

Abacavir

Pediatric Patients: *Therapy-Experienced Pediatric Patients:* Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a ≥5% frequency during therapy with abacavir 8 mg/kg twice daily, lamivudine 4 mg/kg twice daily, and zidovudine 180 mg/m^2 twice daily compared with lamivudine 4 mg/kg twice daily and zidovudine 180 mg/m^2 twice daily from CNA3006 are listed in Table 3.

Table 3. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Experienced Pediatric Patients (CNA3006) Through 16 Weeks of Treatment

Adverse Reaction	Abacavir plus Lamivudine plus Zidovudine (n = 102)	Lamivudine plus Zidovudine (n = 103)
Fever and/or chills	9%	7%
Nausea and vomiting	9%	2%
Skin rashes	7%	1%
Ear/nose/throat infections	5%	1%
Pneumonia	4%	5%
Headache	1%	5%

Laboratory abnormalities: In Study CNA3006, laboratory abnormalities (anemia, neutropenia, liver function test abnormalities, and CPK elevations) were observed with similar frequencies as in a study of therapy-naive adults (CNA30024). Mild elevations of blood glucose were more frequent in pediatric patients receiving abacavir (CNA3006) as compared with adult patients (CNA30024).

Other Adverse Events: In addition to adverse reactions listed above, other adverse events observed in the expanded access program for abacavir were pancreatitis and increased GGT.

Lamivudine

Pediatric Patients: *Clinical Trials in HIV-1:* Lamivudine oral solution has been studied in 638 pediatric patients 3 months to 18 years of age in 3 clinical trials.
Selected clinical adverse reactions and physical findings with a ≥5% frequency during therapy with lamivudine 4 mg/kg twice daily plus zidovudine 160 mg/m^2 3 times daily in therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in Table 4.

Table 4. Selected Clinical Adverse Reactions and Physical Findings (≥5% Frequency) in Pediatric Patients in Study ACTG300

Adverse Reaction	Lamivudine plus Zidovudine (n = 236)	Didanosine (n = 235)
Body as a Whole		
Fever	25%	32%
Digestive		
Hepatomegaly	11%	11%
Nausea & vomiting	8%	7%
Diarrhea	8%	6%
Stomatitis	6%	12%
Splenomegaly	5%	8%
Respiratory		
Cough	15%	18%
Abnormal breath sounds/wheezing	7%	9%
Ear, Nose, and Throat		
Signs or symptoms of ears[a]	7%	6%
Nasal discharge or congestion	8%	11%
Other		
Skin rashes	12%	14%
Lymphadenopathy	9%	11%

[a] Includes pain, discharge, erythema, or swelling of an ear.

Pancreatitis: Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced pediatric patients receiving lamivudine alone or in combination with other antiretroviral agents. In an open-label dose-escalation study

(A2002), 14 patients (14%) developed pancreatitis while receiving monotherapy with lamivudine. Three of these patients died of complications of pancreatitis. In a second open-label study (A2005), 12 patients (18%) developed pancreatitis. In Study ACTG300, pancreatitis was not observed in 236 patients randomized to lamivudine plus zidovudine. Pancreatitis was observed in 1 patient in this study who received open-label lamivudine in combination with zidovudine and ritonavir following discontinuation of didanosine monotherapy [see Warnings and Precautions (5.9)].

Paresthesias and Peripheral Neuropathies: Paresthesias and peripheral neuropathies were reported in 15 patients (15%) in Study A2002, 6 patients (9%) in Study A2005, and 2 patients (<1%) in Study ACTG300.

Selected laboratory abnormalities experienced by therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in Table 5.

Table 5. Frequencies of Selected Grade 3-4 Laboratory Abnormalities in Pediatric Patients in Study ACTG300

Test (Threshold Level)	Lamivudine plus Zidovudine	Didanosine
Absolute neutrophil count (<400/mm^3)	8%	3%
Hemoglobin (<7.0 g/dL)	4%	2%
Platelets (<50,000/mm^3)	1%	3%
ALT (>10 x ULN)	1%	3%
AST (>10 x ULN)	2%	4%
Lipase (>2.5 x ULN)	3%	3%
Total Amylase (>2.5 x ULN)	3%	3%

ULN = Upper limit of normal.

Neonates - *Clinical Trials in HIV-1*: Limited short-term safety information is available from 2 small, uncontrolled studies in South Africa in neonates receiving lamivudine with or without zidovudine for the first week of life following maternal treatment starting at Week 38 or 36 of gestation [see Clinical Pharmacology (12.3)]. Selected adverse reactions reported in these neonates included increased liver function tests, anemia, diarrhea, electrolyte disturbances, hypoglycemia, jaundice and hepatomegaly, rash, respiratory infections, and sepsis; 3 neonates died (1 from gastroenteritis with acidosis and convulsions, 1 from traumatic injury, and 1 from unknown causes). Two other nonfatal gastroenteritis or diarrhea cases were reported, including 1 with convulsions; 1 infant had transient renal insufficiency associated with dehydration. The absence of control groups limits assessments of causality, but it should be assumed that perinatally exposed infants may be at risk for adverse reactions comparable to those reported in pediatric and adult HIV-1-infected patients treated with lamivudine-containing combination regimens. Long-term effects of in utero and infant lamivudine exposure are not known.

6.2 Post-Marketing Experience

In addition to adverse reactions reported from clinical studies, the following reactions have been identified during post-marketing use of abacavir, lamivudine, and/or abacavir and lamivudine. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These reactions have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to abacavir, lamivudine, and/or abacavir and lamivudine.

Abacavir:
Cardiovascular: Myocardial infarction.
Skin: Suspected Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients receiving abacavir primarily in combination with medications known to be associated with SJS and TEN, respectively. Because of the overlap of clinical signs and symptoms between hypersensitivity to abacavir and SJS and TEN, and the possibility of multiple drug sensitivities in some patients, abacavir should be discontinued and not restarted in such cases.

There have also been reports of erythema multiforme with abacavir use.

Abacavir and Lamivudine:
Body as a Whole: Redistribution/accumulation of body fat [see WARNINGS AND PRECAUTIONS (5.6)].
Digestive: Stomatitis.
Endocrine and Metabolic: Hyperglycemia.
General: Weakness.
Hemic and Lymphatic: Aplastic anemia, anemia (including pure red cell aplasia and severe anemias progressing on therapy), lymphadenopathy, splenomegaly.
Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis [see Warnings and Precautions (5.2)], post treatment exacerbation of hepatitis B [see WARNINGS AND PRECAUTIONS (5.3)].
Hypersensitivity: Sensitization reactions (including anaphylaxis), urticaria.
Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.
Nervous: Paresthesia, peripheral neuropathy, seizures.
Respiratory: Abnormal breath sounds/wheezing.
Skin: Alopecia, erythema multiforme, Stevens-Johnson syndrome.

