

Abacavir Sulfate Tablets 300 mg
ABAMUNE

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

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 ABAMUNE 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 ABAMUNE IF HYPERSENSITIVITY CANNOT BE RULED OUT, EVEN WHEN OTHER DIAGNOSES ARE POSSIBLE.

FOLLOWING A HYPERSENSITIVITY REACTION TO ABACAVIR, NEVER RESTART ABAMUNE OR ANY OTHER ABACAVIR-CONTAINING PRODUCT BECAUSE MORE SEVERE SYMPTOMS CAN OCCUR WITHIN HOURS AND MAY INCLUDE LIFE-THREATENING HYPOTENSION AND DEATH.

REINTRODUCTION OF ABAMUNE 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).

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING ZIAGEN AND OTHER ANTIRETROVIRALS (see WARNINGS AND PRECAUTIONS).

COMPOSITION

ABAMUNE Tablet 300 mg

Each film-coated tablet contains:

Abacavir sulfate 300 mg

DOSAGE FORM

Oral tablet

PHARMACOLOGY

Pharmacodynamics

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 .

Pharmacokinetics

The pharmacokinetic properties of abacavir have been studied in asymptomatic, HIV-1-infected adult patients after administration of a single intravenous (I.V.) 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 is rapidly and extensively absorbed after oral administration. The geometric mean absolute bioavailability of the tablet is 83%. After oral administration of 300 mg twice daily in 20 patients, the steady-state peak serum abacavir concentration (C_{max} was 3.0 ± 0.89 mcg/mL (mean \pm S.D.) 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 patients, 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 I.V. administration of abacavir is 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 the erythrocytes.

Metabolism: In humans, abacavir is not significantly metabolized by cytochrome (CYP) 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 study following administration of a 600-mg dose of ¹⁴C-abacavir: 99% of the radioactivity was recovered, 1.2% was excreted in the urine as abacavir, 30% as the 5'-carboxylic acid metabolite, 36% as the 5'-glucuronide metabolite, and 15% as unidentified minor metabolites in the urine. Fecal elimination accounted for 16% of the dose.

In single-dose studies, 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: Bioavailability of abacavir tablets was assessed in the fasting and fed states. There was no significant difference in systemic exposure (AUC_{∞}) in the fed and fasting states; therefore, **ABAMUNE Tablets** may be administered with or without food. Systemic exposure to abacavir was comparable after the 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 has been studied in patients 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. A dose of 200 mg (provided by 10 mL of abacavir oral solution) administered twice daily is recommended for patients with mild liver disease. The safety, efficacy, and pharmacokinetics of abacavir have not been studied in patients with moderate or severe hepatic impairment; therefore, **ABAMUNE Tablet** is contraindicated in these patients.

Pediatric Patients: The pharmacokinetics of abacavir have been studied after either single or repeat doses of abacavir in 68 pediatric patients. Following

multiple-dose administration of abacavir 8 mg/kg twice daily, the steady-state AUC_(0–12 hr) and C_{max} were 9.8 ± 4.56 mcg·hr/mL and 3.71 ± 1.36 mcg/mL (mean ± S.D.), respectively (see **WARNINGS AND PRECAUTIONS**).

In addition, to support dosing of abacavir scored tablet (300 mg) for pediatric patients 14 to greater than 30 kg, analysis of actual and simulated pharmacokinetic data indicated comparable exposures are expected following administration of 300 mg scored tablet and the 8 mg/kg dosing regimen using oral solution.

Geriatric Patients: The pharmacokinetics of abacavir has 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) patients 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.

INDICATIONS

ABAMUNE Tablet, in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV-1) infection.

Additional important information on the use of abacavir for treatment of HIV-1 infection:

- Abacavir is one of multiple products containing abacavir. Before starting abacavir, 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.

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.

ABAMUNE Tablet may be taken with or without food.

Adult Patients

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

Pediatric Patients

The recommended oral dose of abacavir in HIV-1-infected pediatric patients aged 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.

Before prescribing abacavir tablet, children should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow abacavir tablet, the oral solution formulation should be prescribed. The recommended oral dosage of abacavir tablet for HIV-1-infected pediatric patients is presented in Table 1.

