

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ABACAVIR and LAMIVUDINE TABLETS safely and effectively. See full prescribing information for ABACAVIR and LAMIVUDINE TABLETS.

ABACAVIR and LAMIVUDINE tablets, for oral use

WARNING: HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, 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 high risk for experiencing a hypersensitivity reaction to abacavir. (5.1)
- Abacavir and Lamivudine tablets are contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients. (4)
- Discontinue Abacavir and Lamivudine tablets as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B*5701 status, permanently discontinue Abacavir and Lamivudine tablets if hypersensitivity cannot be ruled out, even when other diagnoses are possible. (5.1)
- Following a hypersensitivity reaction to Abacavir and Lamivudine tablets, NEVER restart Abacavir and Lamivudine tablets 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 tablets. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.3)

INDICATIONS AND USAGE

Abacavir and Lamivudine tablets, 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, screen for the HLA-B*5701 allele because Abacavir and Lamivudine tablets contains abacavir. (2.1)
- Pediatric Patients 3 Months and Older: Administered either once or twice daily. Dose should be calculated on body weight (kg) and should not exceed 600 mg of abacavir and 300 mg of lamivudine. (2.2)
- Because Abacavir and Lamivudine tablets are a fixed-dose formulation and cannot be dose adjusted, Abacavir and Lamivudine tablets are not recommended in patients requiring dosage adjustment or patients with hepatic impairment. (2.3, 4)

DOSAGE FORMS AND STRENGTHS

Tablets: 60 mg of abacavir USP, and 30 mg of lamivudine USP. (3)

CONTRAINDICATIONS

- Presence of HLA-B*5701 allele. (4)
- Prior hypersensitivity reaction to abacavir or lamivudine. (4)
- Moderate or severe hepatic impairment. (4, 8.7)

WARNINGS AND PRECAUTIONS

- Hepatic decompensation, some fatal, has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy and interferon alfa with or without ribavirin. Discontinue Abacavir and Lamivudine tablets as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.4)
- Immune reconstitution syndrome (5.5) and redistribution/accumulation of body fat have been reported in patients treated with combination antiretroviral therapy. (5.6)
- Abacavir and Lamivudine tablets are not recommended with other lamivudine- or zidovudine-containing products or emtricitabine-containing products. (5.8)
- Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue treatment as clinically appropriate. (5.9)

ADVERSE REACTIONS

- Abacavir and Lamivudine: The most commonly reported adverse reactions of at least moderate intensity (incidence greater than 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 greater than or equal to 5%) in pediatric HIV-1 clinical trials were fever and/or chills, nausea and vomiting, skin rashes, and ear/nose/throat infections (6.2)
- Lamivudine: The most commonly reported adverse reactions (incidence greater than or equal to 15%) in pediatric subjects were fever and cough (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Hetero Labs Limited at 1-866-495-1995 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)

USE IN SPECIFIC POPULATIONS

- Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION

WARNING: 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.

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 tablets are 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 tablets or reinitiation of therapy with Abacavir and Lamivudine tablets, unless patients have a previously documented HLA-B*5701 allele assessment. Discontinue Abacavir and Lamivudine tablets immediately if a hypersensitivity reaction is suspected, regardless of HLA-B*5701 status and even when other diagnoses are possible [see Contraindications (4), Warnings and Precautions (5.1)].

Following a hypersensitivity reaction to Abacavir and Lamivudine tablets, NEVER restart Abacavir and Lamivudine tablets 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

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 tablets 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, which is one component of Abacavir and Lamivudine tablets. 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 tablets 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, in combination with other antiretroviral agents, are indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection.

2 DOSAGE AND ADMINISTRATION

2.1 Screening for HLA-B*5701 Allele Prior to Starting Abacavir and Lamivudine tablets

Screen for the HLA-B*5701 allele prior to initiating therapy with Abacavir and Lamivudine tablets [see *Boxed Warning, Warnings and Precautions (5.1)*].

2.2 Recommended Dosage for Pediatric Patients

The recommended dosage of Abacavir and Lamivudine scored tablets in HIV-1-infected pediatric patients aged 3 months and older is abacavir 8 mg per kg taken orally twice-daily or abacavir 16 mg per kg taken orally once-daily (up to a maximum of 600 mg daily) and lamivudine 4 mg per kg taken orally twice-daily or lamivudine 8 mg per kg taken orally once-daily (up to a maximum of 300 mg daily), administered in combination with other antiretroviral agents, with or without food, is provided in Table 1.

