Abacavir Sulfate and Lamivudine Tablets
(60 mg/30 mg)
Rx only

AUROBINDO

WARNINGS

Abacavir Sulfate and Lamivudine Tablets contain 2 nucleoside analogues (abacavir sulfate and lamivudine) and are intended only for patients whose regimen would otherwise include these 2 components.

Hypersensitivity Reactions: Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate, a component of Abacavir Sulfate and Lamivudine Tablets. Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups: (1) fever, (2) rash, (3) gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain), (4) constitutional (including generalized malaise, fatigue, or achiness), and (5) respiratory (including dyspnea, cough, or pharyngitis). Discontinue Abacavir Sulfate and Lamivudine Tablets as soon as a hypersensitivity reaction is suspected.

Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, screening for the HLA-B*5701 allele is recommended; this approach has been found to decrease the risk of hypersensitivity reaction. Screening is also recommended prior to reinitiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. HLA-B*5701-negative patients may develop a suspected hypersensitivity reaction to abacavir; however, this occurs significantly less frequently than in HLA-B*5701-positive patients.

Regardless of HLA-B*5701 status, permanently discontinue Abacavir Sulfate and Lamivudine Tablets if hypersensitivity cannot be ruled out, even when other diagnoses are possible.

Following a hypersensitivity reaction to abacavir, NEVER restart Abacavir Sulfate and Lamivudine Tablets or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.

Reintroduction of Abacavir Sulfate and Lamivudine Tablets or any other abacavir-containing product, even in patients who have no identified history or unrecognized symptoms of hypersensitivity to abacavir therapy, can result in serious or fatal hypersensitivity reactions. Such reactions can occur within hours (see WARNINGS and PRECAUTIONS: Information for Patients).

Lactic Acidosis and Severe Hepatomegaly: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir, lamivudine, and other antiretrovirals (see WARNINGS).

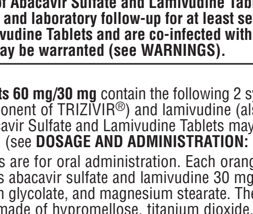
Exacerbations of Hepatitis B: Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV) and have discontinued lamivudine, which is one component of Abacavir Sulfate and Lamivudine Tablets. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue Abacavir Sulfate and Lamivudine Tablets and are co-infected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted (see WARNINGS).

DESCRIPTION

Abacavir Sulfate and Lamivudine Tablets 60 mg/30 mg contain the following 2 synthetic nucleoside analogues: abacavir sulfate (ZIAGEN®, also a component of TRIZIVIR®) and lamivudine (also known as EPIVIR® or 3TC) with inhibitory activity against HIV. Abacavir Sulfate and Lamivudine Tablets may be swallowed or dispersed in water immediately before administration (see **DOSAGE AND ADMINISTRATION: Method of Preparation**).

Abacavir Sulfate and Lamivudine Tablets are for oral administration. Each orange, film-coated tablet contains the active ingredients abacavir 60 mg as abacavir sulfate and lamivudine 30 mg, and the inactive ingredients: microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. The tablets are coated with a film (opadry orange YS-1-13065-A) that is made of hypromellose, titanium dioxide, polysorbate 80, polyethylene glycol 400, and FD&C yellow #6 aluminum lake.

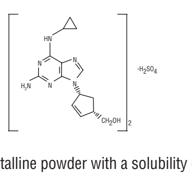
Abacavir Sulfate: The chemical name of abacavir sulfate is (1*S*,*cis*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1). Abacavir sulfate is the enantiomer with 1*S*, 4*R* absolute configuration on the cyclopentene ring. It has a molecular formula of $(C_{14}H_{18}N_6O)_2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



Abacavir sulfate is a white to off-white crystalline powder with a solubility of approximately 77 mg/mL in distilled water at 25°C.

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

Lamivudine: The chemical name of lamivudine is (-)-1-[(2*R*, 5*S*)-2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. 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 daltons. It has the following structural formula:



Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg/mL in water at 20°C.

MICROBIOLOGY

Mechanism of Action

Abacavir: Abacavir is a carbocyclic synthetic nucleoside analogue. Abacavir is converted by cellular enzymes to the active metabolite, carbovir triphosphate (CBV-TP), an analogue of deoxyguanosine-5'-triphosphate (dGTP). CBV-TP inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation into viral DNA. The lack of a 3'-OH group in the incorporated nucleotide analogue prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation, and therefore, the viral DNA growth is terminated. CBV-TP is a weak inhibitor of cellular DNA polymerases α, β, and γ.

Lamivudine: Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue. CBV-TP and 3TC-TP are weak inhibitors of cellular DNA polymerases α, β, and γ.

Antiviral Activity

Abacavir: The antiviral activity of abacavir against HIV-1 was evaluated against a T-cell tropic laboratory strain HIV-1IIIB in lymphoblastic cell lines, a monocyte/macrophage tropic laboratory strain HIV-1BaL in primary monocytes/macrophages, and clinical isolates in peripheral blood mononuclear cells. The concentration of drug necessary to effect viral replication by 50 percent (EC_{50}) ranged from 3.7 to 5.8 μM (1 μM = 0.28 mcg/mL) and 0.07 to 1.0 μM against HIV-1IIIB and HIV-1BaL, respectively, and was 0.26 ± 0.18 μM against 8 clinical isolates. The EC_{50} values of abacavir against different HIV-1 clades (A-G) ranged from 0.0015 to 1.05 μM, and against HIV-2 isolates, from 0.024 to 0.49 μM. Ribavirin (50 μM) had no effect on the anti-HIV-1 activity of abacavir in cell culture.

Lamivudine: The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. EC_{50} values were in the range of 0.003 to 15 μM (1 μM = 0.23 mcg/mL). HIV from therapy-naive subjects with no mutations associated with resistance gave median EC_{50} values of 0.426 μM (range: 0.200 to 2.007 μM) from Virco (n = 93 baseline samples from COLA40263) and 2.35 μM (1.44 to 4.08 μM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC_{50} values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120 μM, and against HIV-2 isolates from 0.003 to 0.120 μM in peripheral blood mononuclear cells. Ribavirin (50 μM) decreased the anti-HIV-1 activity of lamivudine by 3.5 fold in MT-4 cells. In HIV-1-infected MT-4 cells, lamivudine in combination with zidovudine at various ratios exhibited synergistic antiretroviral activity.

The combination of abacavir and lamivudine has demonstrated antiviral activity in cell culture against non-subtype B isolates and HIV-2 isolates with equivalent antiviral activity as for subtype B isolates. Abacavir/lamivudine had additive to synergistic activity in cell culture in combination with the nucleoside reverse transcriptase inhibitors (NRTIs: emtricitabine, stavudine, tenofovir, zidovudine), the non-nucleoside reverse transcriptase inhibitors (NNRTIs: delavirdine, efavirenz, nevirapine), the protease inhibitors (PIs: amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir), or the fusion inhibitor, enfuvirtide. Ribavirin, used in combination with interferon for the treatment of HCV infection, decreased the anti-HIV potency of abacavir/lamivudine reproducibly by 2- to 6-fold in cell culture.

Resistance

HIV-1 isolates with reduced susceptibility to the combination of abacavir and lamivudine have been selected in cell culture and have also been obtained from patients failing abacavir/lamivudine-containing regimens. Genotypic characterization of abacavir/lamivudine-resistant viruses selected in cell culture identified amino acid substitutions M184V/I, K65R, L74V, and Y115F in HIV-1 RT.

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compared to 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 to the 150 mg twice-daily regimen.

Inter-subject variability was greater for intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough concentrations. The clinical significance of observed differences for both plasma lamivudine concentrations and intracellular lamivudine triphosphate concentrations is not known.

In humans, abacavir and lamivudine are not significantly metabolized by cytochrome P450 enzymes.

The pharmacokinetic properties of abacavir and lamivudine in fasting patients are summarized in Table 1.

Table 1. Pharmacokinetic Parameters* for Abacavir and Lamivudine in Adults

ParameterAbacavir			Lamivudine	
Oral bioavailability (%)	86 ± 25	n = 6	86 ± 16	n = 12
Apparent volume of distribution (L/kg)	0.86 ± 0.15	n = 6	1.3 ± 0.4	n = 20
Systemic clearance (L/hr/kg)	0.8 ± 0.24	n = 6	0.33 ± 0.06	n = 20
Renal clearance (L/hr/kg)	.007 ± .008	n = 6	0.22 ± 0.06	n = 20
Elimination half-life (hr)	1.45 ± 0.32	n = 20	5 to 7†	

* Data presented as mean ± standard deviation except where noted.

† Approximate range.

Effect of Food on Absorption of Abacavir Sulfate and Lamivudine Tablets

Abacavir Sulfate and Lamivudine Tables may be administered with or without food. Administration with a high-fat meal in a single-dose bioavailability study resulted in no change in AUC last, AUC_∞, and C_{max} for lamivudine. Food did not alter the extent of systemic exposure to abacavir (AUC_∞), but the rate of absorption (C_{max}) was decreased approximately 24% compared to fasted conditions (n = 25). These results are similar to those from previous studies of the effect of food on abacavir and lamivudine tablets administered separately.

Special Populations

Renal Impairment

Abacavir Sulfate and Lamivudine: The pharmacokinetic properties of abacavir sulfate have not been determined in patients with impaired renal function. Renal excretion of unchanged abacavir is a minor route of elimination in humans. Lamivudine requires dose adjustment in the presence of renal insufficiency. Because Abacavir Sulfate and Lamivudine Tablets are a fixed-dose combination and cannot be dose adjusted, Abacavir Sulfate and Lamivudine Tablets are contraindicated for patients with renal impairment (see **PRECAUTIONS**).

