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 for oral suspension 60 mg/30 mg

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

Scored tablets for oral suspension 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 Cipla Ltd. at 91-22-2578 7825 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Ethanol: Decreases elimination of abacavir. (7.2)
- Methadone: An increased methadone dose may be required in a small number of patients. (7.4)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE.

Revised: May 2011

Abacavir Sulfate and
Lamivudine tablets
for oral suspension
60 mg/30 mg
J022 A

FULL PRESCRIBING INFORMATION: CONTENTS*

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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 FOR ORAL SUSPENSION. 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 tablet for oral suspension, 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 for oral suspension 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.
- Take abacavir and lamivudine on an empty stomach.

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 is provided in Table 1.

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

Weight (kg)	Dosage Regimen Using Scored Abacavir Sulfate and Lamivudine Tablets for Oral Suspension, 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)[a]	5 tablets (300 mg A/150 mg L)[a]	600A/300L

A= abacavir sulfate; L= lamivudine

[a]= For recommended doses of abacavir 300 mg twice daily and lamivudine 150 mg twice daily (adult maximum daily dose), the adult formulations (abacavir 300 mg tablet and lamivudine 150 mg tablet) can be used.

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 FOR ORAL SUSPENSION WITH ANY LIQUID OTHER THAN WATER.

2.2 Dose Adjustment

Because abacavir sulfate and lamivudine tablets for oral suspension 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

Abacavir sulfate and lamivudine tablets for oral suspension contain 60 mg of abacavir as abacavir sulfate and 30 mg of lamivudine. The tablets are scored, white to off white colored, capsule shaped, biconvex, and uncoated tablets with central breakline on one side and 'C' debossed on other side.

4 CONTRAINDICATIONS

Abacavir sulfate and lamivudine tablets for oral suspension 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.

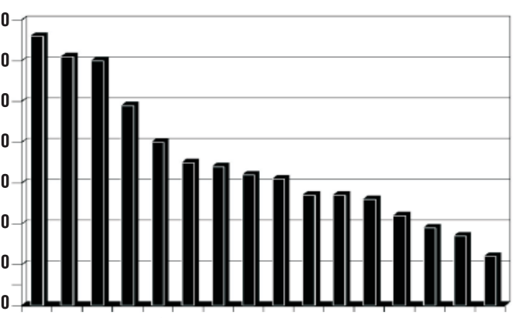
Signs and symptoms of Hypersensitivity: Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in two or more of the following groups:

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-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected subjects [see Clinical Pharmacology (12.3)], 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. Patients receiving interferon alfa with or without ribavirin and abacavir sulfate 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.

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 for oral suspension 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).

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/m² twice daily compared with lamivudine 4 mg/kg twice daily and zidovudine 180 mg/m² 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/m² 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/mm³)	8%	3%
Hemoglobin (<7.0 g/dL)	4%	2%
Platelets (<50,000/mm³)	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 HIV0-1:* 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)], posttreatment 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 for oral suspension [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 lamivudine: 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.

8.2 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.**

8.3 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)].

8.4 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)].

8.5 Patients With Impaired Renal Function

Abacavir and lamivudine tablets for oral suspension 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.

8.6 Patients With Impaired Hepatic Function

Abacavir and lamivudine tablets for oral suspension 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

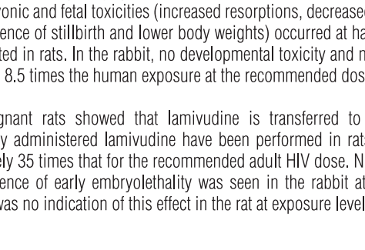
Abacavir: There is no known antidote for abacavir. It is not known whether abacavir can be removed by peritoneal dialysis or hemodialysis.

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

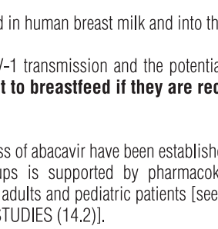
Abacavir sulfate and lamivudine tablet for oral suspension 60/30mg contain the following 2 synthetic nucleoside analogues: abacavir sulfate and lamivudine with inhibitory activity against HIV-1. Abacavir sulfate and lamivudine tablets are for oral administration. Each uncoated tablet contains the active ingredients 60 mg of abacavir as abacavir sulfate and 30 mg lamivudine and the inactive ingredients microcrystalline cellulose, sodium starch glycolate, hypromellose, corn starch, strawberry cream (PHS132963), aspartame, colloidal silicon dioxide, magnesium stearate, and purified water.

Abacavir Sulfate: The chemical name of abacavir sulfate is (*1S, cis*)-4-[2-amino-6-(cyclopropylamino)-*9H*-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 $(C_{14}H_{18}N_6O)_2 \bullet H_2SO_4$ 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 a 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 for oral suspension (60 mg/30 mg) were bioequivalent to EPZICOM Tablets of GlaxoSmithKline USA, when single doses of 600 mg/300 mg) were administered to healthy volunteers under fasting 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.

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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)	.007 ± .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 for oral suspension:__ The effect of food on abacavir sulfate and lamivudine tablets for oral suspension was not determined; therefore, this product must be administered on an empty stomach.

__Special Populations:__ *Renal Impairment:* Because lamivudine requires dose adjustment in the presence of renal insufficiency, abacavir and lamivudine tablets for oral suspension are not recommended for use in patients with creatinine clearance <50 mL/min [see Dosage and Administration 2.2)].

Hepatic Impairment: Abacavir and lamivudine tablets for oral suspension 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.