Table 1. Dosing Recommendations for Abacavir and Lamivudine Scored Tablets

Weight (kg)	Once-daily Dosing Regimen ^a	Twice-daily Dosing Regimen		
		AM Dose	PM Dose	Total Daily Dose (mg)
5 to less than 6	1 ½ tablets (90 mg A/45 mg L)	½ tablet (30 mg A/15 mg L)	1 tablet (60 mg A/30 mg L)	90A/45L
6 to less than 9	2 tablets (120 mg A/60 mg L)	1 tablet (60 mg A/30 mg L)	1 tablet (60 mg A/30 mg L)	120A/60L
9 to less than 12	3 tablets (180 mg A/90 mg L)	1.5 tablets (90 mg A/45 mg L)	1.5 tablets (90 mg A/45 mg L)	180A/90L
12 to less than 17	4 tablets (240 mg A/ 120 mg L)	2 tablets (120 mg A/60 mg L)	2 tablets (120 mg A/60 mg L)	240A/120L
17 to less than 20	5 tablets (300 mg A/150 mg L)	2.5 tablets (150 mg A/75 mg L)	2.5 tablets (150 mg A/75 mg L)	300A/150L
20 to less than 25	6 tablets (360 mg A/180 mg L)	3 tablets (180 mg A/90 mg L)	3 tablets (180 mg A/90 mg L)	360A/180L
25 to less than 29	7 tablets (420 mg A/210 mg L)	3.5 tablets (210 mg A/105 mg L)	3.5 tablets (210 mg A/105 mg L)	420A/210L
29 to less than 35	8 tablets (480 mg A/240 mg L)	4 tablets (240 mg A/120 mg L)	4 tablets (240 mg A/120 mg L)	480A/240L
35 and greater	10 tablets (600 mg A/300 mg L) ^c	5 tablets (300 mg A/150 mg L) ^b	5 tablets (300 mg A/150 mg L) ^b	600A/300L

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 doses of abacavir 300 mg twice-daily and lamivudine 150 mg twice-daily (adult maximum daily dose), the adult formulations (abacavir 300 mg tablet and lamivudine 150 mg tablet) can be used.

- ^c 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 in water. The following procedure can be used:

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

DO NOT MIX THE ABACAVIR AND LAMIVUDINE TABLETS WITH ANY LIQUID OTHER THAN WATER. SPLIT TABLETS WHEN NEEDED. STORE UNUSED HALF TABLETS IN A SEPARATE BAG OR BOTTLE AND USE AS SOON AS PRACTICAL.

2.3 Not Recommended Due to Lack of Dosage Adjustment

Because Abacavir and Lamivudine tablets are a fixed-dose combination and cannot be dose adjusted, Abacavir and Lamivudine tablets are not recommended for:

- patients with creatinine clearance less than 50 mL per minute [*see Use in Specific Populations (8.6)*].
- patients with mild hepatic impairment. Abacavir and Lamivudine tablets are contraindicated in patients with moderate or severe hepatic impairment [*see Contraindications (4), Use in Specific Populations (8.7)*].

3 DOSAGE FORMS AND STRENGTHS

Abacavir and Lamivudine functionally scored tablets contain 60 mg of abacavir as abacavir (equivalent to 70.3 mg of abacavir sulfate USP) and 30 mg of lamivudine USP. The tablets are orange, oval, biconvex, film-coated tablets, debossed with 'H' on one side with score line and 'A and 9' separated by a score line on other side.

4 CONTRAINDICATIONS

Abacavir and Lamivudine tablets are contraindicated in patients with:

- who have the HLA-B*5701 allele [*see Warnings and Precautions (5.1)*].
- with prior hypersensitivity reaction to abacavir [*see Warnings and Precautions (5.1)*] 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, a component of Abacavir and Lamivudine tablets. 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 tablets or reinitiation of therapy with Abacavir and Lamivudine tablets, unless patients have a previously documented HLA-B*5701 allele assessment.
- Abacavir and Lamivudine tablets is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients.
- Before starting Abacavir and Lamivudine tablets, review medical history for prior exposure to any abacavir-containing product. NEVER restart Abacavir and Lamivudine tablets 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 tablets 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 tablets 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 tablets. 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 tablets 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 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. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Caution should be exercised when administering Abacavir and Lamivudine tablets to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with Abacavir and Lamivudine tablets 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

Posttreatment 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 subjects 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 subjects who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

5.4 Use With Interferon- and Ribavirin-based Regimens

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine, a component of Abacavir and Lamivudine tablets. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected patients [see *Clinical Pharmacology (12.3)*], 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. Patients receiving interferon alfa with or without ribavirin and Abacavir and Lamivudine tablets should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of Abacavir and Lamivudine tablets 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 the complete prescribing information for interferon and ribavirin).