Hepatic Impairment

Abacavir Sulfate and Lamivudine: Abacavir Sulfate is contraindicated in patients with moderate to severe hepatic impairment and dose reduction is required in patients with mild hepatic impairment. Because Abacavir Sulfate and Lamivudine Tablets are a fixed-dose combination and cannot be dose adjusted, Abacavir Sulfate and Lamivudine Tablets are contraindicated for patients with hepatic impairment.

Pregnancy

Abacavir Sulfate and Lamivudine: No data are available on the pharmacokinetics of abacavir or lamivudine during pregnancy (see **PRECAUTIONS: Pregnancy**).

Nursing Mothers

Abacavir: No data are available on the pharmacokinetics of abacavir in nursing mothers (see **PRECAUTIONS: Nursing Mothers**).

Lamivudine: Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine (see **PRECAUTIONS: Nursing Mothers**).

Pediatric Patients

Abacavir Sulfate: The pharmacokinetics of abacavir have been studied after either single or repeat doses of abacavir sulfate in 68 pediatric patients. Following multiple-dose administration of abacavir sulfate 8 mg/kg twice daily, steady-state $AUC_{(0\text{-}12\ hr)}$ and C_{max} were 9.8 ± 4.56 mcg•hr/mL and 3.71 ± 1.36 mcg/mL (mean ± SD), respectively (see **PRECAUTIONS: Pediatric Use**).

Lamivudine: The pharmacokinetic properties of lamivudine were assessed in 57 HIV-infected pediatric patients (age range: 4.8 months to 16 years, weight range: 5 to 66 kg) after oral and IV administration of 1, 2, 4, 8, 12, and 20 mg/kg/day. In the 9 infants and children (range: 5 months to 12 years of age) receiving oral solution 4 mg/kg twice daily, absolute bioavailability was 66% ± 26% (mean ± SD), which was less than the 86% ± 16% (mean ± SD) observed in adults. The mechanism for the diminished absolute bioavailability of lamivudine in infants and children is unknown. Systemic clearance decreased with increasing age in pediatric patients.

After oral administration of an oral solution of lamivudine 4 mg/kg twice daily to 11 pediatric patients ranging from 4 months to 14 years of age, Cmax was 1.1 ± 0.6 mcg/mL and half-life was 2.0 ± 0.6 hours. (In adults with similar blood sampling, the half-life was 3.7 ± 1 hours.) Total exposure to lamivudine, as reflected by mean AUC values, was comparable between pediatric patients receiving an 8 mg/kg/day dose and adults receiving a 4 mg/kg/day dose (see **PRECAUTIONS: Pediatric Use)**.

Limited, uncontrolled pharmacokinetic and safety data are available from administration of lamivudine (and zidovudine) to 36 infants up to 1 week of age in 2 studies in South Africa. In these studies, lamivudine clearance was substantially reduced in 1-week-old neonates relative to pediatric patients (>3 months of age) studied previously. There is insufficient information to establish the time course of changes in clearance between the immediate neonatal period and the age-ranges >3 months old (see the **ADVERSE REACTIONS**).

Geriatric Patients

The pharmacokinetics of abacavir and lamivudine have not been studied in patients over 65 years of age.

Gender

Abacavir: A population pharmacokinetic analysis in HIV-infected male (n = 304) and female (n = 67) patients showed no gender differences in abacavir AUC normalized for lean body weight.

Lamivudine: A pharmacokinetic study in healthy male (n = 12) and female (n = 12) subjects showed no gender differences in lamivudine AUC_∞ normalized for body weight.

Race

Abacavir: There are no significant differences between blacks and Caucasians in abacavir pharmacokinetics.

Lamivudine: There are no significant racial differences in lamivudine pharmacokinetics.

Drug Interactions

See **PRECAUTIONS: Drug Interactions**. The drug interactions described are based on studies conducted with the individual nucleoside analogues. In humans, abacavir and lamivudine are not significantly metabolized by cytochrome P450 enzymes nor do they inhibit or induce this enzyme system; therefore, it is unlikely that clinically significant drug interactions will occur with drugs metabolized through these pathways.

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

In a study of 11 HIV-infected patients receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of abacavir sulfate twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI 6% to 42%). 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.

Lamivudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q 12 hr). Lamivudine pharmacokinetics are not significantly affected by abacavir.

Table 2. Effect of Coadministered Drugs on Abacavir and Lamivudine AUC*

Note: ROUTINE DOSE MODIFICATION OF ABACAVIR AND LAMIVUDINE IS NOT WARRANTED WITH COADMINISTRATION OF THE FOLLOWING DRUGS.

Drugs That May Alter Abacavir Blood Concentrations					
Coadministered Drug and Dose	Abacavir Dose	n	Abacavir Concentrations: AUC	Abacavir Concentrations: Variability	Concentration of Coadministered Drug
Ethanol 0.7 g/kg	Single 600 mg	24	↑41%	90% CI: 35% to 48%	↔
Drugs That May Alter Lamivudine Blood Concentrations					
Coadministered Drug and Dose	**Lamivudine Dose**	**n**	**Lamivudine Concentrations: AUC**	**Lamivudine Concentrations: Variability**	**Concentration of Coadministered Drug**
Nelfinavir 750 mg q 8 hr x 7 to 10 days	Single 150 mg	11	↑10%	95% CI: 1% to 20%	↔
Trimethoprim 160 mg/ Sulfamethoxazole 800 mg daily x 5 days	Single 300 mg	14	↑43%	90% CI: 32% to 55%	↔

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

*See **PRECAUTIONS: Drug Interactions** for additional information on drug interactions.

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/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/HCV co-infected patients (see **WARNINGS**).

INDICATIONS AND USAGE

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

Additional important information on the use of Abacavir Sulfate and Lamivudine Tablets for treatment of HIV-1 infection:

- Abacavir Sulfate and Lamivudine Tablets are one of multiple products containing abacavir. Before starting Abacavir Sulfate and Lamivudine Tablets, review medical history for prior exposure to any abacavir-containing products in order to avoid reintroduction in a patient with a history of hypersensitivity to abacavir.
- In one controlled study (CNA30021), more patients taking abacavir sulfate 600 mg once daily had severe hypersensitivity reactions compared to patients taking abacavir sulfate 300 mg twice daily.
- As part of a triple-drug regimen, Abacavir Sulfate and Lamivudine Tablets are recommended for use with antiretroviral agents from different pharmacological classes and not with other nucleoside/nucleotide reverse transcriptase inhibitors.

See **WARNINGS, ADVERSE REACTIONS**, and **Description of Clinical Studies.**

Description of Clinical Studies

The following studies were conducted with the individual components of Abacavir Sulfate and Lamivudine Tablets.

Pediatric Patients

Abacavir: CNA3006 was a randomized, double-blind study comparing abacavir 8 mg/kg twice daily plus lamivudine 4 mg/kg twice daily plus zidovudine 180 mg/m² twice daily versus lamivudine 4 mg/kg twice daily plus zidovudine 180 mg/m² twice daily. Two hundred and five therapy-experienced pediatric patients were enrolled: female (56%), Caucasian (17%), black (50%), Hispanic (30%), median age of 5.4 years, baseline CD4+ cell percent >15% (median = 27%), and median baseline plasma HIV-1 RNA of 4.6 log_{10} copies/mL. Eighty percent and 55% of patients had prior therapy with zidovudine and lamivudine, respectively, most often in combination. The median duration of prior nucleoside analogue therapy was 2 years. At 16 weeks the proportion of patients responding based on plasma HIV-1 RNA ≤400 copies/mL was significantly higher in patients receiving abacavir plus lamivudine plus zidovudine compared with patients receiving lamivudine plus zidovudine, 13% versus 2%, respectively. Median plasma HIV-1 RNA changes from baseline were -0.53 log_{10} copies/mL in the group receiving abacavir plus lamivudine plus zidovudine compared with -0.21 log_{10} copies/mL in the group receiving lamivudine plus zidovudine. Median CD4+ cell count increases from baseline were 69 cells/mm³ in the group receiving abacavir plus lamivudine plus zidovudine and 9 cells/mm³ in the group receiving lamivudine plus zidovudine.

Lamivudine: ACTG300 was a multi-center, randomized, double-blind study that provided for comparison of lamivudine plus zidovudine with didanosine monotherapy. A total of 471 symptomatic, HIV-1-infected therapy-naive (≤56 days of antiretroviral therapy) pediatric patients were enrolled in these 2 treatment arms. The median age was 2.7 years (range: 6 weeks to 14 years), 58% were female, and 86% were non-Caucasian. The mean baseline CD4+ cell count was 868 cells/mm³ (mean: 1,060 cells/mm³ and range: 0 to 4,650 cells/mm³ for patients ≤5 years of age; mean: 419 cells/mm³ and range: 0 to 1,555 cells/mm³ for patients >5 years of age) and the mean baseline plasma HIV-1 RNA was 5.0 log_{10} copies/mL. The median duration on study was 10.1 months for the patients receiving lamivudine plus zidovudine and 9.2 months for patients receiving didanosine monotherapy. Results are summarized in Table 3.

Table 3. Number of Patients (%) Reaching a Primary Clinical Endpoint (Disease Progression or Death)

Endpoint	Lamivudine plus Zidovudine (n = 236)	Didanosine (n = 235)
HIV -1 disease progression or death (total)	15 (6.4%)	37 (15.7%)
Physical growth failure	7 (3.0%)	6 (2.6%)
Central nervous system deterioration	4 (1.7%)	12 (5.1 %)
CDC Clinical Category C	2 (0.8%)	8 (3.4%)
Death	2 (0.8%)	11 (4.7%)

CONTRAINDICATIONS

Abacavir Sulfate and Lamivudine Tablets are contraindicated in patients with previously demonstrated hypersensitivity to abacavir or to any other component of the product (see WARNINGS). NEVER restart Abacavir Sulfate and Lamivudine Tablets or any other abacavir-containing product following a hypersensitivity reaction to abacavir, regardless of HLA-B*5701 status (see WARNINGS, PRECAUTIONS and ADVERSE REACTIONS).

