3062-2015-12
Abacavir Oral Solution USP
2032867

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ABACAVIR Oral Solution, USP

Initial U.S. Approval: 1998

WARNING: HYPERSENSITIVITY REACTIONS, and LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY

See full prescribing information for complete boxed warning.

Hypersensitivity Reactions

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

Lactic Acidosis and Severe Hepatomegaly with Steatosis

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. (5.2)**

RECENT MAJOR CHANGES

Boxed Warning	09/2015
Indications and Usage (1)	09/2015
Dosage and Administration, Screening for HLA B*5701 Allele prior to Starting abacavir (2.1)	09/2015
Dosage and Administration, Recommended Dosage for Pediatric Patients (2.3)	03/2015
Contraindications (4)	09/2015
Warnings and Precautions, Hypersensitivity Reactions (5.1)	09/2015
Warnings and Precautions, Related Products that are Not Recommended (5.6)	03/2015

INDICATIONS AND USAGE

Abacavir oral solution, USP a nucleoside analogue human immunodeficiency virus (HIV 1) reverse transcriptase inhibitor, is indicated in combination with other antiretroviral agents for the treatment of HIV 1 infection. (1)

DOSAGE AND ADMINISTRATION

- Before taking abacavir, screen for the HLA B*5701 allele. (2.1)
- Adults: 600 mg daily, administered as either 300 mg twice daily or 600 mg once daily. (2.2)
- Pediatric Patients Aged 3 Months and Older: Administered either once or twice daily. Dose should be calculated on body weight (kg) and should not exceed 600 mg daily. (2.3)
- Patients with Hepatic Impairment: Mild hepatic impairment 200 mg twice daily. (2.4)

DOSAGE FORMS AND STRENGTHS

- Oral Solution: 20 mg per mL (3)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Immune reconstitution syndrome and redistribution/accumulation of body fat have been reported in patients treated with combination antiretroviral therapy. (5.3, 5.4)
- Administration of abacavir oral solution with other products containing abacavir is not recommended. (5.6)

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Hetero Labs Limited at 1 866 495 1995 or FDA at 1 800 FDA 1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Methadone: An increased methadone dose may be required in a small number of patients. (7.1)

USE IN SPECIFIC POPULATIONS

- Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: HYPERSENSITIVITY REACTIONS, and LACTIC ACIDOSIS, AND SEVERE HEPATOMEGALY

Hypersensitivity Reactions

Serious and sometimes fatal hypersensitivity reactions, with multiple organ involvement, have occured with abacavir.

Patients who carry the HLA B*5701 allele are at a higher risk of a hypersensitivity reaction to abacavir; although, hypersensitivity reactions have occurred in patients who do not carry the HLA B*5701 allele *[see Warnings and Precautions (5.1)]*.

Abacavir oral solution is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA B*5701 positive patients *[see Contraindications (4), Warnings and Precautions (5.1)]*. All patients should be screened for the HLA B*5701 allele prior to initiating therapy with abacavir oral solution or reinitiation of therapy with abacavir oral solution, unless patients have a previously documented HLA B*5701 allele assessment. Discontinue abacavir oral solution immediately if a hypersensitivity reaction is suspected, regardless of HLA B*5701 status and even when other diagnoses are possible *[see Contraindications (4), Warnings and Precautions (5.1)]*.

Following a hypersensitivity reaction to abacavir, NEVER restart abacavir oral solution or any other abacavir containing product because more severe symptoms, including death can occur within hours. Similar severe reactions have also occurred rarely following the reintroduction of abacavir containing products in patients who have no history of abacavir hypersensitivity *[see Warnings and Precautions (5.1)]*.

Lactic Acidosis and Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues and other antiretrovirals. Discontinue abacavir if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

Abacavir oral solution, USP in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV 1) infection.

2 DOSAGE AND ADMINISTRATION

2.1 Screening for HLAB*5701 Allele prior to Starting Abacavir

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

2.2 Recommended Dosage for Adults patients

The recommended oral dose of abacavir sulfate tablet for adults is 600 mg daily, administered as either 300 mg twice daily or 600 mg once daily, in combination with other antiretroviral agents.

2.3 Recommended Dosage for Pediatric Patients

The recommended dosage of abacavir oral solution in HIV 1 infected pediatric patients aged 3 months and older is 8 mg per kg orally twice daily or 16 mg per kg orally once daily (up to a maximum of 600 mg daily) in combination with other antiretroviral agents.

