

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Abacavir and Lamivudine Tablets for Oral Suspension safely and effectively. See full prescribing information for Abacavir and Lamivudine Tablets for Oral Suspension.

### Abacavir and Lamivudine Tablets for Oral Suspension 120 mg/60 mg

#### WARNINGS: HYPERSENSITIVITY REACTIONS AND EXACERBATIONS OF HEPATITIS B

See full prescribing information for complete boxed warning.

##### Hypersensitivity Reactions

- Serious and sometimes fatal hypersensitivity reactions have occurred 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 higher risk of experiencing a hypersensitivity reaction to abacavir. (5.1)
- Abacavir and lamivudine Tablet for Oral Suspension is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B\*5701-positive patients. (4)
- Discontinue abacavir and lamivudine as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B\*5701 status, permanently discontinue abacavir 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 and lamivudine or any other abacavir-containing product. (5.1)

##### 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, a component of abacavir and lamivudine. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.2)

#### INDICATIONS AND USAGE

Abacavir 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

- Before initiating abacavir and lamivudine tablets for oral suspension, screen for the HLA-B\*5701 allele

- Pediatric patients 3 months and older: Dosage should be based on body weight. (2.1)
- Do not prescribe for patients requiring a dosage adjustment or patients with hepatic impairment. (2.2)

#### DOSAGE FORMS AND STRENGTHS

Tablets for oral suspension contain 120 mg of abacavir and 60 mg of lamivudine with functional scoring. (3)

#### CONTRAINDICATIONS

- Prior hypersensitivity reaction to abacavir or lamivudine (4, 5.1)
- Presence of HLA-B\*5701 allele. (4)
- Moderate or severe Hepatic impairment. (4)

#### WARNINGS AND PRECAUTIONS

- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. (5.3)
- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. (5.4)
- .
- Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue treatment as clinically appropriate. (5.6)
- Inform patients with phenylketonuria that abacavir and lamivudine contain phenylalanine, a component of aspartame (5.7)

#### ADVERSE REACTIONS

- Abacavir and lamivudine: The most commonly reported adverse reactions of at least moderate intensity (incidence >5%) in an adult HIV-1 clinical trial 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 trials 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 1-866-604-3268 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

- Methadone: An increased methadone dose may be required in a small number of patients. (7.1)
- Sorbitol: Coadministration of lamivudine and sorbitol may decrease lamivudine concentrations; when possible, avoid chronic coadministration. (7.2)
- Riociguat: The riociguat dose may need to be reduced. (7.3)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE.

Revised: 8/2021

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### WARNING: HYPERSENSITIVITY REACTIONS AND EXACERBATIONS OF HEPATITIS B

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Pediatric Patients

2.2 Dose Adjustment

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reaction

5.2 Patients With Hepatitis B Virus Co-Infection

5.3 Lactic Acidosis/Severe Hepatomegaly With Steatosis

5.4 Immune Reconstitution Syndrome

5.5 Myocardial Infarction

5.6 Pancreatitis

5.7 Risks in Patients with Phenylketonuria

#### 6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Post-marketing Experience

#### 7 DRUG INTERACTIONS

7.1 Methadone

7.2 Sorbitol

7.3 Riociguat

- 8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.6 Patients With Impaired Renal Function
- 8.7 Patients With Impaired Hepatic Function

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics
- 12.4 Microbiology

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 Adults
- 14.2 Pediatrics Patients

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

## FULL PRESCRIBING INFORMATION

### **WARNINGS: HYPERSENSITIVITY REACTIONS AND EXACERBATIONS OF HEPATITIS B**

#### **HYPERSENSITIVITY REACTIONS**

**SERIOUS AND SOMETIMES FATAL HYPERSENSITIVITY REACTIONS, WITH MULTIPLE ORGAN INVOLVEMENT, HAVE OCCURRED WITH ABACAVIR, A COMPONENT OF ABACAVIR AND LAMIVUDINE TABLETS FOR ORAL SUSPENSION. PATIENTS WHO CARRY THE HLA-B\*5701 ALLELE ARE AT A HIGHER RISK OF A HYPERSENSITIVITY REACTION TO ABACAVIR; ALTHOUGH, HYPERSENSITIVITY REACTIONS HAVE OCCURRED IN PATIENTS WHO DO NOT CARRY THE HLA-B\*5701 ALLELE [SEE WARNINGS AND PRECAUTIONS (5.1)]. ABACAVIR AND LAMIVUDINE IS CONTRAINDICATED IN PATIENTS WITH A PRIOR HYPERSENSITIVITY REACTION TO ABACAVIR AND IN HLA-B\*5701-POSITIVE PATIENTS [SEE CONTRAINDICATIONS (4), WARNINGS AND PRECAUTIONS (5.1)]. ALL PATIENTS SHOULD BE SCREENED FOR THE HLA-B\*5701 ALLELE PRIOR TO INITIATING THERAPY WITH ABACAVIR AND LAMIVUDINE OR REINITIATION OF THERAPY WITH ABACAVIR AND LAMIVUDINE, UNLESS PATIENTS HAVE A PREVIOUSLY DOCUMENTED HLA-B\*5701 ALLELE ASSESSMENT. DISCONTINUE ABACAVIR AND LAMIVUDINE IMMEDIATELY IF A HYPERSENSITIVITY REACTION IS SUSPECTED, REGARDLESS OF HLA-B\*5701 STATUS AND 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, INCLUDING DEATH, CAN OCCUR WITHIN HOURS. SIMILAR SEVERE REACTIONS HAVE ALSO OCCURRED RARELY FOLLOWING THE REINTRODUCTION OF ABACAVIR-CONTAINING PRODUCTS IN PATIENTS WHO HAVE NO HISTORY OF ABACAVIR HYPERSENSITIVITY [SEE WARNINGS AND PRECAUTIONS (5.1)].**

## **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, A 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 (5.2)].**

## **1 INDICATIONS AND USAGE**

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

## **2 DOSAGE AND ADMINISTRATION**

- Screen for the HLA-B\*5701 allele prior to initiating therapy with abacavir and lamivudine [see *Boxed Warning, Warnings and Precautions (5.1)*].
- Abacavir and Lamivudine Tablets for Oral Suspension should be taken without food.

### **2.1 Recommended Dosage for Pediatric Patients**

The recommended oral once daily dosing regimen of abacavir and lamivudine in HIV-1-infected pediatric patients 3 months and older and weighing at least 6 kg is provided in Table 1.

**Table 1. Dosing Recommendations for Abacavir and Lamivudine Scored Tablets for Oral Suspension, 120 mg/60 mg**

<b>Weight (kg)</b>	<b>Once-daily Dosing Regimen<sup>a</sup></b>	<b>Total Daily Dose (mg)</b>
6 to less than 9	1 tablet (120 mg A/60 mg L)	120A/60L
9 to less than 12	1 ½ tablets (180 mg A/90 mg L)	180A/90L
12 to less than 17	2 tablets (240 mg A/120 mg L)	240A/120L
17 to less than 20	2 ½ tablets (300 mg A/150 mg L)	300A/150L
20 to less than 25	3 tablets (360 mg A/180 mg L)	360A/180L
25 to less than 29	3 ½ tablets (420 mg A/210 mg L)	420A/210L
29 to less than 35	4 tablets (480 mg A/240 mg L)	480A/240L
35 and greater	5 tablets (600 mg A/300 mg L) <sup>b</sup>	600A/300L

A= abacavir; L= lamivudine

<sup>a</sup> Data regarding the efficacy of once-daily dosing is limited to subjects who transitioned from twice-daily dosing to once-daily dosing after 36 weeks of treatment [see *Clinical Studies (14.2)*].