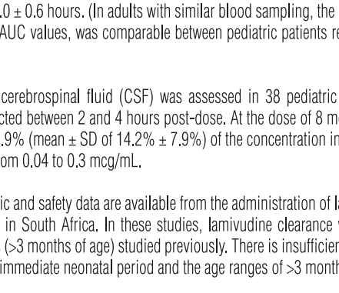
Pediatric Patients

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 bioavailabilty 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					
			Lamivudine Concentrations		**Concentration of Coadministered**
Coadministered Drug and Dose	**Lamivudine Dose**	**n**	**AUC**	**Variability**	**Drug**
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 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 had 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/mm³ (range: 21 to 918 cells/mm³) 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/mm³ in the group receiving abacavir 600 mg once daily and 200 cells/mm³ 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/m² twice daily versus lamivudine 4 mg/kg twice daily plus zidovudine 180 mg/m² 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/mm³ in the group receiving abacavir plus lamivudine plus zidovudine and 9 cells/mm³ 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/mm³ (mean: 1,060 cells/mm³ and range: 0 to 4,650 cells/mm³ for patients ≤5 years of age; mean: 419 cells/mm³ and range: 0 to 1,555 cells/mm³ 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 are available as tablets for oral suspension. Each tablet contains 60 mg of abacavir as abacavir sulfate and 30 mg of lamivudine. The tablets are scored, white to off white colored, capsule shaped, biconvex, and uncoated tablets with central breakline on one side and 'C' debossed on other side. They are packaged as follows:

Bottle of 60 tablets
Bottle of 120 tablets
Carton of 60 (6 x 10) unit of use tablets

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 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 and lamivudine 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).

Co-infection With HIV-1 and HBV: 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)].

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 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. Advise patients that the use of abacavir sulfate and lamivudine has not been shown to reduce the risk of transmission of HIV-1 to others through sexual contact or blood contamination. Patients should be informed to take all HIV medications exactly as prescribed.

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

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MEDICATION GUIDE

Abacavir Sulfate and Lamivudine tablets for oral suspension 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 for oral suspension?

1. **Serious Allergic Reaction (hypersensitivity reaction).** Abacavir sulfate and lamivudine contain abacavir. Patients taking abacavir sulfate and lamivudine 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 because of an allergic reaction, NEVER take abacavir sulfate and lamivudine or any other abacavir-containing medicine again. If your child or you take abacavir sulfate and lamivudine 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 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 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 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.**

- Take or give abacavir sulfate and lamivudine exactly as prescribed.
- Do not run out of abacavir sulfate and lamivudine.
- Do not stop abacavir sulfate and lamivudine 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.

What are abacavir sulfate and lamivudine tablets for oral suspension?

Abacavir sulfate and lamivudine tablets for oral suspension 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 does not cure HIV infection or AIDS.**
- It is not known if abacavir sulfate and lamivudine 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.

Who should not take abacavir sulfate and lamivudine tablets for oral suspension?

Do not take abacavir sulfate and lamivudine if you or your child:

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

What should I tell my healthcare provider before taking or giving abacavir sulfate and lamivudine tablets for oral suspension?

Before you take or give abacavir sulfate and lamivudine 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 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.** Abacavir sulfate and lamivudine can pass into your breast milk. You should not breastfeed if you are taking abacavir sulfate and lamivudine. If you are a woman who has or will have a baby while taking abacavir sulfate and lamivudine, talk to your healthcare provider about the best way to feed your baby. The Center for Disease Control and Prevention (CDC) recommend that HIV-infected mothers **not** breastfeed to avoid the risk of passing HIV infection to your baby.
- **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)
- 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 may affect the way other medicines work, and other medicines may affect how abacavir sulfate and lamivudine 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 for oral suspension?

- **Take or give abacavir sulfate and lamivudine 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 FOR ORAL SUSPENSION 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 for Oral Suspension Pediatric Patients

Weight (kg)	Dosage Regimen Using Scored Abacavir Sulfate and Lamivudine Tablets for Oral Suspension, 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)[a]	5 tablets (300 mg A/150 mg L)[a]	600A/300L

A= abacavir sulfate; L= lamivudine

[a]= For recommended doses of abacavir 300 mg twice daily and lamivudine 150 mg twice daily (adult maximum daily dose), the adult formulations (abacavir 300 mg tablet and lamivudine 150 mg tablet) can be used.

- Do not skip doses.
- Take or give abacavir sulfate and lamivudine on an empty stomach.
- **Do not let your abacavir sulfate and lamivudine run out.**

If your child or you stop the anti-HIV drugs, 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, 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 for oral suspension?**__

- **Abacavir sulfate and lamivudine 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 for oral suspension?"**
- **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. 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. 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 for oral suspension?**__

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 and all medicines out of the reach of children.

__**General information for safe and effective use of abacavir sulfate and Lamivudine tablets for oral suspension**__

Abacavir sulfate and lamivudine do not stop you or your child from spreading HIV to other people by sex, sharing needles, or being exposed to you or your child's blood. Talk with your healthcare provider about safe sexual practices that protect your partner. Never share needles. Do not share personal items that can have blood or body fluids on them, like toothbrushes or razor blades.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guides. Do not use abacavir sulfate and lamivudine for a condition for which it was not prescribed. Do not give abacavir sulfate and lamivudine 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. 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 that is written for healthcare professionals.

What are the ingredients in abacavir sulfate and lamivudine tablets for oral suspension?

Active ingredients: abacavir sulfate and lamivudine

Inactive ingredients: microcrystalline cellulose, sodium starch glycolate, hypromellose, corn starch, strawberry cream (PHS132963), aspartame, colloidal silicondioxide, magnesium stearate, and purified water.

Other brands listed are the registered trademarks of their respective owners and are not of Cipla Ltd.