7 DRUG INTERACTIONS

No drug interaction studies have been conducted using Abacavir sulfate and Lamivudine Tablets [see Clinical Pharmacology (12.3)].

7.1 Ethanol

Abacavir: Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol decreases the elimination of abacavir causing an increase in overall exposure [see Clinical Pharmacology (12.3)].

7.2 Interferon- and Ribavirin-Based Regimens

Lamivudine: Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected subjects, hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected subjects receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin [see Warnings and Precautions (5.4), Clinical Pharmacology (12.3)].

7.3 Methadone

Abacavir: The addition of methadone has no clinically significant effect on the pharmacokinetic properties of abacavir. In a study of 11 HIV-1-infected subjects receiving methadone-maintenance therapy with 600 mg of abacavir twice daily (twice the currently recommended dose), oral methadone clearance increased [see Clinical Pharmacology (12.3)]. 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.

7.4 Trimethoprim/Sulfamethoxazole (TMP/SMX)

Lamivudine: No change in dose of either drug is recommended [see Clinical Pharmacology (12.3)]. There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used to treat PCP.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Abacavir and lamivdine: Pregnancy Category C. There are no adequate and well-controlled studies of abacavir and lamivudine in pregnant women. Reproduction studies with abacavir and lamivudine have been performed in animals (see abacavir and lamivudine sections below). Abacavir and lamivudine should be used during pregnancy only if the potential benefits outweigh the risks.

Abacavir: Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. Fetal malformations (increased incidences of fetal anasarca and skeletal malformations) and developmental toxicity (depressed fetal body weight and reduced crown-rump length) were observed in rats at a dose which produced 35 times the human exposure, based on AUC. Embryonic and fetal toxicities (increased resorptions, decreased fetal body weights) and toxicities to the offspring (increased incidence of stillbirth and lower body weights) occurred at half of the above-mentioned dose in separate fertility studies conducted in rats. In the rabbit, no developmental toxicity and no increases in fetal malformations occurred at doses that produced 8.5 times the human exposure at the recommended dose based on AUC.

Lamivudine: Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. Reproduction studies with orally administered lamivudine have been performed in rats and rabbits at doses producing plasma levels up to approximately 35 times that for the recommended adult HIV dose. No evidence of teratogenicity due to

lamivudine was observed. Evidence of early embryolethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 35 times those in humans.

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

Abacavir: Abacavir is secreted into the milk of lactating rats.

Lamivudine: Lamivudine is excreted in human breast milk and into the milk of lactating rats.

Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving abacavir and lamivudine.**

8.4 Pediatric Use

Abacavir: The safety and effectiveness of abacavir have been established in pediatric patients 3 months to 13 years of age. Use of abacavir in these age groups is supported by pharmacokinetic studies and evidence from adequate and well-controlled studies of abacavir in adults and pediatric patients [see DOSAGE AND ADMINISTRATION (2.1), CLINICAL PHARMACOLOGY (12.3, CLINICAL STUDIES (14.2)].

Lamivudine: The safety and effectiveness of twice-daily lamivudine in combination with other antiretroviral agents have been established in pediatric patients 3 months of age and older [see ADVERSE REACTIONS (6.1), CLINICAL PHARMACOLOGY (12.3), CLINICAL STUDIES (14.2)].

8.5 Geriatric Use

Clinical studies of abacavir and lamivudine did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy [see Dosage and Administration (2.2), Use in Specific Populations (8.6, 8.7)].

8.6 Patients With Impaired Renal Function

Abacavir sulfate and Lamivudine Tablets are not recommended for patients with impaired renal function (creatinine clearance <50 mL/min) because the formulation is a fixed dose combination and the dosage of the individual components cannot be adjusted.

8.7 Patients With Impaired Hepatic Function

Abacavir sulfate and Lamivudine Tablets are contraindicated for patients with hepatic impairment because abacavir sulfate is contraindicated in patients with moderate or

severe hepatic impairment and because the dose of the individual components of the fixed-dose combination cannot be adjusted for patients with mild hepatic impairment.

10 OVERDOSAGE

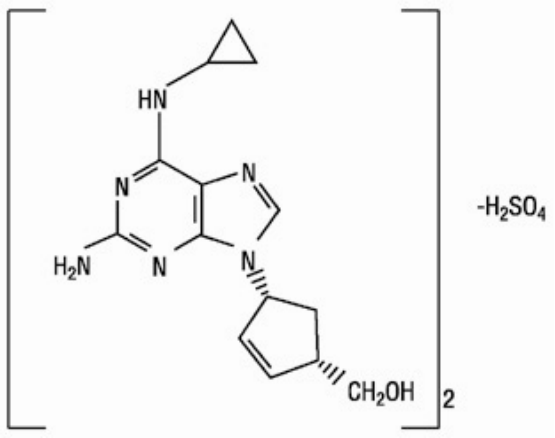
Abacavir: There is no known antidote for abacavir. It is not known whether abacavir can be removed by peritoneal dialysis or hemodialysis.

Lamivudine: One case of an adult ingesting 6 grams of lamivudine was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. It is not known whether lamivudine can be removed by peritoneal dialysis or hemodialysis.

11 DESCRIPTION

Abacavir sulfate and Lamivudine Tablets are a fixed dose combination tablet containing two synthetic nucleoside analogues: abacavir sulfate and lamivudine. Both have inhibitory activity against HIV. Abacavir sulfate and Lamivudine Tablets are for oral administration. Each tablet contains 60 mg of abacavir as abacavir sulfate and 30 mg of lamivudine as active ingredients. The tablets include the following inactive ingredients: magnesium stearate, microcrystalline cellulose, colloidal silicon dioxide and sodium starch glycolate. The tablets are coated with a film (Opadry® Yellow 13B92524) that is made of FD&C Yellow No. 6, hypromellose, polyethylene glycol 400, polysorbate 80, titanium dioxide and iron oxide yellow.

