HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ABACAVIR and LAMIVUDINE tablets for oral suspension safely and effectively. See full prescribing information for ABACAVIR and LAMIVUDINE tablets for oral suspension.

ABACAVIR and LAMIVUDINE tablets for oral suspension
Initial U.S. Approval: 2004

WARNING: HYPERSENSITIVITY REACTIONS and EXACERBATIONS OF HEPATITIS B
See full prescribing information for complete boxed warning.

Hypersensitivity Reactions

- **Serious and sometimes fatal hypersensitivity reactions have occurred with abacavir-containing products. (5.1)**
- **Hypersensitivity to abacavir is a multi-organ clinical syndrome. (5.1)**
- **Patients who carry the HLA-B*5701 allele are at a higher risk of experiencing a hypersensitivity reaction to abacavir. (5.1)**
- **Abacavir and lamivudine tablets for oral suspension are contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients. (4)**
- **Discontinue abacavir and lamivudine tablets for oral suspension as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B*5701 status, permanently discontinue abacavir and lamivudine tablets for oral suspension if hypersensitivity cannot be ruled out, even when other diagnoses are possible. (5.1)**
- **Following a hypersensitivity reaction to abacavir and lamivudine tablets for oral suspension, NEVER restart abacavir and lamivudine tablets for oral suspension or any other abacavir-containing product. (5.1)**

Exacerbations of Hepatitis B

- **Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus type 1 (HIV-1) and have discontinued lamivudine, a component of abacavir and lamivudine tablets for oral suspension. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.2)**

---------- INDICATIONS AND USAGE ----------
Abacavir and lamivudine tablets for oral suspension, a combination of abacavir and lamivudine, both nucleoside analogue HIV-1 reverse transcriptase inhibitors, is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients aged 3 months and older and weighing at least 5 kg. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- Before initiating treatment, screen for the HLA-B*5701 allele because abacavir and lamivudine tablets for oral suspension contain abacavir. (2.1)
- Pediatric patients aged 3 months and older and weighing at least 5 kg: Administered either once or twice daily with or without food. Dosage should be based on body weight (kg) and should not exceed 600 mg of abacavir and 300 mg of lamivudine daily. (2.2)
- May be dispersed in water, swallowed whole or broken in half along the score. Do not chew. (2.3).
- Because the abacavir and lamivudine tablets for oral suspension is a fixed-dose product and cannot be dose adjusted, abacavir and lamivudine tablets for oral suspension is not recommended in patients requiring dosage adjustment or patients with hepatic impairment. (2.4)

---------- DOSAGE FORMS AND STRENGTHS ----------
Tablets for Oral Suspension: 60 mg of abacavir and 30 mg of lamivudine, functionally scored. (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 ----------

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

---------- ADVERSE REACTIONS ----------
The most commonly reported adverse reactions of at least moderate intensity (incidence greater than or equal to 5%) in adult HIV-1 clinical trials were dreams/sleep disorders, drug hypersensitivity, headaches/migraine, nausea, fatigue/malaise, diarrhea, rashes, abdominal pain/gastritis/gastrointestinal signs and symptoms, depressive disorders, dizziness, and musculoskeletal pain. (6.1)

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. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Mylan at 1-877-446-3679 (1-877-4-INFO-RX) 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)
- Sorbitol: Coadministration of lamivudine and sorbitol may decrease lamivudine concentrations; when possible, avoid chronic coadministration. (7.2)
- Riociguat: The riociguat dose may need to be reduced. (7.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: HYPERSENSITIVITY REACTIONS and EXACERBATIONS OF HEPATITIS B
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Screening for HLA-B*5701 Allele Prior to Starting Abacavir and Lamivudine Tablets for Oral Suspension
2.2 Recommended Dosage for Pediatric Patients Aged 3 Months and Older and Weighing at Least 5 kg
2.3 Important Administration and Preparation Instructions
2.4 Not Recommended Due to Lack of Dosage Adjustment
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity Reactions
5.2 Patients with Hepatitis B Virus Co-infection
5.3 Lactic Acidosis and Severe Hepatomegaly with Steatosis
5.4 Immune Reconstitution Syndrome
5.5 Myocardial Infarction
5.6 Pancreatitis
5.7 Lower Virologic Suppression Rates and Increased Risk of Viral Resistance with Oral Solution
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Methadone
7.2 Sorbitol
7.3 Riociguat
7.4 Drugs Inhibiting Organic Cation Transporters
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.3 Pharmacokinetics
12.4 Microbiology
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 Adult Trials
14.2 Pediatric Trials
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

WARNING: HYPERSENSITIVITY REACTIONS and EXACERBATIONS OF HEPATITIS B

Hypersensitivity Reactions: Serious and sometimes fatal hypersensitivity reactions, with multiple organ involvement, have occurred with abacavir, a component of abacavir and lamivudine tablets for oral suspension. Patients who carry the HLA-B*5701 allele are at a higher risk of a hypersensitivity reaction to abacavir; although, hypersensitivity reactions have occurred in patients who do not carry the HLA-B*5701 allele *[see Warnings and Precautions (5.1)]*.

Abacavir and lamivudine tablets for oral suspension 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 tablets for oral suspension or reinitiation of therapy with abacavir and lamivudine tablets for oral suspension, unless patients have a previously documented HLA-B*5701 allele assessment. Discontinue abacavir and lamivudine tablets for oral suspension 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 for oral suspension, NEVER restart abacavir and lamivudine tablets for oral suspension or any other abacavir-containing product because more severe symptoms, including death, can occur within hours. Similar severe reactions have also occurred rarely following the reintroduction of abacavir-containing products in patients who have no history of abacavir hypersensitivity *[see Warnings and Precautions (5.1)]*.

Exacerbations of Hepatitis B: Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus type 1 (HIV-1) and have discontinued lamivudine, which is a component of abacavir and lamivudine tablets for oral suspension. 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 for oral suspension and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

Abacavir and lamivudine tablets for oral suspension, in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in pediatric patients 3 months of age and older and weighing at least 5 kg.

2 DOSAGE AND ADMINISTRATION

2.1 Screening for HLA-B*5701 Allele Prior to Starting Abacavir and Lamivudine Tablets for Oral Suspension

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

2.2 Recommended Dosage for Pediatric Patients Aged 3 Months and Older and Weighing at Least 5 kg

The recommended oral dosage of abacavir and lamivudine tablets for oral suspension in HIV-1-infected pediatric patients 3 months of age and older and weighing at least 5 kg is based on body weight (see Table 1).

Abacavir and lamivudine tablets for oral suspension can be taken as once daily dosing or twice daily dosing with or without food *[see Clinical Pharmacology (12.3)]*.
Recommended dosage is:

- Once daily dosing: abacavir 16 mg/kg and lamivudine 8 mg/kg, OR
- Twice daily dosing: abacavir 8 mg/kg and lamivudine 4 mg/kg in combination with other antiretroviral agents.

The maximum daily dose of abacavir is 600 mg and the maximum daily dose of lamivudine is 300 mg.

Table 1. Dosing Recommendations for Abacavir and Lamivudine Scored Tablets for Oral Suspension for Pediatric Patients 3 Months of Age and Older and Weighing at Least 5 kg

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

ABC = abacavir; 3TC = 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)]*.

2.3 Important Administration and Preparation Instructions

Abacavir and lamivudine tablets for oral suspension may be taken with or without food.

Abacavir and lamivudine tablets for oral suspension may be dispersed in water. It may also be swallowed whole or broken in half along the score. Do not chew. Do not use or take tablets if they are damaged, broken, or expired.

Method of Preparation:
For children unable to swallow tablets, prepare the dispersion using the following procedure:

1. Place the required number of abacavir and lamivudine tablets for oral suspension in a container and add two teaspoons (10 mL) of drinking water per tablet. One teaspoon (5 mL) of drinking water should be used for ½ tablet.
2. Stir with a spoon or swirl the container (approximately 2-3 minutes) 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. Do not chew the tablet(s).
3. Drink the mixture immediately upon preparation but no later than 1 hour after mixing. If not administered immediately upon preparation, stir with a spoon or swirl the container (approximately 2-3 minutes) before administration. Discard the mixture if not used within 1 hour.
4. Rinse the container with an additional small amount of water (approximately one to two teaspoons [(5 mL to 10 mL) per tablet] and drink the contents to ensure that the entire dosage is taken.