Issued: May 2011

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

Cipla Ltd.
Mumbai Central, Mumbai, INDIA

J022 A

PACKAGING DEVELOPMENT

Product Name : aba lami	**Item Code :** JQ22A	**Item :** enclosures	**Date :** 03 oct 12
Cordinator : namrata	**Artist :** james	**Software :** illustrator CS2	

Fonts :

Colours :
BLUE WOOL TEST VALUE 5-8
(LIGHT FASTENING DATA)
■ black

Spectro-Densitometer Delta-E reading (△E) for colour: NOT MORE THAN dE2.5
Glossmeter reading (for white surface): NOT LESS THAN 80 %

Supersedes / Reference : GB60A / doc **Screen : #** __ **Unwinding Direction :**

Tuck flap: mm **Side / Collar flap overlap:** mm **Caliper (Thickness) for Board:**

Links :

Pharmacode / 2D code : 2415 mini
Design : folded with perforated tear here tape

Material : 42 GSM ITC paper twin pack
English & French pack ineserts affixed one above the other by means of glue
Varnish :

Actual Size : 595 x 490 mm
Size after Folding : 35x35 mm

Print repeat length :

Grain Direction : Perpendicular to Crease / Perpendicular to Pasting Flap / Parallel to length

Reference / Instructions / Remark / Braille Text Embossing:

Artwork Print Size: ☐ **actual** ☐ **scaled**

Path : james F:1609/release/JQ22A eng.ai

Checked by	**Artist**	**Cordinator**	**Section Head**	**File Copied by:**	**file loaded in BCT HO**
Pharma Code	☐	☐			
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Barcode Code	☐	☐			
Artwork	☐	☐			
Spell check	☐	☐		**Date:**	

NOTE TO THE PRINTER :

- **Return approved artwork alongwith the proof.**
- **The proof must be verified against the approved hardcopy, should be certified and signed by an authorised QA person. The unsigned proof will not be accepted.**
- **Colour scheme must be as approved by packaging development co-ordinator.**
- **Any deviation must be brought to the notice of packaging development co-ordinator immediately.**
- **For any clarification, please contact packaging development co-ordinator immediately.**

Sulfate d'abacavir et Lamivudine Comprimés pour suspension buvable 60mg/30mg

JQ22 A

RÉSUMÉ DE L'INFORMATION POSOLOGIQUE

Ce résumé ne comprend pas toutes les informations nécessaires pour utiliser le sulfate d'abacavir et la lamivudine de manière sûre et efficace. Veuillez lire l'intégralité de l'information posologique du sulfate d'abacavir et de la lamivudine.

Sulfate d'abacavir et Lamivudine Comprimés pour suspension buvable 60mg/30mg

MISES EN GARDE : RISQUE DE RÉACTIONS D'HYPERSENSIBILITÉ, D'ACIDOSE LACTIQUE ET D'HÉPATOMEGALIE GRAVE, ET D'EXACERBATIONS DE L'HÉPATITE

Veuillez lire l'intégralité de l'information posologique afin d'obtenir une description détaillée de l'encadré intitulé Mises en garde.

- **Des réactions d'hypersensibilité graves et parfois fatales ont été associées avec des produits contenant de l'abacavir. (5.1)**
- **L'hypersensibilité à l'abacavir est un syndrome clinique de dysfonction multiple des organes. (5.1)**
- **Les patients porteurs de l'allèle HLA-B*5701 sont plus exposés à une réaction d'hypersensibilité à l'abacavir. (5.1)**
- **Arrêtez immédiatement de prendre Sulfate d'abacavir et lamivudine dès qu'une réaction d'hypersensibilité est suspectée. Sans égard au statut de l'allèle HLA-B*5701, interrompez définitivement la prise de Sulfate d'abacavir et lamivudine si l'hypersensibilité ne peut être exclue, même lorsque d'autres diagnostics sont possibles. (5.1)**
- **Suite à une réaction hypersensibilité à l'abacavir, NE JAMAIS reprendre le traitement par Sulfate d'abacavir et lamivudine ou tout produit contenant de l'abacavir. (5.1)**
- **Des cas d'acidose lactique et d'hépatomégalie grave avec stéatose, y compris des cas fatals, ont été signalés lors de l'utilisation d'analogues nucléosidiques. (5.2)**
- **es cas d'exacerbations aiguës graves de l'hépatite B ont été signalés chez les patients infectés à la fois par le virus de l'hépatite B (VHB) et le virus de l'immunodéficience humaine (VIH-1) et qui ont cessé de prendre la lamivudine, un composant de Sulfate d'abacavir et lamivudine. Chez ces patients, la fonction hépatique doit être étroitement contrôlée et, le cas échéant, instaurez un traitement anti-hépatite B. (5.3)**

-----INDICATIONS ET UTILISATION-----

Sulfate d'abacavir et lamivudine, une association de l'abacavir et de la lamivudine, deux inhibiteurs nucléosidiques de la transcriptase inverse du VIH-1, est indiqué en association avec d'autres agents antirétroviraux pour le traitement de l'infection par le VIH-1. (1)

----- POSOLOGIE ET MODE D'ADMINISTRATION -----

- Un guide de thérapeutique et une fiche de mise en garde doivent être distribués à chaque nouvelle prescription et renouvellement.(2)
- Enfants de 3 mois et plus : La posologie doit être basée sur le poids corporel (2.2)
- Ne pas prescrire aux patients nécessitant une adaptation posologique ou aux patients atteints d'insuffisance hépatique. (2.2)

----- FORMES PHARMACEUTIQUES ET CONCENTRATIONS -----

Chaque comprimé sécable pour suspension buvable contient 60 mg d'abacavir et 30 mg de lamivudine. (3)

----- CONTRE–INDICATIONS -----

- Hypersensibilité précédemment démontrée à l'abacavir ou à tout autre composant du produit (4, 5.1)
- Insuffisance hépatique. (4)