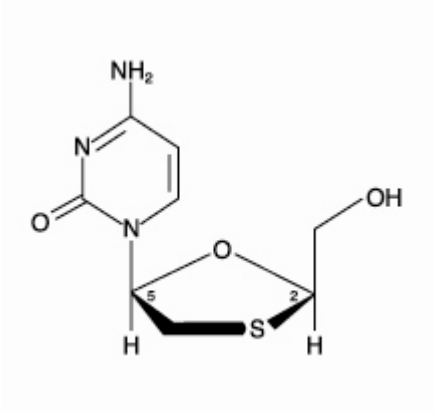
Abacavir Sulfate: The chemical name of abacavir sulfate is *(1S,cis)*-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1). Abacavir sulfate is the enantiomer with *1S*, *4R* absolute configuration on the cyclopentene ring. It has a molecular formula of $(C_{14}H_{18}N_6O)_2 \cdot H_2SO_4$ and a molecular weight of 670.76 daltons. It has the following structural formula:



Abacavir sulfate is a white to off-white solid with a solubility of approximately 77 mg/mL in distilled water at 25°C.

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

Lamivudine: The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2',3'-dideoxy, 3'-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.3 daltons. It has the following structural formula:



Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg/mL in water at 20°C.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Abacavir and lamivudine are antiviral drugs (*see* CLINICAL PHARMACOLOGY (12.4)).

12.3 Pharmacokinetics

Pharmacokinetics in Adults

Abacavir sulfate and lamivudine combination tablets (60 mg/30 mg) are compositionally proportional to abacavir sulfate and lamivudine combination tablets (600 mg/300 mg). Abacavir sulfate and lamivudine combination tablets (600 mg/300 mg) were bioequivalent to EPZICOM Tablets of GlaxoSmithKline USA, when single doses of 600 mg/300 mg) were administered to healthy volunteers under fasting and fed conditions.

Abacavir and lamivudine: In a single-dose, 3-way crossover bioavailability study of 1 abacavir sulfate and lamivudine tablet (600 mg/300 mg) versus 2 abacavir sulfate tablets (2 x 300 mg) and 2 lamivudine tablets (2 x 150 mg) administered simultaneously in healthy subjects (n = 25), there was no difference in the extent of absorption, as measured by the area under the plasma concentration-time curve (AUC) and maximal peak concentration (C_{max}), of each component.

Abacavir: Following oral administration, abacavir is rapidly absorbed and extensively distributed. After oral administration of a single dose of 600 mg of abacavir in

20 subjects, C_{max} was 4.26 ± 1.19 mcg/mL (mean ± SD) and AUC_{∞} was 11.95 ± 2.51 mcg•hr/mL. Binding of abacavir to human plasma proteins is approximately 50% and was independent of concentration. Total blood and plasma drug-related radioactivity concentrations are identical, demonstrating that abacavir readily distributes into erythrocytes. The primary routes of elimination of abacavir are metabolism by alcohol dehydrogenase to form the 5′-carboxylic acid and glucuronyl transferase to form the 5′-glucuronide.

Lamivudine: Following oral administration, lamivudine is rapidly absorbed and extensively distributed. After multiple-dose oral administration of lamivudine 300 mg once daily for 7 days to 60 healthy volunteers, steady-state C_{max} ($C_{max,ss}$) was 2.04 ± 0.54 mcg/mL (mean ± SD) and the 24-hour steady-state AUC ($AUC_{24,ss}$) was 8.87 ± 1.83 mcg•hr/mL. Binding to plasma protein is low. Approximately 70% of an intravenous dose of lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours).

The steady-state pharmacokinetic properties of the lamivudine 300-mg tablet once daily for 7 days compared with the lamivudine 150-mg tablet twice daily for 7 days were assessed in a crossover study in 60 healthy volunteers. Lamivudine 300 mg once daily resulted in lamivudine exposures that were similar to lamivudine 150 mg twice daily with respect to plasma $AUC_{24,ss}$; however, $C_{max,ss}$ was 66% higher and the trough value was 53% lower compared with the 150-mg twice-daily regimen. Intracellular lamivudine triphosphate exposures in peripheral blood mononuclear cells were also similar with respect to $AUC_{24,ss}$ and $C_{max24,ss}$; however, trough values were lower compared with the 150-mg twice-daily regimen. Inter-subject variability was greater for intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough concentrations. The clinical significance of observed differences for both plasma lamivudine concentrations and intracellular lamivudine triphosphate concentrations is not known.

In humans, abacavir and lamivudine are not significantly metabolized by cytochrome P450 enzymes.

The pharmacokinetic properties of abacavir and lamivudine in fasting subjects are summarized in Table 6.

Table 6. Pharmacokinetic Parameters[a] for Abacavir and Lamivudine in Adults

Parameter	Abacavir		Lamivudine	
Oral bioavailability (%)	86 ± 25	n = 6	86 ± 16	n = 12
Apparent volume of distribution (L/kg)	0.86 ± 0.15	n = 6	1.3 ± 0.4	n = 20
Systemic clearance (L/hr/kg)	0.80 ± 0.24	n = 6	0.33 ± 0.06	n = 20
Renal clearance (L/hr/kg)	0.007 ± 0.008	n = 6	0.22 ± 0.06	n = 20
Elimination half-life (hr)	1.45 ± 0.32	n = 20	5 to 7[b]	

[a] Data presented as mean ± standard deviation except where noted.
[b] Approximate range.

Effect of Food on Absorption of Abacavir sulfate and Lamivudine Tablets: Abacavir sulfate and Lamivudine Tablets may be administered with or without food.

Special Populations: *Renal Impairment:* Because lamivudine requires dose adjustment in the presence of renal insufficiency, Abacavir sulfate and Lamivudine Tablets are not recommended for use in patients with creatinine clearance <50 mL/min [see Dosage and Administration 2.2)].

Hepatic Impairment: Abacavir sulfate and Lamivudine Tablets are contraindicated in patients with hepatic impairment because abacavir sulfate is contraindicated in patients with moderate or severe hepatic impairment and because the dose of the individual components of the fixed-dose combination cannot be dose adjusted.

Pregnancy: See Use in Specific Populations (8.1).
Abacavir and Lamivudine: No data are available on the pharmacokinetics of abacavir or lamivudine during pregnancy.

