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ABAMUNE-L Tablets (Abacavir sulfate + Lamivudine)

Black Box Warnings

Hypersensitivity Reactions, Lactic Acidosis and Severe Hepatomegaly with Steatosis, and Exacerbations of Hepatitis B
Hypersensitivity Reactions
Serious and sometimes fatal hypersensitivity reactions, with multiple organ involvement, have occurred with abacavir, a component of abamune-l (abacavir and lamivudine) tablets.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)
Abacavir and lamivudine is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients (see contraindications, warnings and precautions). All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with abacavir/lamivudine or reinitiation of therapy with abacavir/lamivudine, unless patients have a previously documented HLA-B*5701 allele assessment. Discontinue ABAMUNE L immediately if a hypersensitivity reaction is suspected, regardless of HLA-B*5701 status and even when other diagnoses are possible (see contraindications, warnings and precautions).
Following a hypersensitivity reaction to abacavir and lamivudine, never restart abacavir and lamivudine 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).
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 and lamivudine if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur (see warnings and precautions).
Exacerbations of Hepatitis B
Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis b virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine, which is one component of abacavir and lamivudine. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue abacavir and lamivudine and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted (see warnings and precautions).

Composition

ABAMUNE-L

Each film-coated tablet contains:

Abacavir Sulphate equivalent to

Abacavir.....600mg

Lamivudine USP.....300mg

Description

ABAMUNE-L tablets contain 2 synthetic nucleoside analogues: abacavir and lamivudine with inhibitory activity against HIV-1.

Pharmacology

Pharmacodynamics

Abacavir: 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.
Lamivudine: Lamivudine is a synthetic nucleoside analogue. Intracellularly lamivudine is phosphorylated to its active 5′-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue.

Pharmacokinetics

Pharmacokinetics in Adults
Abacavir/Lamivudine: In a single-dose, 3-way crossover bioavailability trial of 1 abacavir/lamivudine tablet versus 2 abacavir tablets (2 x 300 mg) and 2 lamivudine tablets (2 x 150 mg) administered simultaneously in healthy subjects (n = 25), there was no difference in the extent of absorption, as measured by the area under the plasma concentration-time curve (AUC) and maximal peak concentration (C_{max}), of each component.
Abacavir: Following oral administration, abacavir is rapidly absorbed and extensively distributed. After oral administration of a single dose of 600 mg of abacavir in 20 subjects, C_{max} was 4.26 ± 1.19 mcg/mL (mean ± SD) and AUC_{∞} was 11.95 ± 2.51 mcg•hour per mL. 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. 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.
Lamivudine: Following oral administration, lamivudine is rapidly absorbed and extensively distributed. After multiple-dose oral administration of lamivudine 300 mg once daily for 7 days to 60 healthy subjects, steady-state C_{max} ($C_{max,ss}$) was 2.04 ± 0.54 mcg per mL (mean ± SD) and the 24-hour steady-state AUC ($AUC_{24,ss}$) was 8.87 ± 1.83 mcg•hour per mL. Binding to plasma protein is low. Approximately 70% of an intravenous dose of lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours).
In humans, abacavir and lamivudine are not significantly metabolized by cytochrome P450 enzymes.
The pharmacokinetic properties of abacavir and lamivudine in fasting subjects are summarized in Table 1.

Table 1. Pharmacokinetic parametersa for abacavir and lamivudine in adults

Parameter	Abacavir		Lamivudine	
Oral bioavailability (%)	86 ± 25	n = 6	86 ± 16	n = 12
Apparent volume of distribution (L/kg)	0.86 ± 0.15	n = 6	1.3 ± 0.4	n = 20
Systemic clearance (L/h/kg)	0.80 ± 0.24	n = 6	0.33 ± 0.06	n = 20
Renal clearance (L/h/kg)	0.007 ± 0.008	n = 6	0.22 ± 0.06	n = 20

Elimination half-life (h)	1.45 ± 0.32	n = 20	5 to 7[b]

[a] Data presented as mean ± standard deviation except where noted.

[b] Approximate range.