----- MISES EN GARDE ET PRÉCAUTIONS D'EMPLOI -----

- Voir les mises en garde en encadré pour de plus amples informations sur les points suivants : Réactions d'hypersensibilité, acidose lactique et hépatomégalie grave, et exacerbations aiguës graves de l'hépatite B. (5.1, 5.2, 5.3)
- Une décompensation hépatique, fatale dans certains cas, est survenue chez des patients infectés à la fois par le VIH-1/VHC recevant un traitement par association d'antirétroviraux et l'interféron alpha avec ou sans ribavirine. Interrompez la prise de Sulfate d'abacavir et lamivudine de manière médicalement appropriée et envisagez de diminuer la posologie ou d'interrompre la prise de l'interféron alpha, de la ribavirine, voire des deux. (5.4)
- Des cas de syndrome de reconstitution immunitaire (5.5) et de redistribution / d'accumulation de graisse corporelle ont été signalés chez des patients traités par une association d'antirétroviraux. (5.6)
- Sulfate d'abacavir et lamivudine ne doit pas être administré avec d'autres produits contenant de la lamivudine ou de la zidovudine ou des produits contenant de l'emtricitabine. (5.8)
- Pancréatite : La prudence est de mise chez les patients pédiatriques présentant des antécédents de pancréatite ou d'autres facteurs de risque importants de pancréatite. Interrompez le traitement de manière cliniquement appropriée. (5.9)

----- EFFETS SECONDAIRES -----

- Effets secondaires d'intensité au moins modérée les plus couramment rapportés (incidence ≥ 5%) chez un adulte ayant pris part à l'étude clinique du VIH-1 : hypersensibilité médicamenteuse, insomnie, dépression/humeur dépressive, maux de tête/migraines, fatigue/malaise, étourdissements/vertiges, nausées et diarrhée. (6.1)
- Abacavir : Effets secondaires d'intensité au moins modérée les plus couramment rapportés (incidence ≥ 5%) chez des enfants ayant pris part aux études cliniques du VIH-1 : fièvre et/ou frissons, nausées et vomissements, éruptions cutanées, infections de l'oreille/du nez/ de la gorge (6.1)
- Lamivudine : Effets secondaires les plus couramment rapportés (incidence >15%) chez les patients pédiatriques : fièvre et toux (6.1)

Pour signaler des EFFETS SECONDAIRES SOUPÇONNÉS, contactez Cipla Ltd. au 91-22-25787825 ou l'Agence Fédérale américaine des produits alimentaires et médicamenteux (FDA) au 1-800-FDA-1088 ou rendez-vous sur le site Internet: www.fda.gov/medwatch.

----- INTERACTIONS MÉDICAMENTEUSES -----

- Éthanol : Diminue l'élimination de l'abacavir. (7.2)
- Méthadone : L'augmentation d'une dose de méthadone peut être nécessaire chez un nombre restreint de patients. (7.4)

Voir 17 pour LES RENSEIGNEMENTS SUR LES CONSEILS À DONNER AUX PATIENTS et LE GUIDE DE THÉRAPEUTIQUE

Révision : Mai 2011

INFORMATION POSOLOGIQUE COMPLÈTE : SOMMAIRE*

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  2.2 Adaptation posologique
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4 CONTRE-INDICATIONS
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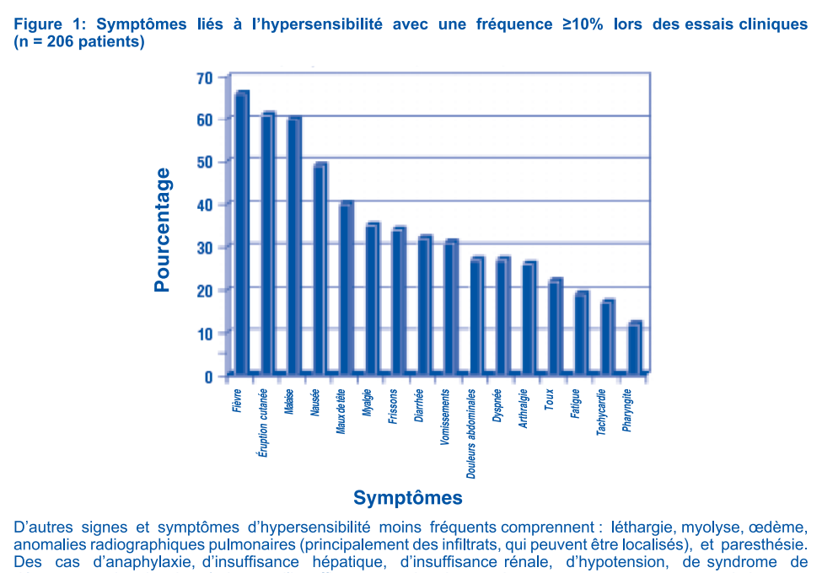
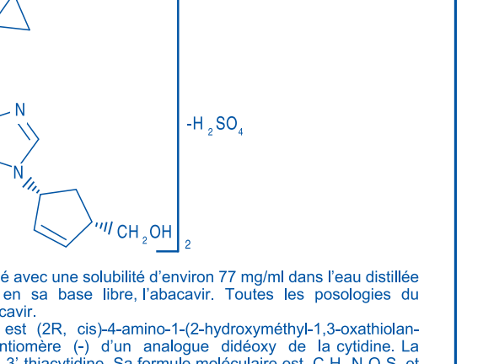
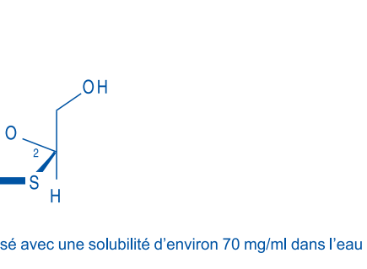
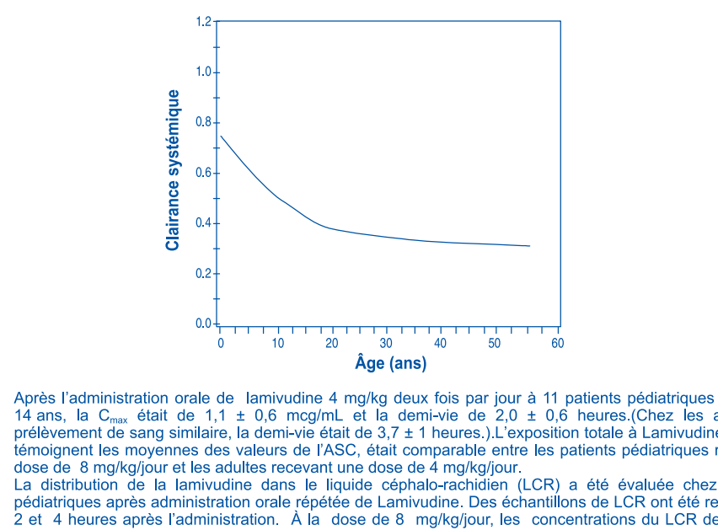
17 RENSEIGNEMENTS SUR LES CONSEILS À DONNER AUX PATIENTS