<sup>b</sup> For recommended dose of abacavir 600 mg once-daily and lamivudine 300 mg once-daily (adult maximum daily dose), the adult fixed-dose combination (abacavir and lamivudine tablets, 600 mg/300 mg) can be used.

## **Method of Preparation**

For children unable to swallow tablets, dispersion can be prepared by dispensing required number of tablets for oral suspension in water, the following procedure can be used:

1. Place the tablet(s) for oral suspension in a container and add two teaspoonful (10 mL) of drinking water per tablet.
2. Swirl the container until the tablet(s) for oral suspension 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 AND LAMIVUDINE TABLETS FOR ORAL SUSPENSION WITH ANY LIQUID OTHER THAN WATER.**

## **2.2 Dose Adjustment**

Because Abacavir 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 and lamivudine tablets for oral suspension contain 120 mg of abacavir equivalent to 140.6 mg of abacavir sulfate and 60 mg of lamivudine. The tablets are white to off white, capsule shaped biconvex, uncoated tablet debossed with 'CJ' on one side and with a functional scoreline on other side.

## **4 CONTRAINDICATIONS**

Abacavir and Lamivudine Tablets for Oral Suspension are contraindicated in patients:

- who have the HLA-B\*5701 allele [*see Warnings and Precautions (5.1)*].
- with prior hypersensitivity reaction to abacavir or lamivudine [*see Warnings and Precautions (5.1)*].
- with moderate or severe hepatic impairment [*see Use in Specific Populations (8.7)*].

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Hypersensitivity Reaction**

Serious and sometimes fatal hypersensitivity reactions have occurred with abacavir. These hypersensitivity reactions have included multi-organ failure and anaphylaxis and typically occurred within the first 6 weeks of treatment with abacavir (median time to onset was 9 days); although abacavir hypersensitivity reactions have occurred any time during treatment [*see Adverse Reactions (6.1)*]. Patients who carry the HLA-B\*5701 allele are at a higher risk of abacavir hypersensitivity reactions; although, patients who do not carry the HLA-B\*5701 allele have developed hypersensitivity reactions.

Hypersensitivity to abacavir was reported in approximately 206 (8%) of 2,670 patients in 9 clinical trials with abacavir-containing products where HLA-B\*5701 screening was not performed. The incidence of suspected abacavir hypersensitivity reactions in clinical trials was 1% when subjects carrying the HLA-B\*5701 allele were excluded. In any patient treated with abacavir, the clinical diagnosis of hypersensitivity reaction must remain the basis of clinical decision making.

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

- All patients should be screened for the HLA-B\*5701 allele prior to initiating therapy with abacavir and lamivudine or reinitiation of therapy with abacavir and lamivudine, unless patients have a previously documented HLA-B\*5701 allele assessment.
- Abacavir and lamivudine tablets for oral suspension is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B\*5701-positive patients.
- Before starting abacavir and lamivudine, review medical history for prior exposure to any abacavir containing product. NEVER restart abacavir and lamivudine or any other abacavir-containing product following a hypersensitivity reaction to abacavir, regardless of HLA-B\*5701 status.
- To reduce the risk of a life-threatening hypersensitivity reaction, regardless of HLA-B\*5701 status, discontinue abacavir and lamivudine immediately if a hypersensitivity reaction is suspected, even when other diagnoses are possible (e.g. acute onset respiratory diseases such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions to other medications).
- If a hypersensitivity reaction cannot be ruled out, do not restart abacavir and lamivudine or any other abacavir-containing products because more severe symptoms, which may include life-threatening hypotension and death, can occur within hours.
- If a hypersensitivity reaction is ruled out, patients may restart abacavir and lamivudine. Rarely, patients who have stopped abacavir for reasons other than symptoms of hypersensitivity have also experienced life-threatening reactions within hours of reinitiating abacavir therapy. Therefore, reintroduction of abacavir and lamivudine or any other abacavir-containing product is recommended only if medical care can be readily accessed.
- A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill.

## **5.2 Patients With Hepatitis B Virus Co-Infection**

**Post-treatment Exacerbations of Hepatitis:** 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 postmarketing 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.

**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. 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.

### **5.3 Lactic Acidosis and Severe Hepatomegaly with Steatosis**

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues, including abacavir and lamivudine. A majority of these cases have been in women. Female sex and obesity may be risk factors for the development of lactic acidosis and severe hepatomegaly with steatosis in patients treated with antiretroviral nucleoside analogues. See full prescribing information for abacavir and lamivudine. 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.

### **5.4 Immune Reconstitution Syndrome**

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

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barre syndrome) have been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.

### **5.5 Myocardial Infarction**

Several prospective, observational, epidemiological studies have reported an association with the use of abacavir and the risk of myocardial infarction (MI). Meta-analyses of randomized, controlled clinical trials have observed no excess risk of MI in abacavir-treated subjects as compared with control subjects. To date, there is no established biological mechanism to explain the potential increase in risk. In totality, the available data from the observational studies and from controlled clinical trials show inconsistency; therefore, evidence for a causal relationship between abacavir treatment and the risk of MI is inconclusive. As a precaution, the underlying risk of coronary heart disease should be considered when prescribing antiretroviral therapies,

including abacavir, and action taken to minimize all modifiable risk factors (e.g., hypertension, hyperlipidemia, diabetes mellitus, smoking).

### **5.6 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, one component of abacavir and lamivudine tablets for oral suspension, should be used with caution. Treatment with abacavir and lamivudine tablets for oral suspension should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur [*see Adverse Reactions (6.1)*].

### **5.7 Risks in Patients with Phenylketonuria**

Phenylalanine can be harmful to patients with phenylketonuria (PKU). Abacavir and lamivudine tablets for oral suspension contains phenylalanine, a component of aspartame. Each 120/60mg tablet contains 6.7 mg of phenylalanine. Before prescribing abacavir and lamivudine tablets for oral suspension in a patient with PKU, consider the combined daily amount of phenylalanine from all sources, including the daily dose of abacavir and lamivudine tablets for oral suspension.

## **6 ADVERSE REACTIONS**

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

- Serious and sometimes fatal hypersensitivity reactions [*see Boxed Warning, Warnings and Precautions (5.1)*].
- Exacerbations of hepatitis B [*see Boxed Warning, Warnings and Precautions (5.2)*].
- Lactic acidosis and severe hepatomegaly [*see Boxed Warning, Warnings and Precautions (5.3)*].
- Immune reconstitution syndrome [*see Warnings and Precautions (5.4)*].
- Myocardial infarction [*see Warnings and Precautions (5.5)*].
- Pancreatitis [*see Warnings and Precautions (5.6)*].

### **6.1 Clinical Trials Experience**

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

#### **Serious and Fatal Abacavir-associated Hypersensitivity Reactions**

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

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

### Abacavir and lamivudine

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

**Table 2. Treatment-emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2-4, Greater than or Equal to 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)
<b>Drug hypersensitivity<sup>a,b</sup></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 <sup>a</sup>	5%	6%
Rash	5%	5%
Pyrexia	5%	3%
Abdominal pain/gastritis	4%	5%
Abnormal dreams	4%	5%
Anxiety	3%	5%

<sup>a</sup> 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.