5.5 Immune Reconstitution Syndrome

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

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

5.6 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 (MI) in patients on combination antiretroviral therapy, the use of abacavir

within the previous 6 months was correlated with an increased risk of MI. In a sponsor-conducted pooled analysis of clinical trials, no excess risk of MI 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, smoking).

5.8 Related Products that are Not Recommended

Abacavir and Lamivudine tablets contain fixed doses of 2 nucleoside analogue reverse transcriptase inhibitors (abacavir and lamivudine); concomitant administration of Abacavir and Lamivudine tablets with other products containing abacavir or lamivudine is not recommended. In addition, do not administer Abacavir and Lamivudine tablets in combination with products containing emtricitabine.

5.9 Pancreatitis

In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, lamivudine, a component of Abacavir and Lamivudine tablets, should be used with caution. Treatment with Abacavir and Lamivudine tablets should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur.

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 with steatosis [*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 (5.9)*].

6.1 Clinical Trials Experience in Adult Subjects

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

Additional Adverse Reactions with Use of Abacavir and Lamivudine

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)
Drug hypersensitivity ^{a,b}	9%	7%
Insomnia	7%	9%
Depression/Depressed mood	7%	7%
Headache/Migraine	7%	6%
Fatigue/Malaise	6%	8%
Dizziness/Vertigo	6%	6%
Nausea	5%	6%
Diarrhea ^a	5%	6%
Rash	5%	5%
Pyrexia	5%	3%
Abdominal pain/gastritis	4%	5%
Abnormal dreams	4%	5%
Anxiety	3%	5%

^a Subjects receiving abacavir 600 mg once daily, experienced a significantly higher incidence of severe drug hypersensitivity reactions and severe diarrhea compared with subjects who received abacavir 300 mg twice daily. Five percent (5%) of subjects receiving abacavir 600 mg once daily had severe drug hypersensitivity reactions compared with 2% of subjects receiving abacavir 300 mg twice daily. Two percent (2%) of subjects receiving abacavir 600 mg once daily had severe diarrhea while none of the subjects receiving abacavir 300 mg twice daily had this event.

^b 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 trials 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.

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.

6.2 Clinical Trials Experience in Pediatric Subjects

Abacavir

Therapy-experienced Pediatric Subjects (Twice-daily Dosing)

Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a greater than or equal to 5% frequency during therapy with abacavir 8 mg per kg twice daily, lamivudine 4 mg per kg twice daily, and zidovudine 180 mg per m² twice daily compared with lamivudine 4 mg per kg twice daily and zidovudine 180 mg per m² twice daily from CNA3006 are listed in Table 3.

Table 3. Treatment-emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2-4, Greater than or Equal to 5% Frequency) in Therapy-experienced Pediatric Subjects (CNA3006) through 16 Weeks of Treatment

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

Laboratory Abnormalities: In 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 and laboratory abnormalities reported in Table 3, other adverse reactions observed in the expanded access program were pancreatitis and increased GGT.

Abacavir and Lamivudine

Pediatric Subjects Once-daily versus Twice-daily Dosing (COL105677)

The safety of once-daily compared with twice-daily dosing of abacavir and lamivudine, administered as either single products or as a combination of abacavir and lamivudine, 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)*].

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 (5.9)*].

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

Neonates: Limited short-term safety information is available from 2 small, uncontrolled trials 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.

6.3 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 exposures.

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: Lactic acidosis and hepatic steatosis [see *Warnings and Precautions (5.2)*], posttreatment exacerbation of hepatitis B [see *Warnings and Precautions (5.3)*].

Hypersensitivity: Sensitization reactions (including anaphylaxis), urticaria.

Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.

Nervous: Paresthesia, peripheral neuropathy, seizures.

Respiratory: Abnormal breath sounds/wheezing.

Skin: Alopecia, erythema multiforme, Stevens-Johnson syndrome.