*Les sections ou les paragraphes omis de l'information posologique complète ne sont pas énumérés.









Redistribution / accumulation de tissus adipeux : Informer les patients que la redistribution ou une accumulation de tissus adipeux peut survenir chez les patients recevant un traitement antirétroviral et que la cause et les effets à long terme de ces états ne sont pas connus pour le moment [voir Mises en garde et précautions d'emploi (5.6)]

Risque de pancréatite : Les parents ou tuteurs doivent surveiller les patients pédiatriques pour des signes et des symptômes de pancréatite [voir Mises en garde et précautions d'emploi (5.9)].

Information sur l'infection par le VIH-1 : Sulfate d'abacavir et lamivudine n'est pas un remède contre l'infection par le VIH-1 et les patients peuvent continuer à avoir des maladies associées à l'infection par le VIH-1, y compris les infections opportunistes. Les patients doivent rester sous surveillance d'un médecin lors de l'utilisation de Sulfate d'abacavir et de lamivudine. Informer les patients que l'utilisation de Sulfate d'abacavir et lamivudine n'a pas présentés de réduction de risque de transmission du VIH-1 à d'autres personnes par contact sexuel ou contamination sanguine. Les patients doivent respecter la prescription des médicaments contre le VIH.

Importance du respect de la prescription d'Abacavir et Lamivudine : Les patients doivent prendre Sulfate d'abacavir et de Lamivudine selon un programme posologique régulier et éviter de rater les doses. Sulfate d'abacavir et lamivudine comprimés pour suspension buvable sont destinés pour une ingestion orale uniquement. COMBIVIR, EPIVIR, EPIVIR-HBV, EPZICOM, TRIZIVIR, ATRIPLA, EMTRIVA, TRUVADA, and ZIAGEN sont des marques déposées de leurs propriétaires respectifs et non des marques de Cipla Limited.

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Cipla Ltd.
Mumbai Central, Mumbai, INDE

GUIDE DE THÉRAPEUTIQUE
Sulfate d'abacavir et Lamivudine Comprimés pour suspension buvable 60mg/30mg

Lisez le Guide de thérapeutique avant que vous ou votre enfant commenciez à prendre Sulfate d'abacavir et lamivudine et à chaque fois que votre enfant ou vous obtenez un renouvellement. De nouvelles informations peuvent y figurer. Ces informations ne remplacent pas le fait de parler à votre professionne de santé au sujet de votre état de santé ou de votre traitement ou celui de votre enfant.. Assurez-vous d'être toujours en possession de la Fiche de mises en garde de Sulfate d'abacavir et lamivudine.

Quelles sont les informations les plus importantes que je dois connaître à propos de Sulfate d'abacavir et lamivudine comprimés pour suspension buvable ?

1. Réaction allergique grave (réaction d'hypersensibilité). Sulfate d'abacavir et lamivudine contient de l'abacavir. Les patients sous Sulfate d'abacavir et lamivudine peuvent avoir une réaction allergique grave (réaction d'hypersensibilité) qui peut causer la mort. **Le risque de cette réaction allergique est beaucoup plus élevé si votre enfant ou vous avez une variation génétique appelée HLA-B*5701. Votre professionnel de santé peut déterminer par une analyse sanguine si votre enfant ou vous avez cette variation génétique.**

Si votre enfant ou si vous ressentez un symptôme de 2 ou plusieurs des groupes suivants pendant la prise de Sulfate d'abacavir et lamivudine, appelez immédiatement votre médecin pour savoir si votre enfant ou vous devez arrêter de prendre ce médicament.

	Symptôme(s)
Groupe 1	**Fièvre**
Groupe 2	**Éruption cutanée**
Groupe 3	**Nausées, vomissements, diarrhée ou douleurs abdominales (région de l'estomac)**
Groupe 4	**Sensation de malaise général, fatigue extrême ou courbatures**
Groupe 5	**Essoufflement, toux, maux de gorge**

Une liste de ces symptômes se trouve sur la Fiche de mises en garde remise par votre pharmacien. Ayez toujours avec vous cette Fiche de mises en garde.

Si votre enfant ou vous arrêtez Sulfate d'abacavir et lamivudine à la suite d'une réaction allergique, NE reprenez JAMAIS Sulfate d'abacavir et lamivudine ou tout autre médicament contenant de l'abacavir. Si votre enfant ou vous reprenez Sulfate d'abacavir et lamivudine ou tout autre médicament contenant de l'abacavir après que vous ou votre enfant ayez eu une réaction allergique, **DURANT LES HEURES** qui suivent la prise, votre enfant ou vous pouvez avoir des symptômes pouvant être mortels, et qui peuvent inclure une **tension artérielle très basse ou la mort**.