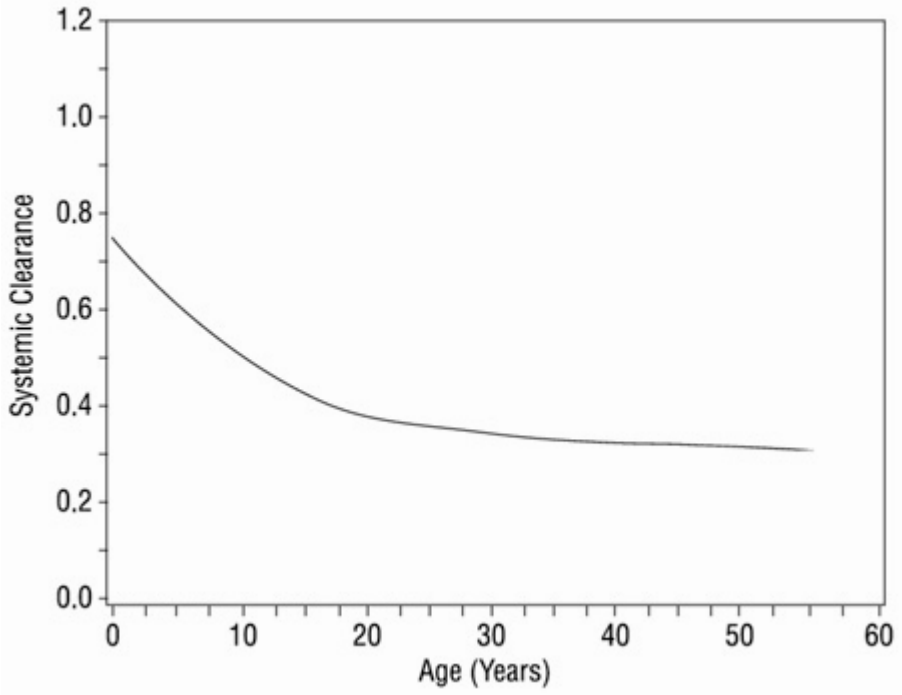
Nursing Mothers: See Use in Specific Populations (8.3).
Abacavir: No data are available on the pharmacokinetics of abacavir in nursing mothers.
Lamivudine: Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

Pediatric Patients
Abacavir: The pharmacokinetics of abacavir have been studied after either single or repeat doses of abacavir in 68 pediatric patients. Following multiple-dose administration of abacavir 8 mg/kg twice daily, steady-state $AUC_{(0\text{-}12\ hr)}$ and C_{max} were 9.8 ± 4.56 mcg•hr/mL and 3.71 ± 1.36 mcg/mL (mean ± SD), respectively [see Use in Specific Populations (8.4)].

Lamivudine: In Study NUCA2002, the pharmacokinetic properties of lamivudine were assessed in a subset of 57 HIV-1-infected pediatric patients (age range: 4.8 months to 16 years, weight range: 5 to 66 kg) after oral and I.V. administration of 1, 2, 4, 8, 12, and 20 mg/kg/day. In the 9 infants and children (range: 5 months to 12 years of age) receiving oral solution 4 mg/kg twice daily (the usual recommended pediatric dose), absolute bioavailability was 66% ± 26% (mean ± SD), which was less than the 86% ± 16% (mean ± SD) observed in adults. The mechanism for the diminished absolute bioavailability of lamivudine in infants and children is unknown.

Systemic clearance decreased with increasing age in pediatric patients, as shown in Figure 2.

Figure 2: Systemic Clearance (L/hr.kg) of Lamivudine in Relation to Age



After oral administration of lamivudine 4 mg/kg twice daily to 11 pediatric patients ranging from 4 months to 14 years of age, C_{max} was 1.1 ± 0.6 mcg/mL and the half-life was 2.0 ± 0.6 hours. (In adults with similar blood sampling, the half-life was 3.7 ± 1 hour.) Total exposure to lamivudine, as reflected by mean AUC values, was comparable between pediatric patients receiving an 8 mg/kg/day dose and adults receiving a 4 mg/kg/day dose.

Distribution of lamivudine into the cerebrospinal fluid (CSF) was assessed in 38 pediatric patients after multiple oral dosing with lamivudine. CSF samples were collected between 2 and 4 hours post-dose. At the dose of 8 mg/kg/day, CSF lamivudine concentrations in 8 patients ranged from 5.6% to 30.9% (mean ± SD of 14.2% ± 7.9%) of the concentration in a simultaneous serum sample, with CSF lamivudine concentrations ranging from 0.04 to 0.3 mcg/mL.

Limited, uncontrolled pharmacokinetic and safety data are available from the administration of lamivudine (and zidovudine) to 36 infants, up to 1 week of age, in two studies in South Africa. In these studies, lamivudine clearance was substantially reduced in 1-week-old neonates relative to pediatric patients (>3 months of age) studied previously. There is insufficient information to establish the time course of changes in clearance between the immediate neonatal period and the age ranges of >3 months old [see Adverse Reactions (6.1)].

Geriatric Patients: The pharmacokinetics of abacavir and lamivudine have not been studied in subjects over 65 years of age.

Gender: *Abacavir:* A population pharmacokinetic analysis in HIV-1-infected male (n = 304) and female (n = 67) subjects showed no gender differences in abacavir AUC normalized for lean body weight.
Lamivudine: A pharmacokinetic study in healthy male (n = 12) and female (n = 12) subjects showed no gender differences in lamivudine AUC_{∞} normalized for body weight.

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

Drug Interactions: The drug interactions described are based on studies conducted with the individual nucleoside analogues. In humans, abacavir and lamivudine are not significantly metabolized by cytochrome P450 enzymes nor do they inhibit or induce this enzyme system; therefore, it is unlikely that clinically significant drug interactions will occur with drugs metabolized through these pathways.

Abacavir: *Lamivudine and Zidovudine:* Fifteen HIV-1-infected subjects were enrolled in a crossover-designed drug interaction study 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.
Methadone: In a study of 11 HIV-1-infected subjects receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of abacavir twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI: 6% to 42%) [see Drug Interactions (7.3)].

Lamivudine: *Zidovudine:* No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-1-infected adult subjects given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q 12 hr).
Ribavirin: In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected subjects [see Warnings and Precautions (5.4)].

The effects of other coadministered drugs on abacavir or lamivudine are provided in Table 7.

Table 7. Effect of Coadministered Drugs on Abacavir and Lamivudine AUC
Note: ROUTINE DOSE MODIFICATION OF ABACAVIR AND LAMIVUDINE IS NOT WARRANTED WITH COADMINISTRATION OF THE FOLLOWING

DRUGS.