Abacavir Sulfate and Lamivudine Tablets are contraindicated in patients with renal and hepatic impairment (see **CLINICAL PHARMACOLOGY**).

WARNINGS

Abacavir

Hypersensitivity Reaction: Serious and sometimes fatal hypersensitivity reactions have been associated with Abacavir Sulfate and Lamivudine and other abacavir-containing products. Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, screening for the HLA-B*5701 allele is recommended; this approach has been found to decrease the risk of a hypersensitivity reaction. Screening is also recommended prior to reinitiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. For HLA-B*5701-positive patients, treatment with an abacavir-containing regimen is not recommended and should be considered only with close medical supervision and under exceptional circumstances when the potential benefit outweighs the risk.

HLA-B*5701-negative patients may develop a hypersensitivity reaction to abacavir; however, this occurs significantly less frequently than in HLA-B*5701-positive patients. Regardless of HLA-B*5701 status, permanently discontinue Abacavir Sulfate and Lamivudine Tablets if hypersensitivity cannot be ruled out, even when other diagnoses are possible. Important information on signs and symptoms of hypersensitivity, as well as clinical management, is presented below.

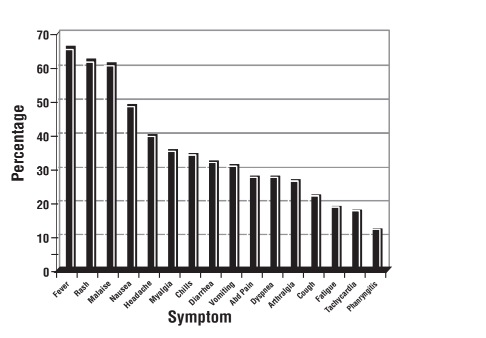
Signs and Symptoms of Hypersensitivity: Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups.

Group 1: Fever
Group 2: Rash
Group 3: Gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain)
Group 4: Constitutional (including generalized malaise, fatigue, or achiness)
Group 5: Respiratory (including dyspnea, cough, or pharyngitis)

Hypersensitivity to abacavir following the presentation of a single sign or symptom has been reported infrequently.

Hypersensitivity to abacavir was reported in approximately 8% of 2,670 patients (n = 206) in 9 clinical trials (range: 2% to 9%) with enrollment from November 1999 to February 2002. Data on time to onset and symptoms of suspected hypersensitivity were collected on a detailed data collection module. The frequencies of symptoms are shown in Figure 1. Symptoms usually appeared within the first 6 weeks of treatment with abacavir, although the reaction may occur at any time during therapy. Median time to onset was 9 days; 89% appeared within the first 6 weeks; 95% of patients reported symptoms from 2 or more of the 5 groups listed above.

Figure 1: Hypersensitivity-Related Symptoms Reported with ≥10% Frequency in Clinical Trials (n = 206 Patients)



Other less common signs and symptoms of hypersensitivity include lethargy, myolysis, edema, abnormal chest x-ray findings (predominantly infiltrates, which can be localized), and paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure, and death have occurred in association with hypersensitivity reactions. In one study, 4 patients (11%) receiving abacavir sulfate 600 mg once daily experienced hypotension with a hypersensitivity reaction compared with 0 patients receiving abacavir sulfate 300 mg twice daily.

Physical findings associated with hypersensitivity to abacavir in some patients include lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and rash. The rash usually appears maculopapular or urticarial, but may be variable in appearance. There have been reports of erythema multiforme. Hypersensitivity reactions have occurred without rash.

Laboratory abnormalities associated with hypersensitivity to abacavir in some patients include elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, and lymphopenia.

Clinical Management of Hypersensitivity: **Discontinue Abacavir Sulfate and Lamivudine Tablets as soon as a hypersensitivity reaction is suspected. To minimize the risk of a life-threatening hypersensitivity reaction, permanently discontinue Abacavir Sulfate and Lamivudine Tablets if hypersensitivity cannot be ruled out, 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).**

Following a hypersensitivity reaction to abacavir, NEVER restart Abacavir Sulfate and Lamivudine Tablets or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.

When therapy with Abacavir Sulfate and Lamivudine Tablets has been discontinued for reasons other than symptoms of a hypersensitivity reaction, and if reinitiation of Abacavir Sulfate and Lamivudine Tablets or any other abacavir-containing product is under consideration, carefully evaluate the reason for discontinuation of Abacavir Sulfate and Lamivudine Tablets to ensure that the patient did not have symptoms of a hypersensitivity reaction. If the patient is of unknown HLA-B*5701 status, screening for the allele is recommended prior to reinitiation of Abacavir Sulfate and Lamivudine Tablets. If hypersensitivity cannot be ruled out, DO NOT reintroduce Abacavir Sulfate and Lamivudine Tablets or any other abacavir-containing product. Even in the absence of the HLA-B*5701 allele, it is important to permanently discontinue Abacavir Sulfate and Lamivudine Tablets and not rechallenge with any other abacavir-containing product if a hypersensitivity reaction cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

If symptoms consistent with hypersensitivity are not identified, reintroduction can be undertaken with continued monitoring for symptoms of a hypersensitivity reaction. Make patients aware that a hypersensitivity reaction can occur with reintroduction of Abacavir Sulfate and Lamivudine Tablets or any other abacavir-containing product and that reintroduction of Abacavir Sulfate and Lamivudine Tablets or introduction of any other abacavir-containing product needs to be undertaken only if medical care can be readily accessed by the patient or others.

Risk Factor: HLA-B*5701 Allele: Studies have shown that carriage of the HLA-B*5701 allele is associated with a significantly increased risk of a hypersensitivity reaction to abacavir.

CNA106030 (PREDICT-1), a randomized, double-blind study, evaluated the clinical utility of prospective HLA-B*5701 screening on the incidence of abacavir hypersensitivity reaction in abacavir-naive HIV-1-infected adults (n = 1,650). In this study, use of pre-therapy screening for the HLA-B*5701 allele and exclusion of subjects with this allele reduced the incidence of clinically suspected abacavir hypersensitivity reactions from 7.8% (66/847) to 3.4% (27/803). Based on this study, it is estimated that 61% of patients with the HLA-B*5701 allele will develop a clinically suspected hypersensitivity reaction during the course of abacavir treatment compared with 4% of patients who do not have the HLA-B*5701 allele.

Screening for carriage of the HLA-B*5701 allele is recommended prior to initiating treatment with Abacavir Sulfate and Lamivudine Tablets. Screening is also recommended prior to reinitiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. For HLA-B*5701-positive patients, initiating or reinitiating treatment with an abacavir-containing regimen is not recommended and should be considered only with close medical supervision and under exceptional circumstances where potential benefit outweighs the risk.

Skin patch testing is used as a research tool and should not be used to aid in the clinical diagnosis of abacavir hypersensitivity.

In any patient treated with abacavir, the clinical diagnosis of hypersensitivity reaction must remain the basis of clinical decision-making. Even in the absence of the HLA-B*5701 allele, it is important to permanently discontinue abacavir and not rechallenge with abacavir if a hypersensitivity reaction cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

Lamivudine

Pancreatitis: In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, lamivudine should be used with caution. Treatment with lamivudine should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur (see ADVERSE REACTIONS).

Posttreatment Exacerbations of Hepatitis: In clinical trials in non-HIV-infected patients treated with lamivudine for chronic HBV, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence of HBV DNA. Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from post-marketing experience after changes from lamivudine-containing HIV treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters the course of posttreatment exacerbations of hepatitis.

Use With Interferon- and Ribavirin-Based Regimens: *In vitro* studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine, a component of abacavir sulfate/lamivudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV/HCV co-infected patients (see **CLINICAL PHARMACOLOGY: Drug Interactions**), **hepatic decompensation (some fatal) has occurred in HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon alfa with or without ribavirin.** Patients receiving interferon alfa with or without ribavirin and Abacavir Sulfate and Lamivudine Tablets should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of Abacavir Sulfate and Lamivudine Tablets should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Childs Pugh >6) (see the complete prescribing information for interferon and ribavirin).

Abacavir and Lamivudine

Lactic Acidosis/Severe Hepatomegaly with Steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir and lamivudine and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering Abacavir Sulfate and Lamivudine Tablets to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with Abacavir Sulfate and Lamivudine Tablets should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Other: Abacavir Sulfate and Lamivudine Tablets contain fixed doses of 2 nucleoside analogues, abacavir and lamivudine, and should not be administered concomitantly with other abacavir-containing products (ZIAGEN®, EPZICOM, or TRIZIVIR®) and/or lamivudine-containing products (EPIVIR®, EPIVIR-HBV®, COMBIVIR®, EPZICOM™, ATRIPLA®, TRUVADA® or TRIZIVIR®).

The complete prescribing information for all agents being considered for use with Abacavir Sulfate and Lamivudine Tablets should be consulted before combination therapy with Abacavir Sulfate and Lamivudine Tablets is initiated.

PRECAUTIONS

Therapy-Experienced Patients

Abacavir: In clinical trials, patients with prolonged prior NRTI exposure or who had HIV-1 isolates that contained multiple mutations conferring resistance to NRTIs had limited response to abacavir. The potential for cross-resistance between abacavir and other NRTIs should be considered when choosing new therapeutic regimens in therapy-experienced patients (see **MICROBIOLOGY: Cross-Resistance**).