Si votre enfant ou vous arrêtez de prendre Sulfate d'abacavir et lamivudine pour toute autre raison, même pour quelques jours, et si votre enfant ou vous n'êtes pas allergique au Sulfate d'abacavir et lamivudine, parlez-en avec votre professionnel de santé avant de reprendre le médicament ou de le redonner à votre enfant. La reprise de Sulfate d'abacavir et lamivudine peut provoquer une réaction allergique grave, voire mortelle, même si vous n'avez jamais eu de réaction allergique à ce médicament auparavant.

Si votre professionnel de santé vous indique que vous pouvez reprendre Sulfate d'abacavir et lamivudine ou le donner à nouveau à votre enfant, commencez le traitement lorsque votre enfant ou vous disposez d'une assistance médicale ou de personnes qui peuvent faire appel à un professionnel de santé si votre enfant ou vous en avez besoin.

2. Acidose lactique (accumulation d'acide dans le sang). Certains médicaments anti-virus de l'immunodéficience humaine (VIH), y compris Sulfate d'abacavir et lamivudine, peuvent provoquer une maladie rare mais grave appelée acidose lactique. L'acidose lactique est une urgence médicale grave qui peut entraîner la mort et doit être traitée à l'hôpital.

Appelez immédiatement votre professionnel de santé si vous ressentez l'un des signes ou symptômes suivants d'acidose lactique :

- Vous vous sentez très faible ou fatigué
- Vous avez des douleurs musculaires inhabituelles (anormales)
- Vous avez des difficultés à respirer
- Vous avez des maux d'estomac avec des nausées et des vomissements
- Vous avez froid, surtout au niveau des bras et des jambes
- Vous ressentez des vertiges ou vous vous sentez étourdi
- Vous avez un rythme cardiaque rapide ou irrégulier

3. Troubles hépatiques graves. Certaines personnes qui ont pris des médicaments comme Sulfate d'abacavir et lamivudine ont développé des troubles hépatiques graves appelés hépatotoxicité, avec l'élargissement du foie (hépatomégalie) et la présence de graisse dans le foie (stéatose). L'hépatomégalie avec stéatose est une urgence médicale grave qui peut causer la mort.

Appelez immédiatement votre professionnel de santé si vous ressentez l'un des signes ou symptômes suivants **de troubles hépatiques** :

- Votre peau ou le blanc de vos yeux devient jaune (jaunisse)
- Votre urine devient foncée
- Vos selles (excréments) deviennent de couleur claire
- Vous n'avez pas envie de manger de la nourriture pendant plusieurs jours, voire plus
- Vous ressentez des maux d'estomac (nausées)
- Vous ressentez une douleur au niveau de la zone inférieure de l'estomac (abdominale)

Vous pouvez être plus susceptibles d'avoir une acidose lactique ou des troubles hépatiques graves si vous êtes une femme, en surcharge pondérale ou si vous avez pris des analogues nucléosidiques pendant une longue période.

4. Utilisation avec des traitements à base d'interféron et de ribavirine. L'aggravation de la maladie hépatique (entraînant parfois la mort) s'est produite chez des patients infectés par le VIH et le virus de l'hépatite C, qui prennent des médicaments anti-VIH et sont également traités pour l'hépatite C par l'interféron avec ou sans ribavirine. Si vous ou votre enfant prenez Sulfate d'abacavir et lamivudine, y compris de l'interféron avec ou sans ribavirine et que vous ou votre enfant présentez des effets secondaires, n'oubliez pas de le signaler à votre professionnel de santé.

5. Si vous ou votre enfant souffrez d'une infection par le VIH et d'une infection par le virus de l'hépatite B, l'infection par le virus de l'hépatite B peut s'aggraver si vous ou votre enfant arrêtez de prendre Sulfate d'abacavir et lamivudine.

- Prendre ou donner Sulfate d'abacavir et lamivudine conformément à la prescription médicale.
- Veiller à ne pas manquer de Sulfate d'abacavir et lamivudine.
- Ne pas interrompre Sulfate d'abacavir et lamivudine sans en parler à votre professionnel de santé.
- Si vous arrêtez de prendre Sulfate d'abacavir et lamivudine, votre professionnel de santé doit surveiller votre santé et prescrire des analyses sanguines régulières pour vérifier votre foie.

Qu'est-ce que Sulfate d'abacavir et lamivudine comprimés pour suspension buvable ?

Sulfate d'abacavir et lamivudine comprimés pour suspension buvable contient 2 médicaments obtenus sur ordonnance, l'abacavir et la lamivudine, tous les deux utilisés pour le traitement de l'infection par le VIH. Ces deux médicaments sont appelés inhibiteurs nucléosidiques de la transcriptase inverse (INTI).

- **Sulfate d'abacavir et lamivudine ne guérit pas l'infection par le VIH ou le SIDA.**
- On ignore si Sulfate d'abacavir et lamivudine aidera votre enfant ou vous à vivre plus longtemps ou à connaître moins de problèmes médicaux que rencontrent les personnes vivants avec le VIH ou le SIDA.
- Il est très important de consulter votre professionnel de santé de manière régulière pendant que votre enfant ou vous prenez Sulfate d'abacavir et lamivudine.

Qui ne doit pas prendre Sulfate d'abacavir et lamivudine comprimés pour suspension buvable ?

Ne pas prendre Sulfate d'abacavir et lamivudine si vous ou votre enfant :

- **Etes allergique à l'abacavir ou l'un des composants de Sulfate d'abacavir et lamivudine. Voir la fin de ce guide de thérapeutique pour une liste complète des excipients contenus dans Sulfate d'abacavir et lamivudine.**
- **Avez des troubles hépatiques avérés.**

Que devrais-je mentionner à mon professionnel de santé avant de prendre ou de donner Sulfate d'abacavir et lamivudine comprimés pour suspension buvable?