Abacavir is also available as a scored tablet for HIV 1 infected pediatric patients weighing greater than or equal to 14 kg for whom a solid dosage form is appropriate. Before prescribing abacavir tablets, children should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow abacavir tablets, the oral solution formulation should be prescribed. The recommended oral dosage of abacavir tablets for HIV 1 infected pediatric patients is presented in Table 1.

Table 1. Dosing Recommendations for Abacavir Scored Tablets in Pediatric Patients

Weight (kg)	Once daily Dosing Regimen[a]	Twice daily Dosing Regimen		
		AM Dose	PM Dose	Total Daily Dose
14 to <20	1 tablet (300 mg)	½ tablet (150 mg)	½ tablet (150 mg)	300 mg
≥20 to <25	1½tablets(450mg)	½ tablet (150 mg)	1 tablet (300 mg)	450 mg
≥25	2 tablets (600 mg)	1 tablet (300 mg)	1 tablet (300 mg)	600 mg

[a] Data regarding the efficacy of once daily dosing is limited to subjects who transitioned from twice daily dosing to once daily dosing after 36 weeks of treatment *[see Clinical Studies (14.2)]*.

2.4 Recommended Dosage for Patients with Hepatic Impairment

The recommended dose of abacavir in patients with mild hepatic impairment (Child Pugh Class A) is 200 mg twice daily. To enable dose reduction, abacavir oral solution (10 mL twice daily) should be used for the treatment of these patients. The safety, efficacy, and pharmacokinetic properties of abacavir have not been established in patients with moderate to severe hepatic impairment; therefore, abacavir is contraindicated in these patients.

3 DOSAGE FORMS AND STRENGTHS

Abacavir Oral Solution, USP contains 20 mg per mL of abacavir as abacavir sulfate, USP. The solution is clear yellowish, strawberry banana flavored liquid filled in 250 cc HDPE opaque bottles.

4 CONTRAINDICATIONS

Abacavir oral solution is contraindicated in patients:

- who have the HLA B*5701 allele *[see Warnings and Precautions (5.1)]*.
- with prior hypersensitivity reaction to abacavir *[see Warnings and Precautions (5.1)]*.
- with moderate or severe hepatic impairment *[see Use in Specific Populations (8.6)]*

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Serious and sometimes fatal hypersensitivity reactions have occurred with abacavir. These hypersensitivity reactions have included multi organ failure and anaphylaxis and typically occurred within the first 6 weeks of treatment with abacavir (median time to onset was 9 days); although abacavir hypersensitivity reactions have occurred any time during treatment *[see Adverse Reactions (6.1)].* Patients who carry the HLA B*5701 allele are at a higher risk of abacavir hypersensitivity reactions; although, patients who do not carry the HLA B*5701 allele have developed hypersensitivity reactions. Hypersensitivity to abacavir was reported in approximately 206 (8%) of 2,670 patients in 9 clinical trials with abacavir containing products where HLA B*5701 screening was not performed. The incidence of suspected abacavir hypersensitivity reactions in clinical trials was 1% when subjects carrying the HLA B*5701 allele were excluded. In any patient treated with abacavir, the clinical diagnosis of hypersensitivity reaction must remain the basis of clinical decision making.

Due to the potential for severe, serious, and possibly fatal hypersensitivity reactions with abacavir:

- All patients should be screened for the HLA B*5701 allele prior to initiating therapy with abacavir or reinitiation of therapy with abacavir, unless patients have a previously documented HLA B*5701 allele assessment.
- Abacavir oral solution is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA B*5701 positive patients.
- Before starting abacavir oral solution, review medical history for prior exposure to any abacavir containing product. NEVER restart abacavir oral solution or any other abacavir containing product following a hypersensitivity reaction to abacavir, regardless of HLA B*5701 status.
- To reduce the risk of a life threatening hypersensitivity reaction, regardless of HLA B*5701 status, discontinue abacavir immediately if a hypersensitivity reaction is suspected, even when other diagnoses are possible (e.g., acute onset respiratory diseases such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions to other medications).
- If a hypersensitivity reaction cannot be ruled out, do not restart abacavir oral solution or any other abacavir containing products because more severe symptoms which may include life threatening hypotension and death can occur within hours.
- If a hypersensitivity reaction is ruled out, patients may restart abacavir. Rarely, patients who have stopped abacavir for reasons other than symptoms of hypersensitivity have also experienced life threatening reactions within hours of reinitiating abacavir therapy. Therefore, reintroduction of abacavir oral solution or any other abacavir containing product is recommended only if medical care can be readily accessed.
- A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill.