For more details on preparation and administration, see **Instructions for Use**.

2.4 Not Recommended Due to Lack of Dosage Adjustment

Because the abacavir and lamivudine tablets for oral suspension is a fixed-dose product and cannot be dose adjusted, abacavir and lamivudine tablets for oral suspension is not recommended for:

- patients with creatinine clearance less than 30 mL/min and pediatric patients with a similar degree of renal impairment based on age-appropriate renal function assessment. There are no data available on the use of lamivudine, a component of abacavir and lamivudine tablets for oral suspension, in pediatric patients with renal impairment *[see Use in Specific Populations (8.6)]*.
- patients with mild hepatic impairment. Abacavir and lamivudine tablets for oral suspension is contraindicated in patients with moderate or severe hepatic impairment *[see Contraindications (4), Use in Specific Populations (8.7)]*.

Use of lamivudine oral solution or tablets and abacavir oral solution may be considered.

3 DOSAGE FORMS AND STRENGTHS

Abacavir and Lamivudine Tablets for Oral Suspension contain 60 mg of abacavir and 30 mg of lamivudine.

The tablets are white to off-white, round, scored tablets debossed with **AL** above the score and **7** below the score on one side of the tablet and **M** on the other side. The tablets are functionally scored.

4 CONTRAINDICATIONS

Abacavir and lamivudine tablets for oral suspension is contraindicated in patients:

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Serious and sometimes fatal hypersensitivity reactions have occurred with abacavir, a component of abacavir and lamivudine tablets for oral suspension. 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 for oral suspension or reinitiation of therapy with abacavir and lamivudine tablets for oral suspension, unless patients have a previously documented HLA-B*5701 allele assessment.
- Abacavir and lamivudine tablets for oral suspension are contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients.
- Before starting abacavir and lamivudine tablets for oral suspension, review medical history for prior exposure to any abacavir-containing product. NEVER restart abacavir and lamivudine tablets for oral suspension 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 for oral suspension 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 for oral suspension 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 for oral suspension. 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 for oral suspension or any other abacavir-containing product is recommended only if medical care can be readily accessed.
- A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill.

5.2 Patients with Hepatitis B Virus Co-infection

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 been reported in HIV-1-infected subjects who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

5.3 Lactic Acidosis and Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues, including abacavir and lamivudine (components of abacavir and lamivudine tablets for oral suspension). A majority of these cases have been in women. Female sex and obesity may be risk factors for the development of lactic acidosis and severe hepatomegaly with steatosis in patients treated with antiretroviral nucleoside analogues. Treatment with abacavir and lamivudine tablets for oral suspension should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity, which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations.

5.4 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including abacavir and lamivudine tablets for oral suspension. 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, Guillain-Barré syndrome, and autoimmune hepatitis) 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.

5.5 Myocardial Infarction

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

As a precaution, the underlying risk of coronary heart disease should be considered when prescribing antiretroviral therapies, including abacavir, and action taken to minimize all modifiable risk factors (e.g., hypertension, hyperlipidemia, diabetes mellitus, smoking).

5.6 Pancreatitis

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

5.7 Lower Virologic Suppression Rates and Increased Risk of Viral Resistance with Oral Solution

Pediatric subjects who received lamivudine oral solution (at weight band-based doses approximating 8 mg per kg per day) concomitantly with other antiretroviral oral solutions at any time in the ARROW trial had lower rates of virologic suppression, lower plasma lamivudine exposure, and developed viral resistance more frequently than those receiving lamivudine tablets *[see Clinical Pharmacology (12.3), Microbiology (12.4), Clinical Studies (14.2)]*.

6 ADVERSE REACTIONS

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

- Serious and sometimes fatal hypersensitivity reactions *[see Boxed Warning, Warnings and Precautions (5.1)]*.
- Exacerbations of hepatitis B *[see Boxed Warning, Warnings and Precautions (5.2)]*.

- Lactic acidosis and severe hepatomegaly with steatosis *[see Warnings and Precautions (5.3)]*.
- Immune reconstitution syndrome *[see Warnings and Precautions (5.4)]*.
- Myocardial infarction *[see Warnings and Precautions (5.5)]*.
- Pancreatitis *[see Warnings and Precautions (5.6)].*

6.1 Clinical Trials Experience

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

The safety of abacavir and lamivudine tablets for oral solution has been established from adequate and well-controlled studies of *abacavir and lamivudine* in adult patients with HIV-1 infection *[see Clinical Studies (14)]*. Below is a display of the adverse reactions of *abacavir and lamivudine* in these adequate and well-controlled studies in adults.

Clinical Trials Experience in Adults

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 for oral suspension *[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 300 mg twice daily or zidovudine 300 mg twice daily, both in combination with lamivudine 150 mg twice daily and efavirenz 600 mg once daily, from CNA30024 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-Naïve Adults (CNA30024[a]) through 48 Weeks of Treatment

Adverse Event	Abacavir plus Lamivudine plus Efavirenz (n = 324)	Zidovudine plus Lamivudine plus Efavirenz (n = 325)
Dreams/sleep disorders	10%	10%
Drug hypersensitivity	9%	< 1%[b]
Headache/migraine	7%	11%
Nausea	7%	11%
Fatigue/malaise	7%	10%
Diarrhea	7%	6%
Rashes	6%	12%
Abdominal pain/gastritis/ gastrointestinal signs and symptoms	6%	8%
Depressive disorders	6%	6%
Dizziness	6%	6%
Musculoskeletal pain	6%	5%
Bronchitis	4%	5%
Vomiting	2%	9%

a This trial 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.

b Ten (3%) cases of suspected drug hypersensitivity were reclassified as not being due to abacavir following unblinding.

Abacavir Once Daily versus Abacavir Twice Daily (CNA30021): Treatment-emergent clinical adverse reactions (rated by the investigator as at least moderate) with a 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, from CNA30021 were similar. For hypersensitivity reactions, subjects receiving abacavir once daily showed a rate of 9% in comparison with a rate of 7% for subjects receiving abacavir twice daily. However, 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.

Laboratory Abnormalities*:* Laboratory abnormalities (Grades 3-4) in therapy-naive adults during therapy with abacavir 300 mg twice daily or zidovudine 300 mg twice daily, both in combination with lamivudine 150 mg twice daily and efavirenz 600 mg once daily, from CNA30024 are listed in Table 3.

Table 3. Laboratory Abnormalities (Grades 3-4) in Therapy-Naive Adults (CNA30024) through 48 Weeks of Treatment

Grade 3/4 Laboratory Abnormalities	Abacavir plus Lamivudine plus Efavirenz (n = 324)	Zidovudine plus Lamivudine plus Efavirenz (n = 325)
Elevated CPK (>4 X ULN)	8%	8%
Elevated ALT (>5 X ULN)	6%	6%
Elevated AST (>5 X ULN)	6%	5%
Hypertriglyceridemia (>750 mg/dL)	6%	5%
Hyperamylasemia (>2 X ULN)	4%	5%
Neutropenia (ANC <750/mm^3)	2%	4%
Anemia (Hgb ≤6.9 gm/dL)	<1%	2%
Thrombocytopenia (Platelets <50,000/mm^3)	1%	<1%
Leukopenia (WBC ≤1,500/mm^3)	<1%	2%

ULN = Upper limit of normal.
n = Number of subjects assessed.

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

Clinical Trial in Pediatrics

Therapy-Experienced Pediatric Subjects (Twice-Daily Dosing): Abacavir and Lamivudine

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/kg twice daily, and zidovudine 180 mg/m^2 twice daily compared with lamivudine 4 mg/kg twice daily and zidovudine 180 mg/m^2 twice daily from CNA3006 are listed in Table 4.

Table 4. 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).

Pediatric Subjects Once-Daily versus Twice-Daily Dosing

The safety of once-daily compared with twice-daily dosing of abacavir and lamivudine, administered as either single products or as a fixed-dose combination, was assessed in the ARROW trial (COL105677) (n=336). Primary safety assessment in the ARROW 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 (5.4)]*.

*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.

6.2 Postmarketing Experience

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

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

Cardiovascular: Myocardial infarction.

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 (5.3)]*, posttreatment exacerbations of hepatitis B *[see Warnings and Precautions (5.2)]*.

Hypersensitivity: Sensitization reactions (including anaphylaxis), urticaria.

Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.

Nervous: Paresthesia, peripheral neuropathy, seizures.

Respiratory: Abnormal breath sounds/wheezing.

Skin: Alopecia, erythema multiforme, pruritus, Stevens-Johnson syndrome. 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)]*.

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.

7.2 Sorbitol

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

7.3 Riociguat

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

7.4 Drugs Inhibiting Organic Cation Transporters

Lamivudine is predominantly eliminated in the urine by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system (e.g., trimethoprim) *[see Clinical Pharmacology (12.3)]*. No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry:

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to abacavir and lamivudine tablets for oral suspension during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary:

Available data from the APR show no difference in the overall risk of birth defects for abacavir or lamivudine compared with the background rate for birth defects of 2.7% in the Metropolitan Atlanta Congenital Defects Program (MACDP) reference population *(see Data)*. The APR uses the MACDP as the U.S. reference population for birth defects in the general population. The MACDP evaluates women and infants from a limited geographic area and does not include outcomes for births that occurred at less than 20 weeks' gestation. The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15% to 20%. The background risk for major birth defects and miscarriage for the indicated population is unknown.

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

Data:

Human Data:

Abacavir: Based on prospective reports to the APR of exposures to abacavir during pregnancy resulting in live births (including over 1,400 exposed in the first trimester and over 1,300 exposed in second/third trimester), there was no difference between the overall risk of birth defects for abacavir compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of defects in live births was 3.2% (95% CI: 2.4% to 4.3%) following first trimester exposure to abacavir-containing regimens and 3.0% (95% CI: 2.2% to 4.1%) following second/third trimester exposure to abacavir-containing regimens.

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

Lamivudine: Based on prospective reports to the APR of exposures to lamivudine during pregnancy resulting in live births (including over 5,600 exposed in the first trimester and over 7,500 exposed in the second/third trimester), there was no difference between the overall risk of birth defects for lamivudine compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of defects in live births was 3.1% (95% CI: 2.6% to 3.6%) following first trimester exposure to lamivudine-containing regimens and 2.9% (95% CI: 2.5%, 3.3%) following second/third trimester exposure to lamivudine-containing regimens.

Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical trials conducted in South Africa. The trials assessed pharmacokinetics in 16 women at 36 weeks' gestation using 150 mg lamivudine twice daily with zidovudine, 10 women at 38 weeks' gestation using 150 mg lamivudine twice daily with zidovudine, and 10 women at 38 weeks' gestation using lamivudine 300 mg twice daily without other antiretrovirals. These trials were not designed or powered to provide efficacy information. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, amniotic fluid specimens were collected following natural rupture of membranes and confirmed that lamivudine crosses the placenta in humans. Based on limited data at delivery, median (range) amniotic fluid concentrations of lamivudine were 3.9 (1.2 to 12.8)-fold greater compared with paired maternal serum concentration (n = 8).

Animal Data

Abacavir: Abacavir was administered orally to pregnant rats (at 100, 300, and 1000 mg/kg/day) and rabbits (at 125, 350, or 700 mg/kg/day) during organogenesis (on Gestation Days 6 through 17 and 6 through 20, respectively). Fetal malformations (increased incidences of fetal anasarca and skeletal malformations) or developmental toxicity (decreased fetal body weight and crown-rump length) were observed in rats at doses up to 1000 mg/kg/day, resulting in exposures approximately 35 times the human exposure (AUC) at the recommended daily dose. No developmental effects were observed in rats at 100 mg/kg/day, resulting in exposures (AUC) 3.5 times the human exposure at the recommended daily dose. In a fertility and early embryo-fetal development study conducted in rats (at 60, 160, or 500 mg/kg/day), embryonic and fetal toxicities (increased resorptions, decreased fetal body weights) or toxicities to the offspring

(increased incidence of stillbirth and lower body weights) occurred at doses up to 500 mg/kg/day. No developmental effects were observed in rats at 60 mg/kg/day, resulting in exposures (AUC) approximately 4 times the human exposure at the recommended daily dose. Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. In pregnant rabbits, no developmental toxicities and no increases in fetal malformations occurred at up to the highest dose evaluated, resulting in exposures (AUC) approximately 9 times the human exposure at the recommended dose.

Lamivudine: Lamivudine was administered orally to pregnant rats (at 90, 600, and 4000 mg/kg/day) and rabbits (at 90, 300 and 1000 mg/kg/day and at 15, 40, and 90 mg/kg/day) during organogenesis (on Gestation Days 7 through 16 [rat] and 8 through 20 [rabbit]). No evidence of fetal malformations due to lamivudine was observed in rats and rabbits at doses producing plasma concentrations (C_{max}) approximately 35 times higher than human exposure at the recommended daily dose. Evidence of early embryolethality was seen in the rabbit at systemic exposures (AUC) similar to those observed in humans, but there was no indication of this effect in the rat at plasma concentrations (C_{max}) 35 times higher than human exposure at the recommended daily dose. Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. In the fertility/pre- and postnatal development study in rats, lamivudine was administered orally at doses of 180, 900, and 4000 mg/kg/day from prior mating through postnatal Day 20). In the study, development of the offspring, including fertility and reproductive performance, were not affected by the maternal administration of lamivudine.

8.2 Lactation

Risk Summary

Abacavir and lamivudine are present in human milk. There is no information on the effects of abacavir and lamivudine on the breastfed infant or the effects of the drug on milk production.

Potential risks of breastfeeding include: (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults.

8.4 Pediatric Use

The safety and effectiveness of abacavir and lamivudine tablets for oral suspension in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients 3 months of age and older has been established through studies of abacavir and lamivudine, both components of abacavir and lamivudine tablets for oral suspension. Use of abacavir and lamivudine tablets for oral suspension is supported by evidence from adequate and well-controlled studies of individual components in adults with additional pharmacokinetics, safety, and virologic data in pediatric subjects with HIV-1 infection 3 months of age and older *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.2)].*

The safety and effectiveness of abacavir and lamivudine tablets for oral suspension has not been established in pediatric patients younger than 3 months of age.

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

8.6 Renal Impairment
Abacavir and lamivudine tablets for oral suspension is not recommended for patients with creatinine clearance less than 30 mL/min because abacavir and lamivudine tablets for oral suspension is 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 tablets for oral suspension, is required for patients with creatinine clearance less than 30mL/min, then the individual components should be used *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment
Abacavir and lamivudine tablets for oral suspension is 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 for oral suspension, 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 for oral suspension is contraindicated in these patients *[see Contraindications (4)]*.

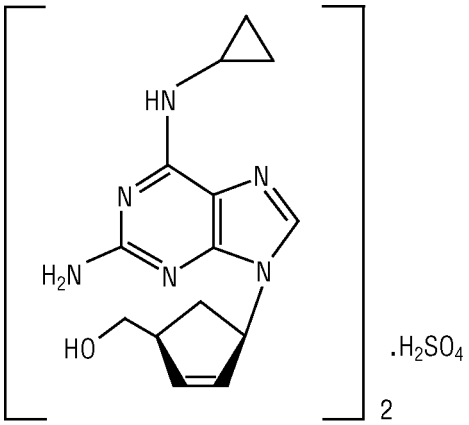
10 OVERDOSAGE
There is no known specific treatment for overdose with abacavir and lamivudine tablets for oral suspension. If overdose occurs, the patient should be monitored, and standard supportive treatment applied as required.

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.

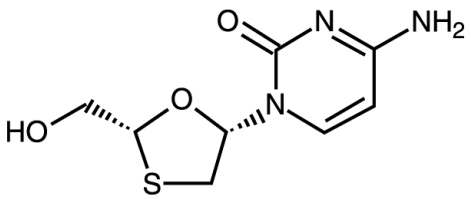
11 DESCRIPTION
Abacavir and lamivudine tablets for oral suspension contain abacavir sulphate and lamivudine (3TC), synthetic nucleoside analogues with inhibitory activity against HIV-1.

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



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

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



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

Abacavir and lamivudine tablets for oral suspension: Each scored white to off-white tablet contains the active ingredients 60 mg of abacavir (equivalent to 70.2 mg of abacavir sulfate) and 30 mg of lamivudine, and the inactive ingredients crospovidone, microcrystalline cellulose, sodium stearyl fumarate, strawberry cream flavor permaseal (maltodextrin, modified starch, natural identical flavoring substance, natural flavoring substance and propylene glycol) and sucralose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Abacavir and lamivudine tablets for oral suspension is an antiretroviral agent *[see Microbiology (12.4)]*.