Drugs That May Alter Abacavir Blood Concentrations					
Coadministered Drug and Dose	**Abacavir Dose**	**n**	**Abacavir Concentrations**		**Concentration of Coadministered Drug**
			AUC	**Variability**	
Ethanol 0.7 g/kg	Single 600 mg	24	↑41%	90% CI: 35% to 48%	↔
Drugs That May Alter Lamivudine Blood Concentrations					
Coadministered Drug and Dose	**Lamivudine Dose**	**n**	**Lamivudine Concentrations**		**Concentration of Coadministered Drug**
			AUC	**Variability**	
Nelfinavir 750 mg q 8 hr x 7 to 10 days	Single 150 mg	11	↑10%	95% CI: 1% to 20%	↔
Trimethoprim 160 mg/ Sulfamethoxazole 800 mg daily x 5 days	Single 300 mg	14	↑43%	90% CI: 32% to 55%	↔

↑ = Increase; ↔ = no significant change; AUC = area under the concentration versus time curve; CI = confidence interval.

12.4 Microbiology

Mechanism of Action: ***Abacavir:*** Abacavir is a carbocyclic synthetic nucleoside analogue. Abacavir is converted by cellular enzymes to the active metabolite, carbovir 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 α, β, and γ.

Lamivudine: Lamivudine is a synthetic nucleoside analogue. Intracellularly lamivudine is phosphorylated to its active 5′-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue. CBV-TP and 3TC-TP are weak inhibitors of cellular DNA polymerases α, β, and γ.

Antiviral Activity:

Abacavir: The antiviral activity of abacavir against HIV-1 was evaluated against a T-cell tropic laboratory strain HIV-1_{IIIB} in lymphoblastic cell lines, a monocyte/macrophage tropic laboratory strain HIV-1_{BaL} in primary monocytes/macrophages, and clinical isolates in peripheral blood mononuclear cells. The concentration of drug necessary to effect viral replication by 50 percent (EC_{50}) ranged from 3.7 to 5.8 μM (1 μM = 0.28 mcg/mL) and 0.07 to 1.0 μM against HIV-1_{IIIB} and HIV-1_{BaL}, respectively, and was 0.26

± 0.18 μM against 8 clinical isolates. The EC_{50} values of abacavir against different HIV-1 clades (A-G) ranged from 0.0015 to 1.05 μM, and against HIV-2 isolates, from 0.024 to 0.49 μM. Ribavirin (50 μM) had no effect on the anti–HIV-1 activity of abacavir in cell culture.

Lamivudine: The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. EC_{50} values were in the range of 0.003 to 15 μM (1 μM = 0.23 mcg/mL). HIV-1 from therapy-naive subjects with no amino acid substitutions associated with resistance gave median EC_{50} values of 0.429 μM (range: 0.200 to 2.007 μM) from Virco (n = 92 baseline samples from COLA40263) and 2.35 μM (1.37 to 3.68 μM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC_{50} values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120 μM, and against HIV-2 isolates from 0.003 to 0.120 μM in peripheral blood mononuclear cells. Ribavirin (50 μM) decreased the anti–HIV-1 activity of lamivudine by 3.5 fold in MT-4 cells.

The combination of abacavir and lamivudine has demonstrated antiviral activity in cell culture against non-subtype B isolates and HIV-2 isolates with equivalent antiviral activity as for subtype B isolates. Abacavir and lamivudine had additive to synergistic activity in cell culture in combination with the nucleoside reverse transcriptase inhibitors (NRTIs) emtricitabine, stavudine, tenofovir, zalcitabine, zidovudine; the non-nucleoside reverse transcriptase inhibitors (NNRTIs) delavirdine, efavirenz, nevirapine; the protease inhibitors (PIs) amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir; or the fusion inhibitor, enfuvirtide. Ribavirin, used in combination with interferon for the treatment of HCV infection, decreased the anti-HIV-1 potency of abacavir and lamivudine reproducibly by 2- to 6-fold in cell culture.

Resistance: HIV-1 isolates with reduced susceptibility to the combination of abacavir and lamivudine have been selected in cell culture and have also been obtained from patients failing abacavir and lamivudine- containing regimens. Genotypic characterization of abacavir and lamivudine-resistant viruses selected in cell culture identified amino acid substitutions M184V/I, K65R, L74V, and Y115F in HIV-1 RT.

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 HIV-1 RT contributed to abacavir resistance. Genotypic analysis of isolates selected in cell culture and recovered from lamivudine-treated subjects showed that the resistance was due to a specific amino acid substitution in HIV-1 RT at codon 184 changing the methionine to either isoleucine or valine (M184V/I). In a study of therapy-naive adults receiving abacavir 600 mg once daily (n = 384) or 300 mg twice daily (n = 386) in a background regimen of lamivudine 300 mg and efavirenz 600 mg once daily (Study CNA30021), 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 study showed that the RT substitutions that emerged during abacavir and lamivudine once-daily and twice-daily therapy were K65R, L74V,

Y115F, and M184V/I. The abacavir- and lamivudine-associated resistance substitution M184V/I was the most commonly observed substitution in virologic failure isolates from subjects receiving abacavir and lamivudine 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 >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). Fifty-six percent **(**10/18) of the virologic failure isolates in the once-daily abacavir group compared with 41% (7/17) of the failure isolates in the twice-daily abacavir group had a >2.5-fold decrease in lamivudine susceptibility with median-fold changes of 81 (range 0.79 to >116) and 1.1 (range 0.68 to >116) in the once-daily and twice-daily abacavir arms, respectively.

Cross-Resistance: Cross-resistance has been observed among NRTIs. Viruses containing abacavir and lamivudine resistance-associated amino acid substitutions, namely, K65R, L74V, M184V, and Y115F, exhibit 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.

The combination of abacavir and lamivudine has demonstrated decreased susceptibility to viruses with the substitutions K65R with or without the M184V/I substitution, viruses with L74V plus the M184V/I substitution, and viruses with thymidine analog mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219 E/R/H/Q/N) plus M184V. An increasing number of TAMs is associated with a progressive reduction in abacavir susceptibility.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity:

Abacavir: 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.

Lamivudine: Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at the recommended therapeutic dose for HIV-1

infection. It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Mutagenicity: Abacavir: 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.

Lamivudine: Lamivudine was mutagenic in an L5178Y mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was not mutagenic in a microbial mutagenicity assay, in an in vitro cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver.

Impairment of Fertility: Abacavir or lamivudine induced no adverse effects on the mating performance or fertility of male and female rats at doses producing systemic exposure levels approximately 8 or 130 times, respectively, higher than those in humans 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

Abacavir and lamivudine: There have been no clinical studies conducted with abacavir and lamivudine.

The following studies were conducted with the individual components of abacavir and lamivudine.

14.1 Adults

Therapy-Naive Adults: **CNA30021** was an international, multi-center, double-blind, controlled study in which 770 HIV-1-infected, therapy-naive 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. Study 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^3 (range: 21 to

918 cells/mm^3) and the median baseline plasma HIV-1 RNA was 4.89 $\log_{10}$ copies/mL (range: 2.60 to 6.99 $\log_{10}$ copies/mL).

