HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use abacavir sulfate and lamivudine safely and effectively. See full prescribing information for abacavir sulfate and lamivudine.

Abacavir Sulfate and Lamivudine tablets for oral suspension 60 mg/30 mg

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

See full prescribing information for complete boxed warning.

- **Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir-containing products (5.1)**
- **Hypersensitivity to abacavir is a multiorgan clinical syndrome. (5.1)**
- **Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. (5.1)**
- **Discontinue abacavir sulfate and lamivudine as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B*5701 status, permanently discontinue abacavir sulfate and lamivudine if hypersensitivity cannot be ruled out, even when other diagnoses are possible. (5.1)**
- **Following a hypersensitivity reaction to abacavir, NEVER restart abacavir sulfate and lamivudine or any other abacavir-containing product. (5.1)**
- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. (5.2)**
- **Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine, a component of abacavir sulfate and lamivudine. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.3)**

INDICATIONS AND USAGE

Abacavir sulfate and lamivudine, a combination of abacavir and lamivudine, both nucleoside analogues HIV-1 reverse transcriptase inhibitors, are indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. (1)

DOSAGE AND ADMINISTRATION

- A medication guide and warning card should be dispensed with each new prescription and refill. (2)
- Pediatric patients 3 months and older: Dosage should be based on body weight (2,2)
- Do not prescribe for patients requiring a dosage adjustment or patients with hepatic impairment. (2,2)

DOSAGE FORMS AND STRENGTHS

Scored tablets for oral suspension contain 60 mg of abacavir and 30 mg of lamivudine. (3)

CONTRAINDICATIONS

- Previously demonstrated hypersensitivity to abacavir or any other component of the product. (4, 5.1)
- Hepatic impairment. (4)

WARNINGS AND PRECAUTIONS

- See boxed warning for information about the following: hypersensitivity reactions, lactic acidosis and severe hepatomegaly, and severe acute exacerbations of hepatitis B. (5.1, 5.2, 5.3)
- Hepatic decompensation, some fatal, has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy and interferon alfa with or without ribavirin. Discontinue abacavir sulfate and lamivudine as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.4)
- Immune reconstitution syndrome (5.5) and osteonecrosis (5.6) have been reported in patients treated with combination antiretroviral therapy. (5.5)
- Mitochondrial dysfunction: avoid use in combination with other lamivudine- or zidovudine-containing products or ribavirin-containing products. (5.7)
- Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue treatment as clinically appropriate. (5.8)

ADVERSE REACTIONS

- The most commonly reported adverse reactions of at least moderate intensity (incidence ≥5%) in adult HIV-1 clinical study were drug hypersensitivity, insomnia, depression, depressed mood, headache/migraine, fatigue/malaise, diaphoresis/night sweats, and diarrhea. (6.1)
- Abacavir: The most common reported adverse reactions of at least moderate intensity (incidence ≥5%) in pediatric HIV-1 clinical trials were fever/chills, nausea and vomiting, skin eruptions, and upper/lower respiratory infections (6.1)
- Lamivudine: The most commonly reported adverse reactions (incidence ≥5%) in pediatric patients were fever and cough (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Cipla Ltd. at 91-22-2578 7825 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Ethanol: Decrease elimination of abacavir. (7.2)
- Methadone: Increased methadone dose may be required in a small number of patients. (7.4)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE.

Revised: May 2011

Abacavir Sulfate and Lamivudine tablets for oral suspension 60 mg/30 mg

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: RISK OF HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, AND EXACERBATIONS OF HEPATITIS B

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FULL PRESCRIBING INFORMATION

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

HYPERSENSITIVITY REACTIONS, SERIOUS AND SOMETIMES FATAL HYPERSENSITIVITY REACTIONS HAVE BEEN ASSOCIATED WITH ABACAVIR SULFATE, A COMPONENT OF ABACAVIR SULFATE AND LAMIVUDINE TABLETS FOR ORAL SUSPENSION. 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); OR CONSTITUTIONAL (INCLUDING GENERALIZED MALAISE, FATIGUE, OR ACHIEVES). AND (3) RESPIRATORY (INCLUDING DYSPNEA, COUGH, OR PHARYNGITIS). DISCONTINUE ABACAVIR AND LAMIVUDINE 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. DATA APPROACHING 100% PREDICTIVITY HAVE BEEN FOUND TO DECREASE THE RISK OF HYPERSENSITIVITY REACTIONS. SCREENING IS ALSO RECOMMENDED PRIOR TO RE-INITIATION OF ABACAVIR IN PATIENTS OF UNKNOWN HLA-B*5701 STATUS WHO HAVE PREVIOUSLY TOLERATED ABACAVIR. HLA-B*5701-NEGATIVE PATIENTS MAY DEVELOP A SUSPECTED WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE ABACAVIR AND LAMIVUDINE AND ARE CO-INFECTED WITH HIV-1 AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS AND PRECAUTIONS (5.3)).

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 AND PRECAUTIONS (5.2)).

EXACERBATIONS OF HEPATITIS B: SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED WITH HEPATITIS B VIRUS (HBV) AND HUMAN IMMUNODEFICIENCY VIRUS (HIV-1) AND HAVE DISCONTINUED LAMIVUDINE, WHICH IS ONE COMPONENT OF ABACAVIR AND LAMIVUDINE. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE ABACAVIR AND LAMIVUDINE AND ARE CO-INFECTED WITH HIV-1 AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS AND PRECAUTIONS (5.3)).

1 INDICATIONS AND USAGE

Abacavir sulfate and lamivudine, a combination of abacavir and lamivudine, both nucleoside analogue HIV-1 reverse transcriptase inhibitors, are indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. (1)

2 DOSAGE AND ADMINISTRATION

- A medication guide and warning card should be dispensed with each new prescription and refill. (2)
- Pediatric patients 3 months and older: Dosage should be based on body weight (2,2)
- Do not prescribe for patients requiring a dosage adjustment or patients with hepatic impairment. (2,2)

Scored tablets for oral suspension contain 60 mg of abacavir and 30 mg of lamivudine. (3)

4 CONTRAINDICATIONS

- Previously demonstrated hypersensitivity to abacavir or any other component of the product. (4, 5.1)
- Hepatic impairment. (4)

5 WARNINGS AND PRECAUTIONS

- See boxed warning for information about the following: hypersensitivity reactions, lactic acidosis and severe hepatomegaly, and severe acute exacerbations of hepatitis B. (5.1, 5.2, 5.3)
- Hepatic decompensation, some fatal, has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy and interferon alfa with or without ribavirin. Discontinue abacavir sulfate and lamivudine as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.4)
- Immune reconstitution syndrome (5.5) and osteonecrosis (5.6) have been reported in patients treated with combination antiretroviral therapy. (5.5)
- Mitochondrial dysfunction: avoid use in combination with other lamivudine- or zidovudine-containing products or ribavirin-containing products. (5.7)
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6 ADVERSE REACTIONS

- The most commonly reported adverse reactions of at least moderate intensity (incidence ≥5%) in adult HIV-1 clinical study were drug hypersensitivity, insomnia, depression, depressed mood, headache/migraine, fatigue/malaise, diaphoresis/night sweats, and diarrhea. (6.1)
- Abacavir: The most commonly reported adverse reactions of at least moderate intensity (incidence ≥5%) in pediatric HIV-1 clinical trials were fever/chills, nausea and vomiting, skin eruptions, and upper/lower respiratory infections (6.1)
- Lamivudine: The most commonly reported adverse reactions (incidence ≥5%) in pediatric patients were fever and cough (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Cipla Ltd. at 91-22-2578 7825 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

7 DRUG INTERACTIONS

- Ethanol: Decrease elimination of abacavir. (7.2)
- Methadone: Increased methadone dose may be required in a small number of patients. (7.4)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE.

Revised: May 2011

1 INDICATIONS AND USAGE

Abacavir sulfate and lamivudine, a combination of abacavir and lamivudine, both nucleoside analogue HIV-1 reverse transcriptase inhibitors, are indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. (1)

2 DOSAGE AND ADMINISTRATION

- A medication guide and warning card should be dispensed with each new prescription and refill. (2)
- Take abacavir and lamivudine once daily. (2)

Scored tablets contain 60 mg of abacavir and 30 mg of lamivudine.

Consult full prescribing information on the use of abacavir sulfate and lamivudine for treatment of HIV-1 infection.

- Abacavir sulfate and lamivudine tablets are available in scored tablets containing abacavir. Before crushing abacavir sulfate and lamivudine, consider medical history for prior exposure to any abacavir-containing product in order to avoid sensitization in a patient with a history of hypersensitivity to abacavir (See Warnings and Precautions (5.1), Adverse Reactions (6)).
- As part of a dosing regimen, abacavir sulfate and lamivudine tablets in oral suspension are recommended for use with antiretroviral agents from different pharmacological classes and not with other nucleoside/nucleotide reverse transcriptase inhibitors.

2 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.
- Take abacavir and lamivudine once daily.

2.1 Pediatric Patients

The recommended oral dosage of abacavir sulfate and lamivudine in HIV-1-infected pediatric patients 3 months and older 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 is provided in Table 1.

Table 1. Dosing Recommendations for Abacavir Sulfate and Lamivudine Tablets for Oral Suspension Pediatric Patients

Weight (kg)	Dosage Regimen Using Scored Abacavir Sulfate and Lamivudine tablets for Oral Suspension, 60 mg/30 mg		Total Daily Dose (mg)
	AM Dose (mg)	PM Dose (mg)	
5	1 tablet (60 mg A/30 mg L)	1 tablet (60 mg A/30 mg L)	120A/60L
6 – 9	1 tablet (60 mg A/30 mg L)	1 tablet (60 mg A/30 mg L)	120A/60L
9 – 12	2 tablets (120 mg A/60 mg L)	1 tablet (60 mg A/30 mg L)	180A/90L
12 – 14	2 tablets (120 mg A/60 mg L)	2 tablets (120 mg A/60 mg L)	240A/120L
14 – 20	2 tablets (120 mg A/60 mg L)	2 tablets (120 mg A/60 mg L)	240A/120L
20 – 25	3 tablets (180 mg A/90 mg L)	2 tablets (120 mg A/60 mg L)	300A/150L
25 – 30	3 tablets (180 mg A/90 mg L)	3 tablets (180 mg A/90 mg L)	360A/180L
30 – 35	4 tablets (240 mg A/120 mg L)	3 tablets (180 mg A/90 mg L)	420A/210L
35 – 40	4 tablets (240 mg A/120 mg L)	4 tablets (240 mg A/120 mg L)	480A/240L
≥40	5 tablets (300 mg A/150 mg L)	5 tablets (300 mg A/150 mg L)	600A/300L

A = abacavir sulfate; L = lamivudine

* For recommended doses of abacavir 300 mg twice daily and lamivudine 150 mg twice daily (adult maximum daily dose), the adult forms tablets (abacavir 300 mg tablet and lamivudine 150 mg tablet) can be used.

Method of Preparation

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

1. Place the tablet(s) in a container and add two teaspoonfuls (10 ml) of drinking water per tablet.
2. Crush the tablet(s) with the back of the tablet(s) using a spoon until enough for the dose of 10 ml is available. A spoon can be used to crush the tablets, if needed.
3. Drink the mixture within 1 hour.
4. Rinse the container with a small amount of water and drink the contents to assure that the entire dosage is taken.

DO NOT CRUSH THE ABACAVIR SULFATE AND LAMIVUDINE TABLETS FOR ORAL SUSPENSION WITH ANY LIQUID OTHER THAN WATER.

2.2 Dose Adjustment

Because abacavir sulfate and lamivudine tablets are supplied as a fixed-dose combination, it should not be prescribed for:

- patients requiring dosage adjustment such as those with creatinine clearances <50 mL/min
- patients with hepatic impairment.

