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

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. (5.1)
- 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)

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

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. (5.3)

INDICATIONS AND USAGE
Abacavir and lamivudine, a combination of abacavir and lamivudine, both nucleoside analogue HIV-1 reverse transcriptase inhibitors, are indicated in:
- Patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine, a component of an abacavir and lamivudine. (5.1)

DOSE 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)

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

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

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
- Hepatic decompensation, some fatal, has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy and interferon alpha with or without ribavirin. Discontinue abacavir and lamivudine as medically appropriate and consider dose reduction or discontinuation of interferon alpha, 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 and lamivudine should not be administered with other lamivudine- or zidovudine-containing products or emtricitabine-containing products.
- Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue treatment as clinically appropriate. (5.8)
- Inform patients with phenylketonuria that abacavir and lamivudine contain phenylalanine, a component of aspartame (5.9)

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.

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

FULL PRESCRIBING INFORMATION: CONTENTS
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2 DOSAGE AND ADMINISTRATION
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2.2 Dose Adjustment
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Reference ID: 4080925
WARNINGS: HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, 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)].

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS
LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES AND OTHER ANTIRETROVIRALS. DISCONTINUE ABACAVIR AND LAMIVUDINE IF CLINICAL OR LABORATORY FINDINGS SUGGESTIVE OF LACTIC ACIDOSIS OR PRONOUNCED HEPATOTOXICITY OCCUR [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, 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 (5.3)].

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

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

A= abacavir; L= lamivudine

a 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)].

b 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.
- 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 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 and other antiretrovirals.

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 Hepatitis B Virus Co-Infection

Post-treatment Exacerbations of Hepatitis: Clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. 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 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

Patients receiving interferon alfa with or without ribavirin and abacavir and lamivudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of abacavir and lamivudine should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh greater than 6) (See full prescribing-information for interferon and ribavirin).

5.5 Immune Reconstitution Syndrome

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

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

5.6 Fat Redistribution

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

5.7 Myocardial Infarction
In a published prospective, observational, epidemiological trial designed to investigate the rate of myocardial infarction in patients on combination antiretroviral therapy, the use of abacavir within the previous 6 months was correlated with an increased risk of myocardial infarction (MI). 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 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)].

5.9 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)].
- Lactic acidosis and severe hepatomegaly [see Boxed Warning, Warnings and Precautions (5.2)].
- 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 (5.8)].

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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Abacavir 600 mg q.d. plus Lamivudine plus Efavirenz (n = 384)</th>
<th>Abacavir 300 mg b.i.d. plus Lamivudine plus Efavirenz (n = 386)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug hypersensitivity&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>7%</td>
<td>9%</td>
</tr>
<tr>
<td>Depression/Depressed mood</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Headache/Migraine</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Fatigue/Malaise</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>Dizziness/Vertigo</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Diarrhea&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Rash</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Abdominal pain/gastritis</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3%</td>
<td>5%</td>
</tr>
</tbody>
</table>

<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-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 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-naive 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 (A2002), 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 (A2005), 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 (5.8)].

Paresthesias and Peripheral Neuropathies: Paresthesias and peripheral neuropathies were reported in 15 subjects (15%) in A2002, 6 subjects (9%) in A2005, 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 Post-Marketing 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 [see Warnings and Precautions (5.6)].
**Digestive:** Stomatitis.
**Endocrine and Metabolic:** Hyperglycemia.
**General:** Weakness.
**Hemic and Lymphatic:** Aplastic anemia, anemia (including pure red cell aplasia and severe anemias progressing on therapy), lymphadenopathy, splenomegaly.
**Hepatic and Pancreatic:** Lactic acidosis and hepatic steatosis [see Warnings and Precautions (5.2)], post treatment exacerbation of hepatitis B [see Warnings and Precautions (5.3)].
**Hypersensitivity:** Sensitization reactions (including anaphylaxis), urticaria.
**Musculoskeletal:** Muscle weakness, CPK elevation, rhabdomyolysis.
**Nervous:** Paresthesia, peripheral neuropathy, seizures.
**Respiratory:** Abnormal breath sounds/wheezing.
**Skin:** Alopecia, erythema multiforme, Stevens-Johnson syndrome.
7 DRUG INTERACTIONS
Drug interaction trials have been conducted with abacavir and lamivudine, the individual components of Abacabir 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.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Available data from the Antiretroviral Pregnancy Registry show no difference in the risk of overall major birth defects for abacavir or lamivudine compared with the background rate for major birth defects of 2.7% in the US reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). Abacavir produced fetal malformations and other embryonic and fetal toxicities in rats at 35 times the human exposure at the recommended clinical dose. Lamivudine produced embryonic toxicity in rabbits at a dose that produced similar human exposures to the recommended clinical dose. The relevance of animal findings to human pregnancy registry data is not known.