- <sup>b</sup> CNA30024 was a multi-center, double-blind, controlled trial in which 649 HIV-1-infected, therapy-naïve adults were randomized and received either abacavir (300 mg twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once daily); or zidovudine (300 mg twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once daily). CNA30024 used double-blind ascertainment of suspected hypersensitivity reactions. During the blinded portion of the trial, suspected hypersensitivity to abacavir was reported by investigators in 9% of 324 subjects in the abacavir group and 3% of 325 subjects in the zidovudine group.

**Laboratory Abnormalities:** Laboratory abnormalities observed in clinical trials of abacavir 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 CNA30021.

## **Abacavir and Lamivudine**

### **Pediatric Patients:**

The safety of once-daily compared with twice-daily dosing of abacavir and lamivudine, administered as either single products or as a combination, was assessed in the ARROW trial (n = 336). Primary safety assessment in the ARROW (COL105677) trial was based on Grade 3 and Grade 4 adverse events. The frequency of Grade 3 and 4 adverse events was similar among subjects randomized to once-daily dosing compared with subjects randomized to twice-daily dosing. One event of Grade 4 hepatitis in the once-daily cohort was considered as uncertain causality by the investigator and all other Grade 3 or 4 adverse events were considered not related by the investigator. No additional safety issues were identified in pediatric subjects receiving abacavir and lamivudine once-daily compared with historical data in adults [*see Adverse Reactions (6.1)*].

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

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

(NUCA2002), 14 subjects (14%) developed pancreatitis while receiving monotherapy with lamivudine. Three of these subjects died of complications of pancreatitis. In a second open-label trial (NUCA2005), 12 subjects (18%) developed pancreatitis. In trial ACTG300, pancreatitis was not observed in 236 subjects randomized to lamivudine plus zidovudine. Pancreatitis was observed in 1 subject in this trial who received open-label lamivudine in combination with zidovudine and ritonavir following discontinuation of didanosine monotherapy [see *Warnings and Precautions* (5.6)].

***Paresthesias and Peripheral Neuropathies:*** Paresthesias and peripheral neuropathies were reported in 15 subjects (15%) in trial NUCA2002, 6 subjects (9%) in NUCA2005, and 2 subjects (<1%) in ACTG300.

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

## **6.2 Postmarketing Experience**

The following adverse reactions have been identified during postmarketing use. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

### ***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 [see *Adverse Reactions* (6.1)].

### ***Abacavir and Lamivudine:***

**Body as a Whole:** Redistribution/accumulation of body fat.

**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* (5.3)], post treatment exacerbation of hepatitis B [see *Warnings and Precautions* (5.2)].

**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

Drug interaction trials have been conducted with abacavir and lamivudine, the individual components of Abacavir and Lamivudine Tablets for Oral Suspension [see *Clinical Pharmacology* (12.3)].

### 7.1 Methadone

In a trial 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.

### 7.2 Sorbitol

Coadministration of single doses of lamivudine and sorbitol resulted in a sorbitol dose-dependent reduction in lamivudine exposures. When possible, avoid use of sorbitol-containing medicines with lamivudine-containing medicines [see *Clinical Pharmacology* (12.3)].

### 7.3 Riociguat

Coadministration with fixed-dose abacavir/dolutegravir/lamivudine resulted in increased riociguat exposure, which may increase the risk of riociguat adverse reactions [see *Clinical Pharmacology* (12.3)]. The riociguat dose may need to be reduced. See full prescribing information for riociguat.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Available data from the Antiretroviral Pregnancy Registry (APR) show no difference in the overall risk of birth defects for abacavir or lamivudine compared with the background rate for birth defects of 2.7% in the Metropolitan Atlanta Congenital Defects Program

(MACDP) reference population [see Data]. The APR uses the MACDP as the U.S. reference population for birth defects in the general population. The MACDP evaluates women and infants from a limited geographic area and does not include outcomes for births that occurred at less than 20 weeks' gestation. The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15% to 20%. The background risk for major birth defects and miscarriage for the indicated population is unknown.

In animal reproduction studies, oral administration of abacavir to pregnant rats during organogenesis resulted in fetal malformations and other embryonic and fetal toxicities at exposures 35 times the human exposure (AUC) at the recommended clinical daily dose. However, no adverse developmental effects were observed following oral administration of abacavir to pregnant rabbits during organogenesis, at exposures approximately 9 times the human exposure (AUC) at the recommended clinical dose. Oral administration of lamivudine to pregnant rabbits during organogenesis resulted in embryoletality at systemic exposure (AUC) similar to the recommended clinical dose; however, no adverse development effects were observed with oral administration of lamivudine to pregnant rats during organogenesis at plasma concentrations ( $C_{max}$ ) 35 times the recommended clinical dose (see Data).

#### Data

*Human Data: Abacavir:* Based on prospective reports to the APR of exposures to abacavir during pregnancy resulting in live births (including over 1,300 exposed in the first trimester and over 1,300 exposed in the second/third trimester), there was no difference between the overall risk of birth defects for abacavir compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of defects in live births was 3.2% (95% CI: 2.3% to 4.3%) following first trimester exposure to abacavir-containing regimens and 2.9% (95% CI: 2.1% to 4.0%) following second/third trimester exposure to abacavir-containing regimens.

Abacavir has been shown to cross the placenta and concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery [see *Clinical Pharmacology* (12.3)].

*Lamivudine:* Based on prospective reports to the APR of exposures to lamivudine during pregnancy resulting in live births (including over 5,300 exposed in the first trimester and over 7,400 exposed in the second/third trimester), there was no difference between the overall risk of birth defects for lamivudine compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of birth defects in live births was 3.1% (95% CI: 2.7% to 3.6%) following first trimester exposure to lamivudine-containing regimens and 2.9% (95% CI: 2.5%, 3.3%) following second/third trimester exposure to lamivudine containing regimens.

Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical trials conducted in South Africa. The trials assessed pharmacokinetics in 16 women at 36 weeks gestation using 150 mg lamivudine twice daily with zidovudine, 10 women at 38 weeks gestation using 150 mg lamivudine twice daily with zidovudine, and 10 women at 38 weeks gestation using lamivudine 300 mg twice daily without other antiretrovirals.

These trials were not designed or powered to provide efficacy information. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, amniotic fluid specimens were collected following natural rupture of membranes and confirmed that lamivudine crosses the placenta in humans. Based on limited data at delivery, median (range) amniotic fluid concentrations of lamivudine were 3.9 (1.2 to 12.8)–fold greater compared with paired maternal serum concentration (n = 8).

#### Animal Data:

**Abacavir:** Abacavir was administered orally to pregnant rats (at 100, 300, and 1,000 mg per kg per day) and rabbits (at 125, 350, or 700 mg per kg per day) during organogenesis (on Gestation Days 6 through 17 and 6 through 20, respectively). Fetal malformations (increased incidences of fetal anasarca and skeletal malformations) or developmental toxicity (decreased fetal body weight and crown-rump length) were observed in rats at doses up to 1,000 mg per kg per day, resulting in exposures approximately 35 times the human exposure (AUC) at the recommended daily dose. No developmental effects were observed in rats at 100 mg per kg per day, resulting in exposures (AUC) 3.5 times the human exposure at the recommended daily dose. In a fertility and early embryo-fetal development study conducted in rats (at 60, 160, or 500 mg per kg per day), embryonic and fetal toxicities (increased resorptions, decreased fetal body weights) or toxicities to the offspring (increased incidence of stillbirth and lower body weights) occurred at doses up to 500 mg per kg per day. No developmental effects were observed in rats at 60 mg per kg per day, resulting in exposures (AUC) approximately 4 times the human exposure at the recommended daily dose. Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. In pregnant rabbits, no developmental toxicities and no increases in fetal malformations occurred at up to the highest dose evaluated, resulting in exposures (AUC) approximately 9 times the human exposure at the recommended dose.