The outcomes of randomized treatment are provided in Table 8.

Table 8. Outcomes of Randomized Treatment Through Week 48 (CNA30021)

Outcome	Abacavir 600 mg q.d. plus Lamivudine plus Efavirenz (n = 384)	Abacavir 300 mg b.i.d. plus Lamivudine plus Efavirenz (n = 386)
Responder[a]	64% (71%)	65% (72%)
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 <50 copies/mL (<400 copies/mL) through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR® standard test version 1.0).
[b] Includes viral rebound, failure to achieve confirmed <50 copies/mL (<400 copies/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/mm^3 in the group receiving abacavir 600 mg once daily and 200 cells/mm^3 in the group receiving abacavir 300 mg twice daily. Through Week 48, 6 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 study medications.

14.2 Pediatric Patients

Therapy-Experienced Pediatric Patients: CNA3006 was a randomized, double-blind study comparing abacavir 8 mg/kg twice daily plus lamivudine 4 mg/kg twice daily plus zidovudine 180 mg/m^2 twice daily versus lamivudine 4 mg/kg twice daily plus zidovudine 180 mg/m^2 twice daily. Two hundred and five therapy-experienced pediatric patients 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 $\log_{10}$ copies/mL. Eighty percent and 55% of patients 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 patients responding based on plasma HIV-1 RNA less than or equal to 400 copies/mL was significantly higher in patients receiving abacavir plus lamivudine plus zidovudine compared with patients receiving lamivudine plus zidovudine, 13% versus 2%, respectively. Median plasma HIV-1 RNA changes from baseline were -0.53 $\log_{10}$ copies/mL in the group receiving abacavir plus lamivudine plus zidovudine compared with -0.21 $\log_{10}$ copies/mL in the group receiving lamivudine plus

zidovudine. Median CD4+ cell count increases from baseline were 69 cells/mm^3 in the group receiving abacavir plus lamivudine plus zidovudine and 9 cells/mm^3 in the group receiving lamivudine plus zidovudine.

Clinical Endpoint Study: ACTG300 was a multi-center, randomized, double-blind study that provided for comparison of lamivudine plus zidovudine with didanosine monotherapy. A total of 471 symptomatic, HIV-1-infected therapy-naive (≤56 days of antiretroviral therapy) pediatric patients were enrolled in these 2 treatment arms. The median age was 2.7 years (range: 6 weeks to 14 years), 58% were female, and 86% were non-Caucasian. The mean baseline CD4+ cell count was 868 cells/mm^3 (mean: 1,060 cells/mm^3 and range: 0 to 4,650 cells/mm^3 for patients ≤5 years of age; mean: 419 cells/mm^3 and range: 0 to 1,555 cells/mm^3 for patients >5 years of age) and the mean baseline plasma HIV-1 RNA was 5.0 $\log_{10}$ copies/mL. The median duration on study was 10.1 months for the patients receiving lamivudine plus zidovudine and 9.2 months for patients receiving didanosine monotherapy. Results are summarized in Table 9.

Table 9. Number of Patients (%) Reaching a Primary Clinical Endpoint (Disease Progression or Death)

Endpoint	Lamivudine plus Zidovudine (n = 236)	Didanosine (n = 235)
HIV-1 disease progression or death (total)	15 (6.4%)	37 (15.7%)
Physical growth failure	7 (3.0%)	6 (2.6%)
Central nervous system deterioration	4 (1.7%)	12 (5.1%)
CDC Clinical Category C	2 (0.8%)	8 (3.4%)
Death	2 (0.8%)	11 (4.7%)

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 sulfate and lamivudine tablets are supplied as yellow colored, biconvex, film coated tablet, debossed with "M26" on one side and score line on the other side. Each bottle contains 30 tablets, activated silica gel desiccant, induction sealed liner and closed with child-resistant closure (NDC 65015-118-30).

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature).

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Abacavir: 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 lamivudine, 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 and lamivudine. (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 doctor right away to determine if they should stop taking abacavir sulfate and lamivudine.
- that a hypersensitivity reaction can worsen and lead to hospitalization or death if abacavir sulfate and lamivudine is not immediately discontinued.
- **to not restart abacavir sulfate and lamivudine 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 and lamivudine is stopped right away.
- that if they have interrupted abacavir sulfate and lamivudine 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.
- that in one study, more severe hypersensitivity reactions were seen when abacavir was dosed 600 mg once daily.
- **to not restart abacavir sulfate and lamivudine or any other abacavir-containing product without medical consultation and that restarting abacavir needs to be undertaken only if medical care can be readily accessed by the patient or others.**
- Abacavir sulfate and Lamivudine Tablets should not be administered concomitantly with EPZICOM (abacavir sulfate and lamivudine), ATRIPLA (efavirenz, emtricitabine, and tenofovir disoproxil fumarate), COMBIVIR (lamivudine/zidovudine), EMTRIVA (lamivudine/zidovudine), EPIVIR (lamivudine), EPIVIR-HBV (lamivudine), TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine), TRUVADA (emtricitabine and tenofovir disoproxil fumarate), or ZIAGEN (abacavir sulfate) , or COMPLERA® (rilpivirine/emtricitabine/tenofovir).

HIV-1/ HBVCo-infection*:* Patients co-infected with HIV-1 and HBV should be informed that deterioration of liver disease has occurred in some cases when treatment with lamivudine was discontinued. Patients should be advised to discuss any changes in regimen with their physician [see Warnings and Precautions (5.3)].

HIV-1/HCV Co-Infection: Patients co-infected with HIV-1/HCV co-infection should be informed that hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-

infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin [see Warnings and Precautions (5.4)].

Lactic Acidosis/Hepatomegaly: Inform patients that some HIV-1 medicines, including abacavir sulfate and lamivudine, 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 (5.6)].

Risk of Pancreatitis: Parents or guardians should be advised to monitor pediatric patients for signs and symptoms of pancreatitis [see Warnings and Precautions (5.9)].

Information About HIV-1 Infection: Abacavir sulfate and lamivudine 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 and lamivudine. 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 or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed**. Lamivudine is excreted in human breast milk. It is not known if abacavir 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.

Importance of Taking Abacavir sulfate and Lamivudine Tablets as Prescribed: Inform patients to take Abacavir sulfate and Lamivudine Tablets on a regular dosing schedule and to avoid missing doses. Abacavir sulfate and Lamivudine Tablets are for oral ingestion only.