Effect of Food on Absorption of Abacavir/Lamivudine

Abacavir/lamivudine may be administered with or without food. Administration with a high-fat meal in a single-dose bioavailability trial resulted in no change in AUC_{last}, AUC_{∞}, and C_{max} for lamivudine. Food did not alter the extent of systemic exposure to abacavir (AUC_{∞}), but the rate of absorption (C_{max}) was decreased approximately 24% compared with fasted conditions (n = 25). These results are similar to those from previous trials of the effect of food on abacavir and lamivudine tablets administered separately.

Special Populations

Patients with Renal Impairment

Abacavir/lamivudine: The effect of renal impairment on the combination of abacavir and lamivudine has not been evaluated (see the prescribing information for the individual abacavir and lamivudine components).

Patients with Hepatic Impairment

Abacavir/lamivudine: The effect of hepatic impairment on the combination of abacavir and lamivudine has not been evaluated (see the prescribing information for the individual abacavir and lamivudine components)

Pregnant Women

Abacavir: Abacavir pharmacokinetics were studied in 25 pregnant women during the last trimester of pregnancy receiving abacavir 300 mg twice daily. Abacavir exposure (AUC) during pregnancy was similar to those in postpartum and in HIV-infected non-pregnant historical controls. Consistent with passive diffusion of abacavir across the placenta, abacavir concentrations in neonatal plasma cord samples at birth were essentially equal to those in maternal plasma at delivery.

Lamivudine: Lamivudine pharmacokinetics were studied in 36 pregnant women during 2 clinical trials conducted in South Africa. Lamivudine pharmacokinetics in pregnant women were similar to those seen in non-pregnant adults and in postpartum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples.

Geriatric Patients

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

Gender

There are no significant or clinically relevant gender differences in the pharmacokinetics of the individual components (abacavir or lamivudine) based on the available information that was analyzed for each of the individual components.

Race

There are no significant or clinically relevant racial differences in pharmacokinetics of the individual components (abacavir or lamivudine) based on the available information that was analyzed for each of the individual components.

Indications

ABAMUNE-L tablet is indicated for the treatment of HIV-1 infection in adults.

Dosage And Administration

▶ Screening for HLA-B*5701 Allele Prior to Starting ABAMUNE L

Screen for the HLA-B*5701 allele prior to initiating therapy with ABAMUNE L (see BOXED WARNING, WARNINGS

AND PRECAUTIONS).

▶ Recommended Dosage for Adult Patients

The recommended dosage of ABAMUNE-L for adults is one tablet taken orally once daily, in combination with other antiretroviral agents with or without food.

▶ Not Recommended Due to Lack of Dosage Adjustment

Because ABAMUNE L is a fixed-dose tablet and cannot be dose adjusted, ABAMUNE L is not recommended for:
patients with creatinine clearance less than 50 mL per minute(see USE IN SPECIAL POPULATIONS)
patients with mild hepatic impairment. ABAMUNE L is contraindicated in patients with moderate or severe hepatic impairment (see CONTRAINDICATIONS, USE IN SPECIALC POPULATIONS)

Contraindications

ABAMUNE-L tablet is contraindicated in patients
who have the HLA-B*5701 allele (see WARNINGS AND PRECAUTIONS).
with prior hypersensitivity reaction to abacavir (see WARNINGS AND PRECAUTIONS) or lamivudine.
with moderate or severe hepatic impairment. (see USE IN SPECIAL POPULATIONS).

Warnings And Precautions

▶ Drug Interactions

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. 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.
Sorbitol
Coadministration of single doses of lamivudine and sorbitol resulted in a sorbitol dose-dependent reduction in lamivudine exposures. When possible, avoid use of sorbitol-containing medicines with lamivudine-containing medicines.

▶ Hypersensitivity Reactions

Serious and sometimes fatal hypersensitivity reactions have occurred with abacavir, a component of Abacavir/lamivudine. 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 UNDESIRABLE EFFECTS). Patients who carry the HLA-B*5701 allele are at 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/lamivudine or reinitiation of therapy with Abacavir/lamivudine, unless patients have a previously documented HLA-B*5701 allele

assessment.

• Abacavir/lamivudine is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients.

• Before starting Abacavir/lamivudine, review medical history for prior exposure to any abacavir containing product. NEVER restart Abacavir/lamivudine 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/lamivudine 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/lamivudine 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/lamivudine. 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/lamivudine or any other abacavir-containing product is recommended only if medical care can be readily accessed.

