

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Abacavir sulfate Tablets for Oral Suspension 60mg

WARNING: HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS, AND SEVERE HEPATOMEGALY
See full prescribing information for complete boxed warning.

- Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate. (5.1)
- Hypersensitivity to abacavir is a multi-organ clinical syndrome. (5.1)
- Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. (5.1)
- Discontinue abacavir sulfate as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B*5701 status, permanently discontinue abacavir sulfate if hypersensitivity cannot be ruled out, even when other diagnoses are possible. (5.1)
- Following a hypersensitivity reaction to abacavir, NEVER restart abacavir sulfate 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)

-----INDICATIONS AND USAGE-----

Abacavir sulfate, a nucleoside analogue, is 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 Aged 3 Months and Older: Dose should be calculated on body weight (kg) and should not exceed 300 mg twice daily. (2.2)
- Patients with Hepatic Impairment: Mild hepatic impairment – 200 mg twice daily; moderate/severe hepatic impairment – contraindicated. (2.3)

-----DOSAGE FORMS AND STRENGTHS-----

Tablets for Oral Suspension: 60 mg, scored; (3)

-----CONTRAINDICATIONS-----

- Previously demonstrated hypersensitivity to abacavir. (4, 5.1)
- Moderate or severe hepatic impairment. (4)

-----WARNINGS AND PRECAUTIONS-----

- Hypersensitivity: Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate and other abacavir-containing products. Read full prescribing information section 5.1 before prescribing abacavir sulfate. (5.1)
- Lactic acidosis and severe hepatomegaly with steatosis have been reported with the use of nucleoside analogues. (5.2)
- Immune reconstitution syndrome (5.3) and redistribution/accumulation of body fat have been reported in patients treated with combination antiretroviral therapy. (5.4)

-----ADVERSE REACTIONS-----

- The most commonly reported adverse reactions of at least moderate intensity (incidence ≥10%) in adult HIV-1 clinical trials were nausea, headache, malaise and fatigue, nausea and vomiting, and dreams/sleep disorders. (6.1)
- The most commonly reported adverse reactions of at least moderate intensity (incidence ≥5%) in pediatric HIV-1 clinical trials were fever and/or chills, nausea and vomiting, skin rashes, and ear/nose/throat infections. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Cipla Ltd. at 1-866-604-3268 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

- Ethanol: Decreases elimination of abacavir. (7)
- Methadone: An increased methadone dose may be required in a small number of patients. (7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION

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

Hypersensitivity Reactions: Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate.

Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups: (1) fever, (2) rash, (3) gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain), (4) constitutional (including generalized malaise, fatigue, or achiness), and (5) respiratory (including dyspnea, cough, or pharyngitis). Discontinue abacavir sulfate tablets for oral suspension as soon as a hypersensitivity reaction is suspected.

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

Regardless of HLA-B*5701 status, permanently discontinue abacavir sulfate tablets for oral suspension if hypersensitivity cannot be ruled out, even when other diagnoses are possible.

Following a hypersensitivity reaction to abacavir, NEVER restart abacavir sulfate tablets for oral suspension or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.

Reintroduction of abacavir sulfate tablets for oral suspension or any other abacavir-containing product, even in patients who have no identified history or unrecognized symptoms of hypersensitivity to abacavir therapy, can result in serious or fatal hypersensitivity reactions. Such reactions can occur within hours [*see Warnings and Precautions (5.1)*].

Lactic Acidosis and Severe Hepatomegaly: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir sulfate and other antiretrovirals [*see Warnings and Precautions (5.2)*].

1 INDICATIONS AND USAGE

Abacavir sulfate tablets for oral suspension, in combination with other antiretroviral agents, are indicated for the treatment of human immunodeficiency virus (HIV-1) infection.

Additional important information on the use of abacavir sulfate for treatment of HIV-1 infection: Abacavir sulfate tablets for oral suspension is one of multiple products containing abacavir. Before starting abacavir sulfate tablets for oral suspension, review medical history for prior exposure to any abacavir-containing product in order to avoid reintroduction in a patient with a history of hypersensitivity to abacavir [see *Warnings and Precautions (5.1), Adverse Reactions (6)*].

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.
- Abacavir sulfate tablets for oral suspension are recommended to be taken on an empty stomach.

2.2 Pediatric Patients

The recommended oral dosage of abacavir sulfate in HIV-1-infected pediatric patients 3 months and older is 8 mg/kg twice daily (up to a maximum of 300 mg twice daily) in combination with other antiretroviral agents is presented in Table 1.

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

| Weight (kg) | Dosage Regimen Using Scored 60 mg Tablets | | Total Daily Dose |
|-------------|---|---------------------------------|------------------|
| | AM Dose | PM Dose | |
| 5 - < 6 | ½ tablet (30 mg) | 1 tablet (60 mg) | 90 mg |
| 6 - < 9 | 1 tablet (60 mg) | 1 tablet (60 mg) | 120 mg |
| 9 - < 12 | 1.5 tablets (90 mg) | 1.5 tablets (90 mg) | 180 mg |
| 12 - < 17 | 2 tablets (120 mg) | 2 tablets (120 mg) | 240 mg |
| 17 - < 20 | 2.5 tablets (150 mg) | 2.5 tablets (150 mg) | 300 mg |
| 20 - < 25 | 3 tablets (180 mg) | 3 tablets (180 mg) | 360 mg |
| 25- < 29 | 3.5 tablets (210 mg) | 3.5 tablets (210 mg) | 420 mg |
| 29 - <35 | 4 tablets (240 mg) | 4 tablets (240 mg) | 480 mg |
| ≥35 | 5 tablets (300 mg) ^a | 5 tablets (300 mg) ^a | 600 mg |

a For recommended doses of 300 mg twice daily (adult maximum daily dose), the adult formulation (300 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 water per tablet.
2. Swirl the container until 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 one 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 ABACAVIR TABLET FOR ORAL SUSPENSION WITH ANY LIQUID OTHER THAN WATER.