5.2 Lactic Acidosis and Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Caution should be exercised when administering abacavir 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 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. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

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

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

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

5.6 Related Products that are Not Recommended

Abacavir oral solution is one of multiple abacavir containing products. Concomitant administration of abacavir oral solution with other products containing abacavir is not recommended.

6 ADVERSE REACTIONS

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

- Serious and sometimes fatal hypersensitivity reaction *[see Boxed Warning, Warnings and Precautions (5.1)]*.
- Lactic acidosis and severe hepatomegaly with steatosis *[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 in Adult Subjects

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

Serious and Fatal Abacavir associated Hypersensitivity Reactions

In clinical trials, serious and sometimes fatal hypersensitivity reactions have occurred with abacavir *[see Boxed Warning, Warnings and Precautions (5.1)]*. These reactions have been characterized by 2 or more of the following signs or symptoms: (1) fever; (2) rash; (3) gastrointestinal symptoms (including nausea, vomiting, diarrhea, or abdominal pain); (4) constitutional symptoms (including generalized malaise, fatigue, or achiness); (5) respiratory symptoms (including dyspnea, cough, or pharyngitis). Almost all abacavir hypersensitivity reactions include fever and/or rash as part of the syndrome.

Other signs and symptoms have included lethargy, headache, myalgia, edema, arthralgia, and paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure, myolysis, and death have occurred in association with these hypersensitivity reactions. Physical findings have included lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and maculopapular or urticarial rash (although some patients had other types of rashes and others did not have a rash). There were reports of erythema multiforme. Laboratory abnormalities included elevated liver chemistries, elevated creatine phosphokinase, elevated creatinine, and lymphopenia, and abnormal chest x ray findings (predominantly infiltrates, which were localized).

Additional Adverse Reactions with Use of Abacavir

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 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 to 4, Greater than or Equal to 5% Frequency) in Therapy naive Adults (CNA30024[a]) through 48 Weeks of Treatment

Adverse Reaction	Abacavir 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 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 to 4, Greater than or Equal to 5% Frequency) in Therapy naive Adults (CNA3005) through 48 Weeks of Treatment

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

Laboratory Abnormalities: Laboratory abnormalities (Grades 3 to 4) in therapy naive adults during therapy with abacavir 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 to 4) in Therapy naive Adults (CNA30024) through 48 Weeks of Treatment

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

ULN Upper limit of normal.

n Number of subjects assessed.

Laboratory abnormalities in CNA3005 are listed in Table 5.

Table 5. Treatment emergent Laboratory Abnormalities (Grades 3 to 4) in CNA3005

Grade 3/4 Laboratory Abnormalities	Abacavir plus Lamivudine/Zidovudine (n 262)	Indinavir plus Lamivudine/Zidovudine (n 264)
Elevated CPK (>4 x ULN)	18 (7%)	18 (7%)
ALT (>5 x ULN)	16 (6%)	16 (6%)
Neutropenia (<750/mm^3)	13 (5%)	13 (5%)
Hypertriglyceridemia (>750 mg/dL)	5 (2%)	3 (1%)
Hyperamylasemia (>2 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.

6.2 Clinical Trials Experience in Pediatric Subjects

Therapy experienced Pediatric Subjects (Twice daily Dosing)

Treatment emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a greater than or equal to 5% frequency during therapy with abacavir 8 mg per kg twice daily, lamivudine 4 mg per kg twice daily, and zidovudine 180 mg per m^2 twice daily compared with lamivudine 4 mg per kg twice daily and zidovudine 180 mg per m^2 twice daily from CNA3006 are listed in Table 6.

Table 6. Treatment emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2 to 4, Greater than or Equal to 5% Frequency) in Therapy experienced Pediatric Subjects (CNA3006) through 16 Weeks of Treatment

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

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

Other Adverse Events

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

Pediatric Subjects Once daily vs Twice daily Dosing (COL105677): The safety of once daily compared with twice daily dosing of abacavir was assessed in the ARROW trial. Primary safety assessment in the ARROW trial was based on Grade 3 and Grade 4 adverse events. The frequency of Grade 3 and 4 adverse events was similar among subjects randomized to once daily dosing compared with subjects randomized to twice daily dosing. One event of Grade 4 hepatitis in the once daily cohort was considered as uncertain causality by the investigator and all other Grade 3 or 4 adverse events were considered not related by the investigator.

6.3 Postmarketing Experience

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

Body as a Whole

Redistribution/accumulation of body fat.