▶ 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 including abacavir and lamivudine components of abacavir/lamivudine. A majority of these cases have been in women. Female sex and obesity may be risk factors for the development of lactic acidosis and severe hepatomegaly with steatosis in patients treated with antiretroviral nucleoside analogues See full prescribing information for abacavir and lamivudine. Treatment with Abacavir/lamivudine should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations)

▶ Patients with Hepatitis B Virus Co-Infection

Posttreatment Exacerbations of Hepatitis

Clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. See full prescribing information for lamivudine. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment.

Emergence of Lamivudine-Resistant HBV

Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in subjects dually infected with HIV-1 and HBV. Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-1-infected subjects who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus. See full prescribing information for lamivudine

▶ Use with Interferon- and Ribavirin-Based Regimens

Patients receiving interferon alfa with or without ribavirin and Abacavir/lamivudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of Abacavir/lamivudine should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child Pugh greater than 6) (see the complete prescribing information for interferon and ribavirin).

▶ Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including abacavir /lamivudine. During the initial phase of combination antiretroviral treatment, patients whose immune system respond may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia , 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.

▶ Myocardial Infarction

Several prospective, observational, epidemiological studies have reported an association with the use of abacavir and the risk of myocardial infarction (MI). Meta-analyses of randomized, controlled clinical trials have observed no excess risk of MI in abacavir-treated subjects as compared with control subjects. To date, there is no established biological mechanism to explain the potential increase in risk. In totality, the available data from the observational studies and from controlled clinical trials show inconsistency; therefore, evidence for a causal relationship between abacavir treatment and the risk of MI is 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).

▶ Patients with Impaired Renal Function

Abacavir/lamivudine is not recommended for patients with creatinine clearance <50 mL per min because Abacavir/lamivudine is a fixed-dose combination of (Abacavir/lamivudine) and the dosage of the individual components cannot be adjusted. If a dose reduction of lamivudine, a component of Abacavir/lamivudine, is required for patients with creatinine clearance less than 50 mL per min, then the individual components should be used.

▶ Patients with Impaired Hepatic Function

Abacavir/lamivudine is a fixed-dose combination and the dosage of the individual components cannot be adjusted. If a dose reduction of abacavir, a component of Abacavir/lamivudine, is required for patients with mild hepatic impairment (Child-Pugh Class A), then the individual components should be used.

The safety, efficacy, and pharmacokinetic properties of abacavir have not been established in patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment; therefore, abacavir/lamivudine is contraindicated in these patients (see CONTRAINDICATIONS).

▶ Pregnancy

Risk Summary

Available data from the Antiretroviral Pregnancy Registry show no difference in the overall risk of birth defects for abacavir or lamivudine compared with the background rate for major birth defects of 2.7% in the Metropolitan Atlanta Congenital Defects Program (MACDP) reference population. The APR uses the MACDP as the U.S. reference population for birth defects in the general population. The MACDP evaluates women and infants from a limited geographic area and does not include outcomes for births that occurred at less than 20 weeks gestation. The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15% to 20%. The background risk for major birth defects and miscarriage for the indicated