2.3 Patients with Hepatic Impairment

The recommended dose of abacavir sulfate in patients with mild hepatic impairment (Child-Pugh score 5 to 6) is 200 mg twice daily. The safety, efficacy, and pharmacokinetic properties of abacavir have not been established in patients with moderate to severe hepatic impairment; therefore, abacavir sulfate is contraindicated in these patients.

3 DOSAGE FORMS AND STRENGTHS

Tablets for oral suspension, containing abacavir sulfate equivalent to 60 mg abacavir are scored, white to off white colored, capsule shaped, biconvex, uncoated tablets with central breakline on one side and debossed A on other side.

4 CONTRAINDICATIONS

Abacavir sulfate is contraindicated in patients with:

- previously demonstrated hypersensitivity to abacavir or any other component of the products. NEVER restart abacavir sulfate 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)*].
- moderate or severe hepatic impairment [see *Dosage and Administration (2.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reaction

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

HLA-B*5701-negative patients may develop a hypersensitivity reaction to abacavir; however, this occurs significantly less frequently than in HLA-B*5701-positive patients. Regardless of HLA-B*5701 status, permanently discontinue abacavir sulfate if hypersensitivity cannot be ruled out, even when other diagnoses are possible.

Important information on signs and symptoms of hypersensitivity, as well as clinical management, is presented below.

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

Group 1: Fever

Group 2: Rash

Group 3: Gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain)

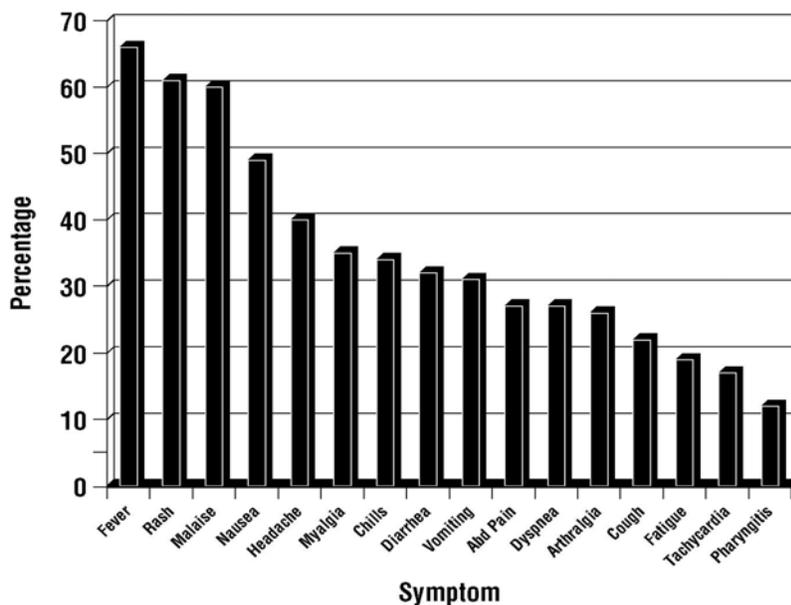
Group 4: Constitutional (including generalized malaise, fatigue, or achiness)

Group 5: Respiratory (including dyspnea, cough, or pharyngitis).

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

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

Figure 1. Hypersensitivity-Related Symptoms Reported With $\geq 10\%$ Frequency in Clinical Trials (n = 206 Subjects)



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

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

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

Clinical Management of Hypersensitivity: Discontinue abacavir sulfate tablets for oral suspension as soon as a hypersensitivity reaction is suspected. To minimize the risk of a life-threatening hypersensitivity reaction, permanently discontinue abacavir sulfate if hypersensitivity cannot be ruled out, even when other diagnoses are possible (e.g., acute onset respiratory diseases such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions to other medications).

Following a hypersensitivity reaction to abacavir, NEVER restart abacavir sulfate tablets for oral suspension or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.

When therapy with abacavir sulfate tablets for oral suspension has been discontinued for reasons other than symptoms of a hypersensitivity reaction, and if reinitiation of abacavir sulfate tablets for oral suspension or any other abacavir-containing product is under consideration, carefully evaluate the reason for discontinuation of abacavir sulfate tablets for oral suspension to ensure that the patient did not have symptoms of a hypersensitivity reaction. If the patient is of unknown HLA-B*5701 status, screening for the allele is recommended prior to reinitiation of abacavir sulfate tablets for oral suspension.

If hypersensitivity cannot be ruled out, DO NOT reintroduce abacavir sulfate 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 rechallenge with abacavir if a hypersensitivity reaction cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

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

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

CNA106030 (PREDICT-1), a randomized, double-blind trial, evaluated the clinical utility of prospective HLA-B*5701 screening on the incidence of abacavir hypersensitivity reaction in abacavir-naive HIV-1-infected adults (n = 1,650). In this trial, use of pre-therapy screening for the HLA-B*5701 allele and exclusion of subjects with this allele reduced the incidence of clinically suspected abacavir hypersensitivity reactions from 7.8% (66/847) to 3.4% (27/803). Based on this trial, 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 rechallenge with abacavir if a hypersensitivity reaction cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

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 and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering abacavir sulfate tablets for oral suspension to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with abacavir sulfate tablets for oral suspension should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

5.3 Immune Reconstitution Syndrome

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

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

5.4 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.

5.5 Myocardial Infarction

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

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

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 trial, once-daily 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)*].
- Immune reconstitution syndrome [*see Warnings and Precautions (5.3)*].
- Fat redistribution [*see Warnings and Precautions (5.4)*].
- Myocardial infarction [*see Warnings and Precautions (5.5)*].

6.1 Clinical Trials Experience

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

Adults: Therapy-Naive Adults: Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a greater than or equal to 5% frequency during therapy with abacavir sulfate 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg daily compared with zidovudine 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg daily from CNA30024 are listed in Table 2.

Table 2. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Naive Adults (CNA30024^a) Through 48 Weeks of Treatment

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

^a This trial used double-blind ascertainment of suspected hypersensitivity reactions. During the blinded portion of the trial, suspected hypersensitivity to abacavir was reported by investigators in 9% of 324 subjects in the abacavir group and 3% of 325 subjects in the zidovudine group.

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

Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a greater than or equal to 5% frequency during therapy with abacavir sulfate 300 mg twice daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily compared with indinavir 800 mg 3 times daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily from CNA3005 are listed in Table 3.

