*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.

Therapy-Experienced Pediatric Patients: Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a ≥5% frequency during therapy with abacavir 8 mg/kg twice daily, lamivudine 4 mg/kg twice daily, and zidovudine 180 mg/m² twice daily compared with lamivudine 4 mg/kg twice daily and zidovudine 180 mg/m² twice daily from CNA3006 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-Experienced Pediatric Patients (CNA3006) Through 16 Weeks of Treatment

Adverse reactions	Abacavir+lamivudine + zidovudine (n=102)	Lamivudine + 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: Laboratory abnormalities (Grades 3-4) 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 3.

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

Grade 3 / 4 laboratory abnormalities	Abacavir + lamivudine + efavirenz (n=324)	Zidovudine + lamivudine + efavirenz (n=325)
Elevated CPK (>4 X ULN)	8%	8%
Elevated ALT (>5 X ULN)	6%	6%
Elevated AST (>5 X ULN)	6%	6%
Hypertriglyceridemia (>750 mg/dL)	6%	6%
Hyperamylasemia (>2 X ULN)	4%	5%
Neutropenia (ANC <750/mm³)	2%	4%
Anaemia (Hgb≤6.9 gm/dL)	<1%	2%
Thrombocytopenia (P1t <50,000/mm³)	1%	<1%
Leukopenia (WBC≤1, 500/mm³)	<1%	2%

ULN = Upper limit of normal
n = Number of patients assessed

Observed During Clinical Practice: In addition to adverse reactions reported from clinical trials, the following events have been identified during use of abacavir in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to their seriousness, frequency of reporting, potential causal connection to abacavir, or a combination of these factors.

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

Hepatic: Lactic acidosis and hepatic steatosis (see WARNINGS and PRECAUTIONS).

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.

Storage
Store below 30°C.

Presentation
ABAMUNE Container of 30 tablets
Container of 60 tablets

Last updated: August 2006

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Abacavir Tablets 300 mg

ABAMUNE

WARNING

HYPERSENSITIVITY REACTIONS: SERIOUS AND SOMETIMES FATAL. HYPERSENSITIVITY REACTIONS HAVE BEEN ASSOCIATED WITH ABACAVIR SULFATE. HYPERSENSITIVITY TO ABACAVIR IS A MULTI-ORGAN CLINICAL SYNDROME USUALLY CHARACTERISED BY A SIGN OR SYMPTOM IN TWO 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. 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: LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING ABAMUNE AND OTHER ANTIRETROVIRALS (SEE WARNINGS AND PRECAUTIONS).

COMPOSITION
Each film-coated tablet contains
Abacavir ..... 300 mg
as Abacavir sulfate

DOSAGE FORM
Oral tablets

PHARMACOLOGY

Pharmacodynamics

Mechanism of Action: Abacavir is a carbocyclic synthetic nucleoside analogue. Intracellularly, abacavir is converted by cellular enzymes to the active metabolite carbovir triphosphate (CBV-TP). (CBV-TP) is 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 nucleoside 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 alpha, beta and gamma.

Pharmacokinetics

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 ± SD) and $AUC_{(0-12\ hr)}$ was 6.02 ± 1.73 mcg·hr/mL. Bioavailability of abacavir tablets was assessed in the fasting and fed states. There was no significant difference in systemic exposure (AUC(infinity)) in the fed and fasting states; therefore, abacavir tablets may be administered with or without food.

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

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

Elimination: Elimination of abacavir was quantified in a mass balance study 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 studies, the observed elimination half-life ($t_{1/2}$) was 1.54 ± 0.63 hours.

DOSAGE AND ADMINISTRATION

ABAMUNE may be taken with or without food.

Adults:
The recommended oral dose for adults is 300 mg twice daily in combination with other antiretroviral agents.

Adolescents and Pediatric Patients:
The recommended oral dose of abacavir for adolescents and pediatric patients 3 months to 16 years of age is 8 mg/kg twice daily (up to a maximum of 300 mg twice daily) in combination with other antiretroviral agents.

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

CONTRAINDICATIONS

ABAMUNE Tablets are contraindicated in patients with previously demonstrated hypersensitivity to abacavir or any other component of the products (see WARNINGS and PRECAUTIONS). Following a hypersensitivity reaction to abacavir, NEVER restart ABAMUNE or any other abacavir-containing product. Fatal rechallenge reactions have been associated with readministration of abacavir to patients with a prior history of a hypersensitivity reaction to abacavir (see WARNINGS and PRECAUTIONS).

ABAMUNE Tablets are contraindicated in patients with moderate or severe hepatic impairment.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Serious and sometimes fatal hypersensitivity reactions have been associated with ABAMUNE and other abacavir-containing products. 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. Important information on signs and symptoms of hypersensitivity, as well as clinical management, is presented below.

Signs and Symptoms of Hypersensitivity: Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in two or more of the following groups.
Group 1: Fever
Group 2: Rash
Group 3: Gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain)
Group 4: Constitutional (including generalized malaise, fatigue, or achiness)
Group 5: Respiratory (including dyspnea, cough, or pharyngitis).
Hypersensitivity to abacavir following the presentation of a single sign or symptom has been reported infrequently.

Hypersensitivity to abacavir was reported in approximately 8% of 2,670 patients (n = 206) in 9 clinical trials (range: 2% to 9%). 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 two or more of the five groups listed above.

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.

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 hypersensitivity cannot be ruled out, DO NOT

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).

Therapy-experienced Patients
In clinical trials, patients with prolonged prior nucleoside reverse transcriptase inhibitor (NRTI) exposure or who had HIV-1 isolates that contained multiple mutations conferring resistance to NRTIs had limited response to abacavir. The potential for cross-resistance to abacavir and other NRTIs should be considered when choosing new therapeutic regimens in therapy – experienced patients.

Immune Reconstitution Syndrome: Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including abacavir sulfate. During the initial phase of combination antiretroviral treatment, patients whose immune system responds 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.

Drug Interactions
Pharmacokinetic properties of abacavir were not altered by the addition of either lamivudine or zidovudine or the combination of lamivudine and zidovudine. No clinically significant changes to lamivudine or zidovudine pharmacokinetics were observed following concomitant administration of abacavir.

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

The addition of methadone has no clinically significant effect on the pharmacokinetic properties of abacavir. In a study of 11 HIV-infected patients receiving methadone-maintenance therapy (40 mg and 90 mg daily) with 600 mg of abacavir 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.

Hepatic Impairment
Insufficient data are available to recommend a dosage of abacavir in patients with hepatic impairment.

Pregnancy
Category C. 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
It is recommended that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV infection. It is not known whether abacavir is excreted in human milk but it is secreted into the milk of lactating rats. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving abacavir.

UNDESIRABLE EFFECTS

Hypersensitivity Reactions

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).

Therapy-naive Adults: Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a e"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 1.

Table 1: Treatment-Emergent (all causality) Adverse Events of at Least Moderate Intensity (grades 2-4, ≥ 5% frequency) in Therapy-naïve adults (CNA30024*) Through 48 weeks of Treatment

Adverse Reactions	Abacavir + lamivudine + efavirenz (n=324)	Zidovudine + lamivudine + efavirenz (n=325)
Dreams/sleep disorders	10%	10%
Drug hypersensitivity	9%	<1%†
Headaches/migraine	7%	11%
Nausea	7%	11%
[illegible]	7%	10%