Avant de prendre ou de donner Sulfate d'abacavir et lamivudine, signalez à votre professionnel de santé si votre enfant ou vous:

- **avez été testé et savez si oui ou non votre enfant ou vous avez une variation génétique particulière appelée HLA-B*5701.**
- **êtes enceinte ou prévoyez de tomber enceinte**. On ignore si Sulfate d'abacavir et lamivudine nuira à votre bébé à venir. Parlez à votre professionnel de santé si vous êtes enceinte ou prévoyez de tomber enceinte.

allaitez ou prévoyez d'allaiter. Sulfate d'abacavir et lamivudine peut passer dans le lait maternel. Vous ne devez pas allaiter si vous prenez Sulfate d'abacavir et lamivudine. Si vous êtes une femme qui a ou va avoir un bébé et sous traitement par Sulfate d'abacavir et lamivudine, parlez-en à votre professionnel quant à la meilleure façon de nourrir votre bébé. Les centres pour le contrôle et la prévention des maladies (CDC) recommandent aux mères infectées par le VIH de **ne pas** allaiter afin d'éviter le risque de transmission postnatale du VIH.

- **êtes atteint de l'infection par le virus de l'hépatite B ou avez d'autres troubles hépatiques.**
- **avez des problèmes rénaux.**

Informez votre professionnel de santé de tous les médicaments que vous prenez, y compris les médicaments obtenus sur ordonnance et sans ordonnance, les vitamines et les suppléments à base de plantes.

Dites surtout à votre professionnel de santé si vous ou votre enfant prenez :

- de l'alcool
- des médicaments utilisés pour le traitement des virus de l'hépatite tels que l'interféron ou la ribavirine.
- de la méthadone
- EPZICOM® (Sulfate d'abacavir et lamivudine)
- ATRIPLA® (Éfavirenz, emtricitabine, et ténofovir)
- COMBIVIR® (Lamivudine et zidovudine)
- EMTRIVA® (Emtricitabine)
- EPIVIR ou EPIVIR-HBV® (Lamivudine, 3TC)
- TRIZIVIR (Sulfate d'abacavir, lamivudine, et zidovudine)
- TRUVADA® (Emtricitabine et ténofovir)
- ZIAGEN (Sulfate d'abacavir)

Si vous n'êtes pas sûr de prendre un médicament énuméré ci-dessus, demandez à votre professionnel de santé.

Sulfate d'abacavir et lamivudine peut affecter la façon dont d'autres médicaments agissent, et d'autres médicaments peuvent affecter la façon dont Sulfate d'abacavir et lamivudine agit.

Gardez en mémoire les médicaments que vous prenez. Gardez-en une liste pour la présenter à votre médecin et votre pharmacien lorsqu'un nouveau médicament vous est prescrit.

Comment dois-je prendre ou donner à mon enfant Sulfate d'abacavir et lamivudine comprimés pour suspension buvable?

- **Prenez ou donnez sulfate d'abacavir et lamivudine exactement comme votre professionnel de santé vous dit de le prendre ou de le donner.**
- Le professionnel de santé vous indiquera la dose appropriée à prendre ou à donner à votre enfant. La dose de votre enfant dépendra de son poids. Pour les très jeunes enfants qui ne peuvent pas avaler les comprimés, la procédure suivante peut être utilisée

Méthode de préparation :

1. Placer le(s) comprimé (s) dans un flacon et ajouter deux cuillères à café (10 ml) d›eau potable par comprimé.
2. Agiter le flacon jusqu'à ce que le(s) comprimé(s) se décompose(nt) en petits morceaux pour que l'enfant puisse avaler. Une cuillère peut être utilisée pour écraser les morceaux, si nécessaire.
3. Boire le mélange dans l'heure qui suit la préparation du mélange.
4. Rincer le flacon avec une petite quantité supplémentaire d'eau et boire le contenu pour s'assurer que la dose entière est prise.

NE PAS MÉLANGER SULFATE D'ABACAVIR ET LAMIVUDINCOMPRIMÉS POUR SUSPENSION BUVABLE AVEC TOUT LIQUIDE AUTRE QUE L'EAU.

- Les enfants plus âgés, qui peuvent avaler des comprimés de manière fiable, peuvent recevoir la dose appropriée à avaler (voir Tableau 1).

Tableau 1. Recommandations posologiques de Sulfate d'abacavir et lamivudine comprimés pour suspension buvable chez les patients pédiatriques

Poids (Kg)	Schéma posologique utilisant Sulfate d'abacavir et lamivudine comprimés sécables pour suspension buvable 60 mg/30 mg		Dose quotidienne totale (mg)
	Dose du matin (mg)	Dose du soir (mg)	
5	½ comprimé (30 mg A/15 mg L)	1 comprimé (60 mg A/30 mg L)	90A/45L
6 - < 9	1 comprimé (60 mg A/30 mg L)	1 comprimé (60 mg A/30 mg L)	120A/60L
9 - < 12	1,5 comprimé 90 mg A/45 mg L)	1,5 comprimé 90 mg A/45 mg L)	180A/90L
12 - < 17	2 comprimés (120 mg A/60 mg L)	2 comprimés (120 mg A/60 mg L)	240A/120L
17 - < 20	2,5 comprimés (150 mg A/75 mg L)	2,5 comprimés (150 mg A/75 mg L)	300A/150L
20 - < 25	3 comprimés (180 mg A/90 mg L)	3 comprimés (180 mg A/90 mg L)	360A/180L
25 - < 29	3,5 comprimés (210 mg A/105 mg L)	3,5 comprimés (210 mg A/105 mg L)	420A/210L
29 - < 35	4 comprimés (240 mg A/120 mg L)	4 comprimés (240 mg A/120 mg L)	480A/240L
≥35	5 comprimés (300 mg A/150 mg L)[a]	5 comprimés (300 mg A/150 mg L)[a]	600A/300L

A= Sulfate d'abacavir; L= Lamivudine

[a]= Pour les doses recommandées d'abacavir 300 mg deux fois par jour et de lamivudine 150 mg deux fois par jour (dose quotidienne maximale adulte), les formulations pour adultes (comprimé de 300 mg d'abacavir et comprimé de 150 mg de lamivudine) peuvent être utilisées.