Data

Human Data: Abacavir: Based on prospective reports from the Antiretroviral Pregnancy Registry of over 2,000 exposures to abacavir during pregnancy resulting in live births (including over 900 exposed in the first trimester), there was no difference between abacavir and overall birth defects compared with the background birth defect rate of 2.7% in the US reference population of the MACDP. The prevalence of defects in the first trimester was 3.0% (95% CI: 2.0% to 4.4%).

Lamivudine: Based on prospective reports from the Antiretroviral Pregnancy Registry of over 11,000 exposures to lamivudine during pregnancy resulting in live births (including over 4,300 exposed in the first trimester), there was no difference between lamivudine and overall birth defects compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of defects in the first trimester was 3.1% (95% CI: 2.6% to 3.7%).

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
pharmacokinetics in pregnant women were similar to those seen in non-pregnant adults and in postpartum women. Lamivudine concentrations were e subjects, amniotic fluid specimens were collected following natural rupture of membranes and confirmed that lamivudine crosses the placenta in humans. Amniotic fluid concentrations of lamivudine were typically 2 times greater than maternal serum levels and ranged from 1.2 to 2.5 mcg per mL (150 mg twice daily) and 2.1 to 5.2 mcg per mL (300 mg twice daily).

Animal Data:

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

**Lamivudine:** Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. Reproduction studies with orally administered lamivudine have been performed in rats and rabbits at doses producing plasma levels up to approximately 35 times that for the recommended adult HIV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryolethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 35 times those in humans.

### 8.3 Nursing Mothers

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

Because of the potential for HIV-1 transmission, mothers should be instructed not to breastfeed.

### 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 (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 (C14H18N6O)2•H2SO4 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 (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 C₈H₁₁N₃O₃S 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, $C_{\text{max}}$ was $4.26 \pm 1.19 \text{ mcg/mL (mean \pm SD)}$ and $AUC_{\infty}$ was $11.95 \pm 2.51 \text{ mcg\cdot hr/mL}$. 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 $C_{\text{max}}$ ($C_{\text{max,ss}}$) was $2.04 \pm 0.54 \text{ mcg/mL (mean \pm SD)}$ and the 24-hour steady-state AUC ($AUC_{24,ss}$) was $8.87 \pm 1.83 \text{ mcg\cdot hr/mL}$. 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$^a$ for Abacavir and Lamivudine in Adults |
|-----------------------------|-----------------------------|-----------------------------|
| Parameter                  | Abacavir                  | Lamivudine                  |
| Oral bioavailability (%)   | $86 \pm 25$ n = 6         | $86 \pm 16$ n = 12          |
| Apparent volume of         | $0.86 \pm 0.15$ n = 6     | $1.3 \pm 0.4$ n = 20        |
| distribution (L/kg)        |                            |                            |
| 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    | 5 to 7$^b$                  |

$^a$ Data presented as mean $\pm$ standard deviation except where noted.

$^b$ 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.

**Special Populations:** *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).

*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).

**Pregnancy:** See Use in Specific Populations (8.1).

**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.

**Gender:** 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.

**Race:** 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.

Cytochrome P450 Enzymes: 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/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.