population is unknown.
In animal reproduction studies, oral administration of abacavir to pregnant rats during organogenesis resulted in fetal malformations and other embryonic and fetal toxicities at exposures 35 times the human exposure (AUC) at the recommended clinical daily dose. However, no adverse developmental effects were observed following oral administration of abacavir to pregnant rabbits during organogenesis, at exposures approximately 9 times the human exposure (AUC) at the recommended clinical dose. Oral administration of lamivudine to pregnant rabbits during organogenesis resulted in embryolethality at systemic exposure (AUC) similar to the recommended clinical dose; however, no adverse development effects were observed with oral administration of lamivudine to pregnant rats during organogenesis at plasma concentrations (C_{max}) 35 times the recommended clinical dose.
Data
Human Data
Abacavir: Based on prospective reports to the Antiretroviral Pregnancy Registry of over 2,000 exposures to abacavir during pregnancy resulting in live births (including over 1,000 exposed in the first trimester), there was no difference between the overall risk of birth defects for abacavir compared with the background birth defect rate of 2.7% in the US reference population of the MACDP. The prevalence of defects in live births was 2.9% (95% CI: 2.0% to 4.1%) following first trimester exposure to abacavir-containing regimens and 2.7% (95% CI: 1.9% to 3.7%) following second/third trimester exposure to abacavir-containing regimens.
Abacavir has been shown to cross the placenta and concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery.
Lamivudine: Based on prospective reports from the Antiretroviral Pregnancy Registry of over 11,000 exposures to lamivudine during pregnancy resulting in live births (including over 4,500 exposed in the first trimester), there was no difference between the overall risk of birth defects for lamivudine compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of birth defects in live births was 3.1% (95% CI: 2.6% to 3.6%) following first trimester exposure to lamivudine-containing regimens and 2.8% (95% CI: 2.5%, 3.3%) following second/third trimester exposure to lamivudine-containing regimens.
Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical trials conducted in South Africa. The trials assessed pharmacokinetics in 16 women at 36 weeks gestation using 150 mg lamivudine twice daily with zidovudine, 10 women at 38 weeks gestation using 150 mg lamivudine twice daily with zidovudine, and 10 women at 38 weeks gestation using lamivudine 300 mg twice daily without other antiretrovirals. These trials were not designed or powered to provide efficacy information. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, amniotic fluid specimens were collected following natural rupture of membranes and confirmed that lamivudine crosses the placenta in humans. Based on limited data at delivery, median (range) amniotic fluid concentrations of lamivudine were 3.9 (1.2 to 12.8)–fold greater compared with paired maternal serum concentration (n = 8).
Animal Data
Abacavir: Abacavir was administered orally to pregnant rats (at 100, 300, and 1,000 mg per kg per day) and rabbits (at 125, 350, or 700 mg per kg per day) during organogenesis (on gestation Days 6 through 17 and 6 through 20, respectively). Fetal malformations (increased incidences of fetal anasarca and skeletal malformations) or developmental toxicity (decreased fetal body weight and crown-rump length) were observed in rats at doses up to 1,000 mg per kg per day, resulting in exposures approximately 35 times the human exposure (AUC) at the recommended daily dose. No developmental effects were observed in rats at 100 mg per kg per day, resulting in exposures (AUC) 3.5 times the human exposure at the recommended daily dose. In a fertility and early embryo-fetal development study conducted in rats (at 60, 160, or 500 mg per kg per day), embryonic and fetal toxicities (increased resorptions, decreased fetal body weights) or toxicities to the offspring (increased incidence of stillbirth and lower body weights) occurred at doses up to

500 mg per kg per day. No developmental effects were observed in rats at 60 mg per kg per day, resulting in exposures (AUC) approximately 4 times the human exposure at the recommended daily dose. Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. In pregnant rabbits, no developmental toxicities and no increases in fetal malformations occurred at up to the highest dose evaluated, resulting in exposures (AUC) approximately 9 times the human exposure at the recommended dose.

Lamivudine: Lamivudine was administered orally to pregnant rats (at 90, 600, and 4,000 mg per kg per day) and rabbits (at 90, 300 and 1,000 mg per kg per day and at 15, 40, and 90 mg per kg per day) during organogenesis (on gestation Days 7 through 16 and 8 through 20). No evidence of fetal malformations due to lamivudine was observed in rats and rabbits at doses producing plasma concentrations (C_{max}) approximately 35 times higher than human exposure at the recommended daily dose. Evidence of early embryolethality was seen in the rabbit at systemic exposures (AUC) similar to those observed in humans, but there was no indication of this effect in the rat at plasma concentrations (C_{max}) 35 times higher than human exposure at the recommended daily dose. Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. In the pre-and postnatal development study in rats, lamivudine was administered orally at doses of 180, 900, and 4,000 mg per kg per day from prior to mating through postnatal Day 20). In the study, development of the offspring, including fertility and reproductive performance, were not affected by the maternal administration of lamivudine.

▶ Lactation

Risk Summary

The Centers for Disease Control and Prevention recommends that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Abacavir and lamivudine are present in human milk. There is no information on the effects of abacavir and lamivudine on the breastfed infant or the effects of the drug on milk production.

Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) adverse reactions in a breastfed infant, instruct mothers not to breastfeed if they are receiving ABAMUNE L.

▶ Pediatric Use

The dosing recommendations in this population are based on the safety and efficacy established in a controlled trial conducted using either the combination of lamivudine and abacavir or Abacavir/lamivudine. In pediatric patients weighing less than 25 kg, use of abacavir and lamivudine as single products is recommended to achieve appropriate dosing.