12.3 Pharmacokinetics

Pharmacokinetics in Adults

Abacavir and Lamivudine Tablets for Oral Suspension*:* Exposures of abacavir and lamivudine were comparable when single doses of abacavir and lamivudine tablets for oral suspension (60 mg/30 mg), ZIAGEN oral solution (containing abacavir 20 mg/mL) and EPIVIR oral solution (containing lamivudine 10 mg/mL) were administered to healthy volunteers under fed and fasted conditions.

Effect of Food on Abacavir and Lamivudine Tablets for Oral Suspension: Food is unlikely to have a clinically meaningful effect on systemic exposures of abacavir and lamivudine following the administration of abacavir and lamivudine tablets for oral suspension.

Abacavir*:* After oral administration of 300 mg twice daily in 20 subjects, the steady-state peak serum abacavir concentration (C_{max}) was 3.0 ± 0.89 mcg/mL (mean ± SD) and $AUC_{(0\text{-}12\ h)}$ was 6.02 ± 1.73 mcg•hour/mL. After oral administration of a single dose of 600 mg of abacavir in 20 subjects, C_{max} was 4.26 ± 1.19 mcg/mL (mean ± SD) and AUC_{∞} was 11.95 ± 2.51 mcg•hour/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. Abacavir is not significantly metabolized by cytochrome P450 enzymes. 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. Elimination of abacavir was quantified in a mass balance trial following administration of a 600-mg dose of 14C-abacavir: 99% of the radioactivity was recovered, 1.2% was excreted in the urine as abacavir, 30% as the 5′-carboxylic acid metabolite, 36% as the 5′-glucuronide metabolite, and 15% as unidentified minor metabolites in the urine. Fecal elimination accounted for 16% of the dose.

Lamivudine*:* The pharmacokinetics of lamivudine was evaluated in 12 adult HIV-1-infected subjects dosed with lamivudine 150 mg twice daily in combination with other antiretroviral agents. The geometric mean (95% CI) for $AUC_{(0\text{-}12)}$ was 5.53 (4.58, 6.67) mcg.h/mL and for Cmax was 1.40 (1.17, 1.69) mcg/mL. The steady-state pharmacokinetic properties of the lamivudine 300 mg tablet once daily for 7 days compared with the lamivudine 150 mg tablet twice daily for 7 days were assessed in a crossover trial in 60 healthy subjects. Lamivudine 300 mg once daily resulted in lamivudine exposures that were similar to lamivudine 150 mg twice daily with respect to plasma $AUC_{24,ss}$; however, $C_{max,ss}$ was 66% higher and the trough value was 53% lower compared with the 150 mg twice daily regimen. Intracellular lamivudine triphosphate exposures in peripheral blood mononuclear cells were also similar with respect to $AUC_{24,ss}$ and $C_{max24,ss}$; however, trough values were lower compared with the 150 mg twice daily regimen. Inter-subject variability was greater for intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough concentrations.

Binding to plasma protein is less than 36%. In vitro studies showed that over the concentration range of 0.1 to 100 mcg/mL, the amount of lamivudine associated with erythrocytes ranged from 53% to 57% and was independent of concentration. The majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion. 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 most single-dose trials in HIV-1-infected subjects, HBV-infected subjects, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life (t½) ranged from 5 to 7 hours.

Specific Populations

Renal Impairment

Abacavir: The pharmacokinetic properties of abacavir have not been determined in patients with impaired renal function. Renal excretion of unchanged abacavir is a minor route of elimination in humans.

Lamivudine: The pharmacokinetic properties of lamivudine have been determined in a small group of HIV-1-infected adults with impaired renal function. Lamivudine exposures were higher in patients with varying degrees of renal impairment as compared to patients with normal renal function *[see Dosage and Administration (2.3), Use in Specific Populations (8.6), and the U.S prescribing information for lamivudine].* The effects of renal impairment on lamivudine pharmacokinetics in pediatric patients are not known.

Hepatic Impairment

Abacavir: The pharmacokinetics of abacavir have been studied in subjects with mild hepatic impairment (Child-Pugh Class A). There was a mean increase of 89% in the abacavir AUC and an increase of 58% in the half-life of abacavir after a single dose of 600 mg of abacavir. The AUCs of the metabolites were not modified by mild liver disease; however, the rates of formation and elimination of the metabolites were decreased *[see Dosage and Administration (2.3), Contraindications (4), Use in Specific Populations (8.7)].*

Lamivudine: The pharmacokinetic properties of lamivudine have been determined in adults with impaired hepatic function. Pharmacokinetic parameters were not altered by diminishing hepatic function. Safety and efficacy of lamivudine have not been established in the presence of decompensated liver disease.

Pregnant Women

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

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

Pediatric Patients

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

The pharmacokinetics of abacavir dosed once daily in HIV-1-infected pediatric subjects aged 3 months through 12 years was evaluated in 3 trials (PENTA 13 [n = 14], PENTA 15 [n = 18], and ARROW [n = 36]). All 3 trials were 2-period, crossover, open-label pharmacokinetic trials of twice- versus once-daily dosing of abacavir and lamivudine. For the oral solution as well as the tablet formulation, these 3 trials demonstrated that once-daily dosing provides comparable AUC_{0-24} to twice-daily dosing of abacavir at the same total daily dose. The mean C_{max} was approximately 1.6- to 2.3-fold higher with abacavir once-daily dosing compared with twice-daily dosing.

Lamivudine: The pharmacokinetics of lamivudine have been studied after either single or repeat doses of lamivudine in 210 pediatric subjects. Pediatric subjects receiving lamivudine oral solution (dosed at approximately 8 mg/kg/day) achieved approximately 25% lower plasma concentrations of lamivudine compared with HIV-1-infected adults. Pediatric subjects receiving lamivudine oral tablets achieved plasma concentrations comparable to or slightly higher than those observed in adults. 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. Lower lamivudine exposures in pediatric patients receiving lamivudine oral solution is likely due to the interaction between lamivudine and concomitant solutions containing sorbitol (such as abacavir).

The pharmacokinetics of lamivudine dosed once daily in HIV-1-infected pediatric subjects aged 3 months through 12 years was evaluated in 3 trials (PENTA-15 [n = 17], PENTA 13 [n = 19], and ARROW PK [n = 35]). All 3 trials were 2-period, crossover, open-label pharmacokinetic trials of twice- versus once-daily dosing of abacavir and lamivudine. These 3 trials demonstrated that once-daily dosing provides similar AUC_{0-24} to twice-daily dosing of lamivudine at the same total daily dose when comparing the dosing regimens within the same formulation (i.e., either the oral solution or the tablet formulation). The mean C_{max} was approximately 80% to 90% higher with lamivudine once-daily dosing compared with twice-daily dosing.

Table 5. Pharmacokinetic Parameters (Geometric Mean [95% CI]) after Repeat Dosing of Lamivudine in 3 Pediatric Trials

	Trial (Number of Subjects)		
	ARROW PK (n = 35)	**PENTA-13 (n = 19)**	**PENTA-15 (n = 17)[a]**
Age Range	**3-12 years**	**2-12 years**	**3-36 months**
Formulation	**Tablet**	**Solution[b] and Tablet[c]**	**Solution[b]**

Parameter	Once Daily	Twice Daily	Once Daily	Twice Daily	Once Daily	Twice Daily
C_{max} (mcg/mL)	3.17 (2.76, 3.64)	1.80 (1.59, 2.04)	2.09 (1.80, 2.42)	1.11 (0.96, 1.29)	1.87 (1.65, 2.13)	1.05 (0.88, 1.26)
$AUC_{(0-24)}$ (mcg•h/mL)	13.0 (11.4, 14.9)	12.0 (10.7, 13.4)	9.80 (8.64, 11.1)	8.88 (7.67, 10.3)	8.66 (7.46, 10.1)	9.48 (7.89, 11.4)

[a] n = 16 for PENTA-15 C_{max}.
[b] Solution was dosed at 8 mg/kg/day.
[c] Five subjects in PENTA-13 received lamivudine tablets.