7 DRUG INTERACTIONS

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 and 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 as 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 first trimester), there was no difference between lamivudine and overall birth defects compared with the background birth defect rate of 2.7% in the US reference population of 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 300 mg lamivudine twice daily without other antiretrovirals. These trials were not designed or powdered 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 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. 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 embryoletality was seen in the rabbit at exposure levels similar to those observed in humans but there was no indication of this effect in the rat at exposure levels up to 35 times those in humans.

8.2 Lactation

The Centers for Disease Control and Prevention recommended that HIV-1-infected mothers 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 have been established in pediatric patients aged 3 months and older. Use of abacavir is supported by pharmacokinetic trials and evidence from adequate and well-controlled trials of abacavir in adults and pediatric subjects [*see Dosage and Administration (2.2), Adverse Reactions (6.2), Clinical Pharmacology (12.3), Clinical Studies (14.2)*].

Lamivudine

The safety and effectiveness of lamivudine in combination with other antiretroviral agents have been established in pediatric patients aged 3 months and older [*see Dosage and Administration (2.2), Adverse Reactions (6.2), Clinical Pharmacology (12.3), Clinical Studies (14.2)*].

8.5 Geriatric Use

Clinical trials of abacavir and lamivudine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of Abacavir and Lamivudine tablets in elderly

patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy[see *Dosage and Administration (2.2), Use in Specific Populations (8.6, 8.7)*].

8.6 Patients with Impaired Renal Function

Abacavir and Lamivudine tablets are not recommended for patients with creatinine clearance less than 50 mL per min because Abacavir and Lamivudine tablets are a fixed-dose combination and the dosage of the individual components cannot be adjusted. If a dose reduction of lamivudine, a component of Abacavir and Lamivudine, is required for patients with creatinine clearance less than 50 mL per min, then the individual components should be used [see *Clinical Pharmacology (12.3)*].

8.7 Patients with Impaired Hepatic Function

Abacavir and Lamivudine tablets are a fixed-dose combination and the dosage of the individual components cannot be adjusted. If a dose reduction of abacavir, a component of Abacavir and Lamivudine tablets, is required for patients with mild hepatic impairment (Child-Pugh Class A), then the individual components should be used [see *Clinical Pharmacology (12.3)*].

The safety, efficacy, and pharmacokinetic properties of abacavir have not been established in patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment; therefore, Abacavir and Lamivudine tablets is contraindicated in these patients [see *Contraindications (4)*].

10 OVERDOSAGE

There is no known specific treatment for overdose with Abacavir and Lamivudine tablets. 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.

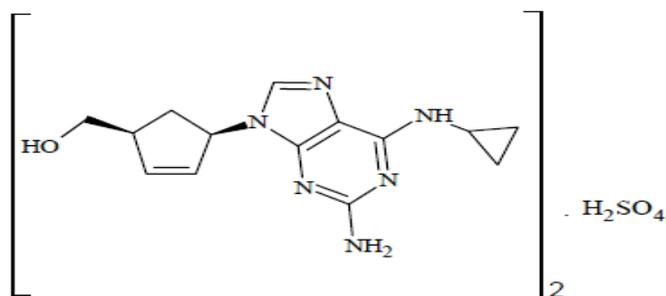
Lamivudine: Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event.

11 DESCRIPTION

Abacavir and Lamivudine tablets: Abacavir and Lamivudine tablets contain the following 2 synthetic nucleoside analogues: abacavir USP and lamivudine USP (also known as 3TC) with inhibitory activity against HIV-1.

Abacavir and Lamivudine tablets are for oral administration. Each orange film-coated tablet contains the active ingredients 60 mg of abacavir (equivalent to 70.3 mg of abacavir sulfate USP) and 30 mg of lamivudine USP. The inactive ingredients are colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablets are coated with opadry orange which contains FD & C Yellow #6/Sunset Yellow FCF Aluminum lake, hypromellose, polyethylene glycol, polysorbate 80, and titanium dioxide.