▶ Geriatric Use

Clinical trials of abacavir and lamivudine 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/lamivudine in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see DOSAGE AND ADMINISTRATION, USE IN SPECIAL POPULATION).

Undesirable Effects

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

Serious and sometimes fatal hypersensitivity reaction. (see BOXED WARNING, WARNINGS AND PRECAUTIONS).

Lactic acidosis and severe hepatomegaly with steatosis (see BOXED WARNING, WARNINGS AND PRECAUTIONS).

Exacerbations of hepatitis B (see BOXED WARNING, WARNINGS AND PRECAUTIONS).

Hepatic decompensation in patients co-infected with HIV-1 and Hepatitis C (see WARNINGS AND PRECAUTIONS).
Immune reconstitution syndrome (see WARNINGS AND PRECAUTIONS).
Myocardial infarction (see WARNINGS AND PRECAUTIONS).

▶ 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 to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Serious and Fatal Abacavir-associated Hypersensitivity Reactions

In clinical trials, serious and sometimes fatal hypersensitivity reactions have occurred with abacavir, a component of Abacavir/lamivudine (see BOXED WARNING, WARNINGS AND PRECAUTIONS). 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/Lamivudine

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 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 are listed in Table 2.

Table 2: Treatment-emergent (all causality) adverse reactions of at least moderate intensity (Grades 2-4 greater than or equal to 5% frequency) in therapy-naïve adults (CNA30021) through 48 weeks of treatment

Adverse Event	Abacavir 600 mg q.d. plus Lamivudine plus Efavirenz (n=384)	Abacavir 300 mg b.i.d. plus Lamivudine plus Efavirenz (n=386)
Drug hypersensitivity[a,b]	9%	7%
Insomnia	7%	9%
Depression/Depressed mood	7%	7%
Headache/migraine	7%	6%
Fatigue/malaise	6%	8%
Dizziness/Vertigo	6%	6%
Nausea	5%	6%

Diarrhea[a]	5%	6%
Rash	5%	5%
Pyrexia	5%	3%
Abdominal pain/gastritis	4%	5%
Abnormal dreams	4%	5%
Anxiety	3%	5%

[a] 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 to 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.

[b] CNA30024 was a multi-center, 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). CNA30024 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.

Laboratory Abnormalities: Laboratory abnormalities observed in clinical trials of abacavir were anemia, neutropenia, liver function test abnormalities, and elevations of CPK, blood glucose, and triglycerides. Additional laboratory abnormalities observed in clinical trials of lamivudine were thrombocytopenia and elevated levels of bilirubin, amylase, and lipase. The frequencies of treatment-emergent laboratory abnormalities were comparable between treatment groups in CNA30021.

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

▶ Postmarketing Experience

The following adverse reactions have been identified during postmarketing use. 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.

Abacavir

Cardiovascular: Myocardial infarction.

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 UNDESIRABLE SIDE EFFECTS).

Abacavir and Lamivudine

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

Digestive: Stomatitis.

Endocrine and Metabolic: Hyperglycemia.

General: Weakness.

Hemic and Lymphatic: Aplastic anemia, anemia (including pure red cell aplasia and severe anemias progressing on therapy), lymphadenopathy, splenomegaly.
Hepatic: Lactic acidosis and hepatic steatosis (see WARNINGS AND PRECAUTIONS), posttreatment exacerbations of hepatitis B (see WARNINGS AND PRECAUTIONS).
Hypersensitivity: Sensitization reactions (including anaphylaxis), urticaria.
Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.
Nervous: Paresthesia, peripheral neuropathy, seizures.
Respiratory: Abnormal breath sounds/wheezing.
Skin: Alopecia, erythema multiforme, Stevens-Johnson syndrome.
If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024.
By reporting side effects, you can help provide more information on the safety of this product.

Overdosage

There is no known specific treatment for overdose with abacavir/lamivudine. If overdose occurs, the patient should be monitored, and standard supportive treatment applied as required.

▶ Abacavir

It is not known whether abacavir can be removed by peritoneal dialysis or hemodialysis.

▶ Lamivudine

Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event.

Storage And Handling Instructions

Store in cool dry place.

Packaging Information

ABAMUNE-L Tablets.....Container of 30 tablets

Last Updated: Nov 2018
Last Reviewed: Nov 2018

ABAMUNE-L Tablets