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

There are no clinically significant differences in the pharmacokinetics of the individual components (abacavir or lamivudine) based on sex, or race/ethnicity based on available information from each of the individual components. The pharmacokinetics of abacavir and lamivudine have not been studied in subjects over 65 years of age.

Drug Interaction Studies
The drug interactions described are based on trials conducted with abacavir or lamivudine as single entities; no drug interaction trials have been conducted with abacavir and lamivudine tablets for oral suspension.

Effect of Abacavir and Lamivudine on the Pharmacokinetics of Other Agents*: In vitro* studies have shown that abacavir has potential to inhibit CYP1A1 and limited potential to inhibit metabolism mediated by CYP3A4. Lamivudine does not inhibit or induce CYP3A4. Abacavir and lamivudine do not inhibit or induce other CYP enzymes (such as CYP2C9 or CYP2D6). Based on *in vitro* study results, abacavir and lamivudine at therapeutic drug exposures are not expected to affect the pharmacokinetics of drugs that are substrates of the following transporters: organic anion transporter polypeptide (OATP)1B1/3, breast cancer resistance protein (BCRP) or P-glycoprotein (P-gp), organic cation transporter (OCT)1, OCT2, OCT3 (lamivudine only), or multidrug and toxic extrusion protein (MATE)1 and MATE2-K.

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

Effect of Other Agents on the Pharmacokinetics of Abacavir or Lamivudine: Abacavir and lamivudine are not significantly metabolized by CYP enzymes; therefore, CYP enzyme inhibitors or inducers are not expected to affect their concentrations.

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

Lamivudine: Lamivudine is a substrate of MATE1, MATE2-K, and OCT2 *in vitro*. Trimethoprim (an inhibitor of these drug transporters) has been shown to increase lamivudine plasma concentrations. This interaction is not considered clinically significant as no dose adjustment of lamivudine is needed. Lamivudine is a substrate of P-gp and BCRP; however, considering its absolute bioavailability (87%), it is unlikely that these transporters play a significant role in the absorption of lamivudine. Therefore, coadministration of drugs that are inhibitors of these efflux transporters is unlikely to affect the disposition and elimination of lamivudine.

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

Lamivudine: Zidovudine*:* No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-1-infected adult subjects given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg every 12 hours).

Other Interactions

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

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

Ribavirin: *In vitro* data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected subjects.

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

The effects of other coadministered drugs on abacavir or lamivudine are provided in Table 6.

Table 6. 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). EC_{50} values ranged from 3.7 to 5.8 microM (1 microM = 0.28 mcg/mL) and 0.07 to 1.0 microM against HIV-1_{IIIB} and HIV-1_{BaL}, respectively, and the mean EC_{50} value was 0.26 ± 0.18 microM against 8 clinical isolates. The median EC_{50} values of abacavir were 344 nM (range: 14.8 to 676

nM), 16.9 nM (range: 5.9 to 27.9 nM), 8.1 nM (range: 1.5 to 16.7 nM), 356 nM (range: 35.7 to 396 nM), 105 nM (range: 28.1 to 168 nM), 47.6 nM (range: 5.2 to 200 nM), 51.4 nM (range: 7.1 to 177 nM), and 282 nM (range: 22.4 to 598 nM) against HIV-1 clades A-G and group O viruses (n = 3 except n = 2 for clade B), respectively. The EC_{50} values against HIV-2 isolates (n = 4) ranged from 24 to 490 nM. The antiviral activity of abacavir in cell culture was not antagonized when combined with the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine or zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, or the protease inhibitor (PI) amprenavir. Ribavirin (50 microM) used in the treatment of chronic HCV infection had no effect on the anti–HIV-1 activity of abacavir in cell culture.

Lamivudine*:* The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines including monocytes and PBMCs using standard susceptibility assays. EC_{50} values were in the range of 0.003 to 15 microM (1 microM = 0.23 mcg per mL). The median EC_{50} 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_{50} values against HIV-2 isolates (n = 4) ranged from 0.003 to 0.120 microM in PBMCs. Lamivudine was not antagonistic to all tested anti-HIV agents. 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.

Resistance

Abacavir: HIV-1 isolates with reduced susceptibility to abacavir have been selected in cell culture. Genotypic analysis of isolates selected in cell culture and recovered from abacavir-treated subjects demonstrated that amino acid substitutions K65R, L74V, Y115F, and M184V/I emerged in HIV-1 RT. M184V or I substitutions resulted in 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.

Thirty-nine percent (7 of 18) of the isolates from subjects who experienced virologic failure in the abacavir once-daily arm had a greater than 2.5-fold mean decrease in abacavir susceptibility with a median-fold decrease of 1.3 (range: 0.5 to 11) compared with 29% (5 of 17) of the failure isolates in the twice-daily arm with a median-fold decrease of 0.92 (range: 0.7 to 13).

Lamivudine: Lamivudine-resistant variants of HIV-1 have been selected in cell culture. Genotypic analysis showed that the resistance was due to a specific amino acid substitution in the HIV-1 reverse transcriptase at codon 184 changing the methionine to either valine or isoleucine (M184V/I).

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from subjects. Susceptibility of clinical isolates to lamivudine and zidovudine was monitored in controlled clinical trials. In subjects receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most subjects became phenotypically and genotypically resistant to lamivudine within 12 weeks.

Pediatrics*:* Pediatric subjects receiving lamivudine oral solution concomitantly with other antiretroviral oral solutions (abacavir, nevirapine/efavirenz, or zidovudine) in ARROW developed viral resistance more frequently than those receiving tablets. At randomization to once-daily or twice-daily dosing of lamivudine plus abacavir, 13% of subjects who started on tablets and 32% of subjects who started on solution had resistance substitutions. The resistance profile observed in pediatrics is similar to that observed in adults in terms of the genotypic substitutions detected and relative frequency, with the most commonly detected substitutions at M184 (V or I) *[see Clinical Studies (14.2)*.

Cross-Resistance

Abacavir:
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.

Lamivudine:
Cross-resistance has been observed among nucleoside reverse transcriptase inhibitors (NRTIs). Lamivudine-resistant HIV-1 mutants were cross-resistant in cell culture to didanosine (ddI). Cross-resistance is also expected with abacavir and emtricitabine as these select M184V substitutions.

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

Lamivudine*:* In a study of reproductive performance, lamivudine administered to rats at doses up to 4,000 mg/kg/day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

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 Adult Trials

The effectiveness of abacavir and lamivudine tablets for oral solution has been established for HIV-1 infection based on adequate and well-controlled studies of *abacavir and lamivudine* in adult patients with HIV-1 infection. Below is a display of the efficacy results of the adequate and well-controlled studies of *abacavir and lamivudine* in adult patients with HIV-1 infection.

Therapy-Naive Adults: CNA30024 was a multicenter, 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). The duration of double-blind treatment was at least 48 weeks. Trial participants were male (81%), white (51%), black (21%), and Hispanic (26%). The median age was 35 years; the median pretreatment CD4+ cell count was 264 cells/mm^3, and median plasma HIV-1 RNA was 4.79 log10 copies/mL. The outcomes of randomized treatment are provided in Table 7.

Table 7. Outcomes of Randomized Treatment through Week 48 (CAN30024)

Outcome	Abacavir plus Lamivudine plus Efavirenz (n = 324)	Zidovudine plus Lamivudine plus Efavirenz (n = 325)

Responder[a]	69% (73%)	69% (71%)
Virologic failures[b]	6%	4%
Discontinued due to adverse reactions	14%	16%
Discontinued due to other reasons[c]	10%	11%

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

b Includes viral rebound, insufficient viral response according to the investigator, and failure to achieve confirmed less than or equal to 50 copies per mL by Week 48.

c Includes consent withdrawn, lost to follow up, protocol violations, those with missing data, clinical progression, and other.

After 48 weeks of therapy, the median CD4+ cell count increases from baseline were 209 cells/mm^3 in the group receiving abacavir and 155 cells/mm^3 in the zidovudine group. Through Week 48, 8 subjects (2%) in the group receiving abacavir (5 CDC classification C events and 3 deaths) and 5 subjects (2%) on the zidovudine arm (3 CDC classification C events and 2 deaths) experienced clinical disease progression.

CNA30021 was an international, multicenter, 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/mm^3 (range: 21 to 918 cells/mm^3) and the median baseline plasma HIV-1 RNA was 4.89 $\log_{10}$ copies/mL (range: 2.60 to 6.99 $\log_{10}$ copies/mL).