Patients With HIV and Hepatitis B Virus Co-infection

Lamivudine: Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients dually infected with HIV and HBV. In non-HIV-infected patients treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected and has been associated with diminished treatment response (see EPIVIR-HBV® package insert for additional information). Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

Patients With Impaired Renal Function

Abacavir Sulfate and Lamivudine Tablets: Because they are fixed-dose tablets, and the dosage of the individual components cannot be altered, Abacavir Sulfate and Lamivudine Tablets are contraindicated in patients with renal impairment.

Patients With Impaired Hepatic Function

Abacavir Sulfate and Lamivudine Tablets: Because they are fixed-dose tablets, and the dosage of the individual components cannot be altered, Abacavir Sulfate and Lamivudine Tablets are contraindicated in patients with hepatic impairment.

Immune Reconstitution Syndrome

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

Fat Redistribution

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

Myocardial Infarction

In a published prospective, observational, epidemiological study designed to investigate the rate of myocardial infarction in patients on combination antiretroviral therapy, the use of abacavir within the previous 6 months was correlated with an increased risk of myocardial infarction (MI).[1] In a sponsor-conducted pooled analysis of clinical trials, no excess risk of myocardial infarction was observed in abacavir-treated subjects as compared with control subjects. In totality, the available data from the observational cohort and from clinical trials are inconclusive.

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

Information for Patients

Abacavir: Hypersensitivity Reaction: Inform patients:

- **that a Medication Guide and Warning Card summarizing the symptoms of the abacavir hypersensitivity reaction and other product information will be dispensed by the pharmacist with each new prescription and refill of Abacavir Sulfate and Lamivudine Tablets, and encourage the patient to read the Medication Guide and Warning Card every time to obtain any new information that may be present about Abacavir Sulfate and Lamivudine Tablets. (The complete text of the Medication Guide is reprinted at the end of this document).**
- **to carry the Warning Card with them.**
- how to identify a hypersensitivity reaction (see **WARNINGS** and **MEDICATION GUIDE**).
- that if they develop symptoms consistent with a hypersensitivity reaction to discontinue treatment with Abacavir Sulfate and Lamivudine Tablets and seek medical evaluation immediately.
- that a hypersensitivity reaction can worsen and lead to hospitalization or death if Abacavir Sulfate and Lamivudine Tablets are not immediately discontinued.
- **to not restart Abacavir Sulfate and Lamivudine Tablets or any other abacavir-containing product following a hypersensitivity reaction because more severe symptoms can occur within hours and may include life threatening hypotension and death.**
- that a hypersensitivity reaction is usually reversible if it is detected promptly and Abacavir Sulfate and Lamivudine Tablets are stopped right away.
- that if they have interrupted Abacavir Sulfate and Lamivudine Tablets for reasons other than symptoms of hypersensitivity (for example, those who have an interruption in drug supply), a serious or fatal hypersensitivity reaction may occur with reintroduction of abacavir.
- that in one study, more severe hypersensitivity reactions were seen when abacavir sulfate was dosed 600 mg once daily.
- **to not restart Abacavir Sulfate and Lamivudine Tablets or any other abacavir containing product without medical consultation and that restarting abacavir needs to be undertaken only if medical care can be readily accessed by the patient or others.**
- Abacavir Sulfate and Lamivudine Tablets should not be coadministered with ZIAGEN®, EPZICOM™ or TRIZIVIR®.

✂ DETACH BEFORE DISPENSING

MEDICATION GUIDE
Abacavir Sulfate and Lamivudine Tablets 60 mg/30 mg

Read the Medication Guide that comes with Abacavir Sulfate and Lamivudine Tablets before you start taking or giving them to your child and each time your child or you get a refill because there may be new information. This information does not take the place of talking to your doctor about your child’s or your medical condition or treatment. Be sure to carry the Abacavir Sulfate and Lamivudine Warning Card with you at all times.

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

- **Serious Allergic Reaction to Abacavir.** Abacavir Sulfate and Lamivudine Tablets contain abacavir (also contained in Ziagen®, Epzicom™ and Trizivir®). Patients taking Abacavir Sulfate and Lamivudine Tablets may have a serious allergic reaction (hypersensitivity reaction) that can cause death. **The risk of this allergic reaction is much higher in persons who have a gene variation called HLA-B*5701 than in those who do not. A blood test can determine if a person has this gene variation. If you get a symptom from 2 or more of the following groups while taking Abacavir Sulfate and Lamivudine Tablets, call your doctor right away to determine if this medicine should be stopped.**

	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.

If your child or you stop Abacavir Sulfate and Lamivudine Tablets because of an allergic reaction, NEVER take Abacavir Sulfate and Lamivudine Tablets or any other abacavir-containing medicine (Ziagen®, Epzicom™ and Trizivir®) again. If your child or you take Abacavir Sulfate and Lamivudine Tablets or any other abacavir-containing medicine again after your child or you have had an allergic reaction, **WITHIN HOURS** your child or you may get **life-threatening symptoms** that may include **very low blood pressure** or **death**.

If your child or you stop Abacavir Sulfate and Lamivudine Tablets for any other reason, even for a few days, and your child or you are not allergic to Abacavir Sulfate and Lamivudine Tablets, talk with your doctor before taking or giving your child Abacavir Sulfate and Lamivudine Tablets again. Taking Abacavir Sulfate and Lamivudine Tablets again can cause a serious allergic or life-threatening reaction, even if your child or you never had an allergic reaction to them before. If the doctor tells your child or you to take Abacavir Sulfate and Lamivudine Tablets again, **start giving or taking them when your child or you are around medical help or people who can call a doctor if your child or you need one.**

- **Lactic Acidosis. Some HIV medicines, including Abacavir Sulfate and Lamivudine Tablets, can cause a rare but serious condition called lactic acidosis with liver enlargement (hepatomegaly).** Nausea and tiredness that don't get better may be symptoms of lactic acidosis. In some cases this condition can cause death. Women, overweight people, and people who have taken HIV medicines like Abacavir Sulfate and Lamivudine Tablets for a long time have a higher chance of getting lactic acidosis and liver enlargement. Lactic acidosis is a medical emergency and must be treated in the hospital.
- **Worsening of hepatitis B virus (HBV) infection.** Patients with HBV infection, who take Abacavir Sulfate and Lamivudine Tablets and then stop it, may get “flare-ups” of their hepatitis. “Flare-up” is when the disease suddenly returns in a worse way than before. If your child or you have HBV infection, your doctor should closely monitor your child’s or your liver function for several months after stopping Abacavir Sulfate and Lamivudine Tablets. Your child or you may need to take anti-HBV medicines.
- **Use with interferon- and ribavirin-based regimens.** Worsening of liver disease (sometimes resulting in death) has occurred in patients infected with both HIV and hepatitis C virus who are taking anti-HIV medicines and are also being treated for hepatitis C with interferon with or without ribavirin. If your child or you are taking Abacavir Sulfate and Lamivudine Tablets as well as interferon with or without ribavirin and your child or you experience side effects, be sure to tell your child’s or your doctor.

Abacavir Sulfate and Lamivudine Tablets can have other serious side effects. Be sure to read the section below entitled **"What are the possible side effects of Abacavir Sulfate and Lamivudine?"**

What are Abacavir Sulfate and Lamivudine Tablets?

Abacavir Sulfate and Lamivudine Tablets are a prescription medicine used to treat HIV infection. Abacavir Sulfate and Lamivudine Tablets include 2 medicines: abacavir and lamivudine (3TC). See the end of this Medication Guide for a complete list of ingredients in Abacavir Sulfate and Lamivudine Tablets. Both of these medicines are called nucleoside analogue reverse transcriptase inhibitors (NRTIs). When used together, they help lower the amount of HIV in your child’s or your blood. This helps to keep your child’s or your immune system as healthy as possible so that it can help fight infection.

Different combinations of medicines are used to treat HIV infection. You and your doctor should discuss which combination of medicines is best for your child or you.

- **Abacavir Sulfate and Lamivudine Tablets do not cure HIV infection or AIDS.** We do not know if Abacavir Sulfate and Lamivudine Tablets will help your child or you live longer or have fewer of the medical problems that people get with HIV or AIDS. It is very important that your child see a doctor regularly while your child or you are taking Abacavir Sulfate and Lamivudine Tablets.
- **Abacavir Sulfate and Lamivudine Tablets do not lower the risk of passing HIV to other people through sexual contact, sharing needles, or being exposed to your blood.** For your health and the health of others, it is important to always practice safe sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood. Never use or share dirty needles.

Who should not take Abacavir Sulfate and Lamivudine Tablets?