**Lamivudine:** Lamivudine was administered orally to pregnant rats (at 90, 600, and 4,000 mg per kg per day) and rabbits (at 90, 300 and 1,000 mg per kg per day and at 15, 40, and 90 mg per kg per day) during organogenesis (on Gestation Days 7 through 16 [rat] and 8 through 20 [rabbit]). No evidence of fetal malformations due to lamivudine was observed in rats and rabbits at doses producing plasma concentrations ( $C_{\max}$ ) approximately 35 times higher than human exposure at the recommended daily dose. Evidence of early embryoletality was seen in the rabbit at systemic exposures (AUC) similar to those observed in humans, but there was no indication of this effect in the rat at plasma concentrations ( $C_{\max}$ ) 35 times higher than human exposure at the recommended daily dose. Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. In the fertility/pre- and postnatal development study in rats, lamivudine was administered orally at doses of 180, 900, and 4,000 mg per kg per day from prior to mating through postnatal Day 20). In the study, development of the offspring, including fertility and reproductive performance, were not affected by the maternal administration of lamivudine.

## 8.2 Lactation

### Risk Summary

The Centers for Disease Control and Prevention recommends that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Abacavir and lamivudine are present in human milk. There is no information on the effects of abacavir and lamivudine on the breastfed infant or the effects of the drug on milk production. Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving abacavir and lamivudine.

### 8.4 Pediatric Use

**Abacavir:** The safety and effectiveness of abacavir has 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)*].

### 8.6 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.

### 8.7 Patients With Impaired Hepatic Function

Abacavir and Lamivudine are contraindicated for patients with hepatic impairment because abacavir 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

There is no known specific treatment for overdose with abacavir and lamivudine tablets for oral suspension. If overdose occurs, the patient should be monitored, and standard supportive treatment applied as required.

**Abacavir:** It is not known whether abacavir can be removed by peritoneal dialysis or hemodialysis.

**Lamivudine:** Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event.

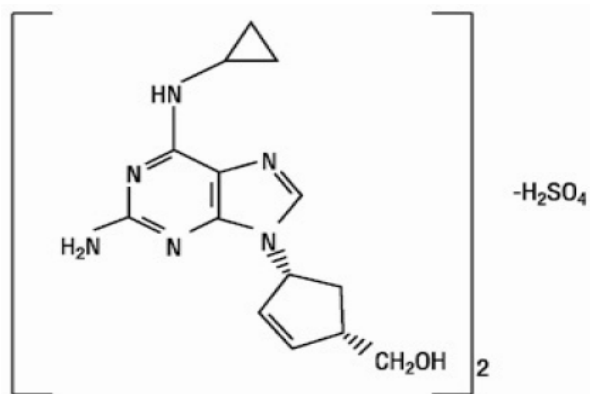
## 11 DESCRIPTION

Abacavir and lamivudine tablet for oral suspension 120 mg/60 mg contain the following two synthetic nucleoside analogues: abacavir and lamivudine with inhibitory activity against HIV-1.

Abacavir and lamivudine tablets are for oral administration. Each uncoated tablet contains the active ingredients 120 mg of abacavir equivalent to 140.6 mg of abacavir sulfate and 60 mg lamivudine and the inactive ingredients microcrystalline cellulose (Avicel PH 101), sodium starch glycolate, hypromellose, microcrystalline cellulose (Avicel PH 102), corn starch, strawberry cream flavour permaseal (PHS-132963), aspartame, colloidal silicon dioxide, magnesium stearate.

### Abacavir Sulfate Drug Substance

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



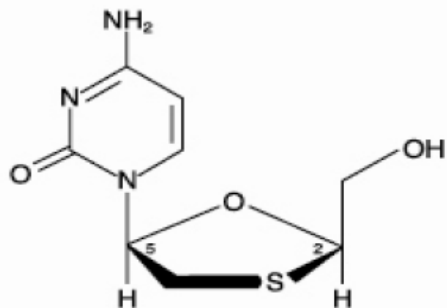
Abacavir sulfate is a white to off-white solid and is soluble in water.

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

### Lamivudine

The chemical name of lamivudine is (2*R*,*cis*)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1*H*)-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 g per mol. It has a structural formula:



Lamivudine is a white to off-white crystalline solid and is soluble in water.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Abacavir and Lamivudine are antiretroviral drugs (*see Microbiology* (12.4)).

### 12.3 Pharmacokinetics

#### Pharmacokinetics in Adults

***Abacavir and Lamivudine Tablets for Oral Suspension:*** Abacavir 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 combination tablets for oral suspension (120 mg/60 mg) is dose proportional formulation to the lower strength i.e. Abacavir and lamivudine tablets for oral suspension (60 mg/30 mg)

***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  $4.26 \pm 1.19$  mcg/mL (mean  $\pm$  SD) and  $AUC_{\infty}$  was  $11.95 \pm 2.51$  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  $2.04 \pm 0.54$  mcg/mL (mean  $\pm$  SD) and the 24-hour steady-state AUC ( $AUC_{24,ss}$ ) was  $8.87 \pm 1.83$  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).

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 3.

**Table 3. Pharmacokinetic Parameters<sup>a</sup> for Abacavir and Lamivudine in Adults**

Parameter	Abacavir		Lamivudine	
Oral bioavailability (%)	$86 \pm 25$	n = 6	$86 \pm 16$	n = 12
Apparent volume of distribution (L/kg)	$0.86 \pm 0.15$	n = 6	$1.3 \pm 0.4$	n = 20
Systemic clearance (L/hr/kg)	$0.80 \pm 0.24$	n = 6	$0.33 \pm 0.06$	n = 20
Renal clearance (L/hr/kg)	$0.007 \pm 0.008$	n = 6	$0.22 \pm 0.06$	n = 20
Elimination half-life (hr)	$1.45 \pm 0.32$	n = 20	13 to 19 <sup>b</sup>	

<sup>a</sup> Data presented as mean  $\pm$  standard deviation except where noted.

<sup>b</sup> Approximate range.

**Effect of Food on Absorption of Abacavir and Lamivudine:** The effect of food on abacavir and lamivudine tablets for oral suspension was not determined; therefore, this product must be administered on an empty stomach.

### **Specific Populations:**

***Patients with Renal Impairment:*** The effect of renal impairment on the combination of abacavir and lamivudine has not been evaluated (see U.S. prescribing information for the individual abacavir and lamivudine components).

***Patients with Hepatic Impairment:*** The effect of hepatic impairment on the combination of abacavir and lamivudine has not been evaluated (see U.S. prescribing information for the individual abacavir and lamivudine components).

***Pregnant Women:*** Abacavir: Abacavir pharmacokinetics were studied in 25 pregnant women during the last trimester of pregnancy receiving abacavir 300 mg twice daily. Abacavir exposure (AUC) during pregnancy was similar to those in postpartum and in HIV-infected non-pregnant historical controls. Consistent with passive diffusion of abacavir across the placenta, abacavir concentrations in neonatal plasma cord samples at birth were essentially equal to those in maternal plasma at delivery.