Table 3. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Naive Adults (CNA3005) Through 48 Weeks of Treatment

| Adverse Reaction | Abacavir sulfate plus Lamivudine/Zidovudine (n = 262) | Indinavir plus Lamivudine/Zidovudine (n = 264) |
|------------------------------|---|--|
| Nausea | 19% | 17% |
| Headache | 13% | 9% |
| Malaise and fatigue | 12% | 12% |
| Nausea and vomiting | 10% | 10% |
| Hypersensitivity reaction | 8% | 2% |
| Diarrhea | 7% | 5% |
| Fever and/or chills | 6% | 3% |
| Depressive disorders | 6% | 4% |
| Musculoskeletal pain | 5% | 7% |
| Skin rashes | 5% | 4% |
| Ear/nose/throat infections | 5% | 4% |
| Viral respiratory infections | 5% | 5% |
| Anxiety | 5% | 3% |
| Renal signs/symptoms | <1% | 5% |
| Pain (non-site-specific) | <1% | 5% |

Five subjects receiving abacavir sulfate in CNA3005 experienced worsening of pre-existing depression compared with none in the indinavir arm. The background rates of pre-existing depression were similar in the 2 treatment arms.

Abacavir sulfate Once Daily Versus Abacavir sulfate Twice Daily (CNA30021):

Treatment-emergent clinical adverse reactions (rated by the investigator as at least moderate) with a greater than or equal to 5% frequency during therapy with abacavir sulfate 600 mg once daily or abacavir sulfate 300 mg twice daily both in combination with lamivudine 300 mg once daily and efavirenz 600 mg once daily from CNA30021, were similar. For hypersensitivity reactions, subjects receiving abacavir sulfate once daily showed a rate of 9% in comparison with a rate of 7% for subjects receiving abacavir sulfate twice daily. However, subjects receiving abacavir sulfate 600 mg once daily, experienced a significantly higher incidence of severe drug hypersensitivity reactions and severe diarrhea compared with subjects who received abacavir sulfate 300 mg twice daily. Five percent (5%) of subjects receiving abacavir sulfate 600 mg once daily had severe drug hypersensitivity reactions compared with 2% of subjects receiving abacavir sulfate 300 mg twice daily. Two percent (2%) of subjects receiving abacavir sulfate 600 mg once daily had severe diarrhea while none of the subjects receiving abacavir sulfate 300 mg twice daily had this event.

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

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

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

ULN = Upper limit of normal.

n = Number of subjects assessed.

Laboratory abnormalities in CNA3005 are listed in Table 5.

Table 5. Treatment-Emergent Laboratory Abnormalities (Grades 3-4) in CNA3005

| Grade 3/4 Laboratory Abnormalities | Number of Subjects by Treatment Group | |
|-------------------------------------|---|--|
| | Abacavir sulfate plus Lamivudine/Zidovudine (n = 262) | Indinavir plus Lamivudine/Zidovudine (n = 264) |
| Elevated CPK (>4 x ULN) | 18 (7%) | 18 (7%) |
| ALT (>5.0 x ULN) | 16 (6%) | 16 (6%) |
| Neutropenia (<750/mm ³) | 13 (5%) | 13 (5%) |
| Hypertriglyceridemia (>750 mg/dL) | 5 (2%) | 3 (1%) |
| Hyperamylasemia (>2.0 x ULN) | 5 (2%) | 1 (<1%) |
| Hyperglycemia (>13.9 mmol/L) | 2 (<1%) | 2 (<1%) |
| Anemia (Hgb ≤6.9 g/dL) | 0 (0%) | 3 (1%) |

ULN = Upper limit of normal.

n = Number of subjects assessed.

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

Pediatric Trials: Therapy-Experienced Pediatric Subjects: Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a greater than or equal to 5% frequency during therapy with abacavir sulfate 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 CNA3006 are listed in Table 6.

Table 6: Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2-4, $\geq 5\%$ Frequency) in Therapy-Experienced Pediatric Subjects (CNA3006) Through 16 Weeks of Treatment

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

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

Other Adverse Events: In addition to adverse reactions and laboratory abnormalities reported in Tables 2, 3, 4, 5, and 6, other adverse reactions observed in the expanded access program were pancreatitis and increased GGT.

6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following reactions have been identified during postmarketing use of abacavir sulfate. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These reactions have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to abacavir sulfate.

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

Cardiovascular: Myocardial infarction.

Hepatic: Lactic acidosis and hepatic steatosis.

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

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

7 DRUG INTERACTIONS

7.1 Ethanol

Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol decreases the elimination of abacavir causing an increase in overall exposure [see *Clinical Pharmacology (12.3)*].

7.2 Methadone

The addition of methadone has no clinically significant effect on the pharmacokinetic properties of abacavir. In a trial of 11 HIV-1-infected subjects receiving methadone-maintenance therapy with 600 mg of abacavir sulfate twice daily (twice the currently recommended dose), oral methadone clearance increased [see *Clinical Pharmacology (12.3)*]. This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

There are no adequate and well-controlled studies in pregnant women. Abacavir sulfate should be used during pregnancy only if the potential benefits outweigh the risk.

8.3 Nursing Mothers

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

Although it is not known if abacavir is excreted in human milk, abacavir is secreted into the milk of lactating rats. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving abacavir sulfate.

8.4 Pediatric Use

The safety and effectiveness of abacavir sulfate have been established in pediatric patients 3 months to 13 years of age. Use of abacavir sulfate in these age groups is supported by pharmacokinetic trials and evidence from adequate and well-controlled trials of abacavir sulfate in adults and pediatric patients [see *Dosage and Administration (2.2)*, *Clinical Pharmacology (12.3)*, *Clinical Studies (14.2)*].