Do not give your child or take Abacavir Sulfate and Lamivudine Tablets if:

- **Your child or you have ever had a serious allergic reaction (a hypersensitivity reaction) to Abacavir Sulfate and Lamivudine Tablets or any other medicine that has abacavir as one of its ingredients (Ziagen®, Epzicom™ and Trizivir®). See the end of this Medication Guide for a complete list of ingredients in Abacavir Sulfate and Lamivudine Tablets. If your child or you have had such a reaction, return all of the unused Abacavir Sulfate and Lamivudine Tablets to the doctor or pharmacist.**
- **Your child or you have a liver that does not function properly.**

Before starting Abacavir Sulfate and Lamivudine Tablets tell the doctor about all your child’s and your medical conditions, including if:

- **Your child or you have been tested and know whether or not your child or you have a particular gene variation called HLA-B*5701.**
- **You are pregnant or planning to become pregnant.** We do not know if Abacavir Sulfate and Lamivudine Tablets will harm your unborn child. You and your doctor will need to decide if Abacavir Sulfate and Lamivudine Tablets are right for you.
- **You are breastfeeding.** Some of the ingredients in Abacavir Sulfate and Lamivudine Tablets can be passed to your baby in your breast milk. It is not known if they could harm your baby. Also, mothers with HIV should not breastfeed because HIV can be passed to the baby in the breast milk.
- **Your child or you have liver problems including hepatitis B virus infection.**
- **Your child or you have kidney problems.**
- **Your child or you have heart problems, smoke, or suffer from diseases that increase your child’s or your risk of heart disease such as high blood pressure, high cholesterol, or diabetes.**

Tell your doctor about all the medicines your child and you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Especially tell your doctor if your child or you take:

- **Methadone**
- **Epivir® or Epivir-HBV® (lamivudine, 3TC), Combivir® (lamivudine and zidovudine), Ziagen® (abacavir sulfate), Epzicom™ (abacavir sulfate and lamivudine) and Trizivir® (abacavir sulfate, lamivudine, and zidovudine).**

How should my child or I take Abacavir Sulfate and Lamivudine Tablets?

- **Give or take Abacavir Sulfate and Lamivudine Tablets by mouth exactly as the doctor prescribes them.** The doctor will tell you the right dose to give or take. The dose will depend on the weight of your child. Do not skip doses. For very young children who cannot swallow tablets, the following procedure can be used:

1. Place the tablet in a container and add two teaspoonfuls (10 mL) of water per tablet.
2. Swirl the container until tablet gets dispersed.
3. Drink the dispersion within 1 hour.
4. Rinse the container with additional small amount of water and drink the contents to assure that the entire dosage is taken.

DO NOT MIX ABACAVIR SULFATE AND LAMIVUDINE TABLET WITH ANY LIQUID OTHER THAN WATER.

- Older children, who can reliably swallow tablets, could be given the appropriate dose (see table) to be swallowed.

P1501370
Abacavir Sulfate and Lamivudine Tablets (60 mg/30 mg) Rx only

Lamivudine: Patients co-infected with HIV and HBV should be informed that deterioration of liver disease has occurred in some cases when treatment with lamivudine was discontinued. Patients should be advised to discuss any changes in regimen with their physician.

Abacavir Sulfate and Lamivudine Tablets: Inform patients that some HIV medicines, including Abacavir Sulfate and Lamivudine Tablets, can cause a rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly).

Abacavir Sulfate and Lamivudine Tablets are not a cure for HIV infection and patients may continue to experience illnesses associated with HIV infection, including opportunistic infections. Patients should remain under the care of a physician when using Abacavir Sulfate and Lamivudine Tablets. Advise patients that the use of Abacavir Sulfate and Lamivudine Tablets has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

Abacavir Sulfate and Lamivudine Tablets are for oral ingestion only.

Patients should be advised of the importance of taking Abacavir Sulfate and Lamivudine Tablets exactly as they are prescribed.

Drug Interactions

Abacavir Sulfate and Lamivudine: No clinically significant changes to pharmacokinetic parameters were observed for abacavir or lamivudine when administered together.

Abacavir: Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol decreases the elimination of abacavir causing an increase in overall exposure (see **CLINICAL PHARMACOLOGY: Drug Interactions**).

The addition of methadone has no clinically significant effect on the pharmacokinetic properties of abacavir. In a study of 11 HIV-infected patients receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of abacavir sulfate twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI 6% to 42%). 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.

Lamivudine: Trimethoprim (TMP) 160 mg/sulfamethoxazole (SMX) 800 mg once daily has been shown to increase lamivudine exposure (AUC). No change in dose of either drug is recommended. The effect of higher doses of TMP/SMX on lamivudine pharmacokinetics has not been investigated (see **CLINICAL PHARMACOLOGY**).

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of Abacavir Sulfate and Lamivudine Tablets in combination with zalcitabine is not recommended.

See **CLINICAL PHARMACOLOGY** for additional drug interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

Abacavir: Abacavir was administered orally at 3 dosage levels to separate groups of mice and rats in 2-year carcinogenicity studies. Results showed an increase in the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver of female rats. In addition, non-malignant tumors also occurred in the liver and thyroid gland of female rats. These observations were made at systemic exposures in the range of 6 to 32 times the human exposure at the recommended dose.

Lamivudine: Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at the recommended therapeutic dose for HIV infection.

It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Mutagenicity

Abacavir: Abacavir induced chromosomal aberrations both in the presence and absence of metabolic activation in an *in vitro* cytogenetic study in human lymphocytes. Abacavir was mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence of metabolic activation in an L5178Y mouse lymphoma assay. Abacavir was clastogenic in males and not clastogenic in females in an *in vivo* mouse bone marrow micronucleus assay. Abacavir was not mutagenic in bacterial mutagenicity assays in the presence and absence of metabolic activation.

Lamivudine: Lamivudine was mutagenic in an L5178Y mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was not mutagenic in a microbial mutagenicity assay, in an *in vitro* cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver.

Impairment of Fertility

Abacavir or lamivudine induced no adverse effects on the mating performance or fertility of male and female rats at doses producing systemic exposure levels approximately 8 or 130 times, respectively, higher than those in humans at the recommended dose based on body surface area comparisons.

Pregnancy

Pregnancy Category C. There are no adequate and well-controlled studies of Abacavir Sulfate and Lamivudine Tablets in pregnant women. Reproduction studies with abacavir and lamivudine have been performed in animals (see ***Abacavir*** and ***Lamivudine*** sections below). Abacavir Sulfate and Lamivudine Tablets should be used during pregnancy only if the potential benefits outweigh the risks.

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

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

Nursing Mothers

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

Abacavir: Abacavir is secreted into the milk of lactating rats.

Lamivudine: Lamivudine is excreted in human breast milk and into the milk of lactating rats.

Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving Abacavir Sulfate and Lamivudine Tablets.**

Pediatric Use

***Abacavir Sulfate and Lamivudine Tablets*:** The safety and effectiveness data described below are based on studies conducted with the individual nucleoside analogues components of Abacavir Sulfate and Lamivudine Tablets.

Abacavir: The safety and effectiveness of abacavir sulfate have been established in pediatric patients 3 months to 13 years of age. Use of abacavir sulfate in these age groups is supported by pharmacokinetic studies and evidence from adequate and well-controlled studies of abacavir sulfate in adults and pediatric patients (see **CLINICAL PHARMACOLOGY: Pharmacokinetics: Special Populations: Pediatric Patients, INDICATIONS AND USAGE: Description of Clinical Studies: Pediatric Patients, WARNINGS, ADVERSE REACTIONS**, and **DOSAGE AND ADMINISTRATION**).

Lamivudine: The safety and effectiveness of twice-daily lamivudine in combination with other antiretroviral agents have been established in pediatric patients 3 months of age and older (see **CLINICAL PHARMACOLOGY: Pharmacokinetics: Special Populations: *Pediatric Patients*, INDICATIONS AND USAGE: Description of Clinical Studies: *Pediatric Patients*, WARNINGS, ADVERSE REACTIONS,** and **DOSAGE AND ADMINISTRATION**).

Geriatric Use

Clinical studies of abacavir and lamivudine did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Abacavir Sulfate and Lamivudine Tablets are not recommended for patients with impaired renal function or impaired hepatic function (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

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 practice.

Abacavir

Hypersensitivity Reaction: **Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate, a component of Abacavir Sulfate and Lamivudine Tablets.**

In one study, once-daily dosing of abacavir sulfate was associated with more severe hypersensitivity reactions (see WARNINGS and PRECAUTIONS: Information for Patients).

Pediatric Patients

Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a ≥5% frequency during therapy with abacavir 8 mg/kg twice daily, lamivudine 4 mg/kg twice daily, and zidovudine 180 mg/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 to 4, ≥5% Frequency) in Therapy-Experienced Pediatric Patients (CNA3006) Through 16 Weeks of Treatment

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

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

Other Adverse Events: In addition to adverse reactions and laboratory abnormalities reported, other adverse reactions observed in the expanded access program were pancreatitis and increased GGT.

Lamivudine

Pediatric Patients

Lamivudine has been studied in 638 pediatric patients 3 months to 18 years of age in 3 clinical trials. Selected clinical adverse events and physical findings with a ≥5% frequency during therapy with lamivudine 4 mg/kg twice daily plus zidovudine 160 mg/m^2 3 times daily compared with didanosine in therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in Table 5.

Table 5. Selected Clinical Adverse Events and Physical Findings (≥5% Frequency) in Pediatric Patients in Study ACTG300

Adverse Event	Lamivudine plus Zidovudine (n = 236)	Didanosine (n = 235)
Body as a Whole		
Fever	25%	32%
Digestive		
Hepatomegaly	11%	11%
Nausea and vomiting	8%	7%
Diarrhea	8%	6%
Stomatitis	6%	12%
Splenomegaly	5%	8%
Respiratory		
Cough	15%	18%
Abnormal breath sounds/ wheezing	7%	9%
Ear, Nose and Throat		
Signs or symptoms of ears*	7%	6%
Nasal discharge or congestion	8%	11%
Other		
Skin rashes	12%	14%
Lymphadenopathy	9%	11%

Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced pediatric patients receiving lamivudine alone or in combination with other antiretroviral agents. In an open-label dose-escalation study (NUCA2002), 14 patients (14%) developed pancreatitis while receiving monotherapy with lamivudine. Three of these patients died of complications of pancreatitis. In a second open-label study (NUCA2005), 12 patients (18%) developed pancreatitis. In Study ACTG300, pancreatitis was not observed in 236 patients randomized to lamivudine plus zidovudine. Pancreatitis was observed in 1 patient in this study who received open-label lamivudine in combination with zidovudine and ritonavir following discontinuation of didanosine monotherapy.