**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 (7.1)].

**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 hr).

**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.

**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 [see Warnings and Precautions (5.4)].

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

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

<table>
<thead>
<tr>
<th>Coadministered Drug and Dose</th>
<th>Drug and Dose</th>
<th>n</th>
<th>Concentrations of Abacavir or Lamivudine</th>
<th>Concentration of Coadministered Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol 0.7 g/kg</td>
<td>Abacavir Single</td>
<td>24</td>
<td>↑41%</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>600 mg</td>
<td></td>
<td></td>
<td>90% CI: 35% to 48%</td>
</tr>
<tr>
<td>Nelfinavir 750 mg every 8 h x 7 to 10 days</td>
<td>Lamivudine Single</td>
<td>11</td>
<td>↑10%</td>
<td>95% CI: 1% to 20%</td>
</tr>
<tr>
<td></td>
<td>150 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethoprim 160 mg/ Sulfamethoxazole 800 mg daily x 5 days</td>
<td>Lamivudine Single</td>
<td>14</td>
<td>↑43%</td>
<td>90% CI: 32% to 55%</td>
</tr>
<tr>
<td></td>
<td>300 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

a 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). EC50 values ranged from 3.7 to 5.8 microM (1 microM = 0.28 mcg/mL) and 0.07 to 1.0 microM against HIV-1HXB and HIV-1Bal, respectively, and the mean EC50 values was 0.26 ± 0.18 microM against 8 clinical isolates. The median EC50 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 EC50 values againstHIV-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. EC50 values were in the range of 0.003 to 15 microM (1 microM = 0.23 mcg per mL). The median EC50...
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 or lamivudine did not affect male or fertility in rats at a dose associated with exposures approximately 8 or 130 times, respectively, higher than the exposures in humans at the doses of 600 mg and 300 mg (respectively).

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/mm³ (range: 21 to 918 cells/mm³) and the median baseline plasma HIV-1 RNA was 4.89 log₁₀ copies/mL (range: 2.60 to 6.99 log₁₀ copies/mL). The outcomes of randomized treatment are provided in Table 5.
Table 5. Outcomes of Randomized Treatment through Week 48 (CNA30021)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Abacavir 600 mg q.d. plus Lamivudine plus Efavirenz (n = 384)</th>
<th>Abacavir 300 mg b.i.d. plus Lamivudine plus Efavirenz (n = 386)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respondera</td>
<td>64% (71%)</td>
<td>65% (72%)</td>
</tr>
<tr>
<td>Virologic failureb</td>
<td>11% (5%)</td>
<td>11% (5%)</td>
</tr>
<tr>
<td>Discontinued due to adverse reactions</td>
<td>13%</td>
<td>11%</td>
</tr>
<tr>
<td>Discontinued due to other reasonsc</td>
<td>11%</td>
<td>13%</td>
</tr>
</tbody>
</table>

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

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

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

After 48 weeks of therapy, the median CD4+ cell count increases from baseline were 200 cells/mm³ 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 to 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 96a (ARROW Randomization 3)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Abacavir plus Lamivudine Twice-daily Dosing (n = 333)</th>
<th>Abacavir plus Lamivudine Once-daily Dosing (n = 336)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA &lt;80 copies/mLb</td>
<td>70%</td>
<td>67%</td>
</tr>
<tr>
<td>HIV-1 RNA ≥80 copies/mLc</td>
<td>28%</td>
<td>31%</td>
</tr>
<tr>
<td>No virologic data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinued due to adverse event or death</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Discontinued study for other reasonsd</td>
<td>0%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Missing data during window but on study</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

a Analyses were based on the last observed viral load data within the Week 96 window.
b Risk difference (95% CI) of response rate is -2.4% (-9% to 5%) at Week 96.
c 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.
d 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)

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 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 (5.3)]. Inform patients with HIV-1/HCV co-infection that hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin [see Warnings and Precautions (5.4)].