8.5 Geriatric Use

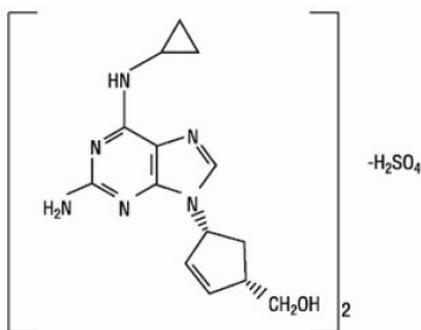
Clinical studies of abacavir sulfate did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE

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

11 DESCRIPTION

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



Abacavir sulfate is a white to off-white solid with a solubility of approximately 77 mg/mL in distilled water at 25°C. It has an octanol/water (pH 7.1 to 7.3) partition coefficient ($\log P$) of approximately 1.20 at 25°C.

Abacavir sulfate tablets for oral suspension are for oral administration. Each tablet contains abacavir sulfate equivalent to 60 mg of abacavir as active ingredient and the following inactive ingredients: microcrystalline cellulose (avicel PH 101), sodium starch glycolate, corn starch, hypromellose, microcrystalline cellulose (avicel PH 102), strawberry cream flavour, aspartame, colloidal silicon dioxide, and magnesium stearate.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Abacavir is an antiviral agent [See *Clinical Pharmacology* (12.4)].

12.3 Pharmacokinetics

Abacavir sulfate from the tablets for oral suspension (60 mg) was bioequivalent to that from ZIAGEN Oral Solution when administered to healthy volunteers under fasting conditions.

Pharmacokinetics in Adults: The pharmacokinetic properties of abacavir have been studied in asymptomatic, HIV-1-infected adult subjects after administration of a single intravenous (IV) dose of 150 mg and after single and multiple oral doses. The pharmacokinetic properties of abacavir were independent of dose over the range of 300 to 1,200 mg/day.

Absorption and Bioavailability: Abacavir was rapidly and extensively absorbed after oral administration. The geometric mean absolute bioavailability of the tablet was 83%. After oral administration of 300 mg twice daily in 20 subjects, the steady-state peak serum abacavir concentration (C_{\max}) was 3.0 ± 0.89 mcg/mL (mean \pm SD) and $AUC_{(0-12 \text{ hr})}$ was 6.02 ± 1.73 mcg•hr/mL. After oral administration of a single dose of 600 mg of abacavir in 20 subjects, C_{\max} was 4.26 ± 1.19 mcg/mL (mean \pm SD) and AUC_{∞} was 11.95 ± 2.51 mcg•hr/mL.

Distribution: The apparent volume of distribution after IV administration of abacavir was 0.86 ± 0.15 L/kg, suggesting that abacavir distributes into extravascular space. In 3 subjects, the CSF $AUC_{(0-6 \text{ hr})}$ to plasma abacavir $AUC_{(0-6 \text{ hr})}$ ratio ranged from 27% to 33%.

Binding of abacavir to human plasma proteins is approximately 50%. Binding of abacavir to plasma proteins was independent of concentration. Total blood and plasma drug-related radioactivity concentrations are identical, demonstrating that abacavir readily distributes into erythrocytes.

Metabolism: In humans, abacavir is not significantly metabolized by cytochrome P450 enzymes. The primary routes of elimination of abacavir are metabolism by alcohol dehydrogenase (to form the 5'-carboxylic acid) and glucuronyl transferase (to form the 5'-glucuronide). The metabolites do not have antiviral activity. In vitro experiments reveal that abacavir does not inhibit human CYP3A4, CYP2D6, or CYP2C9 activity at clinically relevant concentrations.

Elimination: Elimination of abacavir was quantified in a mass balance trial following administration of a 600-mg dose of ^{14}C -abacavir: 99% of the radioactivity was recovered, 1.2% was excreted in the urine as abacavir, 30% as the 5'-carboxylic acid metabolite, 36% as the 5'-glucuronide metabolite, and 15% as unidentified minor metabolites in the urine. Fecal elimination accounted for 16% of the dose.

In single-dose trials, the observed elimination half-life ($t_{1/2}$) was 1.54 ± 0.63 hours. After intravenous administration, total clearance was 0.80 ± 0.24 L/hr/kg (mean \pm SD).

Effects of Food on Oral Absorption of Abacavir Sulfate Tablets for Oral Suspension:

The effect of food on abacavir sulfate tablets for oral suspension was not determined; therefore, this product must be administered on an empty stomach.

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

Hepatic Impairment: The pharmacokinetics of abacavir have been studied in subjects with mild hepatic impairment (Child-Pugh score 5 to 6). Results showed that there was a mean increase of 89% in the abacavir AUC, and an increase of 58% in the half-life of abacavir after a single dose of 600 mg of abacavir. The AUCs of the metabolites were not modified by mild liver disease; however, the rates of formation and elimination of the metabolites were decreased. The safety, efficacy, and pharmacokinetics of abacavir have not been studied in patients with moderate or severe hepatic impairment, therefore abacavir sulfate is contraindicated in these patients.

Pediatric Patients: The pharmacokinetics of abacavir have been studied after either single or repeat doses of abacavir sulfate in 68 pediatric subjects. Following multiple-dose administration of abacavir sulfate 8 mg/kg twice daily, steady-state $AUC_{(0-12 \text{ hr})}$ and C_{max} were 9.8 ± 4.56 mcg•hr/mL and 3.71 ± 1.36 mcg/mL (mean \pm SD), respectively [*see Use in Specific Populations (8.4)*].

Geriatric Patients: The pharmacokinetics of abacavir sulfate have not been studied in patients over 65 years of age.

Gender: A population pharmacokinetic analysis in HIV-1-infected male (n = 304) and female (n = 67) subjects showed no gender differences in abacavir AUC normalized for lean body weight.

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

Drug Interactions: In human liver microsomes, abacavir did not inhibit cytochrome P450 isoforms (2C9, 2D6, 3A4). Based on these data, it is unlikely that clinically significant drug interactions will occur between abacavir and drugs metabolized through these pathways.

Lamivudine and/or Zidovudine: Due to the common metabolic pathways of abacavir and zidovudine via glucuronyl transferase, 15 HIV-1-infected subjects were enrolled in a crossover trial evaluating single doses of abacavir (600 mg), lamivudine (150 mg), and zidovudine (300 mg) alone or in combination. Analysis showed no clinically relevant changes in the pharmacokinetics of abacavir with the addition of lamivudine or zidovudine or the combination of lamivudine and zidovudine. Lamivudine exposure (AUC decreased 15%) and zidovudine exposure (AUC increased 10%) did not show clinically relevant changes with concurrent abacavir.