3 DOSAGE FORMS AND STRENGTHS

Abacavir sulfate and lamivudine tablets for oral suspension contain 60 mg of abacavir as abacavir sulfate and 30 mg of lamivudine. The tablets are scored, white to off-white in color, capsule-shaped, biconvex, and embossed debossed with overall breakline on one side and "A" debossed on other side.

4 CONTRAINDICATIONS

Abacavir sulfate and lamivudine tablets for oral suspension are contraindicated in patients with:

- previously demonstrated hypersensitivity to abacavir or to any other component of the product.

Never restart abacavir and lamivudine or any other abacavir-containing product following a hypersensitivity reaction to abacavir, regardless of HLA-B*5701 status (see WARNINGS AND PRECAUTIONS (5.1), ADVERSE REACTIONS (6)).

- hepatic impairment (see Use in Specific Populations (8.7)).

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reaction

Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir 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 abacavir-containing regimens 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 and lamivudine 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.

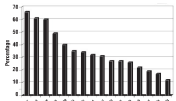
Signs and symptoms of Hypersensitivity: Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in two or more of the following groups:

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 9% of 2,670 patients (n = 206) in 3 clinical trials (range 2% to 9%) with enrollment from November 1999 to February 2002. Based on time to onset and symptoms of suspected hypersensitivity were collected on a medical 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 11 days (IQR = 6 - 20), appeared within the first 6 weeks 95% of patients reported symptoms from 2 or more of the groups listed above.

Figure 1: Hypersensitivity-Related Symptoms Reported with ≥3% Frequency in Clinical Trials (n = 206 Patients)



Other less common signs and symptoms of hypersensitivity include lethargy, myalgias, edema, abnormal chest exam findings (predominantly wheezing), which can be localized, and gastrointestinal findings (liver tender, renal tender, hepatomegaly, gall bladder tender, peritonitis, colitis, diverticulitis, pancreatitis, gastroenteritis, and hepatitis). Laboratory abnormalities, in one study in 4 patients (11%), involving abacavir 600 mg once daily included hepatitis, hepatitis with hepatomegaly, and hepatitis with hepatomegaly and rash. Hypotension (abacavir 300 mg twice daily), lymphadenopathy, and hypersensitivity to abacavir in a patient with Kaposi's sarcoma, resulting in a fatal outcome, have been also reported. Other signs and symptoms of hypersensitivity include lymphadenopathy, edema, and mouth ulceration, and rash, but rash usually appears hypersensitivity reaction during the course of abacavir treatment. These 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 transaminase, elevated bilirubin, elevated creatinine, and myelotoxicity.

Clinical management of hypersensitivity:

Discontinue abacavir and lamivudine as soon as a hypersensitivity reaction is suspected. To minimize the risk of a life-threatening response during reaction, permanently discontinue abacavir and lamivudine if hypersensitivity cannot be ruled out, even when other diagnoses are possible (e.g., acute small respiratory diseases such as pneumonia, bronchitis, pharyngitis, or influenza, gastroenteritis, or reactions to other medications).

Following a hypersensitivity reaction to abacavir, NEVER restart Abacavir and lamivudine or any other abacavir-containing product because they can result in severe symptoms within hours of re-exposure, which can result in life-threatening hospitalization or death.

When therapy with abacavir and lamivudine has been discontinued for reasons other than symptoms of a hypersensitivity reaction, and if sensitization of abacavir and lamivudine or any other abacavir-containing product is under consideration, carefully evaluate the reason for discontinuation of abacavir and lamivudine 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 and lamivudine.

If hypersensitivity cannot be ruled out, DO NOT reintroduce abacavir and lamivudine or any other abacavir-containing product. Even in the absence of the HLA-B*5701 allele, it is important to permanently discontinue abacavir and not re-challenge with abacavir. Subsequent administration of a hypersensitivity reaction cannot be ruled out on clinical grounds, due to the possibility of a severe or even fatal reaction.

Re-exposure in patients with hypersensitivity are not identified, reintroduction can be undertaken with continued monitoring for signs and symptoms of hypersensitivity reaction. Make patients aware that a hypersensitivity reaction can occur with reintroduction of abacavir and lamivudine or any other abacavir-containing product and that abacavir and lamivudine or reintroduction of any other abacavir-containing product needs to be undertaken only if medical care can be readily accessed by the patient or the family.

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 hypersensitivity reaction to abacavir. COMBINATION (PREDICT-1), a randomized, double-blind study, evaluated the clinical utility of prospective HLA-B*5701 screening on the incidence of clinically suspected hypersensitivity reaction in abacavir-naïve HIV-1-infected adults (N = 1,956). In this study, use of pre-therapy screening for the HLA-B*5701 allele and prospective discontinuation of abacavir sulfate and lamivudine tablets for oral suspension in carriers of the HLA-B*5701 allele, and discontinuation of any other abacavir-containing product reduced the incidence of clinically suspected abacavir hypersensitivity reaction from 7.2% (96/847) to 0.6% (2/333). 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. 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 re-challenge with abacavir if a hypersensitivity reaction cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

5.2 Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir sulfate 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 and lamivudine to any patient with known risk factors for liver disease. However, cases have also been reported in patients with no known risk factors. Treatment with Abacavir and lamivudine should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity, which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations.

5.3 Patients With HIV-1 and Hepatitis B Virus Co-Infection

Post-treatment Exacerbation of Hepatitis: B-infected patients treated with lamivudine are at risk for severe acute exacerbations of hepatitis B upon discontinuation of hepatitis B virus-active drug administration. These exacerbations have been detected primarily by serum ALT elevations in addition to reemergence of HBV DNA in serum. Post-treatment exacerbations have been observed in patients who have chronic hepatitis B but who have been exposed to lamivudine for a short duration. Severe acute exacerbations have also been reported in patients who have completed a course of treatment for chronic hepatitis B. Post-treatment exacerbations have been observed in patients who have completed treatment that did prevent HBV from becoming a chronic infection. Post-treatment exacerbations have also been reported in HIV-1-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

5.4 Use With Interferon and Ribavirin-Based Regimens

In vitro studies have shown that ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine, a component of abacavir sulfate and lamivudine tablets. Although no evidence of a pharmacokinetic or pharmacodynamic interaction has been observed in patients who received ribavirin and lamivudine, cases of lactic acidosis with lamivudine in HIV-1/HCV co-infected subjects have Clinical Pharmacology (12.2), hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin. (See Clinical Pharmacology (12.2), Clinical Pharmacology (12.3)).

5.5 Immune Reconstitution Syndrome

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

5.6 Fat Redistribution

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

5.7 Mitocondrial Intoxication

In vitro and in vivo studies have shown that nucleoside analogs may also inhibit mitochondrial DNA synthesis. Mitochondrial dysfunction in patients are contemplation antiretroviral therapy, the use of abacavir within the previous 6 months was associated with an increased risk of peripheral neuropathy (PN). In one retrospective case-control study (n = 386 patients), the duration of exposure to abacavir was also associated with an increased risk of peripheral neuropathy. Mitochondrial dysfunction was observed in abacavir-treated subjects as compared with control subjects. In totality, the available data from the literature suggest that exposure to abacavir may be a risk factor for peripheral neuropathy.

As a precaution, the underlying risk of coronary heart disease should be considered when prescribing antiretroviral therapies, and lipid and glucose levels should be monitored. Non-pharmacologic treatments for coronary heart disease, diabetes mellitus, and smoking.

5.8 Use With Other Abacavir-, Lamivudine-, and/or Emtricitabine-Containing Products

Abacavir sulfate and lamivudine tablets for oral suspension contain fixed dose of 2 nucleoside analogues, abacavir and lamivudine, and should not be administered concomitantly with other abacavir-containing and/or lamivudine-containing products including ZIAGEN® (abacavir sulfate), EPIVIR® and COMBIVIR® (lamivudine), COMBIVIR® (lamivudine and zidovudine), TRIZIVIR® (abacavir sulfate and lamivudine), TRIUMEQ® (abacavir sulfate, lamivudine, and dolutegravir), or emtricitabine-containing products, including EMTRIVA® (emtricitabine), and Truvada® (emtricitabine and tenofovir disoproxil fumarate).

5.9 Pancreatitis

Use with caution with a history of prior antiretroviral treatment exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis. Discontinue treatment with Abacavir and lamivudine tablets for oral suspension and lamivudine, should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur (see Adverse Reactions (6.1)).

6 ADVERSE REACTIONS

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

- Serious and sometimes fatal hypersensitivity reaction. In one study, over 3 days dosing of abacavir was associated with more severe hypersensitivity reactions (see Boxed Warning, Warnings and Precautions (5.1)).
- Lactic acidosis and severe hepatomegaly (see Boxed Warning, Warnings and Precautions (5.2)).
- Acute exacerbations of hepatitis B (see Boxed Warning, Warnings and Precautions (5.3)).
- Hepatic decompensation in patients co-infected with HIV-1 and Hepatitis C (see Warnings and Precautions (5.4)).
- Immune reconstitution syndrome (see Warnings and Precautions (5.5)).
- Fat redistribution (see Warnings and Precautions (5.6)).
- Mitochondrial intoxication (see Warnings and Precautions (5.7)).
- Pancreatitis (see Warnings and Precautions (5.9)).

6.1 Clinical Trials Experience

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

Abacavir and lamivudine

Adults: Therapy-Naïve Adults: Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with ≥ 2% frequency during therapy with abacavir 600 mg once daily or abacavir 300 mg twice daily both in combination with lamivudine 300 mg once daily and zidovudine 300 mg twice daily are listed in Table 2.

Table 2. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2-4, ≥2% Frequency) in Therapy-Naïve Adults (CNA30021) Through 48 Weeks of Treatment

Adverse Event	Abacavir 600 mg Lamivudine Zidovudine (n = 384)	Abacavir 300 mg Lamivudine Zidovudine (n = 386)
Drug hypersensitivity [1]	9%	7%
Insomnia	7%	5%
Depression/Depressed mood	7%	7%
Headache/Migraine	7%	6%
Fatigue/Malaise	6%	8%
Diaphoresis/Nightsweats	6%	6%
Anorexia	5%	6%
Diarrhea[2]	5%	6%
Rash	3%	5%
Myalgia and vomiting	5%	3%
Abnormal dreams/paresthesia	4%	5%
Anemia and dyspnea	4%	5%
Anxiety	3%	5%

[1] Subjects receiving abacavir 600 mg once daily experienced a significantly higher incidence of severe drug hypersensitivity reactions and severe diarrhea compared with subjects who received abacavir 300 mg twice daily. Five percent (7%) of subjects receiving abacavir 600 mg once daily had severe drug hypersensitivity reactions compared with 2% of subjects receiving abacavir 300 mg twice daily. Two percent (7%) of subjects receiving abacavir 600 mg once daily had severe diarrhea compared with 1% of subjects receiving abacavir 300 mg twice daily (not shown).

[2] Study CNA30024 was a multicenter double-blind controlled study in which 649 HIV-1 infected, therapy-naïve adults were randomized and received either abacavir (300 mg twice daily), lamivudine (150 mg twice daily), and zidovudine (300 mg twice daily), or abacavir (300 mg twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once daily). CNA30024 used standard assessment of suspected hypersensitivity reactions. During the blinded portion of the study, suspected hypersensitivity to abacavir were reported by investigators in 9% of 324 subjects in the abacavir group and 3% of 325 subjects in the zidovudine group.

Laboratory Abnormalities: Laboratory abnormalities observed in clinical studies of abacavir sulfate were anemia, neutropenia, leukopenia, and elevations in liver function tests, blood glucose, and triglycerides. Laboratory abnormalities observed in clinical studies of lamivudine were thrombocytopenia and elevated levels of creatine, amylase, and lipase.