Lactic Acidosis/Hepatomegaly: Inform patients that some HIV-1 medicines, including abacavir and lamivudine, can cause a rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly) [see Warnings and Precautions (5.2)].

Immune Reconstitution Syndrome:
In some patients with advanced HIV infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. Advise patients to inform their healthcare provider immediately of any symptoms of infection [see Warnings and Precautions (5.5)].
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 (5.8)].

Phenylketonurics: Inform patients with phenylketonuria that Abacavir and Lamivudine Tablets for Oral Suspension contain phenylalanine, a component of aspartame [see Warnings and Precautions (5.9)].

Information About HIV-1 Infection: Abacavir and lamivudine tablets for oral suspension are not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients must remain on continuous HIV therapy to control HIV-1 infection and decrease HIV-related illness. Inform patients that sustained decreases in plasma HIV-1 RNA have been associated with a reduced risk of progression to AIDS and death.

Advise patients to remain under the care of a physician when using abacavir and lamivudine.
Advise patients to take all HIV medications exactly as prescribed.
Advise patients to avoid doing things that can spread HIV-1 infection to others.
Advise patients not to re-use or share needles or other injection equipment.
Advise patients not to share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.
Advise patients to always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.
Female patients should be advised not to breastfeed. Mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

Instruct patients to read the Medication Guide before starting abacavir and 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
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?

1. **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.

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

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 your child or you take Abacavir and Lamivudine Tablets for Oral Suspension 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 and
Lamivudine Tablets for Oral Suspension for any other reason, even for a few days,
and your child or you are not allergic to abacavir and lamivudine, talk with your
healthcare provider before taking or giving it to your child again. Taking Abacavir
and Lamivudine Tablets for Oral Suspension 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.

2. Lactic Acidosis (buildup of acid in the blood). Some human immunodeficiency
virus (HIV) medicines, including abacavir 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
and Lamivudine Tablets for Oral Suspension 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 and lamivudine tablets for oral suspension 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 and Lamivudine Tablets for Oral Suspension.**
   a. Take or give Abacavir and Lamivudine Tablets for Oral Suspension exactly as prescribed.
   b. Do not run out of Abacavir and Lamivudine Tablets for Oral Suspension.
   c. Do not stop Abacavir and Lamivudine Tablets for Oral Suspension 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 and Lamivudine Tablets for Oral Suspension.

**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 infection. Both of these medicines are called nucleoside analogue reverse transcriptase inhibitors (NRTIs). When used together, they help lower the amount of HIV in your blood.

- **Abacavir and Lamivudine Tablets for Oral Suspension do not cure HIV infection or AIDS.**
- It is not known if Abacavir and Lamivudine Tablets for Oral Suspension 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 and Lamivudine Tablets for Oral Suspension.

**Who should not take Abacavir and Lamivudine Tablets for Oral Suspension?**
Do not take Abacavir and Lamivudine Tablets for Oral Suspension if you or your child:
- are allergic to abacavir or any of the ingredients in Abacavir and Lamivudine Tablets for Oral Suspension. 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.

**What should I tell my healthcare provider before taking or giving Abacavir and Lamivudine Tablets for Oral Suspension?**
Before you take or give Abacavir and Lamivudine Tablets for Oral Suspension tell your healthcare provider if you or 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 and
Lamivudine Tablets for Oral suspension will harm your unborn baby. Talk to your
healthcare provider if you are pregnant or plan to become pregnant.

Do not breastfeed.

have hepatitis B virus infection or have other liver problems.

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.

have phenylketonuria (PKU). Abacavir and lamivudine tablets for oral suspension
contain phenylalanine as part of the artificial sweetener, aspartame. The artificial
sweetener may be harmful to people with PKU.