Ethanol: Due to their common metabolic pathways of abacavir and ethanol via alcohol dehydrogenase, the pharmacokinetic interaction between abacavir and ethanol was studied in 24 HIV-1-infected male subjects. Each subject received the following treatments on separate occasions: a single 600-mg dose of abacavir, 0.7 g/kg ethanol (equivalent to 5 alcoholic drinks), and abacavir 600 mg plus 0.7 g/kg ethanol. Coadministration of ethanol and abacavir resulted in a 41% increase in abacavir AUC_{∞} and a 26% increase in abacavir $t_{1/2}$. In males, abacavir had no

effect on the pharmacokinetic properties of ethanol, so no clinically significant interaction is expected in men. This interaction has not been studied in females.

Methadone: In a trial of 11 HIV-1-infected subjects receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of abacavir sulfate twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI: 6% to 42%). This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients. The addition of methadone had no clinically significant effect on the pharmacokinetic properties of abacavir.

12.4 Microbiology

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

Antiviral Activity: The antiviral activity of abacavir against HIV-1 was evaluated against a T-cell tropic laboratory strain HIV-1_{IIIB} in lymphoblastic cell lines, a monocyte/macrophage tropic laboratory strain HIV-1_{BaL} in primary monocytes/macrophages, and clinical isolates in peripheral blood mononuclear cells. The concentration of drug necessary to effect viral replication by 50 percent (EC₅₀) ranged from 3.7 to 5.8 μM (1 μM = 0.28 mcg/mL) and 0.07 to 1.0 μM against HIV-1_{IIIB} and HIV-1_{BaL}, respectively, and was 0.26 ± 0.18 μM against 8 clinical isolates. The EC₅₀ values of abacavir against different HIV-1 clades (A-G) ranged from 0.0015 to 1.05 μM , and against HIV-2 isolates, from 0.024 to 0.49 μM . Abacavir had synergistic activity in cell culture in combination with the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, and the protease inhibitor (PI) amprenavir; and additive activity in combination with the NRTIs didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine. Ribavirin (50 μM) had no effect on the anti-HIV-1 activity of abacavir in cell culture.

Resistance: HIV-1 isolates with reduced susceptibility to abacavir have been selected in cell culture and were also obtained from subjects treated with abacavir. Genotypic analysis of isolates selected in cell culture and recovered from abacavir-treated subjects demonstrated that amino acid substitutions K65R, L74V, Y115F, and M184V/I in RT contributed to abacavir resistance. In a trial of therapy-naïve adults receiving abacavir sulfate 600 mg once daily (n = 384) or 300 mg twice daily (n = 386), in a background regimen of lamivudine 300 mg once daily and efavirenz 600 mg once daily (CNA30021), the incidence of virologic failure at 48 weeks was similar between the 2 groups (11% in both arms). Genotypic (n = 38) and phenotypic analyses (n = 35) of virologic failure isolates from this trial showed that the RT substitutions that emerged during abacavir once-daily and twice-daily therapy were K65R, L74V, Y115F, and M184V/I. The substitution M184V/I was the most commonly observed substitution in virologic failure isolates from subjects receiving abacavir once daily (56%, 10/18) and twice daily (40%, 8/20).

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

Cross-Resistance: Cross-resistance has been observed among NRTIs. Isolates containing abacavir resistance-associated substitutions, namely, K65R, L74V, Y115F, and M184V, exhibited cross-resistance to didanosine, emtricitabine, lamivudine, tenofovir, and zalcitabine in cell culture and 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. An increasing number of thymidine analogue mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219E/R/H/Q/N) is associated with a progressive reduction in abacavir susceptibility.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity: Abacavir was administered orally at 3 dosage levels to separate groups of mice and rats in 2-year carcinogenicity studies. Results showed an increase in the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver of female rats. In addition, non-malignant tumors also occurred in the liver and thyroid gland of female rats. These observations were made at systemic exposures in the range of 6 to 32 times the human exposure at the recommended dose. It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

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

Abacavir was not mutagenic in bacterial mutagenicity assays in the presence and absence of metabolic activation.

Impairment of Fertility: Abacavir had no adverse effects on the mating performance or fertility of male and female rats at a dose approximately 8 times the human exposure at the recommended dose based on body surface area comparisons.

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

14.1 Adults

Therapy-Naive Adults: CNA30024 was a multicenter, double-blind, controlled trial in which 649 HIV-1-infected, therapy-naive adults were randomized and received either abacavir sulfate (300 mg twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once daily) or zidovudine (300 mg twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once daily). The duration of double-blind treatment was at least 48 weeks. Trial participants were: male (81%), Caucasian (51%), black (21%), and Hispanic (26%). The median age was 35 years, the median pretreatment CD4+ cell count was 264 cells/mm³, and median plasma HIV-1 RNA was 4.79 log₁₀ copies/mL. The outcomes of randomized treatment are provided in Table 7.

Table 7. Outcomes of Randomized Treatment Through Week 48 (CNA30024)

| Outcome | Abacavir sulfate plus Lamivudine plus Efavirenz (n = 324) | Zidovudine plus Lamivudine plus Efavirenz (n = 325) |
|--|--|--|
| Responder ^a | 69% (73%) | 69% (71%) |
| Virologic failures ^b | 6% | 4% |
| Discontinued due to adverse reactions | 14% | 16% |
| Discontinued due to other reasons ^c | 10% | 11% |

^a Subjects achieved and maintained confirmed HIV-1 RNA ≤50 copies/mL (<400 copies/mL) through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR[®] standard test 1.0 PCR).

^b Includes viral rebound, insufficient viral response according to the investigator, and failure to achieve confirmed ≤50 copies/mL by Week 48.

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

After 48 weeks of therapy, the median CD4+ cell count increases from baseline were 209 cells/mm³ in the group receiving abacavir sulfate and 155 cells/mm³ in the zidovudine group. Through Week 48, 8 subjects (2%) in the group receiving abacavir sulfate (5 CDC classification C events and 3 deaths) and 5 subjects (2%) on the zidovudine arm (3 CDC classification C events and 2 deaths) experienced clinical disease progression.