**Lamivudine:** Lamivudine pharmacokinetics were studied in 36 pregnant women during 2 clinical trials conducted in South Africa. Lamivudine pharmacokinetics in pregnant women were similar to those seen in non-pregnant adults and in postpartum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples.

### ***Pediatric Patients***

**Abacavir:** The pharmacokinetics of abacavir have been studied after either single or repeat doses of abacavir in 169 pediatric subjects. Subjects receiving abacavir oral solution according to the recommended dosage regimen achieved plasma concentrations of abacavir similar to adults.

**Lamivudine:** The pharmacokinetics of lamivudine have been studied in 210 pediatric subjects. The absolute bioavailability of both lamivudine tablets and oral solution are lower in children than adults. The relative bioavailability of lamivudine oral solution is approximately 40% lower than tablets containing lamivudine in pediatric subjects despite no difference in adults. The mechanisms for the diminished absolute bioavailability of lamivudine and relative bioavailability of lamivudine solution are unknown. Whether the bioavailability of tablets for oral suspension is diminished in pediatric patients is also unknown.

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

**Male and Female Patients:** There are no significant or clinically relevant gender differences in the pharmacokinetics of the individual components (abacavir or lamivudine) based on the available information that was analyzed for each of the individual components.

**Racial Groups:** There are no significant or clinically relevant racial differences in pharmacokinetics of the individual components (abacavir or lamivudine) based on the available information that was analyzed for each of the individual components.

**Drug Interactions:** The drug interactions described are based on trials conducted with abacavir or lamivudine as single entities.

***Effect of Abacavir and Lamivudine on the Pharmacokinetics of Other Agents:*** In vitro studies have shown that abacavir has potential to inhibit CYP1A1 and limited potential to inhibit metabolism mediated by CYP3A4. Lamivudine does not inhibit or induce CYP3A4. Abacavir and lamivudine do not inhibit or induce other CYP enzymes (such as CYP2C9 or CYP2D6). Based on in vitro study results, abacavir and lamivudine at therapeutic drug exposures are not expected to affect the pharmacokinetics of drugs that are substrates of the following transporters: organic anion transporter polypeptide (OATP)1B1/3, breast cancer resistance protein (BCRP) or P-glycoprotein (P-gp), organic

cation transporter (OCT)1, OCT2, OCT3 (lamivudine only), or multidrug and toxic extrusion protein (MATE)1 and MATE2-K.

*Riociguat:* Coadministration of a single dose of riociguat (0.5 mg) to HIV-1–infected subjects receiving fixed-dose abacavir/dolutegravir/lamivudine is reported to increase riociguat AUC( $\infty$ ) compared with riociguat AUC( $\infty$ ) reported in healthy subjects due to CYP1A1 inhibition by abacavir. The exact magnitude of increase in riociguat exposure has not been fully characterized based on findings from two studies [see *Drug Interactions* (7.3)].

*Effect of Other Agents on the Pharmacokinetics of Abacavir or Lamivudine:* Abacavir and lamivudine are not significantly metabolized by CYP enzymes; therefore, CYP enzyme inhibitors or inducers are not expected to affect their concentrations. In vitro, abacavir is not a substrate of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, MATE1, MATE2-K, multidrug resistance-associated protein 2 (MRP2) or MRP4; therefore, drugs that modulate these transporters are not expected to affect abacavir plasma concentrations. Abacavir is a substrate of BCRP and P-gp in vitro; however, considering its absolute bioavailability (83%), modulators of these transporters are unlikely to result in a clinically relevant impact on abacavir concentrations.

Lamivudine is a substrate of MATE1, MATE2-K, and OCT2 in vitro. Trimethoprim (an inhibitor of these drug transporters) has been shown to increase lamivudine plasma concentrations. This interaction is not considered clinically significant as no dose adjustment of lamivudine is needed.

Lamivudine is a substrate of P-gp and BCRP; however, considering its absolute bioavailability (87%), it is unlikely that these transporters play a significant role in the absorption of lamivudine. Therefore, coadministration of drugs that are inhibitors of these efflux transporters is unlikely to affect the disposition and elimination of lamivudine.

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

*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 every 12 h).

#### Other Interactions

*Ethanol:* Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol decreases the elimination of abacavir causing an increase in overall exposure.

*Interferon Alfa:* There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in a trial of 19 healthy male subjects.

*Methadone:* In a trial of 11 HIV-1-infected subjects receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of abacavir twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI: 6% to 42%) [see *Drug Interactions* (7)]. The addition of methadone has no clinically significant effect on the pharmacokinetic properties of abacavir.

*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.

*Sorbitol (Excipient):* Lamivudine and sorbitol solutions were coadministered to 16 healthy adult subjects in an open-label, randomized-sequence, 4-period, crossover trial. Each subject received a single 300-mg dose of lamivudine oral solution alone or coadministered with a single dose of 3.2 grams, 10.2 grams, or 13.4 grams of sorbitol in solution. Coadministration of lamivudine with sorbitol resulted in dose-dependent decreases of 20%, 39%, and 44% in the AUC(0-24); 14%, 32%, and 36% in the AUC( $\infty$ ); and 28%, 52%, and 55% in the  $C_{max}$  of lamivudine, respectively.

The effects of other coadministered drugs on abacavir or lamivudine are provided in Table 4.

**Table 4. Effect of Coadministered Drugs on Abacavir or Lamivudine**

Coadministered Drug and Dose	Drug and Dose	n	Concentrations of Abacavir or Lamivudine		Concentration of Coadministered Drug
			AUC	Variability	
Ethanol 0.7 g/kg	Abacavir Single 600 mg	24	↑41%	90% CI: 35% to 48%	↔ <sup>a</sup>
Nelfinavir 750 mg every 8 h x 7 to 10 days	Lamivudine Single 150 mg	11	↑10%	95% CI: 1% to 20%	↔
Trimethoprim 160 mg/ Sulfamethoxazole 800 mg daily x 5 days	Lamivudine 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.

<sup>a</sup> The drug-drug interaction was only evaluated in males.

## 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. ***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.

### Antiviral Activity:

***Abacavir*:** The antiviral activity of abacavir against HIV-1 was assessed in a number of cell lines including primary monocytes/macrophages, and peripheral blood mononuclear cells (PBMCs). EC<sub>50</sub> values ranged from 3.7 to 5.8 microM (1 microM = 0.28 mcg/mL) and 0.07 to 1.0 microM against HIV-1<sub>IIIB</sub> and HIV-1<sub>BaL</sub>, respectively, and the mean EC<sub>50</sub> values was 0.26 ± 0.18 microM against 8 clinical isolates. The median EC<sub>50</sub> values of abacavir were 344 nM (range: 14.8 to 676 nM), 16.9 nM (range: 5.9 to 27.9 nM), 8.1 nM (range: 1.5 to 16.7 nM), 356 nM (range: 35.7 to 396 nM), 105 nM (range: 28.1 to 168 nM), 47.6 nM (range: 5.2 to 200 nM), 51.4 nM (range: 7.1 to 177 nM), and 282 nM (range: 22.4 to 598 nM) against HIV-1 clades A-G and group O viruses (n = 3 except n = 2 for clade B), respectively. The EC<sub>50</sub> values against HIV-2 isolates (n=4) ranged from 0.024 to 0.49 microM.