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

Abacavir

Pediatric Patients: Therapy-Experienced Pediatric Patients: Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with ≥ 2% frequency during therapy with abacavir 8 mg/kg twice daily, lamivudine 4 mg/kg twice daily, and zidovudine 180 mg/m² twice daily, compared with lamivudine 4 mg/kg twice daily and zidovudine 180 mg/m² twice daily from CNA30024 are listed in Table 3.

Table 3. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2-4, ≥3% Frequency) in Therapy-Experienced Pediatric Patients (CNA30024) Through 16 Weeks of Treatment

Adverse Reaction	Abacavir plus Lamivudine plus Zidovudine (n = 102)	Lamivudine plus Zidovudine (n = 103)
Fever and/or chills	8%	7%
Nausea and vomiting	5%	2%
Diarrhea	2%	1%
Cutaneous/mucosal reactions	2%	1%
Pharyngitis	4%	5%
Cough	2%	5%

Laboratory abnormalities: In Study CNA30024, laboratory abnormalities (anemia, neutropenia, liver function test abnormalities, and CPK elevations) were observed with similar frequencies as in a study of therapyexperienced CNA30024 (n = 206) adolescent and adult patients were more frequent in pediatric patients receiving abacavir (CNA30024) as compared with adult patients (CNA30021).

Other Adverse Events: In addition to adverse reactions listed above, other adverse events observed in the expanded access program for abacavir were pancreatitis and increased GGT.

Lamivudine

Pediatric Patients: Cohorts from a HIV-1 Lamivudine combination has been studied in 630 pediatric patients 3 months to 16 years of age in 2 clinical trials.

Patient

dose of 600 mg of abacavir in 20 subjects, C_{max} was 4,042 ± 2,19 ng/mL (mean ±SD) and AUC was 14,708 ± 2,8 ng·h/mL. Binding of abacavir to human plasma proteins is approximately 50% and was independent of concentration. Intravenous administration of abacavir 600 mg daily (300 mg twice daily) distributes into cerebrospinal fluid (CSF) with a mean penetration ratio of 0.43 (range 0.2 - 1.1) to plasma. Approximately 2 hours after ingestion of a single oral dose of 600 mg, the CSF to plasma AUC ratio was 0.92 ± 0.3 (range 0.4 - 1.6). The primary metabolite of abacavir is 5-carboxylic acid which is also found in the urine. Metabolite formation is consistent with alcohol dehydrogenase and glucuronyltransferase activity. Abacavir is also metabolized by hydrolytic deamination to the 5-hydroxy and 5-oxo analogs, which are also found in urine as minor metabolites. Intracellular phosphorylation to the 5-monophosphate, followed by conversion to the active 5-triphosphate, is a major pathway of intracellular metabolism. Abacavir 5-triphosphate has a long intracellular half-life of 18 hours. Abacavir 5-triphosphate is a competitive inhibitor of HIV-1 reverse transcriptase and a weak inhibitor of human DNA polymerase beta, gamma and mitochondrial DNA. Intracellular metabolism of abacavir does not interfere with the phosphorylation of other nucleosides. Abacavir 5-triphosphate does not terminate DNA chain elongation. Intracellular metabolism of abacavir does not interfere with the formation of other intracellular 5-triphosphate nucleotides. Elimination of abacavir is primarily by metabolism with a half-life of 1.5 hours. Renal excretion of unchanged abacavir accounts for approximately 2% of the total clearance. Excretion of metabolites in the urine and feces accounts for the remaining clearance. Abacavir 600 mg once daily (300 mg twice daily) administered to 20 HIV-1 infected adult subjects for 7 days, produced a mean (CV%) C_{max} of 4,396 ng/mL (26%), C_{ss} of 2,739 ng/mL (29%), AUC_{24} of 14,981 ng·h/mL (29%) and C_{24} of 0.09 ng/mL (151%). The pharmacokinetics of abacavir administered twice daily were similar to those observed after administration of 600 mg once daily.

Intracellular phosphorylation of abacavir to the active 5-triphosphate was observed in peripheral blood mononuclear cells (PBMC) incubated with abacavir at concentrations consistent with those observed in plasma. Intracellular half-life of the 5-triphosphate was 18 hours. Abacavir 5-triphosphate competitively inhibited HIV-1 reverse transcriptase activity with Ki values of 0.2 and 0.6 μM for the substrates dATP and dGTP, respectively. The Ki for inhibition of human DNA polymerase beta was 4.3 μM, and for human DNA polymerase gamma, 19 μM. Abacavir 5-triphosphate did not inhibit human DNA polymerase alpha or human mitochondrial DNA polymerase at concentrations up to 100 μM. Abacavir 5-triphosphate did not inhibit human DNA polymerase beta at concentrations up to 400 μM. Abacavir 5-triphosphate did not inhibit human DNA polymerase gamma at concentrations up to 200 μM.

Abacavir 600 mg once daily (300 mg twice daily) administered for 7 days to 20 HIV-1 infected adult subjects had no significant effect on the pharmacokinetics of zidovudine (AUC decreased by 9%, C_{max} increased by 3%) or its 5-glucuronyl metabolite (AUC decreased by 6%, C_{max} increased by 3%). The intracellular pharmacokinetics of zidovudine were not determined. Zidovudine administered for 7 days to 20 HIV-1 infected adult subjects had no significant effect on the pharmacokinetics of abacavir (AUC increased by 5%, C_{max} decreased by 9%). The intracellular pharmacokinetics of abacavir were not determined.

Abacavir 600 mg once daily (300 mg twice daily) administered for 7 days to 20 HIV-1 infected adult subjects had no significant effect on the pharmacokinetics of lamivudine (AUC increased by 4%, C_{max} decreased by 9%). The intracellular pharmacokinetics of lamivudine were not determined. Lamivudine administered for 7 days to 20 HIV-1 infected adult subjects had no significant effect on the pharmacokinetics of abacavir (AUC increased by 1%, C_{max} decreased by 4%). The intracellular pharmacokinetics of abacavir were not determined.

Administration of abacavir 600 mg once daily (300 mg twice daily) for 7 days to 20 HIV-1 infected adult subjects had no significant effect on the pharmacokinetics of zidovudine (AUC increased by 3%, C_{max} decreased by 6%). The intracellular pharmacokinetics of zidovudine were not determined.

Administration of abacavir 600 mg once daily (300 mg twice daily) for 7 days to 20 HIV-1 infected adult subjects had no significant effect on the pharmacokinetics of lamivudine (AUC increased by 2%, C_{max} decreased by 9%). The intracellular pharmacokinetics of lamivudine were not determined.

The steady-state pharmacokinetic properties of the lamivudine 300 mg tablet given daily for 7 days compared to the lamivudine 150 mg tablet twice daily for 7 days were analogous to the bioavailability of the 300 mg tablet relative to the 150 mg tablet. Lamivudine exposure was higher in women than in men. Intracellular lamivudine phosphorylation was comparable between men and women. Intracellular lamivudine phosphorylation was 2-fold higher in lymphocytes than in erythrocytes. Intracellular lamivudine half-life in erythrocytes was approximately 19 hours. Lamivudine is primarily eliminated by renal excretion of unchanged drug. Renal clearance accounts for 70% of total clearance. Lamivudine is also cleared by metabolism to the 5-trans-sulfoxide metabolite, which is not a competitive inhibitor of HIV-1 reverse transcriptase. Lamivudine has a long intracellular half-life in lymphocytes (16 hours) and is a competitive inhibitor of HIV-1 reverse transcriptase. Lamivudine 300 mg once daily (150 mg twice daily) administered for 7 days to 20 HIV-1 infected adult subjects had no significant effect on the pharmacokinetics of zidovudine (AUC increased by 3%, C_{max} decreased by 9%). The intracellular pharmacokinetics of zidovudine were not determined.

Administration of zidovudine 300 mg twice daily for 7 days to 20 HIV-1 infected adult subjects had no significant effect on the pharmacokinetics of lamivudine (AUC increased by 3%, C_{max} decreased by 9%). The intracellular pharmacokinetics of lamivudine were not determined.

Administration of lamivudine 300 mg once daily (150 mg twice daily) for 7 days to 20 HIV-1 infected adult subjects had no significant effect on the pharmacokinetics of zidovudine (AUC increased by 2%, C_{max} decreased by 9%). The intracellular pharmacokinetics of zidovudine were not determined.

Table 6. Pharmacokinetic Parameters[1] for Abacavir and Lamivudine in Adults

Parameter	Abacavir	Lamivudine
Oral bioavailability (%)	86 ± 25	86 ± 16
Apparent volume of distribution (L/kg)	0.80 ± 0.15	1.3 ± 0.4
Systemic clearance (L/h/kg)	0.30 ± 0.24	0.4 ± 0.05
Renal clearance (L/h/kg)	0.07 ± 0.08	0.27 ± 0.05
Terminal half-life (h)	1.54 ± 0.63	19.0 *

[1] Values presented as mean ± standard deviation except where noted.
* Approximate mean.

Effect of Food on Absorption of abacavir tablet and lamivudine tablets for oral suspension: The effect of food on abacavir tablet and lamivudine tablet (300 mg) exposure was not determined. Therefore, this product must be taken without an empty stomach.

Special Populations: Renal Impairment: Because lamivudine requires dose adjustment in the presence of renal impairment, abacavir tablet and lamivudine tablets for oral suspension are not recommended for use in patients with creatinine clearance <50 mL/min [see Dosage and Administration (2)].

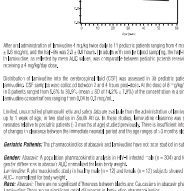
Hepatic Impairment: Abacavir and lamivudine tablets for oral suspension are contraindicated in patients with hepatic decompensation. Because abacavir tablet is contraindicated in patients with moderate or severe hepatic impairment and because the dose of the individual components of the fixed-dose combination cannot be dose adjusted.

Pregnancy: See Use in Specific Populations (8.1).
Abacavir and Lamivudine Pills data are available in the pharmacokinetics of abacavir in Lamivudine during pregnancy.

Nursing Mothers: See Use in Specific Populations (8.3).
Abacavir Pills data are available in the pharmacokinetics of abacavir in nursing mothers.
Lamivudine: Samples of breast milk obtained from 36 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had median lamivudine concentrations of lamivudine.

Pediatric Patients
Abacavir: The pharmacokinetics of abacavir have been studied after either single or repeat dosed of abacavir in HIV-infected pediatric patients. Following multiple dose administration of abacavir (4 mg/kg twice daily) to children (12 - 16 years, mean 15.4 years), C_{max} was 9.4 ± 5.3 mcg/mL and the AUC_{24} was 22.1 ± 7.1 mcg·h/mL. Data from 18 pediatric patients (3 months to 16 years of age) receiving oral abacavir 8 mg/kg twice daily (to a maximum of 300 mg twice daily) for 4 weeks, weight range 5 to 60 kg) gave a mean (CV%) C_{max} of 9.1 mcg/mL (37%), C_{ss} of 2.0 mcg/mL (34%), AUC_{24} of 14.1 mcg·h/mL (29%), and C_{24} of 0.09 mcg/mL (151%). The pharmacokinetic parameters were similar to those observed in adult subjects receiving 300 mg twice daily. The pharmacokinetics of abacavir in children and adults are shown in Figure 2.

Figure 2: Systemic Clearance (L/h/kg) of Lamivudine in Relation to Age



After oral administration of lamivudine 4 mg/kg twice daily to 19 pediatric patients ranging from 6 months to 14 years of age, C_{max} was 1.1 ± 0.6 mcg/mL and the AUC_{24} was 2.9 ± 1.1 mcg·h/mL (mean ± SD). In a study of 23 children (ages 3 months - 12 years) receiving oral lamivudine 4 mg/kg twice daily (to a maximum of 150 mg twice daily), the C_{max} was 1.5 ± 0.7 mcg/mL (47%) and the AUC_{24} was 3.9 ± 1.2 mcg·h/mL (31%). The pharmacokinetic parameters were similar to those observed in adult subjects receiving 150 mg twice daily.