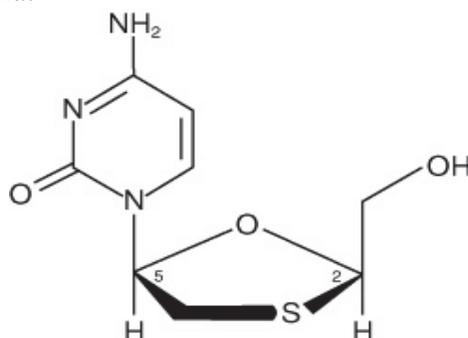
Abacavir Sulfate: The chemical name of abacavir sulfate is (*1S, 4R*)-4-[2-Amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate salt (2:1). Abacavir sulfate is the enantiomer with *1S, 4R* absolute configuration on the cyclopentene ring. It has a molecular formula of (C₁₄H₁₈N₆O)₂•H₂SO₄ and a molecular weight of 670.74 g per mol. It has the following structural formula:



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

Lamivudine

The chemical name of lamivudine is 2(1H) - Pyrimidinone, 4-amino-1- [2- (hydroxymethyl)-1, 3-oxathio-lan-5- yl], (2R-cis)-. Lamivudine has also been referred to as (-)-2'-deoxy-3'-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.26 g per mol. It has the following structural formula:



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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Abacavir and Lamivudine are antiviral agents [see *Microbiology (12.4)*].

12.3 Pharmacokinetics

Pharmacokinetics in Adults:

Abacavir and Lamivudine Tablets: Abacavir and lamivudine combination tablets (600 mg/300 mg) were comparable to Epzicom tablets of ViiV Healthcare USA (containing abacavir 600 mg and lamivudine 300 mg) when single doses were administered to healthy volunteers under fed and fasted conditions.

Abacavir: Following oral administration, abacavir is rapidly absorbed and extensively distributed. After oral administration of a single dose of 600 mg of abacavir in 20 subjects, C_{max} was 4.26 ± 1.19 mcg per mL (mean \pm SD) and AUC_{∞} was 11.95 ± 2.51 mcg·hr per 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 subjects, steady-state C_{\max} ($C_{\max,ss}$) was 2.04 ± 0.54 mcg per mL (mean \pm SD) and the 24-hour steady-state AUC ($AUC_{24,ss}$) was 8.87 ± 1.83 mcg·hr per 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 4.

Table 4. Pharmacokinetic Properties^a for Abacavir and Lamivudine in Adults

Parameter	Abacavir		Lamivudine	
Oral bioavailability (%)	86 ± 25	n = 6	86 ± 16	n = 12
Apparent volume of distribution (L/kg)	0.86 ± 0.15	n = 6	1.3 ± 0.4	n = 20
Systemic clearance (L/hr/kg)	0.80 ± 0.24	n = 6	0.33 ± 0.06	n = 20
Renal clearance (L/hr/kg)	$0.007 \pm .008$	n = 6	0.22 ± 0.06	n = 20
Elimination half-life (hr)	1.45 ± 0.32	n = 20	5 to 7 ^b	

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

^b Approximate range.

Effect of Food on Absorption of Abacavir and Lamivudine:

Abacavir and lamivudine tablets may be administered with or without food. Administration with a high-fat meal in a single-dose bioavailability trial resulted in no change in AUC_{∞} and a 40% decrease in C_{\max} for lamivudine. Food also did not alter the extent of systemic exposure (AUC_{∞}) to abacavir.

Special Populations:

Renal Impairment: Abacavir and Lamivudine tablets: The effect of renal impairment on the combination of abacavir and lamivudine has not been evaluated (see the prescribing information for the individual abacavir and lamivudine components).

Hepatic Impairment: Abacavir and Lamivudine tablets: The effect of hepatic impairment on the combination of abacavir and lamivudine has not been evaluated (see the prescribing information for the individual abacavir and lamivudine components).

Pregnancy: Abacavir: No data are available on the pharmacokinetics of abacavir during pregnancy.

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 and Lamivudine Tablets: The pharmacokinetics of abacavir and lamivudine tablets in pediatric subjects are under investigation. There are insufficient data at this time to recommend a dose.

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; no drug interaction trials have been conducted with combination of abacavir and lamivudine.

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.

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.

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 5.

Table 5. 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%	↔ a
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.

^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 per mL) and 0.07 to 1.0 microM against HIV-1_{IIIB} and HIV-1_{BaL}, respectively, and the mean EC₅₀ value 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 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. 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 EC₅₀ 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 exposures 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 female 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

14.1 Adults

One abacavir and lamivudine tablet given once daily is an alternative regimen to lamivudine tablets 300 mg once daily plus abacavir tablets 2 x 300 mg once daily as a component of antiretroviral therapy.

The following trial was conducted with the individual components of abacavir and lamivudine.

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%), white (54%), black (27%), and American Hispanic (15%). The median baseline CD4+ cell count was 262 cells per mm³ (range: 21 to 918 cells per mm³) and the median baseline plasma HIV-1 RNA was 4.89 log₁₀ copies per mL (range: 2.6 to 6.99 log₁₀ copies per mL).