The outcomes of randomized treatment are provided in Table 8.

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

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

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

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

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

After 48 weeks of therapy, the median CD4+ cell count increases from baseline were 188 cells/mm^3 in the group receiving abacavir 600 mg once daily and 200 cells/mm^3 in the group receiving abacavir 300 mg twice daily. Through Week 48, 6 subjects (2%) in the group receiving abacavir 600 mg once daily (4 CDC classification C events and 2 deaths) and 10 subjects (3%) in the group receiving abacavir 300 mg twice daily (7 CDC classification C events and 3 deaths) experienced clinical disease progression. None of the deaths were attributed to trial medications.

14.2 Pediatric Trials

The effectiveness of abacavir and lamivudine tablets for oral solution has been established for HIV-1 infection based on adequate and well-controlled studies of *abacavir and lamivudine* in adult and pediatric patients with HIV-1 infection. Below is a display of the efficacy results of the adequate and well-controlled studies of *abacavir and lamivudine* in pediatric patients with HIV-1 infection.

Therapy-Experienced Pediatric Subjects: CNA3006 was a randomized, double-blind trial comparing abacavir 8 mg per kg twice daily plus lamivudine 4 mg/kg twice daily plus zidovudine 180 mg/m^2 twice daily versus lamivudine 4 mg per kg twice daily plus zidovudine 180 mg/m^2 twice daily. Two hundred and five therapy-experienced pediatric subjects were enrolled: female (56%), white (17%), black (50%), Hispanic (30%), median age of 5.4 years, baseline CD4+ cell percent greater than 15% (median = 27%), and median baseline plasma HIV-1 RNA of 4.6 $\log_{10}$ copies/mL. Eighty percent and 55% of subjects had prior therapy with zidovudine and lamivudine, respectively, most often in combination. The median duration of prior nucleoside analogue therapy was 2 years. At 16 weeks, the proportion of subjects responding based on plasma HIV-1 RNA less than or equal to 400 copies/mL was significantly higher in subjects receiving abacavir plus lamivudine plus zidovudine compared with subjects receiving lamivudine plus zidovudine, 13% versus 2%, respectively. Median plasma HIV-1 RNA changes from baseline were -0.53 $\log_{10}$ copies/mL in the group receiving abacavir plus lamivudine plus zidovudine compared with -0.21 $\log_{10}$ copies/mL in the group receiving lamivudine plus zidovudine. Median CD4+ cell count increases from baseline were 69 cells/mm^3 in the group receiving abacavir plus lamivudine plus zidovudine and 9 cells/mm^3 in the group receiving lamivudine plus zidovudine.

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

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

The proportions of subjects with HIV-1 RNA less than 80 copies/mL through 96 weeks are shown in Table 9. The differences between virologic responses in the two treatment arms were comparable across baseline characteristics for gender and age.

Table 9. 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/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/mL (or missing).

16 HOW SUPPLIED/STORAGE AND HANDLING

Abacavir and Lamivudine Tablets for Oral Suspension contain 60 mg of abacavir and 30 mg of lamivudine.

The tablets are white to off-white, round, scored tablets debossed with **AL** above the score and **7** below the score on one side of the tablet and **M** on the other side. The tablets are functionally scored and are available as follows:

NDC 0378-0000-00
Bottles of 60 tablets with induction seal and child-resistant cap

Store below 30°C (86°F).

Dispense in the original container and keep the container tightly closed to protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patients, parents or caregivers to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Hypersensitivity Reactions:

Inform patients, parents or caregivers:

- 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 for oral suspension 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 for oral suspension. 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)]*.
- 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 for oral suspension.
- that a hypersensitivity reaction can worsen and lead to hospitalization or death if abacavir and lamivudine tablets for oral suspension is not immediately discontinued.
- to not restart abacavir and lamivudine tablets for oral suspension or any other abacavir-containing product following a hypersensitivity reaction because more severe symptoms can occur within hours and may include life-threatening hypotension and death.
- that if they have a hypersensitivity reaction, they should dispose of any unused abacavir and lamivudine tablets for oral suspension to avoid restarting abacavir.
- that a hypersensitivity reaction is usually reversible if it is detected promptly and abacavir and lamivudine tablets for oral suspension is stopped right away.
- that if they have interrupted abacavir and lamivudine tablets for oral suspension 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 for oral suspension or any other abacavir-containing product without medical consultation and only if medical care can be readily accessed by the patient or others.

Patient with Hepatitis B or C Co-infection:

Advise patients, parents or caregivers of 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, parents or caregivers to discuss any changes in regimen with their physician *[see Warnings and Precautions (5.2)]*.

Lactic Acidosis/Hepatomegaly with Steatosis:

Advise patients, parents or caregivers that lactic acidosis and severe hepatomegaly with steatosis have been reported with use of nucleoside analogues and other antiretrovirals. Advise patients, parents or caregivers to stop abacavir and lamivudine tablets for oral suspension if the child

develops clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity *[see Warnings and Precautions (5.3)]*.

Immune Reconstitution Syndrome:
Advise patients, parents or caregivers to inform their healthcare provider immediately of any signs and symptoms of infection as inflammation from previous infection may occur soon after combination antiretroviral therapy, including when abacavir and lamivudine tablets for oral suspension is started *[see Warnings and Precautions (5.4)]*.

Risk of Pancreatitis:
Advise patients, parents or caregivers to monitor pediatric patients for signs and symptoms of pancreatitis *[see Warnings and Precautions (5.6)]*.

Pregnancy Registry:
Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to abacavir and lamivudine tablets for oral suspension during pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation:
Inform individuals with HIV-1 infection that the risks of breastfeeding include: (1) HIV 1 transmission (in HIV-1–negative infants), (2) developing viral resistance (in HIV-1–positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults *[see Use in Specific Populations (8.2)]*.

Missed Dose:
Instruct patients, parents or caregivers that if the child misses a dose of abacavir and lamivudine tablets for oral suspension, to take it as soon as they remember. Advise parents or caregivers not to double the next dose or take more than the prescribed dose *[see Dosage and Administration (2)]*.

Important Administration and Preparation Instructions:
Instruct patients, parents or caregivers to read the Instructions for Use before preparing and administering abacavir and lamivudine tablets for oral suspension.

Availability of Medication Guide:
Instruct patients, parents or caregivers to read the Medication Guide before their child starts abacavir and lamivudine tablets for oral suspension and to re-read it each time the prescription is renewed. Instruct patients, parents or caregivers to inform their physician or pharmacist if the child develops any unusual symptom, or if any known symptom persists or worsens.

Mylan®

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Hyderabad — 500 096, India

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MEDICATION GUIDE
ABACAVIR and LAMIVUDINE (a bak′ a vir and la miv′ ue deen)
tablets for oral suspension

What is the most important information I should know about abacavir and lamivudine tablets for oral suspension?

Abacavir and lamivudine tablets for oral suspension can cause serious side effects, including:

- **Serious allergic reactions (hypersensitivity reaction)** that can cause death have happened with abacavir and lamivudine tablets for oral suspension 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 for oral suspension, call your healthcare provider right away to find out if you should stop taking abacavir and lamivudine tablets for oral suspension.

	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 for oral suspension because of an allergic reaction, never take abacavir and lamivudine tablets for oral suspension or any other abacavir-containing medicine (EPZICOM®, TRIUMEQ®, TRIUMEQ® PD, TRIZIVIR®, or ZIAGEN®) again.

  - If you have an allergic reaction, dispose of any unused abacavir and lamivudine tablets for oral suspension. Ask your pharmacist how to properly dispose of medicines.
  - If you take abacavir and lamivudine tablets for oral suspension 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 oral suspension for any other reason, even for a few days, and you are not allergic to abacavir and lamivudine tablets for oral suspension, talk with your healthcare provider before taking them 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 them before.

  If your healthcare provider tells you that you can take abacavir and lamivudine tablets for oral suspension again, start taking them when you are around medical help or people who can call a healthcare provider if you need one.

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

What is abacavir and lamivudine tablets for oral suspension?

Abacavir and lamivudine tablets for oral suspension is a prescription medicine used with other HIV-1 medicines to treat HIV-1 infection in children who are at least 3 months of age and older and weigh at least 11 pounds (5 kg).