Distribution of lamivudine into the cerebrospinal fluid (CSF) was assessed in 36 pediatric patients after multiple oral dosing with lamivudine. CSF sampling was collected between 0 and 4 hours post-dose (n=6), 4 to 6 hours post-dose (n=19), and 6 hours post-dose (n=11). Lamivudine CSF concentrations were detectable in all patients, ranged from 0.04 to 0.74 mcg/mL (37% CV), and had a median (95% CI) of 0.12 (0.09, 0.18) mcg/mL. The median ratio of lamivudine CSF to serum concentrations was 0.12 (0.09, 0.18) with a range of 0.06 to 0.42. The median time to peak lamivudine CSF concentration was 3 hours post-dose (range: 2 to 6 hours post-dose).

Limited clinical data in HIV-infected adolescents (ages 16 - 18 years) suggest that the pharmacokinetics of lamivudine administered twice daily (150 mg twice daily) are similar to those observed in children and adults receiving the same dose.

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

Gender: Abacavir: A population pharmacokinetic analysis in (n=47 infected - male (n = 30) and female (n = 17) subjects) showed no gender effect on the abacavir AUC or C_{max} after adjusting for body weight.
Lamivudine: A pharmacokinetic analysis in healthy adult (n = 12) and adolescent (n = 12) subjects showed no gender differences in lamivudine AUC, normalized for body weight.

Race: Abacavir: There were no significant differences between Caucasians in abacavir pharmacokinetics.
Lamivudine: There are no significant racial differences in lamivudine pharmacokinetics.

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: Lamivudine and Zidovudine: Within HIV-1 infected subjects were enrolled in a placebo-controlled drug interaction study evaluating single doses of abacavir (600 mg), lamivudine (150 mg), and zidovudine (300 mg) given in combination, in relation to their pharmacokinetics. Intracellular pharmacokinetics of abacavir with the addition of lamivudine or zidovudine or the combination of lamivudine and zidovudine, lamivudine exposure (AUC) decreased 16% and zidovudine exposure (AUC) increased 127% (2.2-fold) when clinically relevant drug interactions were observed.

Lamivudine: Zidovudine: No clinically significant interactions in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-infected adult subjects given single doses of lamivudine (300 mg) in combination with zidovudine (300 mg) or zidovudine (300 mg) alone.

Abacavir: In vitro data indicate that ethanol increases phosphorylation of lamivudine, zidovudine, and abacavir to a minor extent. However, no clinical interactions with ethanol have been observed in vivo. Methadone: Intracellular and plasma methadone were unaffected by administration of abacavir (600 mg) in 12 opioid-dependent subjects. Abacavir was observed to increase oral clearance and decrease the terminal half-life of methadone. Methadone maintenance treatment did not alter abacavir pharmacokinetics. These interactions are not expected to have any significant clinical consequences. Rifabutin: Administration of rifabutin (300 mg) with abacavir (600 mg) for 14 days in 12 healthy subjects resulted in a 32% increase in abacavir AUC. Interferon: Administration of interferon-alpha (3 million units) with abacavir (600 mg) for 14 days in 12 healthy subjects resulted in a 2-fold increase in abacavir AUC. Ribavirin: Administration of ribavirin (1,200 mg) with abacavir (600 mg) for 14 days in 12 healthy subjects resulted in a 2-fold increase in abacavir AUC. Ribavirin (50 μM) decreased the activity of lamivudine-5-triphosphate by 32-fold in HeLa cells.

Interactions: 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 taking abacavir and lamivudine-containing regimens. Genotypic character isolates of abacavir and lamivudine-resistant viruses selected in cell culture identified the selected substitutions M184V/I, K65R, L74V and Y115F in HIV-1 RT.

Genotypic analysis of isolates selected in cell culture and recovered from abacavir-treated subjects demonstrated the same selected mutations K65R, L74V, Y115F and M184V/I in HIV-1 RT in the majority of virus recoveries. Genotypic analysis of isolates selected in cell culture and recovered from lamivudine-treated subjects showed that the resistance was due to a specific amino acid substitution (M184V/I). Of 8 subjects (5 of 7 receiving the combination of abacavir and lamivudine and 3 of 8 receiving abacavir with no lamivudine) with virus recovered at baseline and at the time of virologic failure, 7 subjects (5 receiving abacavir with no lamivudine) had a 4- to 16-fold increase in the abacavir IC50 and 3 subjects had a 3- to 5-fold increase in the lamivudine IC50. Genotypic analysis of isolates from these 7 subjects showed that the M184V/I substitution was the most common amino acid change observed in combination with other mutations. Of 5 subjects with virus recovered at baseline and at the time of virologic failure, 4 had a 4- to 16-fold increase in the abacavir IC50 and 3 had a 3- to 5-fold increase in the lamivudine IC50.

Cross-Resistance: Cross-resistance has been observed among HIV-1 isolates containing abacavir and lamivudine resistant-associated amino acid substitutions, namely, M184V, L74V, M184V, and Y115F, which also confer resistance to (-)-enantiomer emtricitabine, lamivudine, lamivudine, and didanosine in cell cultures and in vivo in subjects. The K65R substitution can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine; the L74V substitution can confer resistance to abacavir, didanosine, and zalcitabine; and the M184V substitution can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, and zalcitabine.

The combination of abacavir and lamivudine has demonstrated decreased susceptibility in vitro with the substitutions K65R and/or without the M184V/I substitution. Viruses with L74V plus the M184V/I substitution, and in vitro with thymidine analog mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F) or the K65R substitution, are increasingly number of TAMs is associated with a progressive reduction in abacavir susceptibility.

11 NONCLINICAL TOXICOLOGY
11.2 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis:
Abacavir: was administered orally at 3 dosage levels to separate groups of mice and rats in 2-year carcinogenicity studies. Abacavir showed no response in the incidence of malignant and benign tumors in female mice and female rats. Male mice showed increased incidence of vascular tumors (hemangiomas and hemangiosarcomas). Male rats showed increased incidence of malignant schwannomas. Male rats showed increased incidence of benign testicular interstitial cell tumors. The vascular tumors in male mice showed a positive dose response relationship with increasing exposure. These observations were made at systemic exposures in the range of 6 to 32 times the human exposure at the recommended dose.

Lamivudine: Carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 16 times clinical AUC levels in female rats and 26 times clinical AUC levels in male mice. The relevance of these findings to human carcinogenicity is unknown. 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 a human lymphocyte cytogenetic assay. Abacavir was mutagenic in the absence of metabolic activation in one of two in vitro mammalian cell mutagenicity assays. Abacavir was mutagenic in the presence of metabolic activation in one of two in vitro mammalian cell mutagenicity assays. Abacavir was not mutagenic in the presence of metabolic activation in a human lymphocyte cytogenetic assay, Abacavir was not mutagenic in the presence or absence of metabolic activation in the bacterial mutagenicity assays or the assay for unscheduled DNA synthesis in rat hepatocytes.

Lamivudine: Lamivudine was mutagenic in one of 3 in vitro mammalian cell mutagenicity assays, and was not mutagenic in one of 2 in vivo chromosomal aberration assays. Lamivudine was not mutagenic in a bacterial mutagenicity assay, in an in vitro cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in a rat liver and female DNA synthesis in vivo.

Impairment of Fertility: Abacavir: of lamivudine induces no adverse effects on the male or female reproductive or fertility indices and female rats in doses producing systemic exposures levels approximately 8 or 18 times, respectively, higher than those in humans at the recommended dose based on blood plasma area comparisons.

13.2 Animal Toxicology and/or Pharmacology
Microvesicular degeneration was found in mice and rats following administration of abacavir for 2 years. The systemic exposures were equivalent to 12 times and the expected systemic exposure in humans. The clinical relevance of this finding has not been determined.

14.1 Adults
Clinical trial data for **CIMAGRAM** was an international, multicenter, double-blind, controlled study in which 770 HIV-1 infected, treatment-naive adults were randomized and received either abacavir 600 mg once daily or abacavir 300 mg twice daily (both in combination with lamivudine 150 mg twice daily) and zidovudine 300 mg twice daily. Baseline characteristics were comparable between the two arms. Overall, patients had a median age of 37 years, were male (81%), Caucasian (64%), black (21%), and Asian/Pacific Islander (13%). The median CD4+ cell count was 200 cells/mm³ (range: 2 to 318 cells/mm³) and the median baseline plasma HIV-1 RNA was 4.84 log10 copies/mL (range: 2.91 to 6.99 log10 copies/mL).

The outcomes of virologic treatment are presented in Table 7.

Table 7. Outcomes of Randomized Treatment Through Week 48 (CNA30021)

Outcome	Abacavir 300 mg (ABC) + Lamivudine (3TC) + Zidovudine (ZDV) (n = 384)	Abacavir 600 mg (ABC) + Lamivudine (3TC) + Zidovudine (ZDV) (n = 386)
Responder[1]	64% (77%)	66% (77%)
Virologic failure[2]	11% (5%)	11% (5%)
Discontinued due to adverse reactions	13%	17%
Discontinued due to other causes[3]	11%	5%

[1] Subjects achieved and maintained confirmed HIV-1 RNA < 50 copies/mL [<400 copies/mL] through Week 48 (Kaplan-Meier [KM] estimate HIV-1 RNA < 50 copies/mL [<400 copies/mL]).
[2] Includes not evaluable (NE) to achieve confirmed < 50 copies/mL [<400 copies/mL] by Week 48, and insufficient viral load response. Includes one patient who died at week 20 while on study treatment (abacavir and lamivudine).
[3] Subjects achieved and maintained confirmed HIV-1 RNA < 50 copies/mL [<400 copies/mL] through Week 48 (Kaplan-Meier [KM] estimate HIV-1 RNA < 50 copies/mL [<400 copies/mL]).

After 48 weeks of therapy, the median CD4+ cell count increases from baseline were 186 cells/mm³ in the group receiving abacavir 600 mg once daily and 206 cells/mm³ in the group receiving abacavir 300 mg twice daily. The group (Week 48, 6 to 8 weeks [2%] in the group receiving abacavir 600 mg once daily, and 0 in the group receiving abacavir 300 mg twice daily) experienced clinical disease progression. None of the deaths were attributed to drug intolerance.

14.2 Pediatric Patients
Clinical Experience Protocol (Pediatric): PACTG300, was a randomized, double-blind, controlled study in which 290 HIV-1 infected, treatment-naive infants and children received abacavir 8 mg/kg twice daily (to a maximum 300 mg twice daily) or zidovudine 180 mg/m² twice daily, both in combination with lamivudine 4 mg/kg twice daily (to a maximum 150 mg twice daily) and nelfinavir 20 mg/kg twice daily (to a maximum 750 mg twice daily). Baseline characteristics were comparable between the two arms. Overall, patients were male (54%), Caucasian (71%), black (20%), Hispanic (30%), median age of 5.4 years, had an CD4+ cell percent greater than 15% (median = 27%), and median baseline plasma HIV-1 RNA of 5.2 log10 copies/mL. Eighty percent and 93% of patients had prior therapy with nucleoside and protease inhibitor, respectively, most often 1 nucleoside. The median duration of prior antiretroviral exposure was 2 years. At 16 weeks, the proportion of patients responding based on plasma HIV-1 RNA less than 400 copies/mL was 32% higher in the group receiving abacavir plus lamivudine plus nelfinavir compared with patients receiving lamivudine plus zidovudine plus nelfinavir, respectively. Median decline in HIV-1 RNA changes from baseline were −2.5 log10 copies/mL in the group receiving abacavir plus lamivudine plus nelfinavir compared with −2.21 log10 copies/mL in the group receiving lamivudine plus zidovudine plus nelfinavir. Median CD4+ cell count increases from baseline were 131 cells/mm³ in the group receiving abacavir plus lamivudine plus nelfinavir and 160 cells/mm³ in the group receiving lamivudine plus zidovudine plus nelfinavir.