Manufactured by:

Mylan Laboratories Limited,

Hyderabad, INDIA

MEDICATION GUIDE
Abacavir sulfate and Lamivudine Tablets 60 mg/30 mg

Read the Medication Guide before you or your child start taking abacavir sulfate and lamivudine and each time your child or 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 or your child's treatment. Be sure to carry the abacavir sulfate and lamivudine Warning Card with you at all times.

What is the most important information I should know about Abacavir sulfate and Lamivudine Tablets?

1. **Serious Allergic Reaction (hypersensitivity reaction).** Abacavir sulfate and Lamivudine Tablets contain abacavir. Patients taking Abacavir sulfate and Lamivudine Tablets may have a serious allergic reaction (hypersensitivity reaction) that can cause death. The **risk of this allergic reaction is much higher if your child or you have a gene variation called HLA-B*5701. Your healthcare provider can determine with a blood test if your child or you have this gene variation.**

   If your child or you get a symptom from 2 or more of the following groups while taking abacavir sulfate and lamivudine, call your doctor right away to find out if your child or you should stop taking this medicine.

	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 your child or you stop Abacavir sulfate and Lamivudine Tablets because of an allergic reaction, NEVER take Abacavir sulfate and Lamivudine Tablets or any other abacavir-containing medicine again. If your child or you take Abacavir sulfate and Lamivudine Tablets or any other abacavir-containing medicine again after your child or you have had an allergic reaction, **WITHIN HOURS** your child or you may get **life-threatening symptoms** that may include **very low blood pressure or death**. If your child or you stop Abacavir sulfate and Lamivudine Tablets for any other reason, even for a few days, and your child or you are not allergic to abacavir sulfate and lamivudine, talk with your healthcare provider before taking or giving it to your child again. Taking Abacavir sulfate

and Lamivudine 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 or give your child abacavir sulfate and lamivudine again, start taking or giving it when your child or you are around medical help or people who can call a healthcare provider if your child or you need one.

2. **Lactic Acidosis (buildup of acid in the blood). Some human immunodeficiency virus (HIV) medicines, including abacavir sulfate and lamivudine, can cause a rare but serious condition called lactic acidosis**. **Lactic acidosis is a serious medical emergency that can cause death and must be treated in the hospital.**

   Call your healthcare provider right away if you get any of the following signs or symptoms of lactic acidosis:
   - you feel very weak or tired
   - you have unusual (not normal) muscle pain
   - you have trouble breathing
   - you have stomach pain with nausea and vomiting
   - you feel cold, especially in your arms and legs
   - you feel dizzy or light-headed
   - you have a fast or irregular heartbeat

3. **Serious liver problems. Some people who have taken medicines like Abacavir sulfate and Lamivudine Tablets have developed serious liver problems called hepatotoxicity, with liver enlargement (hepatomegaly) and fat in the liver (steatosis). Hepatomegaly with steatosis is a serious medical emergency that can cause death.**

   Call your healthcare provider right away if you get any of the following signs or symptoms of liver problems:
   - your skin or the white part of your eyes turns yellow (jaundice)
   - your urine turns dark
   - your bowel movements (stools) turn light in color
   - you don't feel like eating food for several days or longer
   - you feel sick to your stomach (nausea)
   - you have lower stomach area (abdominal) pain
   - You may be more likely to get lactic acidosis or serious liver problems if you are female, very overweight, or have been taking nucleoside analogue medicines for a long time.

4. **Use with interferon- and ribavirin-based regimens.** Worsening of liver disease (sometimes resulting in death) has occurred in patients infected with both HIV and hepatitis C virus who are taking anti-HIV medicines and are also being treated for

hepatitis C with interferon with or without ribavirin. If you or your child are taking abacavir sulfate and lamivudine as well as interferon with or without ribavirin and you or your child experience side effects, be sure to tell your healthcare provider.

5. **If you or your child have HIV and hepatitis B virus infection, the hepatitis B virus infection may get worse if you or your child stop taking Abacavir sulfate and Lamivudine Tablets.**
    - Take or give Abacavir sulfate and Lamivudine Tablets exactly as prescribed.
    - Do not run out of Abacavir sulfate and Lamivudine Tablets.
    - Do not stop Abacavir sulfate and Lamivudine Tablets without talking to your healthcare provider.
    - Your healthcare provider should monitor your health and do regular blood tests to check your liver if you stop taking Abacavir sulfate and Lamivudine Tablets.

What are Abacavir sulfate and Lamivudine Tablets?

Abacavir sulfate and Lamivudine Tablets contain 2 prescription medicines, abacavir and lamivudine, both used to treat HIV infection. Both of these medicines are called nucleoside analogue reverse transcriptase inhibitors (NRTIs).

- **Abacavir sulfate and Lamivudine Tablets do not cure HIV infection or AIDS.**
- It is not known if Abacavir sulfate and Lamivudine Tablets will help your child or you live longer or have fewer of the medical problems that people get with HIV or AIDS.
- It is very important that you see your healthcare provider regularly while your child or you are taking Abacavir sulfate and Lamivudine Tablets.

Who should not take Abacavir sulfate and Lamivudine Tablets?

Do not take Abacavir sulfate and Lamivudine Tablets if you or your child:

- **are allergic to abacavir or any of the ingredients in Abacavir sulfate and Lamivudine Tablets. See the end of this Medication Guide for a complete list of ingredients in Abacavir sulfate and Lamivudine Tablets.**
- **have certain liver problems.**

What should I tell my healthcare provider before taking or giving Abacavir sulfate and Lamivudine Tablets?

Before you take or give Abacavir sulfate and Lamivudine Tablets tell your healthcare provider if your child or you:

- **have been tested and know whether or not your child or you have a particular gene variation called HLA-B*5701.**
- **are pregnant or plan to become pregnant.** It is not known if Abacavir sulfate and Lamivudine Tablets will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant.

- **are breastfeeding or plan to breastfeed. Do not breastfeed.** Lamivudine is excreted in human breast milk. It is not known if abacavir 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.
- **have hepatitis B virus infection or have other liver problems.**
- **have kidney problems.**

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

Especially tell your healthcare provider if you or your child take:

- alcohol
- medicines used to treat hepatitis viruses such as interferon or ribavirin.
- methadone
- EPZICOM® (abacavir sulfate and lamivudine)
- ATRIPLA® (efavirenz, emtricitabine, and tenofovir)
- COMBIVIR® (lamivudine and zidovudine)
- COMPLERA® (rilpivirine/emtricitabine/tenofovir)
- EMTRIVA® (emtricitabine)
- EPIVIR or EPIVIR-HBV® (lamivudine, 3TC)
- TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine)
- TRUVADA® (emtricitabine and tenofovir)
- ZIAGEN (abacavir sulfate)

Ask your healthcare provider if you are not sure if you take one of the medicines listed above.