Cardiovascular

Myocardial infarction.

Hepatic

Lactic acidosis and hepatic steatosis *[see Warnings and Precautions (5.2)]*.

Skin

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

There have also been reports of erythema multiforme with abacavir use *[see Adverse Reactions (6.1)]*.

7 DRUG INTERACTIONS

7.1 Methadone

In a trial of 11 HIV 1 infected subjects receiving methadone maintenance therapy with 600 mg of abacavir twice daily (twice the currently recommended dose), oral methadone clearance increased *[see Clinical Pharmacology (12.3)]*. This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: *Teratogenic effects:*

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to abacavir during pregnancy. Physicians are encouraged to register patients by calling the Antiretroviral Pregnancy Registry at 1 800 258 4263.

Risk Summary

Available data from the Antiretroviral Pregnancy Registry show no difference in the risk of overall major birth defects for abacavir compared with the background rate for major birth defects of 2.7% in the US reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). Abacavir produced fetal malformations and other embryonic and fetal toxicities in rats at 35 times the human exposure at the recommended clinical dose. The relevance of animal findings to human pregnancy registry data is not known.

Data

Human Data: Based on prospective reports from the Antiretroviral Pregnancy Registry of over 2,000 exposures to abacavir during pregnancy resulting in live births (including over 900 exposed in the first trimester), there was no difference between abacavir and overall birth defects compared with the background birth defect rate of 2.7% in the US reference population of the MACDP. The prevalence of defects in the first trimester was 3% (95% CI: 2% to 4.4%).

Animal Data: 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.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV 1 infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV 1 infection. Because of the potential for HIV 1 transmission, mothers should be instructed not to breastfeed.

8.4 Pediatric Use

The safety and effectiveness of abacavir have been established in pediatric patients aged 3 months and older. Use of abacavir is supported by pharmacokinetic trials and evidence from adequate and well controlled trials of abacavir in adults and pediatric subjects *[see Dosage and Administration (2.2), Adverse Reactions (6.2), Clinical Pharmacology (12.3), Clinical Studies (14.2)]*.

8.5 Geriatric Use

Clinical trials of abacavir did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of abacavir in elderly patient reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Patients with Impaired Hepatic Function

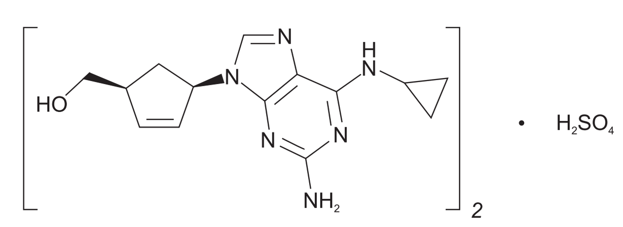
A dose reduction is required for patients with mild hepatic impairment (Child Pugh Class A) *[see Dosage and Administration (2.4)]*. The safety, efficacy, and pharmacokinetic properties of abacavir have not been established in patients with moderate or severe hepatic impairment; therefore, abacavir is contraindicated in these patients *[see Contraindications (4), Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There is no known specific treatment for overdose with abacavir. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required. It is not known whether abacavir can be removed by peritoneal dialysis or hemodialysis.

11 DESCRIPTION

Abacavir sulfate, USP is a synthetic carbocyclic nucleoside analogue with inhibitory activity against HIV 1. The chemical name of abacavir sulfate, USP is (1S,4R) 4 [2 Amino 6 (cyclopropylamino) 9*H* purin 9 yl] 2 cyclopentene 1 methanol sulfate (salt) (2:1). Abacavir sulfate USP is the enantiomer with 1S, *4R* absolute configuration on the cyclopentene ring. It has a molecular formula of $(C_{14}H_{18}N_6O)_2 \cdot H_2SO_4$ and a molecular weight of 670.74 daltons. It has the following structural formula:



Abacavir sulfate, USP is a white to off white powder. Soluble in water, slightly soluble in methanol. It has an octanol per water (pH 3.3) partition coefficient (log *P*) of approximately 1.0 by UV spectrometry at 25°C.f

Abacavir oral solution, USP is for oral administration. Each milliliter (1 mL) of abacavir oral solution, USP contains abacavir sulfate USP equivalent to 20 mg of abacavir (i.e., 20 mg per mL) as active ingredient and the following inactive ingredients: anhydrous citric acid, methylparaben and propylparaben (added as preservatives), propylene glycol, saccharin sodium, sodium citrate (dihydrate), noncrystallizing sorbitol solution, strawberry and banana flavors and water.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Abacavir is an antiretroviral agent *[See Microbiology (12.4)]*.