Table 8. Number of Patients (%) Reaching a Primary Clinical Endpoint (Disease Progression or Death)

Endpoint	Lamivudine (3TC) Zidovudine (n = 206)	Abacavir or Lamivudine (3TC) Zidovudine (n = 209)
HIV-1 disease progression or death (total)	19 (9.2%)	37 (17.7%)
Physical growth failure	1 (0.2%)	6 (2.8%)
Central nervous system* deterioration	4 (1.9%)	12 (5.7%)
CDC Clinical Category C	9 (4.4%)	15 (7.2%)
Death	1 (0.2%)	11 (5.2%)

15 REFERENCES
1. Food Safety Center on Adverse Events of Hiv-1 Drugs (FDACS) Study Group, Lancet, 2000;351:1658(21):1467-1468.

16 HOW SUPPLIED/STORAGE AND HANDLING
Abacavir Tablets and Lamivudine Tablets for oral suspension, Each tablet/for oral suspension, Each tablet/for oral suspension contains 600 mg of abacavir as abacavir sulfate and 300 mg of lamivudine, the tablets are scored, white to off white colour, capsule shaped, biconvex, and uncoated tablets with one end break on one side are in 30 count HDPE bottles with child resistant cap.

Bottle of 60 tablets
Carton of 60 x 10 count unit dose blisters

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

17 PATIENT COUNSELING INFORMATION
See Medication Guide
Abacavir: Hypersensitivity Reaction:
Warn patients that:
- **Read the Medication Guide and Warning Card summarizing the symptoms of the abacavir hypersensitivity reaction and the risk associated with it. Medication will be dispensed to the pharmacist with each new prescription and refill of abacavir sulfate and lamivudine, and encourage the patient to read the Medication Guide and Warning Card every time it is dispensed. Ask the patient to retain the Medication Guide and Warning Card every time it obtains any new information that may be present about abacavir sulfate and lamivudine. (The complete text of the Medication Guide is reprinted at the end of this document).**
- **to carry the Warning Card with them,**
- **how to identify a hypersensitivity reaction** [see WARNINGS AND PRECAUTIONS (5.1), MEDICATION GUIDE],
- that if they develop symptoms consistent with a hypersensitivity reaction they should call their doctor right away to determine if they should stop taking abacavir sulfate and lamivudine,
- that a hypersensitivity reaction can occur even after a hospitalization or clinic visit, abacavir sulfate and lamivudine is not immediately discontinuous,
- **to not restart abacavir sulfate and lamivudine or any other abacavir-containing product following a hypersensitivity reaction because even severe symptoms can occur within hours not may include life-threatening symptoms and death.**
- that a hypersensitivity reaction is usually more but it is detected promptly and abacavir sulfate and lamivudine is stopped right away,
- that if they have interrupted abacavir sulfate and lamivudine for reasons other than symptoms of hypersensitivity (for example, those who have an interruption in drug supply, or serious or life threatening illness, medication may occur with not the reaction of abacavir),
- that the risk of a rechallenge with a medication containing abacavir is extremely high, and
- **to not restart abacavir sulfate and lamivudine or any other abacavir-containing product without medical consultation and that restarting the medication in substance only if medical care can be readily accessed by the patient or others.**
- Abacavir and Lamivudine Pills should not be administered concomitantly with CEREDIM (abacavir sulfate and lamivudine), KIVEXA (abacavir, lamivudine, and dolutegravir), TRIUMEQ (abacavir, dolutegravir, and lamivudine), COMBIVIR (lamivudine/zidovudine), EPIVIR (lamivudine), EPIVIR-HBV (lamivudine), TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine), TRUVADA (emtricitabine and tenofovir disoproxil fumarate), or ATRIPLA (efavirenz, emtricitabine, and tenofovir).
Co-infection With HIV-1 and HBV: Patients co-infected with HIV-1 and HBV should be informed that lamivudine (a component of abacavir sulfate and lamivudine) has been associated with exacerbations of hepatitis after discontinuous. Patients should be advised to discuss any changes in regimen with their physician. See Warnings and Precautions (5.2).

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

Redistribution/Accumulation of Body Fat: Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time [see Warnings and Precautions (5.6)].

Drug Interactions: Zidovudine and lamivudine should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter medicines, vitamins, and herbal supplements.

Information About HIV-1 Infection: Abacavir Sulfate and lamivudine, or a cure, but HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using abacavir sulfate and lamivudine. Advise patients that the use of abacavir sulfate and lamivudine has not been shown to reduce the risk of transmission of HIV-1 to others through sexual contact or blood contamination. Patients should be informed to take all HIV medications exactly as prescribed.

Importance of Taking Abacavir and Lamivudine as Prescribed: Inform patients to take abacavir sulfate and lamivudine on a regular basis, and should avoid missed doses. Advise patients that abacavir sulfate and lamivudine tablets for oral suspension are for oral ingestion only.

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MEDICATION GUIDE

Abacavir Sulfate and Lamivudine tablets for oral suspension 60 mg/30 mg

Read the Medication Guide before you or your child start taking abacavir sulfate and lamivudine and each time you or your child get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your or your child's treatment. Be sure to carry the abacavir 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 for oral suspension?

1. Serious Allergic Reaction (hypersensitivity reaction). Abacavir sulfate and lamivudine contain abacavir. Patients taking abacavir sulfate and lamivudine may have a serious allergic reaction (hypersensitivity reaction) that can cause death. **The risk of this allergic reaction is much higher if your child or you have a gene variation called HLA-B*5701. Your healthcare provider can determine with a blood test if your child or you have this gene variation.**
If your child or you get a symptom from 2 or more of the following groups while taking abacavir sulfate and lamivudine, call your doctor right away to find out if your child or you should stop taking this medicine.

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

A list of these symptoms is on the Warning Card your pharmacist gives you. Carry this Warning Card with you at all times.
If your child or you stop abacavir sulfate and lamivudine because of an allergic reaction, NEVER take abacavir sulfate and lamivudine or any other abacavir-containing medicine again. If your child or you take abacavir sulfate and lamivudine 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 for any other reason, even for a few days, and your child or you are not allergic to abacavir sulfate and lamivudine, talk with your healthcare provider before taking or giving it to your child or again. Taking abacavir sulfate and lamivudine again can cause a serious allergic or life-threatening reaction, even if you never had an allergic reaction up to that time.
If your healthcare provider tells you that you can take or give your child abacavir sulfate and lamivudine again, start taking or giving it when your child or you are around medical help or people who can call a healthcare provider if your child or you need care.

2. Lactic Acidosis (buildup of acid in the blood). Some human immunodeficiency virus (HIV) medicines, including abacavir sulfate and lamivudine, can cause a rare but serious condition called lactic acidosis. Lactic acidosis is a serious medical emergency that can cause death and must be treated in the hospital.
Call your healthcare provider right away if you get any of the following signs or symptoms of lactic acidosis:
- your belly or stomach area (abdomen) pain
- your arms or legs feel very heavy
- your breathing becomes difficult
- your bowel movements (stools) turn light in color
- you have a yellow skin or eyes look for several days or longer
- you feel sick to your stomach (nausea)
- you have lower stomach area (abdominal) pain
- You may be more likely to get lactic acidosis or serious liver problems if you are female, very overweight, or have been taking nucleoside analogue medicines for a long time.

4. Use with interferon- and ribavirin-based regimens. Worsening of liver disease (sometimes resulting in death) has occurred in patients infected with both HIV and hepatitis C virus when are taking and HIV medicines and are also being treated for hepatitis C with interferon with or without ribavirin. If your or your child are taking abacavir sulfate and lamivudine as well as interferon with or without ribavirin and you or your child experience side effects, be sure to tell your healthcare provider.

5. If you or your child have HIV-1 and hepatitis B virus infection the hepatitis B virus infection may get worse if you or your child stop taking abacavir sulfate and lamivudine,
- Take or give abacavir sulfate and lamivudine exactly as prescribed.
- Do not run out of abacavir sulfate and lamivudine.
- Do not stop abacavir sulfate and lamivudine without talking to your healthcare provider.
- Your healthcare provider should monitor your health and do regular blood tests to check your liver if you stop taking abacavir sulfate and lamivudine.

What are abacavir sulfate and lamivudine tablets for oral suspension?
Abacavir sulfate and lamivudine tablets for oral suspension contain 2 prescription medicines, abacavir and lamivudine, both used to treat HIV infection. Both of these medicines are called nucleoside analogue reverse transcriptase inhibitors (NRTIs).
- **Abacavir sulfate and lamivudine does not cure HIV infection or AIDS.**
- It is not known if abacavir sulfate and lamivudine will help your child or you live longer or have fewer of the medical problems that people get with HIV or AIDS.
- It is very important that you see your healthcare provider regularly while your child or you are taking abacavir sulfate and lamivudine.

Who should not take abacavir sulfate and lamivudine tablets for oral suspension?
Do not take abacavir sulfate and lamivudine if you or your child:
- **are allergic to abacavir or any of the ingredients in abacavir sulfate and lamivudine.**
See the end of this Medication Guide for a complete list of ingredients in abacavir sulfate and lamivudine.
- **have certain liver problems.**

What should I tell my healthcare provider before taking or giving abacavir sulfate and lamivudine tablets for oral suspension?
Before you take or give abacavir sulfate and lamivudine tell your healthcare provider 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,**
- **are pregnant or plan to become pregnant.** It is not known if abacavir sulfate and lamivudine will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
- **are breastfeeding or plan to breastfeed.** Abacavir sulfate and lamivudine can pass into your breast milk. You should not breastfeed if you are taking abacavir sulfate and lamivudine. If you are a woman who has or will have a baby while taking abacavir sulfate and lamivudine, talk to your healthcare provider about the best way to feed your baby. The Center for Disease Control and Prevention (CDC) recommend that HIV-infected mothers **not** breastfeed to avoid the risk of passing HIV infection to your baby.
- **have hepatitis B virus infection or have other liver problems.**
- **have kidney problems.**

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.
Especially tell your healthcare provider if you or your child take:
- alcohol
- medicines used to treat hepatitis viruses such as interferon or ribavirin,
- methadone
- COMBIVIR® (abacavir sulfate and lamivudine)
- ATRIPLA® (efavirenz, emtricitabine, and tenofovir)
- COMBIPAK® (lamivudine and zidovudine)
- EMTRIVA® (emtricitabine)
- EPIVIR or EPIVIR-HBV® (lamivudine, 3TC)
- TRIZIVIR® (abacavir sulfate, lamivudine, and zidovudine)
- TRUVADA® (emtricitabine and tenofovir)
- ZIAGEN (abacavir sulfate)

Ask your healthcare provider if you are not sure if you take one of the medicines listed above. Abacavir sulfate and lamivudine may affect the way other medicines work, and other medicines may affect how abacavir sulfate and lamivudine works.
Know the medicines you take. Keep a list of your medicines with you to show to your healthcare provider and pharmacist when you get a new medicine.