### *Lamivudine*:

The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines including monocytes and PBMCs using standard susceptibility assays. EC<sub>50</sub> values were

in the range of 0.003 to 15 microM (1 microM = 0.23 mcg per mL). The median EC<sub>50</sub> values of lamivudine were 60 nM (range: 20 to 70 nM), 35 nM (range: 30 to 40 nM), 30 nM (range: 20 to 90 nM), 20 nM (range: 3 to 40 nM), 30 nM (range: 1 to 60 nM), 30 nM (range: 20 to 70 nM), 30 nM (range: 3 to 70 nM), and 30 nM (range: 20 to 90 nM) against HIV-1 clades A-G and group O viruses (n = 3 except n = 2 for clade B), respectively. The EC<sub>50</sub> values against HIV-2 isolates (n = 4) ranged from 0.003 to 0.120 microM in PBMCs. Ribavirin (50 microM) used in the treatment of chronic HCV infection 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. Neither abacavir nor lamivudine were antagonistic to all tested anti-HIV agents. See full prescribing information for abacavir and lamivudine. Ribavirin, used in the treatment of HCV infection, decreased the anti-HIV-1 potency of abacavir/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 with amino acid substitutions K65R, L74V, Y115F, and M184V/I emerging in HIV-1 RT. M184V or I substitutions resulted in high-level resistance to lamivudine and an approximately 2-fold decrease in susceptibility to abacavir. Substitutions K65R, L74M, or Y115F with M184V or I conferred a 7 to 8-fold reduction in abacavir susceptibility, and combinations of three substitutions were required to confer more than an 8-fold reduction in susceptibility.

**Cross-Resistance:**

Cross-resistance has been observed among nucleoside reverse transcriptase inhibitors (NRTIs). The combination of abacavir/lamivudine has demonstrated decreased susceptibility to viruses with a K65R substitution with or without an M184V/I substitution, viruses with L74V plus the M184V/I substitution, and viruses with thymidine analog mutation substitutions (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219E/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 of 600 mg.

**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) the human exposure at the recommended dose of 300 mg.

**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:** Abacavir did not affect male or female fertility in rats at a dose associated with exposures (AUC) approximately 3.3 times (male) or 4.1 times (female) those in humans at the clinically recommended dose.

**Lamivudine:** Lamivudine did not affect male or female fertility in rats at doses up to 4,000 mg per kg per day, associated with concentrations approximately 42 times (male) or 63 times (female) higher than the concentrations ( $C_{max}$ ) in humans at the dose of 300 mg.

### **13.2 Animal Toxicology and/or Pharmacology**

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

## **14 CLINICAL STUDIES**

The following trials 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 trial 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. Trial participants had a mean age

of 37 years, were: male (81%), Caucasian (54%), black (27%), and American Hispanic (15%). The median baseline CD4+ cell count was 262 cells/mm<sup>3</sup> (range: 21 to 918 cells/mm<sup>3</sup>) and the median baseline plasma HIV-1 RNA was 4.89 log<sub>10</sub> copies/mL (range: 2.60 to 6.99 log<sub>10</sub> copies/mL).

The outcomes of randomized treatment are provided in Table 5.

**Table 5. Outcomes of Randomized Treatment through Week 48 (CNA30021)**

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

<sup>a</sup> Subjects achieved and maintained confirmed HIV-1 RNA less than 50 copies per mL (less than 400 copies per mL) through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR<sup>®</sup> standard test version 1.0).

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

<sup>c</sup> Includes consent withdrawn, lost to follow-up, protocol violations, clinical progression, and other.

After 48 weeks of therapy, the median CD4+ cell count increases from baseline were 200 cells/mm<sup>3</sup> in the group receiving abacavir 300 mg twice daily. Through Week 48, 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**

### **Abacavir and Lamivudine**

ARROW (COL105677) was a 5-year, randomized, multicenter trial which evaluated multiple aspects of clinical management of HIV-1 infection in pediatric subjects. HIV-1–infected, treatment-naïve subjects aged 3 months to 17 years were enrolled and treated with a first-line regimen containing abacavir and lamivudine, dosed twice daily according to World Health Organization recommendations. After a minimum of 36 weeks of treatment, subjects were given the option to participate in Randomization 3 of the ARROW trial, comparing the safety and efficacy of once-daily dosing with twice-daily dosing of abacavir and lamivudine, in combination with a third antiretroviral drug, for an additional 96 weeks. Virologic suppression was not a requirement for participation at baseline for Randomization 3. At baseline for Randomization 3 (following a minimum of 36 weeks of twice-daily treatment), 75% of subjects in the twice-daily cohort were virologically suppressed, compared with 71% of subjects in the once-daily cohort.



Of the 1,206 original ARROW subjects, 669 participated in Randomization 3. Subjects randomized to receive once-daily dosing (n = 336) and who weighed at least 25 kg received abacavir 600 mg and lamivudine 300 mg, as either the single entities or as abacavir and lamivudine combination tablet.

The proportions of subjects with HIV-1 RNA less than 80 copies per mL through 96 weeks are shown in Table 6. The differences between virologic responses in the two treatment arms were comparable across baseline characteristics for gender and age.

**Table 6. Virologic Outcome of Randomized Treatment at Week 96<sup>a</sup> (ARROW Randomization 3)**

<b>Outcome</b>	<b>Abacavir plus Lamivudine Twice-daily Dosing (n = 333)</b>	<b>Abacavir plus Lamivudine Once-daily Dosing (n = 336)</b>
<b>HIV-1 RNA &lt;80 copies/mL<sup>b</sup></b>	70%	67%
<b>HIV-1 RNA ≥80 copies/mL<sup>c</sup></b>	28%	31%
<b>No virologic data</b>		
Discontinued due to adverse event or death	1%	<1%
Discontinued study for other reasons <sup>d</sup>	0%	<1%
Missing data during window but on study	1%	1%

<sup>a</sup> Analyses were based on the last observed viral load data within the Week 96 window.

<sup>b</sup> Risk difference (95% CI) of response rate is -2.4% (-9% to 5%) at Week 96.

<sup>c</sup> Includes subjects who discontinued due to lack or loss of efficacy or for reasons other than an adverse event or death, and had a viral load value of greater than or equal to 80 copies per mL, or subjects who had a switch in background regimen that was not permitted by the protocol.

<sup>d</sup> Other includes reasons such as withdrew consent, loss to follow-up, etc. and the last available HIV-1 RNA less than 80 copies per mL (or missing).

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Abacavir and lamivudine tablets for oral suspension are white to off white, capsule shaped biconvex, uncoated tablet debossed with 'CJ' on one side and with a functional scoreline on the other side.

They are packaged as follows:

Bottle of 60 tablets with desiccant, induction seal and child-resistant cap. (NDC 69097-542-03)

Bottle of 30 tablets with desiccant, induction seal and Non-child-resistant cap. (NDC 69097-542-01)

Store below 30°C (86°F).

## 17 PATIENT COUNSELING INFORMATION

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

### ***Hypersensitivity Reactions:***

Inform patients:

- **that a Medication Guide and Warning Card summarizing the symptoms of the abacavir hypersensitivity reaction and other product information will be dispensed by the pharmacist with each new prescription and refill of abacavir 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 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 and lamivudine.
- that a hypersensitivity reaction can worsen and lead to hospitalization or death if abacavir and lamivudine is not immediately discontinued.
- **to not restart abacavir 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 if they have a hypersensitivity reaction, they should dispose of any unused abacavir and lamivudine to avoid restarting abacavir.
- that a hypersensitivity reaction is usually reversible if it is detected promptly and abacavir and lamivudine is stopped right away.
- that if they have interrupted abacavir 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.
- **to not restart abacavir and lamivudine or any other abacavir-containing product without medical consultation and only if medical care can be readily accessed by the patient or others.**

### **Patients with Hepatitis B or C Co-infection:**

Advise patients co-infected with HIV-1 and HBV that worsening of liver disease has occurred in some cases when treatment with lamivudine was discontinued. Advise patients to discuss any changes in regimen with their physician [*see Warnings and Precautions (5.2)*].