Abacavir sulfate and Lamivudine Tablets may affect the way other medicines work, and other medicines may affect how Abacavir sulfate and Lamivudine Tablets works.

Know the medicines you take. Keep a list of your medicines with you to show to your healthcare provider and pharmacist when you get a new medicine.

How should I or my child take Abacavir sulfate and Lamivudine Tablets?

- **Take or give Abacavir sulfate and Lamivudine Tablets exactly as your healthcare provider tells you to take or give it.**
- The healthcare provider will tell you the right dose to take or give to your child. Your child's dose will depend on the weight of your child. For very young children who cannot swallow tablets, following procedure can be used

Method of preparation:

1. Place the tablet(s) in a container and add two teaspoonfuls (10 mL) of drinking water per tablet.
2. Swirl the container until the tablet(s) breaks up into pieces small enough for the child to swallow. A spoon can be used to crush the pieces, if needed.
3. Drink the mixture within 1 hour.
4. Rinse the container with an additional small amount of water and drink the contents to assure that the entire dosage is taken.

DO NOT MIX THE ABACAVIR SULFATE AND LAMIVUDINE TABLETS WITH ANY LIQUID OTHER THAN WATER.

- Older children, who can reliably swallow tablets, can be given the appropriate dose (see Table 1) to be swallowed.

Table 1. Dosing Recommendations for Abacavir sulfate and Lamivudine Tablets Pediatric Patients

Weight (kg)	Dosage Regimen Using Scored Abacavir Sulfate and Lamivudine Tablets, 60 mg/30 mg		Total Daily Dose (mg)
	AM Dose (mg)	PM Dose (mg)	
5	½ tablet (30 mg A/15 mg L)	1 tablet (60 mg A/30 mg L)	90A/45L
6 - < 9	1 tablet (60 mg A/30 mg L)	1 tablet (60 mg A/30 mg L)	120A/60L
9 - < 12	1.5 tablets (90 mg A/45 mg L)	1.5 tablets (90 mg A/45 mg L)	180A/90L
12 - < 17	2 tablets (120 mg A/60 mg L)	2 tablets (120 mg A/60 mg L)	240A/120L
17 - < 20	2.5 tablets (150 mg A/75 mg L)	2.5 tablets (150 mg A/75 mg L)	300A/150L
20 - < 25	3 tablets (180 mg A/90 mg L)	3 tablets (180 mg A/90 mg L)	360A/180L
25 - < 29	3.5 tablets (210 mg A/105 mg L)	3.5 tablets (210 mg A/105 mg L)	420A/210L
29 - < 35	4 tablets (240 mg A/120 mg L)	4 tablets (240 mg A/120 mg L)	480A/240L
≥ 35	5 tablets (300 mg A/150 mg L)	5 tablets (300 mg A/150 mg L)	600A/300L

A= abacavir sulfate; L= lamivudine

- Do not skip doses.
- Take or give Abacavir sulfate and Lamivudine Tablets with or without food.
- **Do not let your Abacavir sulfate and Lamivudine Tablets run out.**

If your child or you stop the anti-HIV medicines, even for a short time, the amount of virus in the blood may increase and the virus may become harder to treat. If your child or you take too much Abacavir sulfate and Lamivudine Tablets, call the healthcare provider or poison control center or go to the nearest hospital emergency room right away.

What are the possible side effects of Abacavir sulfate and Lamivudine Tablets?

- **Abacavir sulfate and Lamivudine Tablets can cause serious side effects including allergic reactions, lactic acidosis, and liver problems. See "What is the most important information I should know about Abacavir sulfate and Lamivudine Tablets?"**
- **Changes in immune system (Immune Reconstitution Syndrome).** Your and your child's immune system may get stronger and begin to fight infections that have been hidden in your or your child's body for a long time. Tell your healthcare provider if your child or you start having new or worse symptoms of infection after you or your child start taking abacavir sulfate and lamivudine.

- **Changes in body fat (fat redistribution).** Changes in body fat (lipoatrophy or lipodystrophy) can happen in some people taking antiretroviral medicines including Abacavir sulfate and Lamivudine Tablets. The changes may include:
    - more fat in or around your trunk, upper back and neck (buffalo hump), breast, or chest
    - loss of fat in your legs, arms, or face
- **Heart attack (myocardial infarction).** Some HIV medicines including abacavir sulfate and lamivudine may increase your risk of heart attack.

The most common side effects of abacavir sulfate and lamivudine include:

- trouble sleeping
- depression
- headache
- tiredness
- dizziness
- nausea
- diarrhea
- rash
- fever
- cough
- infections of ear, nose, and throat

Tell your healthcare provider if you or your child have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Abacavir sulfate and Lamivudine Tablets. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects.

How should I store Abacavir sulfate and Lamivudine Tablets?

Store Abacavir sulfate and Lamivudine Tablets at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

Keep Abacavir sulfate and Lamivudine Tablets and all medicines out of the reach of children.

General information for safe and effective use of Abacavir sulfate and Lamivudine Tablets

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 or other barrier method to

lower the chance of sexual contact with semen, vaginal secretions, or blood.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guides. Do not use Abacavir sulfate and Lamivudine Tablets for a condition for which it was not prescribed. Do not give Abacavir sulfate and Lamivudine Tablets to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Abacavir sulfate and Lamivudine Tablets. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for the information about Abacavir sulfate and Lamivudine Tablets that is written for healthcare professionals.

What are the ingredients in abacavir sulfate and lamivudine Tablets?
Abacavir sulfate and Lamivudine Tablets are for oral administration. Each film-coated tablet contains the active ingredients 60 mg of abacavir as abacavir sulfate and 30 mg of lamivudine, and the inactive ingredients magnesium stearate, microcrystalline cellulose, colloidal silicon dioxide and sodium starch glycolate. The tablets are coated with a film (Opadry® Yellow 13B92524) that is made of FD&C Yellow No. 6, hypromellose, polyethylene glycol 400, polysorbate 80, titanium dioxide and iron oxide yellow.

Other brands listed are the registered trademarks of their respective owners and are not of Mylan Laboratories Limited.

January 2012

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

Manufactured by:

Mylan Laboratories Limited,

Hyderabad, INDIA