How should I or my child take abacavir sulfate and lamivudine tablets for oral suspension?
- **Take or give abacavir sulfate and lamivudine exactly as your healthcare provider tells you to take or give it.**
- The healthcare provider will tell you the right dose to take or give to your child. Your child's dose will depend on the weight of your child. For very young children who cannot swallow tablets, following procedure can be used

Method of preparation:
1. Place the tablet(s) in a container and add two teaspoonfuls (10 mL) of drinking water per tablet.
2. Seal the container until the tablet(s) breaks up into pieces small enough for the child to swallow. A spoon can be used to crush the pieces, if needed.
3. Drink the mixture within 1 hour.
4. Rinse the container with an additional small amount of water and drink the contents to assure that the entire dosage is taken.
DO NOT MIX THE ABACAVIR SULFATE AND LAMIVUDINE TABLETS FOR ORAL SUSPENSION WITH ANY LIQUID OTHER THAN WATER.
- Other children, who can reliably swallow tablets, can be given the appropriate dose (see Table 1) to be swallowed.

Table 1. Dosing Recommendations for Abacavir Sulfate and Lamivudine Tablets for Oral Suspension Pediatric Patients

Weight (kg)	Dosage Regimen Using Scored Abacavir Sulfate and Lamivudine Tablets for Oral Suspension, 60 mg/30 mg		Total Daily Dose (mg)
	AM Dose (mg)	PM Dose (mg)	
5	1 tablet (30 mg/15 mg)	1 tablet (30 mg/15 mg)

RÉSUMÉ DE L'INFORMATION POSOLOGIQUE

(Si mesure ne comporte pas toutes les informations essentielles pour utiliser le sulfate d'abacavir et la lamivudine de manière sûre et efficace. Veuillez lire l'intégralité de l'information posologique du sulfate d'abacavir et de la lamivudine.

Sulfate d'abacavir et Lamivudine Comprimés pour suspension buvable 60mg/30mg

MISES EN GARDE : RISQUE DE RÉACTIONS D'HYPERSENSIBILITÉ, D'ACIDOSE LACTIQUE ET D'HÉPATOMÉGALIE GRAVE, ET D'ENCÉPHALOPATHIE DE L'HÉPATITE

Veuillez lire l'intégralité de l'information posologique afin d'obtenir une description détaillée de l'avertissement relatif à la mise en garde.

- **Des réactions d'hypersensibilité graves et parfois fatales ont été associées avec des produits contenant de l'abacavir.**
- **L'hypersensibilité est caractérisée par un syndrome clinique de dysfonction multiple des organes. (5.1)**
- **Les patients porteurs de l'allèle HLA-B*5701 sont plus exposés à une réaction d'hypersensibilité à l'abacavir.**
- **Veuillez interrompre immédiatement le premier Sulfate d'abacavir et lamivudine dès qu'une réaction d'hypersensibilité est suspectée. Sans égard au statut d'allèle HLA-B*5701, interrompre définitivement le prise du Sulfate d'abacavir et lamivudine si l'hypersensibilité ne peut être exclue, même lorsque d'autres diagnostics sont possibles. (5.1)**
- **Le test de dépistage de l'allèle HLA-B*5701 AVANT L'ABACAVIR représente le traitement par Sulfate d'abacavir et lamivudine ou tout produit contenant de l'abacavir. (5.1)**
- **Des cas d'acidose lactique et d'hépatomégalie grave avec stéatose, y compris des cas fatals, ont été signalés lors de l'utilisation d'analogues nucléosidiques. (5.2)**
- **Il est recommandé de cesser le traitement par Sulfate d'abacavir et lamivudine chez des patients, lorsque des signes cliniques ou biochimiques d'hépatotoxicité apparaissent, ou lorsque des signes d'acidose lactique sont présents. Il faut faire attention lorsque l'on administre un traitement par Sulfate d'abacavir et lamivudine à des patients présentant un foie anormal, des patients, le fonction hépatique doit être étroitement contrôlée et, le cas échéant, interrompre un traitement anti-hépatite B. (5.3)**

INDICATIONS ET UTILISATION

Sulfate d'abacavir et lamivudine, une association de 2 inhibiteurs de la transcriptase inverse du VIH-1, est indiqué en association avec d'autres agents antirétroviraux pour le traitement de l'infection par le VIH-1. (1)

POSOLOGIE ET MODE D'ADMINISTRATION

- Un guide de thérapeutique du Sulfate de mesure est joint à chaque bouteille prescription et renouvellement. (2)
- Prendre de 2 mesure d'abacavir. La posologie doit être basée sur le poids corporel. (2.2)
- Ne pas prescrire aux patients nécessitant une adaptation posologique du sulfate d'abacavir et lamivudine chez des patients présentant une insuffisance hépatique. (2.3)

FORMES PHARMACEUTIQUES ET CONCENTRATIONS

Chaque comprimé sécable pour suspension buvable contient 60 mg d'abacavir et 30 mg de lamivudine. (3)

CONTRE-INDICATIONS

- Hypersensibilité antérieurement démontrée à l'abacavir ou à tout autre composant du produit. (4, 5.1)
- Insuffisance hépatique. (4)

MISES EN GARDE ET PRÉCAUTIONS D'EMPLOI

- Voir les mises en garde en encadré pour de plus amples informations sur les points suivants : Réactions d'hypersensibilité, acidose lactique et hépatomégalie grave, et encephalopathie aiguë grave de l'hépatite B. (5.1, 5.2, 5.3)
- Hypersensibilité non hépatique, fatale dans certains cas, est survenue chez des patients n'ayant pas été trouvés porteurs de l'allèle HLA-B*5701 ou ayant présenté une association d'autres manifestations d'hypersensibilité dans quelques cas seulement. Interrompre la prise de Sulfate d'abacavir et lamivudine de manière médicalement appropriée et immédiate, même si l'hypersensibilité ne peut être exclue. Ne pas utiliser de formulations de rechallenge, dans des cas fatals. (5.1)
- Rare cas du syndrome de reconstitution immunitaire (5.5) et de redistribution / accumulation de graisse corporelle ont été signalés chez des patients traités par une association antirétrovirale. (5.6)
- Sulfate d'abacavir et lamivudine ne doit pas être administré avec d'autres produits contenant de l'abacavir ou de la lamivudine, sauf en cas de nécessité médicale. (5.7)
- Pancréatite : Il a pu être mis en cause chez des patients pediatriques présentant des antécédents de pancréatite ou d'autres facteurs de risque importants de pancréatite. Interrompre le traitement de manière clinquement appropriée. (5.8)

EFFETS SECONDAIRES

- Effets secondaires d'intensité au moins modérée et peut-être survenant rapporté (fréquence ≥ 5%) chez un adulte ayant pris par le Sulfate d'abacavir de 300mg : hypersensibilité médicamenteuse, insomnie, étourdissement, céphalée, diarrhée, nausée, vomissements, fatigue/malaise, abattement/asthénie/fatigue, faiblesse et diarrhée. (6.1)
- Abacavir : Effets secondaires d'intensité au moins modérée le plus couramment rapportés (fréquence ≥ 5%) chez des patients ayant pris par le Sulfate d'abacavir et lamivudine : nausée, vomissements, anorexie/perte d'appétit, douleur abdominale, céphalées (chez les enfants) et diarrhée. (6.1)
- Lamivudine : Effets secondaires le plus couramment rapportés (fréquence ≥10%) chez des patients pediatriques : fièvre et toux. (6.1)

Pour signaler des EFFETS SECONDAIRES SOUPÇONNÉS, contacter Cipla Ltd. au 1-(22)-6707000 ou l'agence Patients américaine des produits alimentaires et médicamentaux (FDA) au 1-800-FDA-1088 ou rendez-vous sur le site Internet: www.fda.gov/medwatch.

- Chimed (Chimed information médicaux). (7.2)
- Interactions avec d'autres médicaments peut être présumées chez un nombre notable de patients. (7.4)

Voir 17 pour les RENSEIGNEMENTS SUR LES CONSEILS A DONNER AUX PATIENTS et LE GUIDE DE THÉRAPEUTIQUE

Révision : Mai 2011

INFORMATION POSOLOGIQUE COMPLÈTE : SOMMAIRE*

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*Les sections ou les paragraphes dans la Information posologique complète ne sont pas numérotés.

INFORMATION POSOLOGIQUE COMPLÈTE

MISES EN GARDE : RISQUE DE RÉACTIONS D'HYPERSENSIBILITÉ, D'ACIDOSE LACTIQUE ET D'HÉPATOMÉGALIE GRAVE, ET D'ENCÉPHALOPATHIE DE L'HÉPATITE B

RÉACTIONS D'HYPERSENSIBILITÉ : DES RÉACTIONS D'HYPERSENSIBILITÉ GRAVES ET PARFOIS MORTELLES ONT ÉTÉ RAPPORTÉES À L'UTILISATION DU SULFATE D'ABACAVIR, UN COMPOSANT DE SULFATE D'ABACAVIR ET LAMIVUDINE COMPRIMÉS POUR SUSPENSION BUVABLE. L'HYPERSENSIBILITÉ À L'ABACAVIR EST UN SYNDROME CLINIQUE D'INFLAMMATION MULTIPLE DES ORGANES. LA PLUPART DES PATIENTS PORTEURS DE L'ALLÈLE HLA-B*5701 SE SONT APPARITIONNÉS À CE PHÉNOMÈNE GRAVES CHAPITRE. (5) FIÈVRE, DÉCRIPTION CUTANÉE, GASTROINTESTINAL, TY COMPRIS, NAUSÉES, VOMISSEMENTS, DIARRHÉE OU DOULEURS ABDOMINALES, ÉPUISEMENT, ÉTOURDISSEMENT, ÉTOURDISSEMENT, MALAISE, FATIGUE, OU MALAISE GÉNÉRALISÉ). ÉTOURDISSEMENT, ÉTOURDISSEMENT, ÉTOURDISSEMENT, LIMITÉ TOUS, OU PHARYNGÉE. ARRÊTEZ IMMÉDIATEMENT DE PRENDRE ABACAVIR ET LAMIVUDINE DÈS QU'UNE RÉACTION D'HYPERSENSIBILITÉ EST SUSPECTÉE.

LES PATIENTS PORTEURS DE L'ALLÈLE HLA-B*5701 SONT PLUS EXPOSÉS À UNE RÉACTION D'HYPERSENSIBILITÉ À L'ABACAVIR. LE TEST DE DÉPISTAGE DE L'ALLÈLE HLA-B*5701 AVANT L'ABACAVIR, LE DÉPISTAGE PRÉCALABLE DE L'ALLÈLE HLA-B*5701 EST RECOMMANDÉ AU PREMIER CETTE METHODE PERMET DE DIMINUER LE RISQUE D'UNE RÉACTION D'HYPERSENSIBILITÉ. DE MÊME, AVANT DE REPRENDRE L'ABACAVIR, IL EST ÉGALEMENT RECOMMANDÉ DE RÉALISER UN DÉPISTAGE CHEZ LES PATIENTS DONT LE STATUT DE L'ALLÈLE HLA-B*5701 EST INCONNU. LE DÉPISTAGE DE L'ALLÈLE HLA-B*5701 EST ÉGALEMENT UTILE POUR LE RÉSULTATS NÉGATIF AU TEST DE DÉPISTAGE DE L'ALLÈLE HLA-B*5701 PEUVENT DÉVELOPPER UNE RÉACTION D'HYPERSENSIBILITÉ SUSPECTÉE À L'ABACAVIR. TOUTEFOIS, CELA APPARÎT RAREMENT CHEZ LES PATIENTS PORTEURS DE L'ALLÈLE HLA-B*5701 ÉTANT DONNÉ QUE LE TEST DE DÉPISTAGE DE L'ALLÈLE HLA-B*5701 PERMET DÉPISTAGE DU RISQUE DE RÉACTION D'HYPERSENSIBILITÉ DANS GÉNÉRAL, AU STATUT DE L'ALLÈLE HLA-B*5701 INTERROMPRE DÉFINITIVEMENT LA PRISE DE SULFATE D'ABACAVIR ET LAMIVUDINE SI L'HYPERSENSIBILITÉ NE PEUT ÊTRE EXCLUE, MÊME LORSQUE D'AUTRES DIAGNOSTICS SONT POSSIBLES.