**Lactic Acidosis/Hepatomegaly with Steatosis:** Advise patients that lactic acidosis and severe hepatomegaly with steatosis have been reported with use of nucleoside analogues and other antiretrovirals. Advise patients to stop taking abacavir and lamivudine if they develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity [*see Warnings and Precautions (5.3)*].

**Immune Reconstitution Syndrome:**

Advise patients to inform their healthcare provider immediately of any signs and symptoms of infection as inflammation from previous infection may occur soon after combination antiretroviral therapy, including when abacavir and lamivudine is started [see *Warnings and Precautions* (5.4)].

**Risk of Pancreatitis:** Parents or guardians should be advised to monitor pediatric patients for signs and symptoms of pancreatitis [see *Warnings and Precautions* (5.6)].

**Phenylketonurics:** Inform patients with phenylketonuria that Abacavir and Lamivudine Tablets for Oral Suspension contain phenylalanine, a component of aspartame [see *Warnings and Precautions* (5.7)].

**Lactation:** Instruct women with HIV-1 not to breastfeed because HIV-1 can be passed to the baby in the breast milk [see *Use in Special Populations* (8.2)].

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

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

Manufactured by:

**CIPLA LTD.  
MIDC, Patalganga,  
Maharashtra 410 220  
INDIA**

**Revised: 8/2021**

**MEDICATION GUIDE**  
**Abacavir and Lamivudine Tablets for Oral Suspension 120 mg/60 mg**

Read the Medication Guide before you or your child start taking abacavir and lamivudine tablets for oral suspension 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 and lamivudine tablets for oral suspension Warning Card with you at all times.

**What is the most important information I should know about Abacavir and Lamivudine Tablets for Oral Suspension?**

- **Serious Allergic Reaction (hypersensitivity reaction).** Abacavir and Lamivudine Tablets for Oral Suspension contain abacavir. Patients taking Abacavir and Lamivudine Tablets for Oral Suspension 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 and lamivudine tablets for oral suspension, call your healthcare provider right away to find out if your child or you should stop taking this medicine.**

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

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 and Lamivudine Tablets for Oral Suspension because of an allergic reaction, **NEVER** take Abacavir and Lamivudine Tablets for Oral Suspension or any other abacavir-containing medicine again.

- If you have an allergic reaction, dispose of any unused Abacavir and Lamivudine. Ask your pharmacist how to properly dispose of medicines.
- If you take Abacavir and Lamivudine or any other abacavir-containing medicine again after you have had an allergic reaction, within hours you may

get life-threatening symptoms that may include very low blood pressure or death.

- If you stop Abacavir and Lamivudine for any other reason, even for a few days, and you are not allergic to Abacavir and Lamivudine, talk with your healthcare provider before taking it again. Taking Abacavir 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 and lamivudine tablets for oral suspension 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.**

- **Worsening of hepatitis B virus (HBV) infection.** If you or your child has HBV infection and take Abacavir and Lamivudine Tablets for Oral Suspension, your HBV may get worse (flare-up) if you stop taking Abacavir and Lamivudine Tablets for Oral Suspension. A “flare-up” is when your HBV infection suddenly returns in a worse way than before.
  - Do not run out of Abacavir and Lamivudine Tablets for Oral Suspension. Refill your prescription or talk to your healthcare provider before your Abacavir and Lamivudine Tablets for Oral Suspension is all gone.
  - Do not stop Abacavir and Lamivudine Tablets for Oral Suspension without first talking to your healthcare provider.
  - If you stop taking Abacavir and Lamivudine Tablets for Oral Suspension, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your liver function and monitor your HBV infection. It may be necessary to give you a medicine to treat HBV. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking Abacavir and Lamivudine Tablets for Oral Suspension.
- **Resistant HBV.** If you have human immunodeficiency virus-1 (HIV-1) and HBV, the HBV can change (mutate) during your treatment with Abacavir and Lamivudine Tablets for Oral Suspension and become harder to treat (resistant).

### **What are Abacavir and Lamivudine Tablets for Oral Suspension?**

Abacavir and Lamivudine Tablets for Oral Suspension contain 2 prescription medicines, abacavir and lamivudine, both used to treat HIV-1 infection.

HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

### **Do not take Abacavir and Lamivudine Tablets for Oral Suspension if you or your child:**

- have a certain type of gene variation called the HLA-B\*5701 allele. Your healthcare provider will test you for this before prescribing treatment with Abacavir and Lamivudine Tablets for Oral Suspension.

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

**Before you take or give Abacavir and Lamivudine Tablets for Oral Suspension tell your healthcare provider about all of your child or your medical conditions, including if your child or you:**

- have been tested and know whether or not you have a particular gene variation called HLA-B\*5701.
- have or have had liver problems, including hepatitis B or C virus infection.
- have kidney problems.
- have heart problems, smoke, or have diseases that increase your risk of heart disease such as high blood pressure, high cholesterol, or diabetes.
- are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. Do not breastfeed if you take Abacavir and Lamivudine Tablets for Oral Suspension
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.

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

Some medicines interact with Abacavir and Lamivudine Tablets for Oral Suspension.

**Keep a list of your medicines to show your healthcare provider and pharmacist when you get a new medicine.**

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with Abacavir and Lamivudine Tablets for Oral Suspension.
- **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take Abacavir and Lamivudine Tablets for Oral Suspension with other medicines.

**How should I or my child take Abacavir and Lamivudine Tablets for Oral Suspension?**

- **Take or give Abacavir and Lamivudine Tablets for Oral Suspension 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, the following procedure can be used:

**Method of preparation:**

1. Place the tablet(s) for oral suspension in a container and add two teaspoonfuls (10 mL) of drinking water per tablet.
2. Swirl the container until the tablet(s) for oral suspension breaks up into pieces small enough for the child to swallow. A spoon can be used to crush 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 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 and Lamivudine Scored Tablets for Oral Suspension, 120 mg/60 mg**

Weight (kg)	Once-daily Dosing Regimen	Total Daily Dose (mg)
6 to less than 9	1 tablet (120 mg A/60 mg L)	120A/60L
9 to less than 12	1 ½ tablets (180 mg A/90 mg L)	180A/90L
12 to less than 17	2 tablets (240 mg A/120 mg L)	240A/120L
17 to less than 20	2 ½ tablets (300 mg A/150 mg L)	300A/150L
20 to less than 25	3 tablets (360 mg A/180 mg L)	360A/180L
25 to less than 29	3 ½ tablets (420 mg A/210 mg L)	420A/210L
29 to less than 35	4 tablets (480 mg A/240 mg L)	480A/240L
35 and greater	5 tablets (600 mg A/300 mg L) <sup>b</sup>	600A/300L

A= abacavir; L= lamivudine

<sup>a</sup> For recommended dose of abacavir 600 mg once-daily and lamivudine 300 mg once-daily (adult maximum daily dose), the adult fixed-dose combination (abacavir and lamivudine tablets, 600 mg/300 mg) can be used.