12.3 Pharmacokinetics

Pharmacokinetics in Adults

The pharmacokinetic properties of abacavir were independent of dose over the range of 300 to 1,200 mg per day.

Absorption and Bioavailability: Following oral administration, abacavir is rapidly absorbed and extensively distributed. The geometric mean absolute bioavailability of the tablet was 83%. Plasma abacavir AUC was similar following administration of the oral solution or tablets. After oral administration of 300 mg twice daily in 20 subjects, the steady state peak serum abacavir concentration (C_{max}) was 3 ± 0.89 mcg per mL (mean ± SD) and $AUC_{(0\ to\ 12\ hr)}$ was 6.02 ± 1.73 mcg•hr per mL. After oral administration of a single dose of 600 mg of abacavir in 20 subjects, C_{max} was 4.26 ± 1.19 mcg per mL (mean ± SD) and AUC8 was 11.95 ± 2.51 mcg•hr per mL.

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

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

Metabolism and Elimination: 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 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 per hour per kg (mean ± SD).

Effects of Food on Oral Absorption

Bioavailability of abacavir tablets was assessed in the fasting and fed states with no significant difference in systemic exposure (AUC_{∞}); therefore, abacavir tablets may be administered with or without food. Systemic exposure to abacavir was comparable after administration of abacavir oral solution and abacavir tablets. Therefore, these products may be used interchangeably.

Special Populations

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

Hepatic Impairment: The pharmacokinetics of abacavir have been studied in subjects with mild hepatic impairment (Child Pugh Class A). 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 *[see Contraindications (4), Use in Specific Populations (8.6)]*.

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

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

Geriatric Patients: The pharmacokinetics of abacavir have not been studied in subjects older than 65 years.

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

Ethanol: Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol decreases the elimination of abacavir causing an increase in overall exposure. Due to the 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 per kg ethanol (equivalent to 5 alcoholic drinks), and abacavir 600 mg plus 0.7 g per kg ethanol. Coadministration of ethanol and abacavir resulted in a 41% increase in abacavir AUC8 and a 26% increase in abacavir t1/2. 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 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 *[see Drug Interactions (7)]*. 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.

Antiviral Activity

The antiviral activity of abacavir against HIV 1 was assessed in a number of cell lines including primary monocytes/macrophages and peripheral blood mononuclear cells (PBMCs). EC_{50} values ranged from 3.7 to 5.8 µM (1 microM 0.28 mcg per mL) and 0.07 to 1 microM against HIV 1_{IIIB} and HIV 1_{BAL}, respectively, and was 0.26 ± 0.18 microM against 8 clinical isolates. The median EC_{50} values of abacavir were 344 nM (range: 14.8 to 676 nM), 16.9 nM (range: 5.9 to 27.9 nM), 8.1 nM (range: 1.5 to 16.7 nM), 356 nM (range: 35.7 to 396 nM), 105 nM (range: 28.1 to 168 nM), 47.6 nM (range: 5.2 to 200 nM), 51.4 nM (range: 7.1 to 177 nM), and 282 nM (range: 22.4 to 598 nM) against HIV 1 clades A G and group O viruses (n 3 except n 2 for clade B), respectively. The EC50 values against HIV 2 isolates (n 4), ranged from 0.024 to 0.49 microM. The antiviral activity of abacavir in cell culture was not antagonized when combined with the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine or zidovudine, the non nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, or the protease inhibitor (PI) amprenavir. Ribavirin (50 microM) used in the treatment of chronic HCV infection had no effect on the anti HIV 1 activity of abacavir in cell culture.

Resistance

HIV 1 isolates with reduced susceptibility to abacavir have been selected in cell culture. Genotypic analysis of isolates selected in cell culture and recovered from abacavir treated subjects demonstrated that amino acid substitutions K65R, L74V, Y115F, and M184V/I emerged in HIV 1 RT. M184V or I substitutions resulted in an approximately 2 fold decrease in susceptibility to abacavir. Substitutions K65R, L74M, or Y115F with M184V or I conferred a 7 to 8 fold reduction in abacavir susceptibility, and combinations of three substitutions were required to confer more than an 8 fold reduction in susceptibility.

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

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 and tenofovir in cell culture and in subjects. An increasing number of thymidine analogue mutation substitutions (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 of 600 mg.

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 did not affect male or female fertility in rats at a dose associated with exposures approximately 8 times higher than the exposure in humans at the dose of 600 mg.