CNA3005 was a multicenter, double-blind, controlled trial in which 562 HIV-1-infected, therapy-naive adults were randomized to receive either abacavir sulfate (300 mg twice daily) plus COMBIVIR[®] (lamivudine 150 mg/zidovudine 300 mg twice daily), or indinavir (800 mg 3 times a day) plus COMBIVIR twice daily. The trial was stratified at randomization by pre-entry plasma HIV-1 RNA 10,000 to 100,000 copies/mL and plasma HIV-1 RNA greater than 100,000 copies/mL. Trial participants were male (87%), Caucasian (73%), black (15%), and Hispanic (9%). At baseline the median age was 36 years, the median baseline CD4+ cell count was 360 cells/mm³, and median baseline plasma HIV-1 RNA was 4.8 log₁₀ copies/mL. Proportions of subjects with plasma HIV-1 RNA less than 400 copies/mL (using Roche AMPLICOR HIV-1 MONITOR Test) through 48 weeks of treatment are summarized in Table 8.

Table 8. Outcomes of Randomized Treatment Through Week 48 (CNA3005)

| Outcome | Abacavir sulfate plus Lamivudine/Zidovudine (n = 262) | Indinavir plus Lamivudine/Zidovudine (n = 265) |
|--|---|--|
| Responder ^a | 49% | 50% |
| Virologic failure ^b | 31% | 28% |
| Discontinued due to adverse reactions | 10% | 12% |
| Discontinued due to other reasons ^c | 11% | 10% |

^a Subjects achieved and maintained confirmed HIV-1 RNA <400 copies/mL.

^b Includes viral rebound and failure to achieve confirmed <400 copies/mL by Week 48.

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

Treatment response by plasma HIV-1 RNA strata is shown in Table 9.

Table 9. Proportions of Responders Through Week 48 By Screening Plasma HIV-1 RNA Levels (CNA3005)

| Screening HIV-1 RNA (copies/mL) | Abacavir sulfate plus Lamivudine/Zidovudine (n = 262) | | Indinavir plus Lamivudine/Zidovudine (n = 265) | |
|------------------------------------|---|-----|--|-----|
| | <400 copies/mL | n | <400 copies/mL | N |
| ≥10,000 - ≤100,000 | 50% | 166 | 48% | 165 |
| >100,000 | 48% | 96 | 52% | 100 |

In subjects with baseline viral load greater than 100,000 copies/mL, percentages of subjects with HIV-1 RNA levels less than 50 copies/mL were 31% in the group receiving abacavir versus 45% in the group receiving indinavir.

Through Week 48, an overall mean increase in CD4+ cell count of about 150 cells/mm³ was observed in both treatment arms. Through Week 48, 9 subjects (3.4%) in the group receiving abacavir sulfate (6 CDC classification C events and 3 deaths) and 3 subjects (1.5%) in the group receiving indinavir (2 CDC classification C events and 1 death) experienced clinical disease progression.

CNA30021 was an international, multicenter, double-blind, controlled trial in which 770 HIV-1-infected, therapy-naive adults were randomized and received either abacavir 600 mg once daily or abacavir 300 mg twice daily, both in combination with lamivudine 300 mg once daily and efavirenz 600 mg once daily. The double-blind treatment duration was at least 48 weeks. Trial participants had a mean age of 37 years, were: male (81%), Caucasian (54%), black (27%), and American Hispanic (15%). The median baseline CD4+ cell count was 262 cells/mm³ (range 21 to 918 cells/mm³) and the median baseline plasma HIV-1 RNA was 4.89 log₁₀ copies/mL (range: 2.60 to 6.99 log₁₀ copies/mL).

The outcomes of randomized treatment are provided in Table 10.

Table 10. Outcomes of Randomized Treatment Through Week 48 (CNA30021)

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

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

^b Includes viral rebound, failure to achieve confirmed <50 copies/mL (<400 copies/mL) by Week 48, and insufficient viral load response.

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

After 48 weeks of therapy, the median CD4+ cell count increases from baseline were 188 cells/mm³ in the group receiving abacavir 600 mg once daily and 200 cells/mm³ in the group receiving abacavir 300 mg twice daily. Through Week 48, 6 subjects (2%) in the group receiving abacavir sulfate 600 mg once daily (4 CDC classification C events and 2 deaths) and 10 subjects (3%) in the group receiving abacavir sulfate 300 mg twice daily (7 CDC classification C events and 3 deaths) experienced clinical disease progression. None of the deaths were attributed to trial medications.

14.2 Pediatric Trials

Therapy-Experienced Pediatric Subjects: CNA3006 was a randomized, double-blind trial comparing abacavir sulfate 8 mg/kg twice daily plus lamivudine 4 mg/kg twice daily plus zidovudine 180 mg/m² twice daily versus lamivudine 4 mg/kg twice daily plus zidovudine 180 mg/m² twice daily. Two hundred and five therapy-experienced pediatric subjects were enrolled: female (56%), Caucasian (17%), black (50%), Hispanic (30%), median age of 5.4 years, baseline CD4+ cell percent greater than 15% (median = 27%), and median baseline plasma HIV-1 RNA of 4.6 log₁₀ copies/mL. Eighty percent and 55% of subjects had prior therapy with zidovudine and lamivudine, respectively, most often in combination. The median duration of prior nucleoside analogue therapy was 2 years. At 16 weeks the proportion of subjects responding based on plasma HIV-1 RNA less than or equal to 400 copies/mL was significantly higher in subjects receiving abacavir sulfate plus lamivudine plus zidovudine compared with subjects receiving lamivudine plus zidovudine, 13% versus 2%, respectively. Median plasma HIV-1 RNA changes from baseline were -0.53 log₁₀ copies/mL in the group receiving abacavir sulfate plus lamivudine plus zidovudine compared with -0.21 log₁₀ copies/mL in the group receiving lamivudine plus zidovudine. Median CD4+ cell count increases from baseline were 69 cells/mm³ in the group receiving abacavir sulfate plus lamivudine plus zidovudine and 9 cells/mm³ in the group receiving lamivudine plus zidovudine.