Paresthesias and peripheral neuropathies were reported in 15 patients (15%) in Study NUCA2002, 6 patients (9%) in Study NUCA2005, and 2 patients (<1%) in Study ACTG300.

Selected laboratory abnormalities experienced by therapy-naive (56 days of antiretroviral therapy) pediatric patients are listed in Table 6.

Table 6. Frequencies of Selected Laboratory Abnormalities in Pediatric Patients in Study ACTG300

Test (Threshold Level)	Lamivudine plus Zidovudine	Didanosine
Absolute neutrophil count (< 400/mm^3)	8%	3%
Hemoglobin (< 7.0 g/dL)	4%	2%
Platelets (< 50,000/mm^3)	1%	3%
ALT (> 10 x ULN)	1%	3%
AST (> 10 x ULN)	2%	4%
Lipase (> 2.5 x ULN)	3%	3%
Total Amylase (> 2.5 x ULN)	3%	3%

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

Observed During Clinical Practice

The following reactions have been identified during post-approval use of abacavir and lamivudine. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to abacavir and/or lamivudine.

Abacavir: Suspected Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients receiving abacavir primarily in combination with medications known to be associated with SJS and TEN, respectively. Because of the overlap of clinical signs and symptoms between hypersensitivity to abacavir and SJS and TEN, and the possibility of multiple drug sensitivities in some patients, abacavir should be discontinued and not restarted in such cases.

There have also been reports of erythema multiforme with abacavir use.

Abacavir and Lamivudine

Body as a Whole: Redistribution/accumulation of body fat (see **PRECAUTIONS: Fat Redistribution**).

Digestive: Stomatitis.

Endocrine and Metabolic: Hyperglycemia.

General: Weakness.

Hemic and Lymphatic: Aplastic anemia, anemia (including pure red cell aplasia and severe anemias progressing on therapy), lymphadenopathy, splenomegaly.

Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis, pancreatitis, posttreatment exacerbation of hepatitis B (see **WARNINGS**).

Hypersensitivity: Sensitization reactions (including anaphylaxis), urticaria.

Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.

Nervous: Paresthesia, peripheral neuropathy, seizures.

Respiratory: Abnormal breath sounds/wheezing.

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

OVERDOSAGE

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

Lamivudine: One case of an adult ingesting 6 grams of lamivudine was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. It is not known whether lamivudine can be removed by peritoneal dialysis or hemodialysis.

DOSAGE AND ADMINISTRATION

A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill.

Abacavir Sulfate and Lamivudine Tablets can be taken with or without food.

Adolescents and Pediatric Patients

The recommended oral dose of Abacavir Sulfate and Lamivudine Tablets for adolescents and pediatric patients 3 months to up to 16 years of age is abacavir 8 mg/kg twice daily (up to a maximum of 300 mg twice daily) and lamivudine 4 mg/kg twice daily (up to a maximum of 150 mg twice daily) in combination with other antiretroviral agents. This translates as follows in terms of number of tablets:

Weight (kg)	Dosage Regimen Using Scored Abacavir Sulfate and Lamivudine 60 mg/30 mg Tablets*		Total Daily Dose (mg)
	AM Dose (mg)	PM Dose (mg)	
5	½ tablet (30 mg A/15 mg L)	1 tablet (60 mg A/30 mg L)	90A/45L
6 - < 9	1 tablet (60 mg A/30 mg L)	1 tablet (60 mg A/30 mg L)	120A/60L
9 - < 12	1.5 tablets (90 mg A/45 mg L)	1.5 tablets (90 mg A/45 mg L)	180A/90L
12 - < 17	2 tablets (120 mg A/60 mg L)	2 tablets (120 mg A/60 mg L)	240A/120L
17 - < 20	2.5 tablets (150 mg A/75 mg L)	2.5 tablets (150 mg A/75 mg L)	300A/150L
20 - < 25	3 tablets (180 mg A/90 mg L)	3 tablets (180 mg A/90 mg L)	360A/180L
25 - < 29	3.5 tablets (210 mg A/105 mg L)	3.5 tablets (210 mg A/105 mg L)	420A/210L
29 - < 35	4 tablets (240 mg A/120 mg L)	4 tablets (240 mg A/120 mg L)	480A/240L

*A= abacavir sulfate; L= lamivudine

For children younger than 16 years old and weighing ≥ 35 kg, the recommended dose is the adult maximum daily dose, abacavir 300 mg twice daily and lamivudine 150 mg twice daily.

Method of Preparation

For children unable to swallow the tablet, the following procedure can be used:

1. Place the tablet in a container and add two teaspoonfuls (10 mL) of water per tablet.
2. Swirl the container until tablet gets dispersed.
3. Drink the dispersion within 1 hour.
4. Rinse the container with additional small amount of water and drink the contents to assure that the entire dosage is taken.

DO NOT MIX ABACAVIR SULFATE AND LAMIVUDINE TABLET WITH ANY LIQUID OTHER THAN WATER.

Dose Adjustment

Because they are fixed-dose tablets, Abacavir Sulfate and Lamivudine Tablets should not be prescribed for patients with renal and hepatic impairment, or those experiencing dose-limiting adverse events.

HOW SUPPLIED

Abacavir Sulfate and Lamivudine Tablets, 60 mg/30 mg are orange colored, modified capsule shaped film-coated tablets, debossed with 'H' and '38' on either side of the deep break line on one side and deep break line on the other side.

Bottles of 30	NDC 65862-334-30
Bottles of 60	NDC 65862-334-60
Carton of 100 (10 x 10) Unit-of-use Tablets	NDC 65862-334-10

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

ANIMAL TOXICOLOGY

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

REFERENCES

1. Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group. *Lancet*. 2008;371 (9622):1417-1426.

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Issued: December 2008

MEDICATION GUIDE
Abacavir Sulfate and Lamivudine Tablets 60 mg/30 mg

Read the Medication Guide that comes with Abacavir Sulfate and Lamivudine Tablets before you start taking or giving them to your child and each time your child or you get a refill because there may be new information. This information does not take the place of talking to your doctor about your child's or your medical condition or treatment. Be sure to carry the Abacavir Sulfate and Lamivudine Warning Card with you at all times.

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

- **Serious Allergic Reaction to Abacavir.** Abacavir Sulfate and Lamivudine Tablets contain abacavir (also contained in Ziagen®, Epzicom™ and Trizivir®). Patients taking Abacavir Sulfate and Lamivudine Tablets may have a serious allergic reaction (hypersensitivity reaction) that can cause death. **The risk of this allergic reaction is much higher in persons who have a gene variation called HLA-B*5701 than in those who do not. A blood test can determine if a person has this gene variation. If you get a symptom from 2 or more of the following groups while taking Abacavir Sulfate and Lamivudine Tablets, call your doctor right away to determine if this medicine should be stopped.**

	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.

If your child or you stop Abacavir Sulfate and Lamivudine Tablets because of an allergic reaction, NEVER take Abacavir Sulfate and Lamivudine Tablets or any other abacavir-containing medicine (Ziagen®, Epzicom™ and Trizivir®) again. If your child or you take Abacavir Sulfate and Lamivudine Tablets or any other abacavir-containing medicine again after your child or you have had an allergic reaction, **WITHIN HOURS** your child or you may get **life-threatening symptoms** that may include **very low blood pressure** or **death**.

If your child or you stop Abacavir Sulfate and Lamivudine Tablets for any other reason, even for a few days, and your child or you are not allergic to Abacavir Sulfate and Lamivudine Tablets, talk with your doctor before taking or giving your child Abacavir Sulfate and Lamivudine Tablets again. Taking Abacavir Sulfate and Lamivudine Tablets again can cause a serious allergic or life-threatening reaction, even if your child or you never had an allergic reaction to them before. If the doctor tells your child or you to take Abacavir Sulfate and Lamivudine Tablets again, **start giving or taking them when your child or you are around medical help or people who can call a doctor if your child or you need one.**

- **Lactic Acidosis. Some HIV medicines, including Abacavir Sulfate and Lamivudine Tablets, can cause a rare but serious condition called lactic acidosis with liver enlargement (hepatomegaly).** Nausea and tiredness that don't get better may be symptoms of lactic acidosis. In some cases this condition can cause death. Women, overweight people, and people who have taken HIV medicines like Abacavir Sulfate and Lamivudine Tablets for a long time have a higher chance of getting lactic acidosis and liver enlargement. Lactic acidosis is a medical emergency and must be treated in the hospital.
- **Worsening of hepatitis B virus (HBV) infection.** Patients with HBV infection, who take Abacavir Sulfate and Lamivudine Tablets and then stop it, may get "flare-ups" of their hepatitis. "Flare-up" is when the disease suddenly returns in a worse way than before. If your child or you have HBV infection, your doctor should closely monitor your child's or your liver function for several months after stopping Abacavir Sulfate and Lamivudine Tablets. Your child or you may need to take anti-HBV medicines.
- **Use with interferon- and ribavirin-based regimens.** Worsening of liver disease (sometimes resulting in death) has occurred in patients infected with both HIV and hepatitis C virus who are taking anti-HIV medicines and are also being treated for hepatitis C with interferon with or without ribavirin. If your child or you are taking Abacavir Sulfate and Lamivudine Tablets as well as interferon with or without ribavirin and your child or you experience side effects, be sure to tell your child's or your doctor.

Abacavir Sulfate and Lamivudine Tablets can have other serious side effects. Be sure to read the section below entitled **"What are the possible side effects of Abacavir Sulfate and Lamivudine?"**

What are Abacavir Sulfate and Lamivudine Tablets?