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 Adult trials

Therapy naive Adults

CNA30024 was a multicenter, double blind, controlled trial in which 649 HIV 1 infected, therapy naive adults were randomized and received either abacavir (300 mg twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once daily); or zidovudine (300 mg twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once daily). The duration of double blind treatment was at least 48 weeks. Trial participants were male (81%), white (51%), black (21%), and Hispanic (26%). The median age was 35 years; the median pretreatment CD4+ cell count was 264 cells per mm^3, and median plasma HIV 1 RNA was 4.79 log_{10} copies per mL. The outcomes of randomized treatment are provided in Table 7.

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

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

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

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

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

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

CNA3005 was a multicenter, double blind, controlled trial in which 562 HIV 1 infected, therapy naive adults were randomized to receive either abacavir (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 per mL and plasma HIV 1 RNA greater than 100,000 copies per mL. Trial participants were male (87%), white (73%), black (15%), and Hispanic (9%). At baseline the median age was 36 years, the median baseline CD4+ cell count was 360 cells per mm^3, and median baseline plasma HIV 1 RNA was 4.8 log_{10} copies per mL. Proportions of subjects with plasma HIV 1 RNA less than 400 copies per 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 plus Lamivudine/Zidovudine (n 282)	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 less than 400 copies per mL.

[b] Includes viral rebound and failure to achieve confirmed less than 400 copies per 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 plus Lamivudine/Zidovudine (n 282)		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 per mL, percentages of subjects with HIV 1 RNA levels less than 50 copies per 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 per mm^3 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%), white (54%), black (27%), and American Hispanic (15%). The median baseline CD4+ cell count was 262 cells per mm^3 (range 21 to 918 cells per mm^3) and the median baseline plasma HIV 1 RNA was 4.89 log_{10} copies per mL (range: 2.60 to 6.99 log_{10} copies per mL).

The outcomes of randomized treatment are provided in Table 10.

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

Outcome	Abacavir 600 mg q.d. plus EPIVIR® plus Efavirenz (n 384)	Abacavir 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 less than 50 copies per mL (less than400 copies per mL) through Week 48 (Roche AMPLICOR Ultrasensitive HIV 1 MONITOR standard test version 1).

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

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

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

14.2 Pediatric Trials

Therapy experienced Pediatric Subjects

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

Once daily Dosing

ARROW (COL105677) was a 5 year randomized, multicenter trial which evaluated multiple aspects of clinical management of HIV 1 infection in pediatric subjects. HIV 1 infected, treatment naive subjects aged 3 months to 17 years were enrolled and treated with a first line regimen containing abacavir and lamivudine, dosed twice daily according to World Health Organization recommendations. After a minimum of 36 weeks of treatment, subjects were given the option to participate in Randomization 3 of the ARROW trial, comparing the safety and efficacy of once daily dosing with twice daily dosing of abacavir and lamivudine, in combination with a third antiretroviral drug, for an additional 96 weeks. Of the 1,206 original ARROW subjects, 669 participated in Randomization 3. Virologic suppression was not a requirement for participation at baseline for Randomization 3 (following a minimum of 36 weeks of twice daily treatment), 75% of subjects in the twice daily cohort were virologically suppressed compared with 71% of subjects in the once daily cohort.

The proportions of subjects with HIV 1 RNA less than 80 copies per mL through 96 weeks are shown in Table 11. The differences between virologic responses in the two treatment arms were comparable across baseline characteristics for gender and age.

Table 11. Virologic Outcome of Randomized Treatment at Week 96[a] (ARROW Randomization [3])

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

[a] Analyses were based on the last observed viral load data within the Week 96 window.

[b] Predicted difference (95% CI) of response rate is 4.5% (11% to 2%) at Week 96.

[c] Includes subjects who discontinued due to lack or loss of efficacy or for reasons other than an adverse event or death, and had a viral load value of greater than or equal to 80 copies per mL, or subjects who had a switch in background regimen that was not permitted by the protocol.

[d] Other includes reasons such as withdrew consent, loss to follow up, etc. and the last available HIV 1 RNA less than 80 copies per mL (or missing).

16 HOW SUPPLIED/STORAGE AND HANDLING

Abacavir oral solution USP is a clear yellowish, strawberry banana flavored liquid filled in 250 cc HDPE opaque bottles. Each mL of the solution contains abacavir sulfate USP equivalent to 20 mg of abacavir. They are supplied in:

Bottles of 240 mL with Expanded PE Wad (NDC 68554 3062 0).