Table 1. Dosing Recommendations for Abacavir Tablet in Pediatric Patients

Weight (kg)	Dosage Regimen Using Scored Tablet		Total Daily Dose
	AM Dose	PM Dose	
14 to 21	½ tablet (150 mg)	½ tablet (150 mg)	300 mg
>21 to <30	½ tablet (150 mg)	1 tablet (300 mg)	450 mg
≥30	1 tablet (300 mg)	1 tablet (300 mg)	600 mg

Patients with Hepatic Impairment:

The recommended dose of **ABAMUNE** in patients with mild hepatic impairment (Child-Pugh score: 5 to 6) 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 and, therefore, **ABAMUNE** is contraindicated in these patients.

CONTRAINDICATIONS

ABAMUNE is contraindicated in patients with previously demonstrated hypersensitivity to abacavir or any other component of the product. NEVER restart **ABAMUNE** or any other abacavir-containing product following a hypersensitivity reaction to abacavir, regardless of HLA-B*5701 status (**see WARNINGS AND PRECAUTIONS, UNDESIRABLE EFFECTS**).

ABAMUNE is contraindicated in patients with moderate or severe hepatic impairment.

WARNINGS AND PRECAUTIONS

Drug Interactions

Ethanol: Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol decreases the elimination of abacavir causing an increase in overall exposure.

Methadone: The addition of methadone has no clinically significant effect on the pharmacokinetic properties of abacavir. In a study of 11 HIV-1-infected patients receiving methadone-maintenance therapy with 600 mg of abacavir twice daily (twice the currently recommended dose), oral methadone clearance increased.

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.

Hypersensitivity Reaction

Serious and sometimes fatal hypersensitivity reactions have been associated with Abacavir 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 **ABAMUNE** if hypersensitivity cannot be ruled out, even when other diagnoses are possible. Important information on signs and symptoms of hypersensitivity, as well as clinical management, is presented below.

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

Group 1: Fever

Group 2: Rash

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

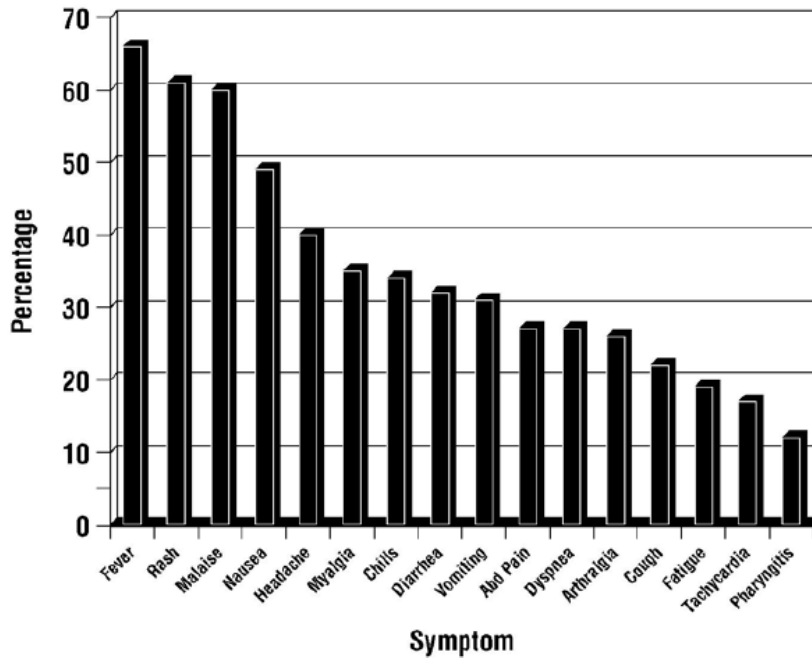
Group 4: Constitutional (including generalized malaise, fatigue, or achiness)