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
- medicines containing abacavir or lamivudine

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

Abacavir and Lamivudine Tablets for Oral suspension may affect the way other
medicines work, and other medicines may affect how Abacavir and Lamivudine Tablets
for Oral Suspension 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 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

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

A= abacavir; L= lamivudine

* 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 skip doses.
- Take or give Abacavir and Lamivudine Tablets for Oral suspension without food.
- **Do not let your Abacavir and Lamivudine Tablets for Oral Suspension run out.**

If your child or you stop the anti-HIV medicines, even for a short time, the amount of virus in the blood may increase and the virus may become harder to treat. If your child or you take too much Abacavir and Lamivudine Tablets for Oral Suspension, 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 and Lamivudine Tablets for Oral Suspension?**

- **Abacavir and Lamivudine Tablets for Oral Suspension 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 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 and lamivudine tablets for oral suspension.

- **Changes in body fat (fat redistribution).** Changes in body fat (lipoatrophy or
lipodystrophy) can happen in some people taking antiretroviral medicines including
Abacavir and Lamivudine Tablets for Oral Suspension. The changes may include:
  o more fat in or around your trunk, upper back and neck (buffalo hump), breast,
or chest
  o loss of fat in your legs, arms, or face

- **Heart attack (myocardial infarction).** Some HIV 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 in adults include:**
- trouble sleeping
- depression
- headache
- tiredness
- dizziness
- nausea
- diarrhea
- rash
- fever

**The most common side effects of abacavir, one component of abacavir and
lamivudine tablets for oral suspension in children include:**
- fever and chills
- nausea
- vomiting
- rash
- infections of ear, nose, and throat

**The most common side effects of lamivudine, one component of abacavir and
lamivudine tablets for oral suspension in children include:**
- fever
- cough

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 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**

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

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

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.

This Medication Guide summarizes the most important information about Abacavir and Lamivudine Tablets for Oral Suspension. If you would like more information, talk with your healthcare provider. 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.

**December 2016**

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

Manufactured by:

CIPLA LTD.
MIDC, Patalganga,
Maharashtra 410 220
INDIA

Reference ID: 4080925
Product Name: Aba Sulf & Lamiv Tab Susp

Actual Size: 100 x 25 mm

Pharmacode: 362_MINI

Date: 12-12-2016

File: RAMA - DATASHIP(ProtectivePaper)Aba & Lamiv Tab for Oral Suspension 06.00mg)
200023 Abacavir Sulfate and Lamivudine Tablet for Oral Suspension (200mg) Label USA.ai
WARNING CARD
Abacavir and Lamivudine tablet
for oral suspension 120/60mg

If you must stop treatment with Abacavir and Lamivudine tablets for oral suspension because you have had an allergic reaction to abacavir, NEVER take Abacavir and Lamivudine tablets for oral suspension or another Abacavir-containing medicine (Ziden® and Truvada®) again. If you take Abacavir and Lamivudine tablets for oral suspension or another 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. You should return all of your unused Abacavir and Lamivudine tablets for oral suspension to your doctor or pharmacist for proper disposal. Please read the Medication Guide for additional information on Abacavir and Lamivudine tablets for oral suspension.

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

Mfg, by Cipla Ltd., MIDC, Patasgama, M.S. 410 220 INDIA

December 2015

WARNING CARD
Abacavir and Lamivudine tablet
for oral suspension 120/60mg

Patients taking Abacavir and Lamivudine tablets for oral suspension may have a serious allergic reaction (hypersensitivity reaction) that can cause death. If you get a symptom from 2 or more of the following groups while taking Abacavir and Lamivudine tablets for oral suspension, stop taking Abacavir and Lamivudine tablets for oral suspension and call your doctor right away.

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

Always carry Warning Card with you to help recognize symptoms of this allergic reaction.

Product Name: Aba Sul and Lam Tab
for oral susp 120 mg/60 mg

Actual Size : 70 x 50 mm

Date: 12-12-2016

Path: RAMA-D:\ATBS\Paused\Peptides\Aba & Lam Tab for Oral Susp 90, 30mg & 120, 60 mg\1215166157 Abacavir Sulfa & Lamivudine Tablets for Oral Suspension 120/60mg Warning Card USA.a