Bottles of 240 mL with Induction Sealing FSE Wad (NDC 68554 3062 1).

This product does not require reconstitution.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. DO NOT FREEZE. May be refrigerated.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA approved patient labeling (Medication Guide).

Hypersensitivity Reactions

Inform patients:

- that a Medication Guide and Warning Card summarizing the symptoms of the abacavir hypersensitivity reaction and other product information will be dispensed by the pharmacist with each new prescription and refill of abacavir oral solution, and instruct the patient to read the Medication Guide and Warning Card every time to obtain any new information that may be present about abacavir. The complete text of the Medication Guide is reprinted at the end of this document.
- to carry the Warning Card with them.
- how to identify a hypersensitivity reaction *[see Warnings and Precautions (5.1), Medication Guide]*.
- that if they develop symptoms consistent with a hypersensitivity reaction they should call their healthcare provider right away to determine if they should stop taking abacavir oral solution.
- that a hypersensitivity reaction can worsen and lead to hospitalization or death if abacavir is not immediately discontinued.
- that in one trial, more severe hypersensitivity reactions were seen when abacavir was dosed 600 mg once daily.
- to not restart abacavir oral solution 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 is stopped right away.
- that if they have interrupted abacavir 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 oral solution or any other abacavir containing product without medical consultation and only if medical care can be readily accessed by the patient or others.

Related Products that are Not Recommended

Inform patients that they should not take abacavir with EPZICOM®, TRIUMEQ®, or TRIZIVIR®.

Lactic Acidosis/Hepatomegaly

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

Immune Reconstitution Syndrome

In some patients with advanced HIV infection, signs and symptoms of inflammation from previous infections may occur soon after anti HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. Advise patients to inform their healthcare provider immediately of any symptoms of infection *[see Warnings and Precautions (5.3)]*.

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

Inform patients that abacavir is not a cure for HIV 1 infection and patients may continue to experience illnesses associated with HIV 1 infection, including opportunistic infections. Patients must remain on continuous HIV therapy to control HIV 1 infection and decrease HIV related illness. Inform patients that sustained decreases in plasma HIV 1 RNA have been associated with a reduced risk of progression to AIDS and death.

Advise patients to remain under the care of a physician when using abacavir.

Advise patients to take all HIV medications exactly as prescribed. Instruct patients that if they miss a dose, they should take it as soon as they remember. If they do not remember until it is time for the next dose, they should be instructed to skip the missed dose and go back to the regular schedule. Patients should not double their next dose or take more than the prescribed dose.

Advise patients to avoid doing things that can spread HIV 1 infection to others.

Advise patients not to re use or share needles or other injection equipment.

Advise patients not to share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.

Advise patients to always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

Female patients should be advised not to breastfeed. Mothers with HIV 1 should not breastfeed because HIV 1 can be passed to the baby in the breast milk.

Instruct patients to read the Medication Guide before starting abacavir and to reread it each time the prescription is renewed. Instruct patients to inform their physician or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.

Manufactured by:
HETERO™
HETERO LABS LIMITED
22 110, I.D.A., Jeedimetla,
Hyderabad 500055, India.

Revised: December, 2015

2032867

MEDICATION GUIDE
Abacavir oral solution USP
(ah-BAH-kah-veer)

What is the most important information I should know about abacavir oral solution?

Abacavir can cause serious side effects, including:

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

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

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

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

If you stop abacavir oral solution because of an allergic reaction, never take abacavir oral solution or any other abacavir containing medicine (EPZICOM, TRIUMEQ and TRIZIVIR) again.

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

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

- **Build up of acid in your blood (lactic acidosis).** Lactic acidosis can happen in some people who take abacavir oral solution. Lactic acidosis is a serious medical emergency that can cause death. **Call your healthcare provider right away if you get any of the following symptoms that could be signs of lactic acidosis:**
  - feel very weak or tired
  - unusual (not normal) muscle pain
  - trouble breathing
  - stomach pain with nausea and vomiting
  - feel cold, especially in your arms and legs
  - feel dizzy or light headed
  - have a fast or irregular heartbeat
- **Serious liver problems** can happen in people who take abacavir. In some cases, these serious liver problems can lead to death. Your liver may become large (hepatomegaly) and you may develop fat in your liver (steatosis) when you take abacavir. **Call your healthcare provider right away if you have any of the following signs of liver problems:**
  - your skin or the white part of your eyes turns yellow (jaundice)
  - dark or "tea colored" urine turns
  - light colored stools (bowel movements)
  - loss of appetite for several days or longer
  - nausea
  - pain, aching, or tenderness on the right side of your stomach area

You may be more likely to get lactic acidosis or serious liver problems if you are female, very overweight (obese), or have been taking nucleoside analogue medicines for a long time.