LORSQUE LA RÉACTION D'HYPERSENSIBILITÉ À L'ABACAVIR, NE JAMAIS REPRENDRE LE TRAITEMENT PAR ABACAVIR ET LAMIVUDINE OU TOUT AUTRE PRODUIT CONTENANT L'ABACAVIR. AU RISQUE DE VIE, LE PRODUIT DE GRAVES SYMPTÔMES DANS LES HEURES QUI SUIVENT LA PRISE DU MÉDICAMENT AU BANC DESQUELS L'HYPOTENSION PEUVENT RÉSULTER FATALE ET LA MORT.

NE JAMAIS REPRENDRE LE SULFATE D'ABACAVIR, LAMIVUDINE OU TOUT AUTRE PRODUIT CONTENANT DE L'ABACAVIR, MÊME CHEZ LES PATIENTS QUI N'ONT AUCUN ANTÉCÉDENT DÉNITRE DE L'ABACAVIR. LE DÉPISTAGE DE L'ALLÈLE HLA-B*5701 PEUVENT PAS ABACAVIR, PEUT-ÊTRE ÉTANT DONNÉ QUE LE RISQUE DE RÉACTION D'HYPERSENSIBILITÉ À L'ABACAVIR PEUT ÊTRE PLUS IMPORTANT POUR CAUSE DES GRAVES DES SUBSTITUTS À PRÉSENT DISPONIBLES.

ACIDOSE LACTIQUE ET HÉPATOMÉGALIE GRAVE : DES CAS D'ACIDOSE LACTIQUE ET D'HÉPATOMÉGALIE GRAVE AVEC STÉATOSE, Y COMPRIS DES CAS MORTELS ONT ÉTÉ RAPPORTÉS À L'UTILISATION D'ANALOGUES NUCLÉOSIDIQUES. DES ÉTUDES ONT ÉTÉ ASSOCIÉES, Y COMPRIS LAMIVUDINE, L'ABACAVIR, ET D'AUTRES ANTIRÉTROVIRAUX (VOIR MISES EN GARDE ET PRÉCAUTIONS D'EMPLOI (5.2)).

ENCÉPHALOPATHIE DE L'HÉPATITE B : DES CAS D'ENCÉPHALOPATHIE ASSOCIÉS À UNE HÉPATITE SÉVÈRE ÉTAIENT DÉCRITS CHEZ LES PATIENTS COINFECTÉS PAR LE VIRUS DE L'HÉPATITE B (VHB) ET LE VIRUS DE L'IMMUNODÉFICIENCE HUMAINE (VIH) ET PAR LEQUEL CE PRENDRE DE LA LAMIVUDINE. DAS ET LAMIVUDINE ET ABACAVIR ET LAMIVUDINE, FONCTIONNELLE ÉTAIENT DOIT ÊTRE ÉTROITEMENT CONTRÔLÉE PAR UN SUIVI CLINIQUE ET DE LABORATOIRE PROLONGÉ (PLUSIEURS MOIS) CHEZ LES PATIENTS ATTEINTS D'HÉPATITE CHRONIQUE. LE TRAITEMENT PAR ABACAVIR ET LAMIVUDINE CHEZ LES PATIENTS COINFECTÉS PAR LE VIRUS DE L'HÉPATITE B (VHB) ET LE VIH, LE CAS CHÉANT, IL POURRAIT AVOIR LIEU D'INTRAITER UN TRAITEMENT ANTI-HÉPATITE B (VOIR MISES EN GARDE ET PRÉCAUTIONS D'EMPLOI (5.3)).

1. INDICATIONS ET UTILISATION

Sulfate d'abacavir et lamivudine comprimés pour suspension buvable, en association avec d'autres agents antirétroviraux, est indiqué pour le traitement de l'infection par le VIH-1.
Informations supplémentaires concernant l'efficacité du Sulfate d'abacavir et lamivudine pour le traitement de l'infection par le VIH-1.

- Sulfate d'abacavir et lamivudine est l'un des multiples produits contenant de l'abacavir. Avant de commencer à prendre Sulfate d'abacavir et lamivudine, il faut tenir compte des caractéristiques médicaux d'association antérieurs à tout produit contenant de l'abacavir afin d'éviter la réintroduction chez des patients présentant des antécédents d'hypersensibilité à l'abacavir. Il est recommandé d'interrompre définitivement la prise de Sulfate d'abacavir et lamivudine chez des patients présentant des antécédents de pancréatite ou d'autres facteurs de risque importants de pancréatite. Interrompre le traitement de manière clinquement appropriée. (5.8)

2. EFFETS SECONDAIRES

- Effets secondaires d'intensité au moins modérée le plus couramment rapportés (fréquence ≥ 5%) chez un adulte ayant pris par le Sulfate d'abacavir de 300mg : hypersensibilité médicamenteuse, insomnie, étourdissement, céphalée, diarrhée, nausée, vomissements, fatigue/malaise, abattement/asthénie/fatigue, faiblesse et diarrhée. (6.1)
- Abacavir : Effets secondaires d'intensité au moins modérée le plus couramment rapportés (fréquence ≥ 5%) chez des patients ayant pris par le Sulfate d'abacavir et lamivudine : nausée, vomissements, anorexie/perte d'appétit, douleur abdominale, céphalées (chez les enfants) et diarrhée. (6.1)
- Lamivudine : Effets secondaires le plus couramment rapportés (fréquence ≥10%) chez des patients pediatriques : fièvre et toux. (6.1)

Pour signaler des EFFETS SECONDAIRES SOUPÇONNÉS, contacter Cipla Ltd. au 1-(22)-6707000 ou l'agence Patients américaine des produits alimentaires et médicamentaux (FDA) au 1-800-FDA-1088 ou rendez-vous sur le site Internet: www.fda.gov/medwatch.

- Chimed (Chimed information médicaux). (7.2)
- Interactions avec d'autres médicaments peut être présumées chez un nombre notable de patients. (7.4)

Voir 17 pour les RENSEIGNEMENTS SUR LES CONSEILS À DONNER AUX PATIENTS et LE GUIDE DE THÉRAPEUTIQUE

Révision : Mai 2011

INFORMATION POSOLOGIQUE COMPLÈTE : SOMMAIRE*

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*Les sections ou les paragraphes dans la Information posologique complète ne sont pas numérotés.

1. INDICATIONS ET UTILISATION

Sulfate d'abacavir et lamivudine, une association de 2 inhibiteurs de la transcriptase inverse du VIH-1, est indiqué en association avec d'autres agents antirétroviraux pour le traitement de l'infection par le VIH-1. (1)

2. POSOLOGIE ET MODE D'ADMINISTRATION

- Un guide de thérapeutique du Sulfate de mesure est joint à chaque bouteille prescription et renouvellement. (2)
- Prendre de 2 mesure d'abacavir. La posologie doit être basée sur le poids corporel. (2.2)
- Ne pas prescrire aux patients nécessitant une adaptation posologique du sulfate d'abacavir et lamivudine chez des patients présentant une insuffisance hépatique. (2.3)

3. FORMES PHARMACEUTIQUES ET CONCENTRATIONS

Chaque comprimé sécable pour suspension buvable contient 60 mg d'abacavir et 30 mg de lamivudine. (3)

4. CONTRE-INDICATIONS

- Hypersensibilité antérieurement démontrée à l'abacavir ou à tout autre composant du produit. (4, 5.1)
- Insuffisance hépatique. (4)

5. MISES EN GARDE ET PRÉCAUTIONS D'EMPLOI

- Voir les mises en garde en encadré pour de plus amples informations sur les points suivants : Réactions d'hypersensibilité, acidose lactique et hépatomégalie grave, et encephalopathie aiguë grave de l'hépatite B. (5.1, 5.2, 5.3)
- Hypersensibilité non hépatique, fatale dans certains cas, est survenue chez des patients n'ayant pas été trouvés porteurs de l'allèle HLA-B*5701 ou ayant présenté une association d'autres manifestations d'hypersensibilité dans quelques cas seulement. Interrompre la prise de Sulfate d'abacavir et lamivudine de manière médicalement appropriée et immédiate, même si l'hypersensibilité ne peut être exclue. Ne pas utiliser de formulations de rechallenge, dans des cas fatals. (5.1)
- Rare cas du syndrome de reconstitution immunitaire (5.5) et de redistribution / accumulation de graisse corporelle ont été signalés chez des patients traités par une association antirétrovirale. (5.6)
- Sulfate d'abacavir et lamivudine ne doit pas être administré avec d'autres produits contenant de l'abacavir ou de la lamivudine, sauf en cas de nécessité médicale. (5.7)
- Pancréatite : Il a pu être mis en cause chez des patients pediatriques présentant des antécédents de pancréatite ou d'autres facteurs de risque importants de pancréatite. Interrompre le traitement de manière clinquement appropriée. (5.8)

6. EFFETS SECONDAIRES

- Effets secondaires d'intensité au moins modérée le plus couramment rapportés (fréquence ≥ 5%) chez un adulte ayant pris par le Sulfate d'abacavir de 300mg : hypersensibilité médicamenteuse, insomnie, étourdissement, céphalée, diarrhée, nausée, vomissements, fatigue/malaise, abattement/asthénie/fatigue, faiblesse et diarrhée. (6.1)
- Abacavir : Effets secondaires d'intensité au moins modérée le plus couramment rapportés (fréquence ≥ 5%) chez des patients ayant pris par le Sulfate d'abacavir et lamivudine : nausée, vomissements, anorexie/perte d'appétit, douleur abdominale, céphalées (chez les enfants) et diarrhée. (6.1)
- Lamivudine : Effets secondaires le plus couramment rapportés (fréquence ≥10%) chez des patients pediatriques : fièvre et toux. (6.1)

Pour signaler des EFFETS SECONDAIRES SOUPÇONNÉS, contacter Cipla Ltd. au 1-(22)-6707000 ou l'agence Patients américaine des produits alimentaires et médicamentaux (FDA) au 1-800-FDA-1088 ou rendez-vous sur le site Internet: www.fda.gov/medwatch.

- Chimed (Chimed information médicaux). (7.2)
- Interactions avec d'autres médicaments peut être présumées chez un nombre notable de patients. (7.4)

Voir 17 pour les RENSEIGNEMENTS SUR LES CONSEILS À DONNER AUX PATIENTS et LE GUIDE DE THÉRAPEUTIQUE

Révision : Mai 2011

2. POSOLOGIE ET MODE D'ADMINISTRATION

- Un guide de thérapeutique du Sulfate de mesure est joint à chaque bouteille prescription et renouvellement.
- Prendre Abacavir et lamivudine deux fois par jour et en fonction du poids corporel.

2.1 Adultes et adolescents

- La posologie recommandée de Sulfate d'abacavir et lamivudine chez des patients pédiatriques de 3 mois et plus, inclusive, ou de 14kg et plus, d'abacavir deux fois par jour jusqu'à un maximum de 300 mg d'abacavir et 150 mg de lamivudine par jour. Ne pas prescrire aux patients nécessitant une adaptation posologique du sulfate d'abacavir et lamivudine chez des patients présentant une insuffisance hépatique. Le dosage recommandé est fourni dans le Tableau 1.

Tableau 1. Recommandations posologiques de Sulfate d'abacavir et lamivudine comprimés pour suspension buvable chez les patients pédiatriques.