Abacavir Sulfate and Lamivudine Tablets are a prescription medicine used to treat HIV infection. Abacavir Sulfate and Lamivudine Tablets include 2 medicines: abacavir and lamivudine (3TC). See the end of this Medication Guide for a complete list of ingredients in Abacavir Sulfate and Lamivudine Tablets. Both of these medicines are called nucleoside analogue reverse transcriptase inhibitors (NRTIs). When used together, they help lower the amount of HIV in your child's or your blood. This helps to keep your child's or your immune system as healthy as possible so that it can help fight infection.

Different combinations of medicines are used to treat HIV infection. You and your doctor should discuss which combination of medicines is best for your child or you.

- **Abacavir Sulfate and Lamivudine Tablets do not cure HIV infection or AIDS.** We do not know if Abacavir Sulfate and Lamivudine Tablets will help your child or you live longer or have fewer of the medical problems that people get with HIV or AIDS. It is very important that your child see a doctor regularly while your child or you are taking Abacavir Sulfate and Lamivudine Tablets.
- **Abacavir Sulfate and Lamivudine Tablets do not lower the risk of passing HIV to other people through sexual contact, sharing needles, or being exposed to your blood.** For your health and the health of others, it is important to always practice safe sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood. Never use or share dirty needles.

Who should not take Abacavir Sulfate and Lamivudine Tablets?

Do not give your child or take Abacavir Sulfate and Lamivudine Tablets if:

- **Your child or you have ever had a serious allergic reaction (a hypersensitivity reaction) to Abacavir Sulfate and Lamivudine Tablets or any other medicine that has abacavir as one of its ingredients (Ziagen®, Epzicom™ and Trizivir®). See the end of this Medication Guide for a complete list of ingredients in Abacavir Sulfate and Lamivudine Tablets. If your child or you have had such a reaction, return all of the unused Abacavir Sulfate and Lamivudine Tablets to the doctor or pharmacist.**
- **Your child or you have a liver that does not function properly.**

Before starting Abacavir Sulfate and Lamivudine Tablets tell the doctor about all your child's and your medical conditions, including if:

- **Your child or you have been tested and know whether or not your child or you have a particular gene variation called HLA-B*5701.**
- **You are pregnant or planning to become pregnant.** We do not know if Abacavir Sulfate and Lamivudine Tablets will harm your unborn child. You and your doctor will need to decide if Abacavir Sulfate and Lamivudine Tablets are right for you.
- **You are breastfeeding.** Some of the ingredients in Abacavir Sulfate and Lamivudine Tablets can be passed to your baby in your breast milk. It is not known if they could harm your baby. Also, mothers with HIV should not breastfeed because HIV can be passed to the baby in the breast milk.
- **Your child or you have liver problems including hepatitis B virus infection.**
- **Your child or you have kidney problems.**
- **Your child or you have heart problems, smoke, or suffer from diseases that increase your child's or your risk of heart disease such as high blood pressure, high cholesterol, or diabetes.**

Tell your doctor about all the medicines your child and you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Especially tell your doctor if your child or you take:

- **Methadone**
- **Epivir® or Epivir-HBV® (lamivudine, 3TC), Combivir® (lamivudine and zidovudine), Ziagen® (abacavir sulfate), Epzicom™ (abacavir sulfate and lamivudine) and Trizivir® (abacavir sulfate, lamivudine, and zidovudine).**

How should my child or I take Abacavir Sulfate and Lamivudine Tablets?

- **Give or take Abacavir Sulfate and Lamivudine Tablets by mouth exactly as the doctor prescribes them.** The doctor will tell you the right dose to give or take. The dose will depend on the weight of your child. Do not skip doses. For very young children who cannot swallow tablets, the following procedure can be used:

1. Place the tablet in a container and add two teaspoonfuls (10 mL) of water per tablet.
2. Swirl the container until tablet gets dispersed.
3. Drink the dispersion within 1 hour.
4. Rinse the container with additional small amount of water and drink the contents to assure that the entire dosage is taken.

DO NOT MIX ABACAVIR SULFATE AND LAMIVUDINE TABLET WITH ANY LIQUID OTHER THAN WATER.

- Older children, who can reliably swallow tablets, could be given the appropriate dose (see table) to be swallowed.

Weight (kg)	Dosage Regimen Using Scored Abacavir Sulfate and Lamivudine 60 mg/30 mg Tablets*		Total Daily Dose (mg)
	AM Dose (mg)	PM Dose (mg)	
5	½ tablet (30 mg A/15 mg L)	1 tablet (60 mg A/30 mg L)	90A/45L
6 - < 9	1 tablet (60 mg A/30 mg L)	1 tablet (60 mg A/30 mg L)	120A/60L
9 - < 12	1.5 tablets (90 mg A/45 mg L)	1.5 tablets (90 mg A/45 mg L)	180A/90L
12 - < 17	2 tablets (120 mg A/60 mg L)	2 tablets (120 mg A/60 mg L)	240A/120L
17 - < 20	2.5 tablets (150 mg A/75 mg L)	2.5 tablets (150 mg A/75 mg L)	300A/150L
20 - < 25	3 tablets (180 mg A/90 mg L)	3 tablets (180 mg A/90 mg L)	360A/180L
25 - < 29	3.5 tablets (210 mg A/105 mg L)	3.5 tablets (210 mg A/105 mg L)	420A/210L
29 - < 35	4 tablets (240 mg A/120 mg L)	4 tablets (240 mg A/120 mg L)	480A/240L

*A= abacavir sulfate; L= lamivudine

- For children younger than 16 years old and weighing ≥ 35 kg, the recommended dose is the adult maximum daily dose, abacavir 300 mg twice daily and lamivudine 150 mg twice daily.
- **Your child or you can take Abacavir Sulfate and Lamivudine Tablets with or without food.**
- **If your child or you miss a dose of Abacavir Sulfate and Lamivudine Tablets, give or take the missed dose right away. Then, give or take the next dose at the usual time.**
- **Do not let Abacavir Sulfate and Lamivudine Tablets run out.**
- **Starting Abacavir Sulfate and Lamivudine Tablets again can cause a serious allergic or life-threatening reaction, even if your child or you never had an allergic reaction to them before.** If your child or you run out of Abacavir Sulfate and Lamivudine Tablets even for a few days, you must ask the doctor if your child or you can start Abacavir Sulfate and Lamivudine Tablets again. If the doctor tells you that your child or you can take Abacavir Sulfate and Lamivudine Tablets again, start taking it when your child or you are around medical help or people who can call a doctor if your child or you need one.
- **If your child or you stop your anti-HIV drugs, even for a short time, the amount of virus in your child's and your blood may increase and the virus may become harder to treat.**
- **If your child or you take too much Abacavir Sulfate and Lamivudine Tablets, call the doctor or poison control center right away.**

What should my child or I avoid while taking Abacavir Sulfate and Lamivudine Tablets?

- Do not take **Epivir® or Epivir-HBV® (lamivudine, 3TC), Combivir® (lamivudine and zidovudine), Ziagen® (abacavir sulfate), Epzicom™ (abacavir sulfate and lamivudine), Trizivir® (abacavir sulfate, lamivudine, and zidovudine), Atripla® (efavirenz, emtricitabine, and tenofovir disoproxil fumarate), or Truvada® (emtricitabine and tenofovir disoproxil fumarate)** while taking Abacavir Sulfate and Lamivudine Tablets. Some of these medicines are already in Abacavir Sulfate and Lamivudine Tablets.

Avoid doing things that can spread HIV infection, as Abacavir Sulfate and Lamivudine Tablets do not stop your child or you from passing the HIV infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** Abacavir Sulfate and Lamivudine Tablets can be passed to babies in breast milk and could harm the baby. Also, mothers with HIV should not breastfeed because HIV can be passed to the baby in the breast milk.

What are the possible side effects of Abacavir Sulfate and Lamivudine Tablets?

Abacavir Sulfate and Lamivudine Tablets can cause the following serious side effects:

- **Serious allergic reaction that can cause death.** (See **"What is the most important information my child and I should know about Abacavir Sulfate and Lamivudine Tablets?"** at the beginning of this Medication Guide.)
- **Lactic acidosis with liver enlargement (hepatomegaly) that can cause death.** (See **"What is the most important information my child and I should know about Abacavir Sulfate and Lamivudine Tablets?"** at the beginning of this Medication Guide.)
- **Worsening of HBV infection.** (See "**What is the most important information my child and I should know about Abacavir Sulfate and Lamivudine Tablets?"** at the beginning of this Medication Guide.)
- **Changes in immune system.** When your child or you start taking HIV medicines, your child's and your immune system may get stronger and could begin to fight infections that have been hidden in your child's and your body, such as pneumonia, herpes virus, or tuberculosis. If your child and you have new symptoms after starting the HIV medicines, be sure to tell your doctor.
- **Changes in body fat.** These changes have happened in patients taking antiretroviral medicines like Abacavir Sulfate and Lamivudine Tablets. The changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the back, chest, and stomach area. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known.

Some HIV medicines including abacavir sulfate may increase your risk of heart attack. If your child or you have heart problems, smoke, or suffer from diseases that increase your child's or your risk of heart disease such as high blood pressure, high cholesterol, or diabetes, tell your doctor.

The most common side effects with Abacavir Sulfate and Lamivudine Tablets in adults are trouble sleeping, depression, headache, tiredness, dizziness, nausea, diarrhea, rash, fever, stomach pain, abnormal dreams, and anxiety. Most of these side effects did not cause people to stop taking Abacavir Sulfate and Lamivudine Tablets.