The outcomes of randomized treatment are provided in Table 6.

Table 6. Outcomes of Randomized Treatment through Week 48 (CNA30021)

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

^a Subjects achieved and maintained confirmed HIV-1 RNA 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).

^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 188 cells per mm³ in the group receiving abacavir 600 mg once daily and 200 cells per mm³ in the group receiving abacavir 300 mg twice daily. Through Week 48, 6 subjects (2%) in the group receiving abacavir 600 mg once daily (4 CDC classification C events and 2 deaths) and 10 subjects (3%) in

the group receiving abacavir 300 mg twice daily (7 CDC classification C events and 3 deaths) experienced clinical disease progression. None of the deaths were attributed to trial medications.

14.2 Pediatric Subjects

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 the combination.

The proportions of subjects with HIV-1 RNA less than 80 copies per mL through 96 weeks are shown in Table 7. The differences between virologic responses in the two treatment arms were comparable across baseline characteristics for gender and age.

Table 7. Virologic Outcome of Randomized Treatment at Week 96^a (ARROW Randomization 3)

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

^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 are available as tablets. The tablets are orange, oval, biconvex, film-coated tablets, debossed with ‘H’ on one side with score line and ‘A and 9’ separated by a score line on other side. They are packaged as follows:

Bottles of 30 Tablets

NDC 68554-5137-0

Blister Card of 10 unit dose tablets (Alu-Alu)

NDC 68554-5137-1

Carton of 10 blisters and each blister card contains 10 unit dose tablets

NDC 68554-5137-4

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 tablets, and instruct 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 tablets. 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 healthcare provider right away to determine if they should stop taking Abacavir and Lamivudine tablets.
- that a hypersensitivity reaction can worsen and lead to hospitalization or death if Abacavir and Lamivudine tablets are not immediately discontinued.
- to not restart abacavir and lamivudine tablets 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 tablets are stopped right away.
- that if they have interrupted Abacavir and Lamivudine tablets 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 tablets or any other abacavir-containing product without medical consultation and only if medical care can be readily accessed by the patient or others.

Related Products that are Not Recommended

Inform patients that they should not take Abacavir and Lamivudine tablets with other products that also contain abacavir, lamivudine, or emtricitabine.

Lactic Acidosis/Hepatomegaly

Inform patients that some HIV medicines, including Abacavir and Lamivudine tablets, can cause a rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly) [*see Warnings and Precautions (5.2)*].

Patients with Hepatitis B or C Co-infection

Inform 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)*].

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)*].

Information about HIV-1 Infection:

Abacavir and Lamivudine tablets 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 tablets.

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 tablets 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.

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Manufactured by:



HETERO™

HETERO LABS LIMITED 2032397

Unit V, Polepally, Jadcherla,
Mahaboob Nagar-509 301, India.

Barcode

Revised: 11/2015

MEDICATION GUIDE

Abacavir and Lamivudine tablets, 60 mg/30 mg

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

Abacavir and Lamivudine tablets can cause serious side effects, including:

- **Serious allergic reactions (hypersensitivity reaction)** that can cause death have happened with Abacavir and Lamivudine tablets and other abacavir-containing products. Your risk of this allergic reaction is much higher if you have a gene variation called HLA-B*5701. Your healthcare provider can determine with a blood test if you have this gene variation.

If you get a symptom from 2 or more of the following groups while taking Abacavir and Lamivudine tablets, call your healthcare provider right away to find out if you should stop taking Abacavir and Lamivudine tablets.

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

A list of these symptoms is on the Warning Card your pharmacist gives you. **Carry this Warning Card with you at all times.**

If you stop Abacavir and Lamivudine tablets because of an allergic reaction, never take Abacavir and Lamivudine tablets or any other abacavir-containing medicine again.

- If you take Abacavir and Lamivudine tablets 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 tablets for any other reason, even for a few days, and you are not allergic to Abacavir and Lamivudine tablets, talk with your healthcare provider before taking it again. Taking Abacavir and Lamivudine tablets again can cause a serious allergic or life-threatening reaction, even if you never had an allergic reaction to it before.

If your healthcare provider tells you that you can take Abacavir and Lamivudine tablets again, start taking it when you are around medical help or people who can call a healthcare provider if you need one.