Poids (kg)	Nombre(s) comprimé(s) de Sulfate d'abacavir et lamivudine comprimés sécables pour suspension buvable: 60 mg/30 mg	Dose quotidienne totale (mg)
	Dose du matin (mg)	Dose du soir (mg)
5	1 comprimé (60 mg A/30 mg L)	1 comprimé (60 mg A/30 mg L)	60A/60L
6 – < 9	1 comprimé (60 mg A/30 mg L)	1 comprimé (60 mg A/30 mg L)	120A/60L
9 – < 14	1 comprimé (60 mg A/30 mg L)	1 comprimé (60 mg A/30 mg L)	120A/60L
14 – < 17	2 comprimés (120 mg A/60 mg L)	2 comprimés (120 mg A/60 mg L)	240A/120L
17 – < 20	2,5 comprimés (150 mg A/75 mg L)	2,5 comprimés (150 mg A/75 mg L)	300A/150L
20 – < 25	3 comprimés (180 mg A/90 mg L)	3 comprimés (180 mg A/90 mg L)	360A/180L
25 – < 29	3,5 comprimés (210 mg A/105 mg L)	3,5 comprimés (210 mg A/105 mg L)	420A/210L
29 – < 34	4 comprimés (240 mg A/120 mg L)	4 comprimés (240 mg A/120 mg L)	480A/240L
≥34	5 comprimés (300 mg A/150 mg L)	5 comprimés (300 mg A/150 mg L)	600A/300L

Air Sulfate d'abacavir, Lin Lamivudine

- Prendre Sulfate d'abacavir et lamivudine (abacavir 300 mg deux fois par jour et de lamivudine 150 mg deux fois par jour) chez adolescents et enfants pesant 60 kg ou plus. Ce dosage est recommandé en fonction du poids corporel de 300 mg d'abacavir et comprimé de 150 mg de lamivudine) peuvent être utilisés.

Méthode de prise du médicament

- Ne pas dépasser la dose d'abacavir et lamivudine (2 comprimés, possible comme suit :
  1. Mettre le(s) comprimé(s) dans un fond de liquide dans quelques millilitres d'eau (10 ml) d'eau potable par comprimé.
  2. Agiter le liquide jusqu'à ce que le(s) comprimé(s) se désintègrent. Ne pas mettre d'autres liquides pour prendre ce(s) comprimé(s) dans quelques millilitres d'eau pour dissoudre les comprimés, si nécessaire.
  3. Ajouter le(s) comprimé(s) dans le reste de l'eau (10 ml).
  4. Prendre le liquide immédiatement après avoir ajouté le(s) comprimé(s) dans le liquide. Ne pas conserver le(s) comprimé(s) dans le liquide.

NE PAS INJECTER SULFATE D'ABACAVIR ET LAMIVUDINE COMPRIMÉS POUR SUSPENSION BUVABLE AVEC TOUT LIQUIDE AUTRE QUE L'EAU.

Dose oubliée

- Si une dose d'abacavir et lamivudine comprimés pour suspension buvable est une association à deux fois par jour dans les prochaines heures :
  - Les patients pédiatriques de 14 kg et plus : prendre une dose d'abacavir et lamivudine comprimés pour suspension buvable.
  - Les patients atteints d'insuffisance hépatique.

3. FORMES PHARMACEUTIQUES ET CONCENTRATIONS

- Sulfate d'abacavir et lamivudine comprimés pour suspension buvable contient 60 mg d'abacavir sous forme de sulfate d'abacavir et 30 mg de lamivudine.
- Les comprimés sont sécables mais ne doivent pas être ouverts sous forme de gélule, broyés, mâchés, pulvérisés ou mélangés avec d'autres aliments.

4. CONTRE-INDICATIONS

- Sulfate d'abacavir et lamivudine comprimés pour suspension buvable est contre-indiqué chez les patients présentant :
  - une hypersensibilité précédemment démontrée à l'abacavir ou à tout autre composant du produit.
  - **Ne jamais reprendre le traitement par Abacavir et lamivudine chez tout patient présentant des signes d'hypersensibilité et ayant présenté le médicament contenant de l'abacavir, quel que soit le statut de l'allèle HLA-B*5701 ou tout autre signe ou symptôme connu pour être associé à une réaction d'hypersensibilité. Le test de dépistage de l'allèle HLA-B*5701 n'est pas recommandé chez les patients ayant présenté des signes d'hypersensibilité à l'abacavir. Toutefois, cette décision sera moins significative que chez les patients ayant présenté des signes d'hypersensibilité à l'abacavir et ne possédant pas l'allèle HLA-B*5701, étant donné que l'hypersensibilité à l'abacavir est différente chez les patients porteurs de l'allèle HLA-B*5701 et l'hypersensibilité à l'abacavir chez les patients dépourvus de l'allèle HLA-B*5701 (voir Mises en garde et précautions d'emploi (5.1)).**
  - Insuffisance hépatique.

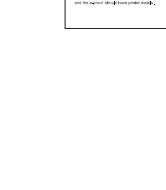
Les informations importantes sur les signes et les symptômes d'hypersensibilité, ainsi que le plan en charge clinique, sont présentées ci-dessous.

- Sulfate d'abacavir et lamivudine comprimés pour suspension buvable est associé à des symptômes diffuses de dysfonction multiple des organes généralement considérés par un signe ou un symptôme apparaissant à deux ou plusieurs des groupes suivants :

Groupe 1: Fièvre
Groupe 2: Éruption cutanée
Groupe 3: Gastrointestinal (y compris nausées, vomissements, diarrhée ou douleurs abdominales)
Groupe 4: Constitutionnel (malaise, fatigue, ou courbatures généralisés)
Groupe 5: Système respiratoire (y compris dyspnée, toux ou pharyngite)

- Les symptômes cliniques de l'hypersensibilité ont été observés principalement après un mois environ. L'hypersensibilité à l'abacavir a été signalée chez environ 5% des 2000 patients (n = 206) ayant reçu de l'abacavir dans les essais cliniques (fréquence 2%, 4.9%) avec les effects suivants de novembre 1999 à février 2000. Les données sur le temps d'apparition des symptômes d'hypersensibilité suspectée ont été recueillies par un medecin collecteur de données détaillées. Les fréquences des symptômes apparaissant à la figure 1 ci-dessous. Les symptômes apparaissant à des fréquences différentes selon le groupe d'âge. Le nombre de patients ayant présenté un problème à l'enquête qui n'avait pas été mentionné au moment du traitement, cependant, il est vraisemblable que ce type, 98% des cas apparus au cours des 6 premières semaines, 95% des patients ont signalé des symptômes apparaissant à au moins trois groupes différents.

Figure 1: Symptômes liés à l'hypersensibilité avec une fréquence ≥10% lors des essais cliniques (n = 206 patients)



Diverses signes et symptômes d'hypersensibilité moins fréquents comprennent: céphalée, myalgie, oedème, anomalies radiographiques pulmonaires (principalement aux infiltrats), anomalies des lymphocytes, et oedème. Des cas d'insuffisance d'insuffisance respiratoire, d'insuffisance rénale, d'hypotension, de syndrome de détresse respiratoire aiguë, d'hépatite, d'éosinophilie, de rhabdomyolyse et de lymphadénopathie ont été rapportés des réactions d'hypersensibilité. Lors d'une étude, 4 patients (1%) recevant 600 mg d'abacavir une fois par jour ont connu une hypotension avec une réaction d'hypersensibilité par rapport à 0 patient traité par 300 mg d'abacavir deux fois par jour. Chez certains patients, les signes cliniques associés à une hypersensibilité à l'abacavir concernent : lymphoadénopathie, lésions des muqueuses, conjonctivite et détresse du système respiratoire. Les signes et symptômes d'hypersensibilité ont été observés chez des patients ne présentant pas d'allèle HLA-B*5701 et ne présentant pas d'antécédents d'hypersensibilité à l'abacavir.

Symptômes

Diverses signes et symptômes d'hypersensibilité moins fréquents comprennent: céphalée, myalgie, oedème, anomalies radiographiques pulmonaires (principalement aux infiltrats), anomalies des lymphocytes, et oedème. Des cas d'insuffisance d'insuffisance respiratoire, d'insuffisance rénale, d'hypotension, de syndrome de détresse respiratoire aiguë, d'hépatite, d'éosinophilie, de rhabdomyolyse et de lymphadénopathie ont été rapportés des réactions d'hypersensibilité. Lors d'une étude, 4 patients (1%) recevant 600 mg d'abacavir une fois par jour ont connu une hypotension avec une réaction d'hypersensibilité par rapport à 0 patient traité par 300 mg d'abacavir deux fois par jour. Chez certains patients, les signes cliniques associés à une hypersensibilité à l'abacavir concernent : lymphoadénopathie, lésions des muqueuses, conjonctivite et détresse du système respiratoire. Les signes et symptômes d'hypersensibilité ont été observés chez des patients ne présentant pas d'allèle HLA-B*5701 et ne présentant pas d'antécédents d'hypersensibilité à l'abacavir chez certains patients présentant d'hypersensibilité à l'abacavir, chez des patients ne présentant pas d'allèle HLA-B*5701 et ne présentant pas d'antécédents d'hypersensibilité à l'abacavir.

Acidose lactique/hépatomégalie grave avec stéatose

Des cas d'acidose lactique et d'hépatomégalie grave avec stéatose, y compris des cas mortels, ont été rapportés avec l'utilisation d'analogues nucléosidiques seuls ou en association, y compris le sulfate d'abacavir et la lamivudine et d'autres antirétroviraux.

Une majorité de ces cas sont survenus chez des femmes. L'obésité et l'exposition prolongée aux nucléosides présentent constituer des facteurs de risques. Une attention particulière doit être accordée lors de la prescription d'analogues nucléosidiques à une personne présentant un foie anormal, des patients, le fonction hépatique. Cependant, cela ne saurait être suffisant chez des patients en apparence exempts de foie. Le traitement par Abacavir et lamivudine doit être interrompu chez tout patient présentant des signes cliniques d'hépatotoxicité, d'hyperlactatémie ou d'acidose lactique, ou présentant des symptômes non spécifiques de dysfonctionnement hépatique, tant majeur que mineur.

Patients infectés par le VHB et le virus de l'hépatite B

- Sulfate d'abacavir et lamivudine comprimés pour suspension buvable est contre-indiqué chez les patients présentant une hépatite B active. Le traitement par Sulfate d'abacavir et lamivudine comprimés pour suspension buvable chez des patients infectés par le VHB et le VIH, le risque de crises de rebond hépatique et de l'aggravation de l'infection consécutive par le virus de l'hépatite B.

5.4 Utilisation avec des traitements à base d'interféron et de ribavirine

Des études in vitro ont montré que la ribavirine peut réduire la phosphorylation d'analogues nucléosidiques inhibiteurs de la transcriptase inverse, par exemple, le sulfate d'abacavir et lamivudine comprimés pour suspension buvable, l'activité in vitro du sulfate d'abacavir et lamivudine comprimés pour suspension buvable. Cependant, la portée de l'antagonisme in vivo, pharmacodynamique, pharmacocinétique, par exemple, la perte de l'activité du sulfate d'abacavir et lamivud

Figure 2: Clairance systémique (L/h/kg) de la lamivudine en fonction de l'âge

Après l'administration orale de lamivudine à raison deux fois par jour à 11 patients pédiatriques de 1 mois à 14 ans, la C_{max} était de 1,3 ± 0,8 mcg/mL, de durée de 2,6 ± 0,4 heures, et la demi-vie d'élimination de 1,3 ± 0,3 heures. La biodisponibilité moyenne était de 57 ± 11 %. Les paramètres pharmacocinétiques étaient comparables à ceux observés chez les adultes. Les données pharmacocinétiques limitées, non contrôlées et descriptives sont disponibles chez les enfants de moins de 3 mois. Elles ont montré une clairance de la lamivudine plus faible chez les nouveau-nés (0,3 ± 0,1 L/h/kg) par rapport à celle observée chez les enfants plus âgés (0,6 ± 0,1 L/h/kg) (voir la figure 2). Des données pharmacocinétiques limitées, non contrôlées et descriptives sont disponibles chez enfants de 3 mois à 3 ans