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

Abacavir and lamivudine tablets for oral suspension contains 2 prescription medicines, abacavir and lamivudine.

It is not known if abacavir and lamivudine tablets for oral suspension is safe and effective in children who are less than 3 months of age.

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

Do not take abacavir and lamivudine tablets for oral suspension 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 for oral suspension.
- are allergic to abacavir, lamivudine, 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.

Before you take abacavir and lamivudine tablets for oral suspension tell your healthcare provider about all of your medical conditions, including 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.
- are pregnant or plan to become pregnant.

  Pregnancy Registry. There is a pregnancy exposure registry for women who take HIV-1 medicines during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.
- are breastfeeding or plan to breastfeed. Abacavir and lamivudine may pass into your breast milk. Talk to your healthcare provider about the following risks to your baby from breastfeeding during or after treatment with abacavir and lamivudine tablets for oral suspension:
  - the HIV-1 virus may pass to your baby if your baby does not have HIV-1 infection.
  - the HIV-1 virus may become harder to treat if your baby has HIV-1 infection.
  - your baby may get side effects from abacavir and lamivudine tablets for oral suspension.

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

Some medicines interact with abacavir and lamivudine tablets for oral suspension. **Keep a list of your medicines to show your healthcare provider and pharmacist when you get a new medicine.**

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with abacavir and lamivudine tablets for oral suspension.
- **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take abacavir and lamivudine tablets for oral suspension with other medicines.

How should I take abacavir and lamivudine tablets for oral suspension?

- **Take abacavir and lamivudine tablets for oral suspension exactly as your healthcare provider tells you to take them.**
- Do not change your dose or stop taking abacavir and lamivudine tablets for oral suspension without talking with your healthcare provider first.
- Your child's healthcare provider will prescribe a dose of abacavir and lamivudine tablets for oral suspension based on your child's weight.
- Take abacavir and lamivudine tablets for oral suspension with or without food.
- Take abacavir and lamivudine tablets for oral suspension by either dispersing the tablet in water to make a suspension, swallowing the tablet whole, or breaking the tablet in half along the line on the tablet (score).
- **Do not** chew abacavir and lamivudine tablets for oral suspension.
- **Do not** use or take tablets if they are damaged, broken, or expired.
- For children who cannot swallow tablets, read the Instructions for Use at the end of this Medication Guide for detailed instructions on how to prepare and take a dose of abacavir and lamivudine tablets for oral suspension.
- If you miss a dose of abacavir and lamivudine tablets for oral suspension, take it as soon as you remember. Do not take 2 doses at the same time or take more than your healthcare provider tells you to take.
- Stay under the care of a healthcare provider during treatment with abacavir and lamivudine tablets for oral suspension.

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

What are the possible side effects of abacavir and lamivudine tablets for oral suspension?

Abacavir and lamivudine tablets for oral suspension can cause serious side effects, including:

- **See "What is the most important information I should know about abacavir and lamivudine tablets for oral suspension?"**
- **Too much lactic acid in your blood (lactic acidosis).** Lactic acidosis is a serious medical emergency that can cause death. **Call your healthcare provider right away if you get any of the following symptoms that could be signs of lactic acidosis:**
  - feel very weak or tired
  - 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.** In some cases, severe liver problems can lead to death. Your liver may become large (hepatomegaly) and you may develop fat in your liver (steatosis). **Call your healthcare provider right away if you get any of the following signs or symptoms of liver problems:**
  - your skin or the white part of your eyes turns yellow (jaundice)
  - 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 or very overweight (obese).

- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having new symptoms after you start taking abacavir and lamivudine tablets for oral suspension.
- **Heart attack.** Some HIV-1 medicines including abacavir and lamivudine tablets for oral suspension may increase your risk of heart attack.
- **Risk of inflammation of the pancreas (pancreatitis).** Children may be at risk for developing pancreatitis during treatment with abacavir and lamivudine tablets for oral suspension if they:
  - have taken nucleoside analogue medicines in the past
  - have a history of pancreatitis
  - have other risk factors for pancreatitis

  Call your healthcare provider right away if your child develops signs and symptoms of pancreatitis including severe upper stomach-area pain, with or without nausea and vomiting. Your healthcare provider may tell you to stop giving abacavir and lamivudine tablets for oral suspension to your child if their symptoms and blood test results show that your child may have pancreatitis.

The most common side effects of abacavir and lamivudine in adults include:

- trouble sleeping or abnormal dreams
- allergic reactions
- headache or migraine
- nausea
- tiredness or weakness
- diarrhea
- rash
- stomach (abdominal) pain or discomfort
- depression
- dizziness
- muscle or bone pain

The most common side effects of abacavir and lamivudine in children include:

- fever and chills
- nausea and vomiting
- rash
- ear, nose, or throat infections

These are not all the possible side effects of abacavir and lamivudine tablets for oral suspension.

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 below 30°C (86°F).
- Keep abacavir and lamivudine tablets for oral suspension in the original bottle and keep the bottle cap tightly closed to protect from moisture so that the tablets stay dry.
- The abacavir and lamivudine tablets for oral suspension bottle contains a child resistant cap.

Keep abacavir and lamivudine tablets for oral suspension and all medicines out of the reach of children.

General information for safe and effective use of abacavir and lamivudine tablets for oral suspension.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use abacavir and lamivudine tablets for oral suspension for a condition for which it was not prescribed. Do not give abacavir and lamivudine tablets for oral suspension to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about abacavir and lamivudine tablets for oral suspension that is written for health professionals.

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

Active ingredients: abacavir sulfate and lamivudine

Inactive ingredients: crospovidone, microcrystalline cellulose, sodium stearyl fumarate, strawberry cream flavor permaseal (maltodextrin, modified starch, natural identical flavoring substance, natural flavoring substance and propylene glycol) and sucralose.

Mylan®

Manufactured by:
Mylan Laboratories Limited
Hyderabad — 500 096, India
For more information, call Mylan at 1-877-446-3679 (1-877-4-INFO-RX).

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MXP:MG:ASLTOS:RX6

INSTRUCTIONS FOR USE

ABACAVIR and LAMIVUDINE (a bak′ a vir and la miv′ ue deen)
tablets for oral suspension

This Instructions for Use contains information on how to prepare and take or give abacavir and lamivudine tablets for oral suspension.

Read this Instructions for Use before you prepare and take or give the first dose of abacavir and lamivudine tablets for oral suspension, each time you get a refill, and as needed. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment. Ask your healthcare provider or pharmacist if you have any questions about how to prepare and take or give a dose of abacavir and lamivudine tablets for oral suspension.

Important Information You Need to Know Before Taking Abacavir and Lamivudine Tablets for Oral Suspension

- For more information about abacavir and lamivudine tablets for oral suspension, see the Medication Guide.
- This Instructions for Use may be used to prepare abacavir and lamivudine tablets for oral suspension and give it to children who cannot swallow tablets.
- Take abacavir and lamivudine tablets for oral suspension by either dispersing the tablet in water to make a suspension, swallowing the tablet whole, or breaking the tablet in half along the line on the tablet (score).
- Your healthcare provider will tell you how many tablets to take or use to prepare an oral suspension.
- Take abacavir and lamivudine tablets for oral suspension with or without food.
- **Do not** chew abacavir and lamivudine tablets for oral suspension.
- **Do not** use tablets if they are damaged, broken, or expired.

Before you prepare a dose of abacavir and lamivudine tablets for oral suspension, gather the following supplies (not included in carton):

- a teaspoon for crushing and stirring
- a measuring spoon for measuring the water
- a drinking cup to place the tablets and water in
- at least an 8-ounce cup of drinking water
- oral syringe (optional)
    - If your child cannot drink from a cup, you may need an oral syringe to give the medicine. Talk to your healthcare provider for advice about the size of oral syringe you should use to give abacavir and lamivudine tablets for oral suspension.

Preparing a dose of abacavir and lamivudine tablets for oral suspension:

Step 1: Choose a clean, flat work surface. Place all supplies on the work surface.	
Step 2: Wash and dry your hands well.	
Step 3: Get the prescribed number of abacavir and lamivudine tablets for oral suspension needed to prepare the dose.	
Step 4: Place the abacavir and lamivudine tablets for oral suspension in the drinking cup. Then, add 2 teaspoons (10 mL) of drinking water for each tablet prescribed. **See Figure A.**	

Note: Add 1 teaspoon (5 mL) of drinking water if you are prescribed a half of a tablet.