- **Build-up of acid in your blood (lactic acidosis).** Lactic acidosis can happen in some people who take Abacavir and Lamivudine tablets. 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
- unusual (not normal) muscle pain
- trouble breathing
- stomach pain with nausea and vomiting
- feel cold, especially in your arms and legs
- feel dizzy or light-headed
- have a fast or irregular heartbeat

- **Serious liver problems** can happen in people who take Abacavir and Lamivudine tablets. In some cases, these serious 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)
- dark or “tea-colored” urine
- light-colored stools (bowel movements)
- loss of appetite for several days or longer
- nausea
- 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, very overweight (obese), or have been taking nucleoside analogue medicines for a long time.

- **Worsening of hepatitis B virus in people who have HIV-1 infection.** If you have HIV-1 and hepatitis B virus (HBV) infection, your HBV may get worse (flare-up) if you stop taking Abacavir and Lamivudine tablets. A “flare-up” is when your HBV infection suddenly returns in a worse way than before. Worsening liver disease can be serious and may lead to death
 - Do not run out of Abacavir and Lamivudine tablets. Refill your prescription or talk to your healthcare provider before your Abacavir and Lamivudine tablets are all gone.
 - Do not stop Abacavir and Lamivudine tablets without first talking to your healthcare provider.
 - If you stop taking Abacavir and Lamivudine tablets, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your liver.
- **Resistant Hepatitis B Virus (HBV).** If you have HIV-1 and hepatitis B, the hepatitis B virus can change (mutate) during your treatment with Abacavir and Lamivudine tablets and become harder to treat (resistant).
- **Use with interferon and ribavirin-based regimens.** Worsening of liver disease that has caused death has happened in people infected with both HIV-1 and hepatitis C virus who are taking antiretroviral medicines and are also being treated for hepatitis C with interferon with or without ribavirin. If you are taking Abacavir and Lamivudine tablets and interferon with or without ribavirin tell your healthcare provider if you have any new symptoms.

What are Abacavir and Lamivudine tablets?

Abacavir and Lamivudine tablets are prescription HIV-1 (Human Immunodeficiency Virus-type 1) medicines used with other antiretroviral medicines to treat HIV-1 infection. HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS). Abacavir and Lamivudine tablets contains 2 prescription medicines, abacavir and lamivudine.

The safety and effectiveness of Abacavir and Lamivudine tablets has not been established in children under 3 months of age.

When used with other antiretroviral medicines to treat HIV-1 infection, Abacavir and Lamivudine tablets may help:

- reduce the amount of HIV-1 in your blood. This is called “viral load”.

- increase the number of CD4+ (T) cells in your blood, that help fight off other infections.

Reducing the amount of HIV-1 and increasing the CD4+ (T) cells in your blood may help improve your immune system. This may reduce your risk of death or getting infections that can happen when your immune system is weak (opportunistic infections).

Abacavir and Lamivudine tablets does not cure HIV-1 infection or AIDS. You must keep taking HIV-1 medicines to control HIV-1 infection and decrease HIV-related illnesses.

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

- Do not share or re-use 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 to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood.

Ask your healthcare provider if you have any questions about how to prevent passing HIV to other people.

Who should not take Abacavir and Lamivudine tablets?

Do not take Abacavir and Lamivudine tablets if you:

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

What should I tell my healthcare provider before taking Abacavir and Lamivudine tablets?

Before you take Abacavir and Lamivudine tablets tell your healthcare provider if 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.
- drink alcohol or take medicines that contain alcohol.
- are pregnant or plan to become pregnant. Taking Abacavir and Lamivudine tablets during pregnancy has not been associated with an increased risk of birth defects. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. **Do not breastfeed if you take Abacavir and Lamivudine tablets.**
 - 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. **Keep a list of your medicines to show your healthcare provider and pharmacist.** You can ask your healthcare provider or pharmacist for a list of medicines that interact with Abacavir and Lamivudine tablets. **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 with other medicines.

You should not take Abacavir and Lamivudine tablets if you take other products that also contain abacavir, lamivudine, or emtricitabine.

Tell your healthcare provider if you take:

- any other medicine to treat HIV-1
- medicines to treat hepatitis viruses such as interferon or ribavirin
- methadone

How should I take Abacavir and Lamivudine tablets?