- Ne pas sauter les doses.
- Prendre ou donner Sulfate d'abacavir et lamivudine à jeun.
- **Veillez à ne pas manquer de Sulfate d'abacavir et de lamivudine.**

Si votre enfant ou vous arrêtez les médicaments anti-VIH, même pour un court laps de temps, la quantité de virus dans le sang peut augmenter et le virus peut devenir plus difficile à traiter. Si votre enfant ou vous prenez trop de Sulfate d'abacavir et lamivudine, appelez votre professionnel de santé ou un centre antipoison ou rendez-vous aux urgences de l'hôpital le plus proche.

Quels sont les effets secondaires possibles de Sulfate d'abacavir et lamivudine comprimés pour suspension buvable?

- **Sulfate d'abacavir et lamivudine peut provoquer des effets secondaires graves, notamment des réactions allergiques, l'acidose lactique, et des troubles hépatiques. Voir "Quelles sont les informations les plus importantes que je dois connaître à propos de Sulfate d'abacavir et lamivudine comprimés pour suspension buvable?"**
- **Changements dans le système immunitaire (syndrome de reconstitution immunitaire).** Votre système immunitaire et celui de votre enfant peuvent devenir plus forts et commencer à combattre les infections dissimulées dans votre corps ou celui de votre enfant pendant une longue période. Signalez à votre professionnel de santé si vous ou votre enfant commencez à ressentir de nouveaux symptômes ou des symptômes s'aggravant d'une infection après que vous ou votre enfant ayez commencé la prise de Sulfate d'abacavir et lamivudine.
- **Modifications des graisses corporelles (redistribution des graisses).** Les modifications des **graisses corporelles** (lipoatrophie ou lipodystrophie) peuvent se produire chez certaines personnes prenant des médicaments antirétroviraux, y compris Sulfate d'abacavir et lamivudine Les modifications peuvent comprendre :
  - plus de graisse au niveau ou autour de votre tronc, du haut du dos et de la nuque (bosse de bison), des seins ou de la poitrine
  - perte de graisse dans les jambes, les bras ou le visage
- **Crise cardiaque (infarctus du myocarde).** Certains médicaments anti-VIH, y compris le sulfate d'abacavir et la lamivudine peuvent augmenter votre risque de crise cardiaque.

Les effets secondaires les plus fréquents de Sulfate d'abacavir et lamivudine incluent :

- troubles du sommeil
- dépression
- maux de tête
- fatigue
- étourdissements
- nausées
- diarrhée
- éruption cutanée
- fièvre
- toux
- infections de l'oreille, du nez et de la gorge

Informez votre professionnel de santé si vous ou votre enfant présentez un effet secondaire qui vous tracasse ou qui ne s'estompe pas. Il ne s'agit pas d'une liste exhaustive des effets secondaires possibles de Sulfate d'abacavir et lamivudine. Pour plus d'informations, adressez-vous à votre professionnel de santé ou votre pharmacien.

Appelez votre professionnel de santé pour un conseil médical relatif aux effets secondaires.

Comment dois-je conserver Sulfate d'abacavir et lamivudine comprimés pour suspension buvable?

Conserver les comprimés de Sulfate d'abacavir et lamivudine à une température de 25°C (77 ° F); limites permises de 15° à 30°C (59° à 86°F) [Voir Température ambiante contrôlée de l'USP].

Garder Sulfate d'abacavir et lamivudine et tous les médicaments hors de la portée des enfants

Informations générales pour une utilisation sûre et efficace de Sulfate d'abacavir et lamivudine comprimés pour suspension buvable

Sulfate d'abacavir et lamivudine ne vous empêche pas ou votre enfant de transmettre le VIH à d'autres personnes par voie sexuelle, partage de seringues, ou en étant exposé à votre sang ou celui de votre enfant.

Discutez avec votre professionnel de santé des pratiques sexuelles sans risque qui protègent votre partenaire. Ne partagez jamais les seringues. Ne partagez pas vos effets personnels qui peuvent contenir du sang ou des fluides corporels, comme les brosses à dents ou les lames de rasoir.

Les médicaments sont quelquefois prescrits à des fins autres que ceux énumérés dans un Guide de thérapeutique. N'utilisez pas Sulfate d'abacavir et lamivudine pour une maladie autre que ce pourquoi il a été prescrit. Ne donnez pas Sulfate d'abacavir et lamivudine à d'autres personnes, même si elles présentent les mêmes symptômes que vous. Il pourrait leur être nocif.

Ce guide de thérapeutique résume les informations les plus importantes concernant Sulfate d'abacavir et lamivudine. Pour de plus amples informations, discutez-en avec votre professionnel de santé. Vous pouvez demander à votre professionnel de santé ou votre pharmacien des informations sur Sulfate d'abacavir et lamivudine qui sont rédigées pour les professionnels de santé.

Quels sont les composants contenus dans Sulfate d'abacavir et lamivudine comprimés pour suspension buvable?

Composants actifs : Sulfate d'abacavir et lamivudine.

Composants inactifs: cellulose microcristalline, glycolate d'amidon sodique, hypromellose, amidon de maïs, crème de fraise (PHS132963), aspartame, dioxyde de silicium colloïdal, stéarate de magnésium et eau purifiée.

Les autres marques mentionnées sont des marques déposées de leurs propriétaires respectifs et ne sont pas de Cipla Ltd.

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