- Do not change your dose or stop taking Abacavir and Lamivudine Tablets for Oral suspension without talking to your healthcare provider.
- If you miss a dose of Abacavir and Lamivudine Tablets for Oral suspension, take it as soon as you remember. Do not take 2 doses at the same time or take more than your healthcare provider tells you to take.
- Stay under the care of a healthcare provider during treatment with Abacavir and Lamivudine Tablets for Oral suspension.
- Take or give Abacavir and Lamivudine Tablets for Oral suspension without food.

- Do not run out of Abacavir and Lamivudine Tablets for Oral suspension. The virus in your blood may increase and the virus may become harder to treat. When your supply starts to run low, get more from your healthcare provider or pharmacy
- If you take too much Abacavir and Lamivudine Tablets for Oral suspension, call your healthcare provider or go to the nearest hospital emergency room right away.

**What are the possible side effects of Abacavir and Lamivudine Tablets for Oral Suspension?**

- **Abacavir and Lamivudine Tablets for Oral Suspension can cause serious side effects. See “What is the most important information I should know about Abacavir and Lamivudine Tablets for Oral Suspension?”**
- **Too much lactic acid in your blood (lactic acidosis).** Lactic acidosis is a serious medical emergency that can cause death. **Call your healthcare provider right away if you get any of the following symptoms that could be signs of lactic acidosis:**
  - feel very weak or tired
  - feel cold, especially in your arms and legs
  - unusual (not normal) muscle pain
  - feel dizzy or light-headed
  - trouble breathing
  - have a fast or irregular heartbeat
  - stomach pain with nausea and vomiting
- **Severe liver problems.** In some cases, severe liver problems can lead to death. Your liver may become large (hepatomegaly) and you may develop fat in your liver (steatosis). **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)
  - loss of appetite for several days or longer
  - dark or “tea-colored” urine
  - nausea
  - light-colored stools (bowel movements)
  - pain, aching, or tenderness on the right side of your stomach area

**You may be more likely to get lactic acidosis or serious liver problems if you are female or very overweight (obese).**

- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having new symptoms after you start taking Abacavir and Lamivudine Tablets for Oral Suspension.
- **Heart attack.** Some HIV-1 medicines including Abacavir and Lamivudine Tablets for Oral Suspension may increase your risk of heart attack.



**The most common side effects of Abacavir and Lamivudine Tablets for Oral Suspension include:**

- |                        |                         |
|------------------------|-------------------------|
| ○ allergic reactions   | ○ tiredness or weakness |
| ○ trouble sleeping     | ○ dizziness             |
| ○ depression           | ○ nausea                |
| ○ headache or migraine | ○ diarrhea              |

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

These are not all the possible side effects of Abacavir and Lamivudine Tablets for Oral Suspension. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store Abacavir and Lamivudine Tablets for Oral suspension?**

Store Abacavir and Lamivudine Tablets for Oral Suspension at Room Temperature below 30°C (86°F)

Keep Abacavir and Lamivudine Tablets for Oral Suspension and all medicines out of the reach of children.

**General information for safe and effective use of Abacavir and Lamivudine Tablets for Oral Suspension**

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

You can ask your healthcare provider or pharmacist for the information about Abacavir and Lamivudine Tablets for Oral Suspension that is written for healthcare professionals.

For more information go to [www.cipla.com](http://www.cipla.com) or call 1-866-604-3268.

**What are the ingredients in Abacavir and Lamivudine Tablets for Oral Suspension?**

Active ingredients: abacavir and lamivudine

Inactive ingredients: microcrystalline cellulose (Avicel PH 101), sodium starch glycolate, hypromellose, microcrystalline cellulose (Avicel PH 102), corn starch, strawberry cream flavour permaseal (PHS-132963), aspartame, colloidal silicon dioxide, magnesium stearate.

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

**August 2021**

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

Manufactured by:

**CIPLA LTD.**

**MIDC, Patalganga,**

**Maharashtra 410 220**

**INDIA**



Product Name: Aba Sulf & Lami Tab Susp

 PANTONE 362 C  PANTONE 186 C  Black

Actual Size: 100 x 25 mm

Ref: 209420




Date: 03-11-2020

Path: PC D : Mukesh\Sachita\PEPFAR\Abacavir and Lamivudine Tablets for Oral Suspension 120 mg\_60 mg  
219471 Abacavir and Lamivudine tablets for oral suspension 120-60mg Label Pefpar.ai



**Note: Warning card (Material No. 21086642) to be affixed inside the carton diagonally with the help of 3 mm glue spot. Warning card should be easily detachable from carton from top side. Please send samples before final pasting.**

**PACKAGING DEVELOPMENT**

Product Name: Abacavir and Lamivudine tablets for oral suspension 120-60mg		Material No.: 21086641	Version: 01	Item: Inner Carton	Co-ordinator: Sachita	Artist: Mukesh	Date: 03-11-2020	
Colours: BLUE WOOL TEST VALUE 5-8 (LIGHT FASTENING DATA)  Black  Pantone 186 C  Pantone 362 C				Ink: Oil Base Colours NBCL Series from SIEGWERK OR Oil based inks from DIC. Varnish: Aqua-Water based OP Ink-High Gloss High Slip(10-603787-2.2660) from SIEGWERK OR HIV-1611-High Gloss Aqua Duct OPV from MICRO INKS				
Spectro-Densitometer Delta-E reading (ΔE) for colour: NOT MORE THAN ΔE2,5		Fonts: ----				Software: Illustrator CC		
Design: Cartonator (CAM)			Links: NA					
Actual Size: 56 x 58 x 110 mm		Pharmacode:		Grain Direction : Perpendicular to Crease		Supersedes/Reference: 21083489		
Tuck flap: 13 mm		Side / Collar flap: 25 mm		Overlap: No		Caliper (Thickness) for Board: NLT 430 micron		
						Screen : #		
Material: 270 GSM CFB board (Cyber XL Premium GC2 from ITC). Overprinting area to be left unvarnished. Warning Card Material No. 21083490 should be pasted inside the carton.				Varnish: Scuff Proof Aqua		Artwork Print Size: <input type="checkbox"/> actual <input type="checkbox"/> scaled		
Path: PC D : Mukesh\Sachita\PEPFAR\Abacavir and Lamivudine Tablets for Oral Suspension 120 mg_60 mg : 21086641 Abacavir and Lamivudine tablets for oral suspension 120-60mg Carton Pepfar.ai								
<b>• Instructions/Remark:</b> • Any deviation must be brought to the notice of packaging development co-ordinator immediately. • For any clarification, please contact packaging development co-ordinator immediately. <b>NO CHANGES IN ARTWORK SHOULD BE DONE BY THE PRINTER.</b> • The printer should verify the e-proof against the approved artwork before submitting for approval and the e-proof should have printer details.				Checked by	Artist	Cordinator	file loaded in Server	Section Head
				Pharma Code	<input type="checkbox"/>	<input type="checkbox"/>		
				2D Code	<input type="checkbox"/>	<input type="checkbox"/>		
				QR Code	<input type="checkbox"/>	<input type="checkbox"/>		
				Bar Code	<input type="checkbox"/>	<input type="checkbox"/>		
				Artwork	<input type="checkbox"/>	<input type="checkbox"/>		
				Spell check	<input type="checkbox"/>	<input type="checkbox"/>		