What is abacavir oral solution?

Abacavir oral solution is a prescription HIV 1 (Human Immunodeficiency Virus type 1) medicine used with other antiretroviral medicines to treat HIV 1 infection. HIV 1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

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

When used with other antiretroviral medicines to treat HIV 1 infection, abacavir oral solution may help:

- reduce the amount of HIV 1 in your blood. This is called "viral load".
- increase the number of CD4+ (T) cells in your blood, that help fight off other infections.

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

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

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

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

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

Who should not take abacavir oral solution?

Do not take abacavir oral solution if you:

- have a certain type of gene variation called the HLA B*5701 allele. Your healthcare provider will test you for this before prescribing treatment with abacavir.
- are allergic to abacavir or any of the ingredients in abacavir oral solution. See the end of this Medication Guide for a complete list of ingredients in abacavir oral solution.
- have liver problems.

What should I tell my healthcare provider before taking abacavir oral solution?

Before you take abacavir oral solution, tell your healthcare providers if you:

- have been tested and know whether or not you have a particular gene variation called HLA B*5701.
- have or have had liver problems, including hepatitis B or C virus infection.
- have 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.
- drink alcohol or take medicines that contain alcohol.
- are pregnant or plan to become pregnant. Taking abacavir during pregnancy has not been associated with an increased risk of birth defects. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
- **Pregnancy Registry.** There is a pregnancy registry for women who take antiretroviral medicines during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.
- are breastfeeding or plan to breastfeed. **Do not breastfeed if you take abacavir.**
- You should not breastfeed if you have HIV 1 because of the risk of passing HIV 1 to your baby.

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

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

You should not take abacavir oral solution if you also take:

- abacavir (EPZICOM, TRIUMEQ, or TRIZIVIR)

Tell your healthcare provider if you take:

- any other medicine to treat HIV 1
- methadone

How should I take abacavir oral solution?

- **Take abacavir oral solution exactly as your healthcare provider tells you.**
- Do not change your dose or stop taking abacavir without talking with your healthcare provider. If you miss a dose of abacavir, take it as soon as you remember. Do not take 2 doses at the same time. If you are not sure about your dosing, call your healthcare provider.
- Stay under the care of a healthcare provider while taking abacavir.
- Abacavir oral solution may be taken with or without food.
- For children aged 3 months and older, your healthcare provider will prescribe a dose of abacavir based on your child's body weight.
- Do not run out of abacavir. The virus in your blood may increase and the virus may become harder to treat. When your supply starts to run out, get more from your healthcare provider or pharmacy.
- If you take too much abacavir, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of abacavir oral solution?

- **Abacavir can cause serious side effects including:**
- **See "What is the most important information I should know about abacavir oral solution?"**
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when your start taking HIV 1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having new or worse symptoms of infection after you start taking abacavir oral solution.
- **Changes in body fat** can happen in people who take HIV 1 medicines. These changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the middle of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The exact cause and long term health effects of these conditions are not known.
- **Heart attack (myocardial infarction).** Some HIV 1 medicines including abacavir may increase your risk of heart attack.

The most common side effects of abacavir in adults include:

- nausea
- headache
- generally not feeling well
- tiredness
- vomiting
- bad dreams or sleep problems

The most common side effects of abacavir in children include:

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

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

These are not all the possible side effects of abacavir. 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 oral solution?

- Store abacavir oral solution at room temperature, between 20° to 25°C (68° to 77°F).
- Do not freeze abacavir oral solution. You may store abacavir oral solution in a refrigerator.

Keep abacavir oral solution and all medicines out of the reach of children.

General information for safe and effective use of abacavir

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

If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for the information about abacavir that is written for healthcare professionals.

What are the ingredients in abacavir oral solution?

Active ingredient: abacavir sulfate USP

Inactive ingredients: anhydrous citric acid, methylparaben and propylparaben (added as preservatives), propylene glycol, saccharin sodium, sodium citrate (dihydrate), noncrystallizing sorbitol solution, strawberry and banana flavors and water.

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

Manufactured by:
HETERO™
HETERO LABS LIMITED
22 110, I.D.A., Jeedimetla,
Hyderabad 500055, India.

Revised: December, 2015