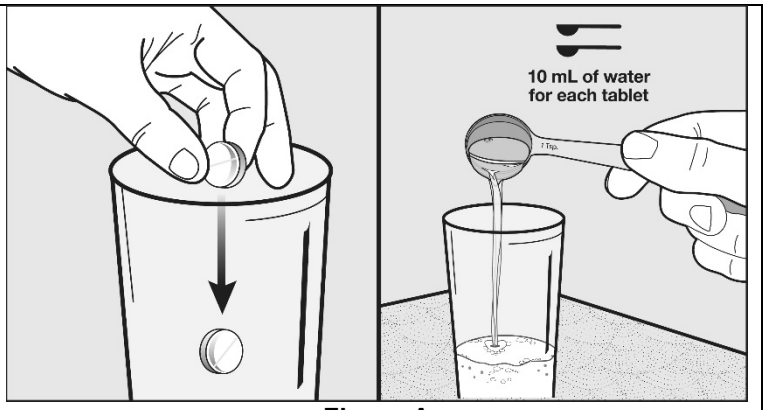

Figure A

Step 5: Stir with a spoon or swirl the drinking cup for about 2 to 3 minutes until the abacavir and lamivudine tablets for oral suspension break up into pieces small enough for a child to swallow. **See Figure B**.

Do not chew the abacavir and lamivudine tablets for oral suspension or pieces of the tablets. Use your teaspoon to crush the pieces, if needed.

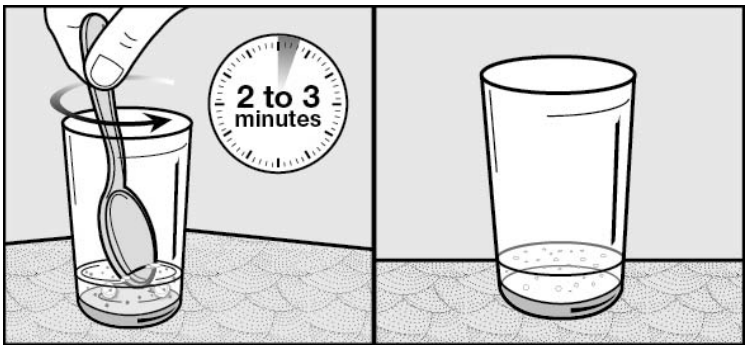

Figure B

Taking or giving abacavir and lamivudine tablets for oral suspension.

Step 6: Drink the mixture within 1 hour. If you do not take the mixture right away after being prepared, stir with a spoon or swirl the drinking cup again for about 2 to 3 minutes before taking. **See Figure C**.

Throw away (discard) the mixture if not used within 1 hour.

Using an oral syringe:
Place the tip of the oral syringe into the prepared medicine and draw up all the medicine into the oral syringe by pulling up on the plunger. **See Figure D**.

Place the tip of the oral syringe against the inside of the child's cheek. Gently push down the plunger to give the dose slowly. **See Figure E**.

Figure C

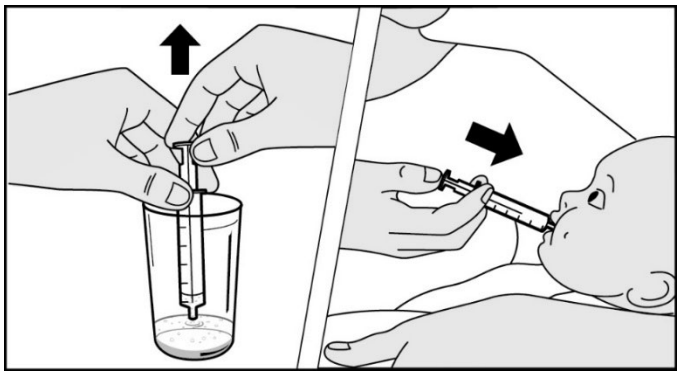

Figure D **Figure E**

Step 7: Rinse the drinking cup with an additional small amount of water. Use about 1 to 2 teaspoons (5 mL to 10 mL) of drinking water for each tablet prescribed and drink or give all the contents to make sure that all the medicine is taken. **See Figure F**.

Using an oral syringe:
Draw up the remaining medicine into the oral syringe and give it all to the child.

Repeat if any medicine remains in the oral syringe to make sure the child gets the full dose.

Allow time for the medicine to be swallowed.

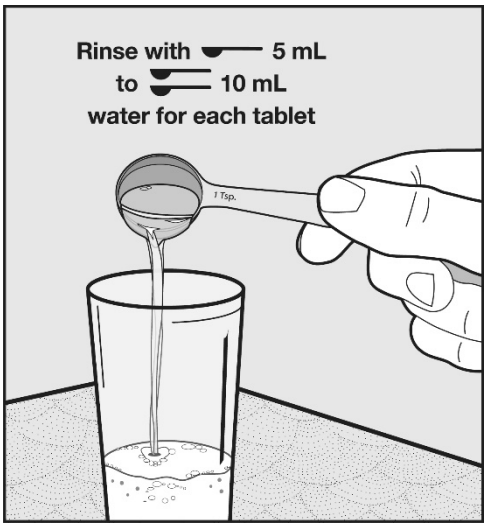

Figure F

Step 8: Wash all the dosing items with water. **See Figure G** and **Figure H**.

If using an oral syringe, pull the plunger out of the syringe and wash the syringe parts separately in water. Allow parts to dry completely before reassembling and storing. **See Figure H**.

All parts will need to be clean before preparing the next dose.

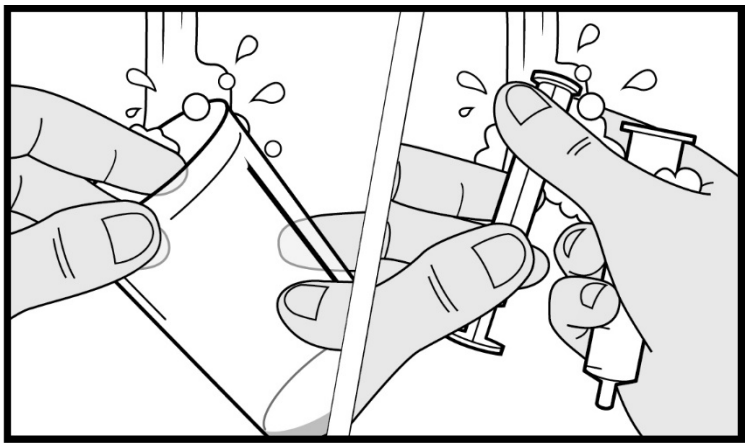

Figure G **Figure H**

Storing abacavir and lamivudine tablets for oral suspension

- Store abacavir and lamivudine tablets for oral suspension below 30°C (86°F).
- Keep abacavir and lamivudine tablets for oral suspension in the original bottle and keep the bottle cap tightly closed to protect from moisture so that the tablets stay dry.
- The abacavir and lamivudine tablets for oral suspension bottle contains a child resistant cap.

Keep abacavir and lamivudine tablets for oral suspension and all medicines out of the reach of children.

Disposing of abacavir and lamivudine tablets for oral suspension
When all the tablets in the bottle have been taken or are no longer needed, throw away the bottle. Dispose of them using your local household waste guidelines.

Mylan®

Manufactured by:
Mylan Laboratories Limited
Hyderabad — 500 096, India
For more information, call Mylan at 1-877-446-3679 (1-877-4-INFO-RX).
This Instructions for Use has been approved by the U.S. Food and Drug Administration. Issued: December 2023
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WARNING CARD (FRONT AND BACK)

Mylan®

WARNING CARD
Abacavir and Lamivudine Tablets for Oral Suspension

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, call your healthcare provider right away to find out if you should stop taking this medicine.

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

(see reverse of card)

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

Mylan®

WARNING CARD
Abacavir and Lamivudine Tablets for Oral Suspension

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 (ZIAGEN®, EPZICOM®, TRIUMEQ®, TRIUMEQ® PD, or TRIZIVIR®) again. If you have an allergic reaction, dispose of any unused abacavir and lamivudine tablets for oral suspension. Ask your pharmacist how to properly dispose of medicines. 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**.

Please read the Medication Guide for additional information on abacavir and lamivudine tablets for oral suspension.

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