The most common side effects with Abacavir Sulfate and Lamivudine Tablets in children include nausea, vomiting, skin rashes, headache, fever and chills, pneumonia, and infections of ear, nose, and throat. Most of these side effects did not cause children to stop taking Abacavir Sulfate and Lamivudine Tablets.

This list of side effects is not complete. Ask your doctor or pharmacist for more information.

How should I store Abacavir Sulfate and Lamivudine Tablets?

- Store Abacavir Sulfate and Lamivudine Tablets at room temperature between 59° to 86°F (15° to 30°C).
- Keep Abacavir Sulfate and Lamivudine Tablets and all medicines out of the reach of children.

General information for safe and effective use of Abacavir Sulfate and Lamivudine Tablets

Medicines are sometimes prescribed for conditions that are not mentioned in Medication Guides. Do not use Abacavir Sulfate and Lamivudine Tablets for a condition for which they were not prescribed. Do not give Abacavir Sulfate and Lamivudine Tablets to other people, even if they have the same symptoms that your child or you have. They may harm them.

This Medication Guide summarizes the most important information about Abacavir Sulfate and Lamivudine Tablets. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for the information that is written for healthcare professionals.

What are the ingredients in Abacavir Sulfate and Lamivudine Tablets?

Active ingredients: abacavir sulfate and lamivudine

Inactive ingredients: Each film-coated Abacavir Sulfate and Lamivudine Tablet contains the inactive ingredients microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. The tablets are coated with a film (opadry orange YS-1-13065-A) that is made of hypromellose, titanium dioxide, polysorbate 80, polyethylene glycol 400, and FD&C yellow #6 aluminum lake.

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

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Issued: December 2008

P1501370

✂ DETACH BEFORE DISPENSING

Weight (kg)	Dosage Regimen Using Scored Abacavir Sulfate and Lamivudine 60 mg/30 mg Tablets*		Total Daily Dose (mg)
	AM Dose (mg)	PM Dose (mg)	
5	½ tablet (30 mg A/15 mg L)	1 tablet (60 mg A/30 mg L)	90A/45L
6 - < 9	1 tablet (60 mg A/30 mg L)	1 tablet (60 mg A/30 mg L)	120A/60L
9 - < 12	1.5 tablets (90 mg A/45 mg L)	1.5 tablets (90 mg A/45 mg L)	180A/90L
12 - < 17	2 tablets (120 mg A/60 mg L)	2 tablets (120 mg A/60 mg L)	240A/120L
17 - < 20	2.5 tablets (150 mg A/75 mg L)	2.5 tablets (150 mg A/75 mg L)	300A/150L
20 - < 25	3 tablets (180 mg A/90 mg L)	3 tablets (180 mg A/90 mg L)	360A/180L
25 - < 29	3.5 tablets (210 mg A/105 mg L)	3.5 tablets (210 mg A/105 mg L)	420A/210L
29 - < 35	4 tablets (240 mg A/120 mg L)	4 tablets (240 mg A/120 mg L)	480A/240L

*A= abacavir sulfate; L= lamivudine

- For children younger than 16 years old and weighing ≥ 35 kg, the recommended dose is the adult maximum daily dose, abacavir 300 mg twice daily and lamivudine 150 mg twice daily.
- **Your child or you can take Abacavir Sulfate and Lamivudine Tablets with or without food.**
- **If your child or you miss a dose of Abacavir Sulfate and Lamivudine Tablets, give or take the missed dose right away. Then, give or take the next dose at the usual time.**
- **Do not let Abacavir Sulfate and Lamivudine Tablets run out.**
- **Starting Abacavir Sulfate and Lamivudine Tablets again can cause a serious allergic or life-threatening reaction, even if your child or you never had an allergic reaction to them before.** If your child or you run out of Abacavir Sulfate and Lamivudine Tablets even for a few days, you must ask the doctor if your child or you can start Abacavir Sulfate and Lamivudine Tablets again. If the doctor tells you that your child or you can take Abacavir Sulfate and Lamivudine Tablets again, start taking it when your child or you are around medical help or people who can call a doctor if your child or you need one.
- **If your child or you stop your anti-HIV drugs, even for a short time, the amount of virus in your child's and your blood may increase and the virus may become harder to treat.**
- **If your child or you take too much Abacavir Sulfate and Lamivudine Tablets, call the doctor or poison control center right away.**

What should my child or I avoid while taking Abacavir Sulfate and Lamivudine Tablets?

- Do not take **Epivir® or Epivir-HBV® (lamivudine, 3TC), Combivir® (lamivudine and zidovudine), Ziagen® (abacavir sulfate), Epzicom™ (abacavir sulfate and lamivudine), Trizivir® (abacavir sulfate, lamivudine, and zidovudine), Atripla® (efavirenz, emtricitabine, and tenofovir disoproxil fumarate), or Truvada® (emtricitabine and tenofovir disoproxil fumarate)** while taking Abacavir Sulfate and Lamivudine Tablets. Some of these medicines are already in Abacavir Sulfate and Lamivudine Tablets.

Avoid doing things that can spread HIV infection, as Abacavir Sulfate and Lamivudine Tablets do not stop your child or you from passing the HIV infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** Abacavir Sulfate and Lamivudine Tablets can be passed to babies in breast milk and could harm the baby. Also, mothers with HIV should not breastfeed because HIV can be passed to the baby in the breast milk.

What are the possible side effects of Abacavir Sulfate and Lamivudine Tablets?

Abacavir Sulfate and Lamivudine Tablets can cause the following serious side effects:

- **Serious allergic reaction that can cause death.** (See **"What is the most important information my child and I should know about Abacavir Sulfate and Lamivudine Tablets?"** at the beginning of this Medication Guide.)
- **Lactic acidosis with liver enlargement (hepatomegaly) that can cause death.** (See **"What is the most important information my child and I should know about Abacavir Sulfate and Lamivudine Tablets?"** at the beginning of this Medication Guide.)
- **Worsening of HBV infection.** (See "**What is the most important information my child and I should know about Abacavir Sulfate and Lamivudine Tablets?"** at the beginning of this Medication Guide.)
- **Changes in immune system.** When your child or you start taking HIV medicines, your child's and your immune system may get stronger and could begin to fight infections that have been hidden in your child's and your body, such as pneumonia, herpes virus, or tuberculosis. If your child and you have new symptoms after starting the HIV medicines, be sure to tell your doctor.
- **Changes in body fat.** These changes have happened in patients taking antiretroviral medicines like Abacavir Sulfate and Lamivudine Tablets. The changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the back, chest, and stomach area. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known.

Some HIV medicines including abacavir sulfate may increase your risk of heart attack. If your child or you have heart problems, smoke, or suffer from diseases that increase your child's or your risk of heart disease such as high blood pressure, high cholesterol, or diabetes, tell your doctor.

The most common side effects with Abacavir Sulfate and Lamivudine Tablets in adults are trouble sleeping, depression, headache, tiredness, dizziness, nausea, diarrhea, rash, fever, stomach pain, abnormal dreams, and anxiety. Most of these side effects did not cause people to stop taking Abacavir Sulfate and Lamivudine Tablets.

The most common side effects with Abacavir Sulfate and Lamivudine Tablets in children include nausea, vomiting, skin rashes, headache, fever and chills, pneumonia, and infections of ear, nose, and throat. Most of these side effects did not cause children to stop taking Abacavir Sulfate and Lamivudine Tablets.

This list of side effects is not complete. Ask your doctor or pharmacist for more information.

How should I store Abacavir Sulfate and Lamivudine Tablets?

- Store Abacavir Sulfate and Lamivudine Tablets at room temperature between 59° to 86°F (15° to 30°C).
- Keep Abacavir Sulfate and Lamivudine Tablets and all medicines out of the reach of children.

General information for safe and effective use of Abacavir Sulfate and Lamivudine Tablets

Medicines are sometimes prescribed for conditions that are not mentioned in Medication Guides. Do not use Abacavir Sulfate and Lamivudine Tablets for a condition for which they were not prescribed. Do not give Abacavir Sulfate and Lamivudine Tablets to other people, even if they have the same symptoms that your child or you have. They may harm them.

This Medication Guide summarizes the most important information about Abacavir Sulfate and Lamivudine Tablets. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for the information that is written for healthcare professionals.

What are the ingredients in Abacavir Sulfate and Lamivudine Tablets?

Active ingredients: abacavir sulfate and lamivudine

Inactive ingredients: Each film-coated Abacavir Sulfate and Lamivudine Tablet contains the inactive ingredients microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. The tablets are coated with a film (opadry orange YS-1-13065-A) that is made of hypromellose, titanium dioxide, polysorbate 80, polyethylene glycol 400, and FD&C yellow #6 aluminum lake.

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

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Issued: December 2008

(Front of Card)

WARNING CARD

Abacavir Sulfate and Lamivudine Tablets 60 mg/30 mg

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

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

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

(Back of Card)

WARNING CARD

Abacavir Sulfate and Lamivudine Tablets 60 mg/30 mg

If your child or you must stop treatment with Abacavir Sulfate and Lamivudine Tablets because your child or you have had an allergic reaction to abacavir, **NEVER** take Abacavir Sulfate and Lamivudine Tablets or another abacavir-containing medicine (Ziagen®, Epzicom and Trizivir®) again. If your child or you take Abacavir Sulfate and Lamivudine Tablets or another abacavir-containing medicine again after your child or you have had an allergic reaction, **WITHIN HOURS** your child or you may get **life-threatening symptoms** that may include **very low blood pressure** or **death**.

Your child or you should return all of the unused Abacavir Sulfate and Lamivudine Tablets to your doctor or pharmacist for proper disposal.

Please read the Medication Guide for additional information on Abacavir Sulfate and Lamivudine Tablets.

Issued: December 2008 P1002670