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Abacavir Sulfate tablets for oral suspension containing 60 mg of abacavir sulfate are scored, white to off white coloured, capsule shaped, biconvex, uncoated tablets with central breakline on one side and debossed A on other side. They are packaged as follows:

Bottles of 60 tablets.

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 FDA-approved patient labeling (Medication Guide)

17.1 Information about Therapy with Abacavir Sulfate

Hypersensitivity Reaction: Inform patients:

- that a Medication Guide and Warning Card summarizing the symptoms of the abacavir hypersensitivity reaction and other product information will be dispensed by the pharmacist with each new prescription and refill of abacavir sulfate, and encourage the patient to read the Medication Guide and Warning Card every time to obtain any new information that may be present about abacavir sulfate. (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 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 tablets for oral suspension.
- that a hypersensitivity reaction can worsen and lead to hospitalization or death if abacavir sulfate tablets for oral suspension is not immediately discontinued.
- that in one trial, more severe hypersensitivity reactions were seen when abacavir sulfate was dosed 600 mg once daily.
- to not restart abacavir sulfate tablets for oral suspension or any other abacavir-containing product following a hypersensitivity reaction because more severe symptoms can occur within hours and may include life-threatening hypotension and death.
- that a hypersensitivity reaction is usually reversible if it is detected promptly and abacavir sulfate tablets for oral suspension is stopped right away.
- that if they have interrupted abacavir sulfate tablets for oral suspension for reasons other than symptoms of hypersensitivity (for example, those who have an interruption in drug supply), a serious or fatal hypersensitivity reaction may occur with reintroduction of abacavir.
- to not restart abacavir sulfate tablets for oral suspension or any other abacavir-containing product without medical consultation and that restarting abacavir needs to be undertaken only if medical care can be readily accessed by the patient or others.

- Abacavir sulfate tablets for oral suspension should not be coadministered with ZIAGEN (abacavir sulfate), EPZICOM[®] (abacavir sulfate and lamivudine) Tablets or TRIZIVIR[®] (abacavir sulfate, lamivudine, and zidovudine) Tablets.

Lactic Acidosis/Hepatomegaly: Inform patients that some HIV medicines, including abacavir sulfate, can cause a rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly) [*see Boxed Warning, 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 (5.4)*].

Information About HIV-1 Infection: Abacavir sulfate is not a cure for 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 tablets for oral suspension.

Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** We do not know if abacavir sulfate can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

Patients should be informed to take all HIV medications exactly as prescribed.

Disclaimer:

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Issued May 2012

**CIPLA LTD.
Mumbai Central, Mumbai INDIA**

MEDICATION GUIDE

Abacavir sulfate tablets for oral suspension 60mg

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

What is the most important information I should know about Abacavir sulfate Tablets for Oral Suspension?

- 1. Serious allergic reaction (hypersensitivity reaction).** Abacavir sulfate tablets for oral suspension 60 mg contains abacavir (also contained in ZIAGEN, EPZICOM[®] and TRIZIVIR[®]). Patients taking abacavir sulfate tablets for oral suspension may have a serious allergic reaction (hypersensitivity reaction) that can cause death. Your risk of this allergic reaction is much higher if you or your child 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 tablets for oral suspension, call your healthcare provider right away to find out if your child or you should stop taking abacavir sulfate tablets for oral suspension.

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

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

If your child or you stop abacavir sulfate tablets for oral suspension because of an allergic reaction, never take abacavir sulfate tablets for oral suspension or any other abacavir-containing medicine (ZIAGEN, EPZICOM and TRIZIVIR) again. If your child or you take abacavir sulfate tablets for oral suspension or any other abacavir-containing medicine again after your child or you have had an allergic reaction, **within hours** your child or you may get **life-threatening symptoms** that may include **very low blood pressure** or **death**. If your child or you stop abacavir sulfate tablets for oral suspension for any other reason, even for a few days and your child or you are not allergic to abacavir sulfate, talk with your healthcare provider before taking or giving your child it again. Taking abacavir sulfate tablets for oral suspension again can cause a serious allergic or life-threatening reaction, even if your child or you never had an allergic reaction to it before.

If your healthcare provider tells you that you can take or give your child abacavir sulfate tablets for oral suspension again, start taking or giving it to your child when your child or you are around medical help or people who can call a healthcare provider if your child or you need one.

- 2. Lactic Acidosis (buildup of acid in the blood). Some human immunodeficiency virus (HIV) medicines, including abacavir sulfate, 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 or your child gets any of the following signs or symptoms of lactic acidosis:

- feel very weak or tired
- have unusual (not normal) muscle pain
- have trouble breathing
- have stomach pain with nausea and vomiting
- feel cold, especially in your arms and legs
- feel dizzy or light-headed
- have a fast or irregular heartbeat

- 3. Serious liver problems. Some people who have taken medicines like tablet for oral suspension have developed serious liver problems called hepatotoxicity, with liver enlargement (hepatomegaly) and fat in the liver (steatosis). Hepatomegaly with steatosis is a serious medical emergency that can cause death.**

Call your healthcare provider right away if you or your child gets any of the following signs or symptoms of liver problems:

- skin or the white part of eyes turns yellow (jaundice)
- urine turns dark
- bowel movements (stools) turn light in color
- don't feel like eating food for several days or longer
- feel sick to your stomach (nausea)
- 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.

What is Abacavir sulfate Tablets for Oral Suspension?

Abacavir sulfate is a prescription medicine used to treat HIV infection. Abacavir Sulfate is a medicine called a nucleoside analogue reverse transcriptase inhibitor (NRTI). Abacavir Sulfate is always used with other anti-HIV medicines. When used in combination with these other medicines, abacavir sulfate helps lower the amount of HIV found in your child's or your blood.

- **Abacavir Sulfate does not cure HIV infection or AIDS.**
- It is not know if abacavir sulfate 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 to see the doctor regularly while your child or you are taking abacavir sulfate tablets for oral suspension.