- **Take Abacavir and Lamivudine tablets exactly as your healthcare provider tells you.**
- Do not change your dose or stop taking Abacavir and Lamivudine tablets without talking with your healthcare provider. If you miss a dose of Abacavir and Lamivudine tablets, take it as soon as you remember. Do not take 2 doses at the same time. If you are not sure about your dosing, call your healthcare provider.
- Stay under the care of a healthcare provider while taking.
- Abacavir and Lamivudine tablets may be taken with or without food.

Children aged 3 months and older, who can reliably swallow tablets, can be given the appropriate dose (see Table 1).

Table 1. Dosing Recommendations for Abacavir and Lamivudine Scored Tablets

Weight (kg)	Once-daily Dosing Regimen ^a	Twice-daily Dosing Regimen		
		AM Dose	PM Dose	Total Daily Dose (mg)
5 to less than 6	1 ½ tablets (90 mg A/45 mg L)	½ tablet (30 mg A/15 mg L)	1 tablet (60 mg A/30 mg L)	90A/45L
6 to less than 9	2 tablets (120 mg A/60 mg L)	1 tablet (60 mg A/30 mg L)	1 tablet (60 mg A/30 mg L)	120A/60L
9 to less than 12	3 tablets (180 mg A/90 mg L)	1.5 tablets (90 mg A/45 mg L)	1.5 tablets (90 mg A/45 mg L)	180A/90L
12 to less than 17	4 tablets (240 mg A/ 120 mg L)	2 tablets (120 mg A/60 mg L)	2 tablets (120 mg A/60 mg L)	240A/120L
17 to less than 20	5 tablets (300 mg A/150 mg L)	2.5 tablets (150 mg A/75 mg L)	2.5 tablets (150 mg A/75 mg L)	300A/150L
20 to less than 25	6 tablets (360 mg A/180 mg L)	3 tablets (180 mg A/90 mg L)	3 tablets (180 mg A/90 mg L)	360A/180L
25 to less than 29	7 tablets (420 mg A/210 mg L)	3.5 tablets (210 mg A/105 mg L)	3.5 tablets (210 mg A/105 mg L)	420A/210L
29 to less than 35	8 tablets (480 mg A/240 mg L)	4 tablets (240 mg A/120 mg L)	4 tablets (240 mg A/120 mg L)	480A/240L
35 and greater	10 tablets (600 mg A/300 mg L) ^c	5 tablets (300 mg A/150 mg L) ^b	5 tablets (300 mg A/150 mg L) ^b	600A/300L

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.

^b For recommended doses of abacavir 300 mg twice-daily and lamivudine 150 mg twice-daily (adult maximum daily dose), the adult formulations (abacavir 300 mg tablet and lamivudine 150 mg tablet) can be used.

^c 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.

- For very young children who cannot swallow tablets, the following procedure can be used:

Method of Preparation

For children unable to swallow tablets, dispersion can be prepared by dispensing required number of tablets in water. The following procedure can be used:

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

DO NOT MIX THE ABACAVIR AND LAMIVUDINE TABLETS WITH ANY LIQUID OTHER THAN WATER. SPLIT TABLETS WHEN NEEDED. STORE UNUSED HALF TABLETS IN A SEPARATE BAG OR BOTTLE AND USE AS SOON AS PRACTICAL.

- Do not run out of Abacavir and Lamivudine tablets. 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, 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?

- **Abacavir and Lamivudine tablets can cause serious side effects including:**
- See “**What is the most important information I should know about Abacavir and Lamivudine tablets?**”
- **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.
- **Changes in body fat** can happen in people who take HIV-1 medicines. These changes may include an increased amount of fat in the upper back and neck (“buffalo hump”), breast, and around the middle of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term health effects of these conditions are not known.
- **Heart attack (myocardial infarction).** Some HIV-1 medicines including Abacavir and Lamivudine tablets may increase your risk of heart attack.

The most common side effects of Abacavir and Lamivudine tablets include:

trouble sleeping
depression

nausea
diarrhea

headache
tiredness
dizziness

rash
fever

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 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?

- Store Abacavir and Lamivudine tablets below 30°C (86°F).

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

General information for safe and effective use of Abacavir and Lamivudine tablets.

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

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 that is written for health professionals.

What are the ingredients in Abacavir and Lamivudine tablets?

Active ingredients: abacavir and lamivudine

Inactive ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablets are coated with opadry orange which contains FD & C Yellow #6/Sunset Yellow FCF Aluminum lake, hypromellose, polyethylene glycol, polysorbate 80, and titanium dioxide.

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Manufactured by:



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

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