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

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

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

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



Other less common signs and symptoms of hypersensitivity include lethargy, myolysis, edema, abnormal chest x-ray findings (predominantly infiltrates, which can be localized), and paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure, and death have occurred in association with hypersensitivity reactions. In one study, 4 patients (11%) receiving abacavir 600 mg once daily experienced hypotension with a hypersensitivity reaction compared with 0 patients receiving abacavir 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 **ABAMUNE** as soon as a hypersensitivity reaction is suspected. To minimize the risk of a life-threatening hypersensitivity reaction, permanently discontinue **ABAMUNE** 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 **ABAMUNE** 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 **ABAMUNE** has been discontinued for reasons other than symptoms of a hypersensitivity reaction, and if reinitiation of **ABAMUNE** or any other abacavir-containing product is under consideration, carefully evaluate the reason for discontinuation of **ABAMUNE** 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 **ABAMUNE**. If hypersensitivity cannot be ruled out, DO NOT reintroduce **ABAMUNE** 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 **ABAMUNE** or any other abacavir-containing product and that reintroduction of **ABAMUNE** 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: Studies have shown that carriage of the HLA-B*5701 allele is associated with a significantly increased risk of a hypersensitivity reaction to abacavir. CNA106030 (PREDICT-1), a randomized, double-blind study, evaluated the clinical utility of prospective HLA-B*5701 screening on the incidence of abacavir hypersensitivity reaction in abacavir-naive HIV-1-infected adults (n = 1,650). In this study, use of pre-therapy screening for the HLA-B*5701 allele and exclusion of subjects with this allele reduced the incidence of clinically suspected abacavir hypersensitivity reactions from 7.8% (66/847) to 3.4% (27/803). Based on this study, it is estimated that 61% of patients with the HLA-B*5701 allele will develop a clinically suspected hypersensitivity reaction during the course of abacavir treatment compared with 4% of patients who do not have the HLA-B*5701 allele. Screening for carriage of the HLA-B*5701 allele is recommended prior to initiating treatment with abacavir. 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.

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 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).

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including **ABAMUNE**. 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.

Fat Redistribution

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

Myocardial Infarction:

In a published prospective, observational, epidemiological study designed to investigate the rate of myocardial infarction in patients on combination antiretroviral therapy, the use of abacavir within the previous 6 months was correlated with an increased risk of myocardial infarction (MI).

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).

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-to-rump length) were observed in rats at a dose which produced 35 times the human exposure, based on the 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 the AUC.

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

Lactation

The Centers for Disease Control and Prevention recommended that HIV-1 infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV infection. Although it is not known whether 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 **ABAMUNE** Tablet.

Pediatric Use

The safety and effectiveness of abacavir have been established in pediatric patients 3 months to 13 years of age. Use of abacavir in these age groups is supported by pharmacokinetic studies and evidence from adequate and well-controlled studies of abacavir in adults and pediatric patients (**see Dosage and Administration**).

Geriatric Use

Clinical studies of abacavir 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.

UNDESIRABLE EFFECTS

Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate. In one study, once-daily dosing of abacavir was associated with more severe hypersensitivity reactions (**see WARNINGS AND PRECAUTIONS**).

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 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) 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%†
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%

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

† 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 2-4, ≥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 patients 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, patients receiving abacavir once daily showed a rate of 9% in comparison with a rate of 7% for

patients receiving abacavir twice daily. However, patients receiving abacavir 600 mg once daily, experienced a significantly higher incidence of severe drug hypersensitivity reactions and severe diarrhea compared with patients who received abacavir 300 mg twice daily. Five percent (5%) of patients receiving abacavir 600 mg once daily had severe drug hypersensitivity reactions compared with 2% of patients receiving abacavir 300 mg twice daily. Two percent (2%) of patients receiving abacavir 600 mg once daily had severe diarrhea while none of the patients receiving abacavir 300 mg twice daily had this event.

Laboratory Abnormalities: Laboratory abnormalities (Grades 3-4) in therapy-naïve 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 3-4) 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%
Elevated AST (>5 X ULN)	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 patients 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 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 patients assessed.

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

Pediatric Patients: Therapy-Experienced Pediatric Patients: 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/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, ≥5% Frequency) in Therapy-Experienced Pediatric Patients (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 Study CNA3006, laboratory abnormalities (anemia, neutropenia, liver function test abnormalities, and CPK elevations) were

observed with similar frequencies as in a study of therapy-naive adults (CNA30024). Mild elevations of blood glucose were more frequent in pediatric patients receiving abacavir (CNA3006) as compared with adult patients (CNA30024).

Other Adverse Events: In addition to adverse reactions and laboratory abnormalities reported in Tables 1, 2, 3, 4, and 5, other adverse reactions observed in the expanded access program were pancreatitis and increased GGT.

Observed During Clinical Practice

In addition to adverse reactions reported from clinical trials, the following reactions have been identified during postmarketing use of abacavir. 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.

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.

OVERDOSAGE

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

PACKAGING INFORMATION

ABAMUNE Tablets 300 mg..... Container of 30 tablets

Last updated: October 2010