Who should not take Abacavir sulfate Tablets for Oral Suspension?

Do not take abacavir sulfate tablets for oral suspension if you or your child:

- **are allergic to abacavir or any of the ingredients in abacavir sulfate tablets for oral suspension. See the end of this Medication Guide for a complete list of ingredients in abacavir sulfate.**
- **have certain liver problems.**

What should I tell my healthcare provider before taking Abacavir sulfate Tablets for Oral Suspension?

Before starting abacavir sulfate, tell the 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**
- **have hepatitis B virus infection or have other liver problems**
- **have heart problems, smoke, or have diseases that increase your risk of heart disease such as high blood pressure, high cholesterol, or diabetes.**
- **are pregnant or plan to become pregnant.** It is not know if abacavir sulfate will harm your unborn child. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
- **are breastfeeding or plan to breast feed. Do not breastfeed.** We do not know if abacavir sulfate can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

Tell your healthcare provider about all the medicines your child or you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

Especially tell your healthcare provider if your child or you take:

- alcohol
- methadone
- ZIAGEN (abacavir sulfate)
- TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine)
- EPZICOM (abacavir sulfate and lamivudine)

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

Abacavir sulfate may affect the way other medicines work, and other medicines may affect how abacavir sulfate 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 Tablets for Oral Suspension?

- **Take or give abacavir sulfate tablets for oral suspension exactly as the healthcare provider tells you to take or give it.** The doctor 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 (See Table 1). For very young children who cannot swallow tablets, the following procedure can be used:

- The child's healthcare professional will decide the right dose and formulation based on the child's weight. The dose should not exceed the recommended adult dose.

Method of Preparation

1. Place the tablet(s) in a container and add two teaspoonfuls (10 mL) of water per tablet.
2. Swirl the container until 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 one 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 ABACAVIR TABLET FOR ORAL SUSPENSION WITH ANY LIQUID OTHER THAN WATER

- Older children, who can reliably swallow tablets, could be given the appropriate dose (see Table 1) to be swallowed.

Table 1: Dosing Recommendations for Abacavir Sulfate Tablets for Oral Suspension in Pediatric Patients

| Weight (kg) range | Dosage Regimen Using Scored 60 mg Tablets | | Total Daily Dose |
|-------------------|---|---------------------------------|------------------|
| | AM Dose | PM Dose | |
| 5 - < 6 | ½ tablet (30 mg) | 1 tablet (60 mg) | 90 mg |
| 6 - < 9 | 1 tablet (60 mg) | 1 tablet (60 mg) | 120 mg |
| 9 - < 12 | 1.5 tablets (90 mg) | 1.5 tablets (90 mg) | 180 mg |
| 12 - < 17 | 2 tablets (120 mg) | 2 tablets (120 mg) | 240 mg |
| 17 - < 20 | 2.5 tablets (150 mg) | 2.5 tablets (150 mg) | 300 mg |
| 20 - < 25 | 3 tablets (180 mg) | 3 tablets (180 mg) | 360 mg |
| 25 - < 29 | 3.5 tablets (210 mg) | 3.5 tablets (210 mg) | 420 mg |
| 29 - < 35 | 4 tablets (240 mg) | 4 tablets (240 mg) | 480 mg |
| ≥35 | 5 tablets (300 mg) ^a | 5 tablets (300 mg) ^a | 600 mg |

a For recommended doses of 300 mg twice daily (adult maximum daily dose), the adult formulation (300 mg tablet) can be used.

- Abacavir sulfate tablets for oral suspension should be taken on an empty stomach.
- Do not skip doses.
- **Do not let your abacavir sulfate tablets for oral suspension run out.**
- If your child or you stop the anti-HIV drugs, even for a short time, the amount of virus in the blood may increase and the virus may become harder to treat. If your child or you take too much abacavir sulfate **tablets for oral suspension**, call the healthcare provider or poison control center or go to the nearest hospital emergency room right away.

What are the possible side effects of Abacavir sulfate Tablets for Oral Suspension?

- **Abacavir Sulfate can cause serious side effects including allergic reactions, lactic acidosis, and liver problems. See "What is the most important information I should know about abacavir sulfate tablets for oral suspension?"**

- **Changes in immune system (Immune Reconstitution Syndrome).** Your immune system may get stronger and begin to fight infections that have been hidden in the body for a long time. Tell the healthcare provider if your child or you start having new or worse symptoms of infection after you or your child start taking abacavir sulfate.
- **Changes in body fat (fat redistribution).** Changes in body fat (lipoatrophy or lipodystrophy) can happen in some people taking antiretroviral medicines including abacavir sulfate Tablets for Oral Suspension.
These changes may include:
 - more fat in or around your trunk, upper back and neck (buffalo hump), breast, or chest
 - loss of fat in your legs, arms, or face
- **Heart attack (myocardial infarction).** Some HIV medicines including abacavir sulfate may increase your risk of heart attack.

The most common side effects of abacavir sulfate tablets for oral suspension in adults include:

- bad dreams or sleep problems
- nausea
- headache
- tiredness
- vomiting

The most common side effects of abacavir sulfate tablets for oral suspension in children include:

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

Tell your healthcare provider if you or your child have any side effect that bothers you or that does not go away.

These are not all the possible side effects of abacavir sulfate tablets for oral suspension. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Abacavir sulfate Tablets for Oral Suspension?

- Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].
- **Keep abacavir sulfate tablets for oral suspension and all medicines out of the reach of children.**

General information for safe and effective use of Abacavir sulfate Tablets for Oral Suspension

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

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

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

This Medication Guide summarizes the most important information about abacavir sulfate tablets for oral suspension. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for the information that is written for healthcare professionals.

For more information go to www.cipla.com or call 1-866-604-3268.

What are the ingredients in Abacavir sulfate Tablets for Oral Suspension?

Tablet for oral suspension:

Active ingredient: abacavir sulfate.

Inactive ingredients: microcrystalline cellulose (avicel PH 101), sodium starch glycolate, corn starch, hypromellose, microcrystalline cellulose (avicel PH 102), strawberry cream flavour, aspartame, colloidal silicon dioxide, and magnesium stearate.

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

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