ABAMUNE-L Tablets (Abacavir sulfate + Lamivudine)

For the use of a Registered Medical Practitioner

Black Box Warning

Hypersensitivity Reactions and Exacerbations of Hepatitis B
Hypersensitivity Reactions
· **Serious and sometimes fatal hypersensitivity reactions have occurred with abacavir-containing products**
· **Hypersensitivity to abacavir is a multi-organ clinical syndrome**
· **Patients who carry the HLA-B*5701 allele are at a higher risk of a hypersensitivity reaction to abacavir.**
· **ABAMUNE-L Tablets is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients.**
· **Discontinue ABAMUNE-L Tablets as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B*5701 status, permanently discontinue ABAMUNE-L Tablets if hypersensitivity cannot be ruled out, even when other diagnoses are possible.**
· **Following a hypersensitivity reaction to ABAMUNE-L Tablets, never restart ABAMUNE-L Tablets or any other abacavir-containing product**

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 a component of ABAMUNE-L Tablets. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment.

Qualitative and Quantitative Composition

ABAMUNE-L Tablets

Each film-coated tablet contains:

Abacavir Sulphate IP equivalent to

Abacavir .....600 mg

Lamivudine IP.....300 mg

Dosage Form and Strength

Film coated tablets of abacavir 600 mg and lamivudine 300 mg.

Clinical Particulars

Therapeutic Indications

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

Posology and Method of Administration

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

Screen for the HLA-B*5701 allele prior to initiating therapy with **ABAMUNE-L Tablets.**

Recommended Dosage for Adult Patients

The recommended dosage of **ABAMUNE-L Tablets** 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 Tablets** is a fixed-dose tablet and cannot be dose adjusted, **ABAMUNE-L Tablets** is not recommended for:

- patients with creatinine clearance less than 50 mL per minute
- patients with mild hepatic impairment. **ABAMUNE-L Tablets** is contraindicated in patients with moderate or severe hepatic impairment

Contraindications

ABAMUNE-L Tablets is contraindicated in patients:

- who have the HLA-B*5701 allele;
- with prior hypersensitivity reaction to abacavir or lamivudine; and
- with moderate or severe hepatic impairment.

Special Warnings and Precautions for Use

Hypersensitivity Reactions

Serious and sometimes fatal hypersensitivity reactions have occurred with abacavir, a component of **ABAMUNE-L Tablets.** 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**.** 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 **ABAMUNE-L Tablets** or reinitiation of therapy with **ABAMUNE-L Tablets**, unless patients have a previously documented HLA-B*5701 allele assessment.

· **ABAMUNE-L Tablets** is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients.

· Before starting **ABAMUNE-L Tablets**, review medical history for prior exposure to any abacavir containing product. NEVER restart **ABAMUNE-L Tablets** 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 **ABAMUNE-L Tablets** 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 **ABAMUNE-L Tablets** 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 **ABAMUNE-L Tablets**. 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 **ABAMUNE-L Tablets** or any other abacavir-containing product is recommended only if medical care can be readily accessed.

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. 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.

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 ABAMUNE-L Tablets). 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. Treatment with ABAMUNE-L Tablets 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-L Tablets**. 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 [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.

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).

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

Co-administration 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 medicine.

Use in Special Populations

Pregnancy

Risk Summary

Available data from the Antiretroviral Pregnancy Registry (APR) 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 (see **Data**).

Data

Human Data

Abacavir:

Based on prospective reports to APR 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 to the APR 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 [rat] and 8 through 20 [rabbit]). 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 Tablets**.

Pediatric Use

ABAMUNE-L Tablets is not indicated for use in pediatrics.

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 **ABAMUNE-L Tablets** in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Patients with Impaired Renal Function

ABAMUNE-L Tablets is not recommended for patients with creatinine clearance less than 50 mL per min because ABAMUNE-L Tablets is a fixed-dose combination and the dosage of the individual components cannot be adjusted. If a dose reduction of lamivudine, a component of ABAMUNE-L Tablets, 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

ABAMUNE-L Tablets is a fixed-dose combination and the dosage of the individual components cannot be adjusted. If a dose reduction of abacavir, a component of ABAMUNE-L Tablets, 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, ABAMUNE-L Tablets is contraindicated in these patients.

Effect on Ability to Drive and Use Machines

No data available.

Undesirable Effects

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

- Serious and sometimes fatal hypersensitivity reactions.
- Exacerbations of hepatitis B.
- Lactic acidosis and severe hepatomegaly with steatosis.
- Immune reconstitution syndrome.
- Myocardial infarction.

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 **ABAMUNE-L Tablets**. 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 ABAMUNE-L Tablets

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 1.

Table 1: 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 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] 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). 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 trial.

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.

Lamivudine

Post-marketing reports of lamivudine received by the National pharmacovigilance program of India (PvPI) include hearing loss.

Abacavir and Lamivudine

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

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. posttreatment exacerbations of hepatitis B.

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 or you can report to Cipla Ltd on 1800 267 7779. By reporting side effects, you can help provide more information on the safety of this product.

Overdose

There is no known specific treatment for overdose with **ABAMUNE-L Tablets**. 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.

Pharmacological Properties

Mechanism of Action

ABAMUNE-L Tablets is an antiretroviral agent.

Pharmacodynamic Properties

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.

Antiviral Activity

Abacavir

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). EC50 values ranged from 3.7 to 5.8 microM (1 microM = 0.28 mcg per mL) and 0.07 to 1.0 microM against HIV-1_{IIIB} and HIV-1_{BaL}, respectively, and the mean EC_{50} value 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 EC_{50} values against HIV-2 isolates (n = 4) ranged from 0.024 to 0.49 microM.

Lamivudine

The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines including monocytes and PBMCs using standard susceptibility assays. EC_{50} values were in the range of 0.003 to 15 microM (1 microM = 0.23 mcg per mL). The median EC_{50} values of lamivudine were 60 nM (range: 20 to 70 nM), 35 nM (range: 30 to 40 nM), 30 nM (range: 20 to 90 nM), 20 nM (range: 3 to 40 nM), 30 nM (range: 1 to 60 nM), 30 nM (range: 20 to 70 nM), 30 nM (range: 3 to 70 nM), and 30 nM (range: 20 to 90 nM) against HIV-1 clades A-G and group O viruses (n = 3 except n = 2 for clade B), respectively. The EC_{50} values against HIV-2 isolates (n = 4) ranged from 0.003 to 0.120 microM in PBMCs. Ribavirin (50 microM) used in the treatment of chronic HCV infection decreased the anti-HIV-1 activity of lamivudine by 3.5-fold in MT-4 cells.

The combination of abacavir and lamivudine has demonstrated antiviral activity in cell culture against non-subtype B isolates and HIV-2 isolates with equivalent antiviral activity as for subtype B isolates. Neither abacavir, nor lamivudine, were antagonistic to all tested anti-HIV agents. See full prescribing information for abacavir and lamivudine. Ribavirin, used in the treatment of HCV infection, decreased the anti-HIV-1 potency of abacavir/lamivudine reproducibly by 2-to 6-fold in cell culture.

Pharmacokinetic Properties

Pharmacokinetics in Adults

In a single-dose, 3-way crossover bioavailability trial of 1 **ABAMUNE-L** 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 2.

Table 2: 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 ABAMUNE-L Tablets

ABAMUNE-L Tablets 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

The effect of renal impairment on the combination of abacavir and lamivudine has not been evaluated*:*

Patients with Hepatic Impairment

The effect of hepatic impairment on the combination of abacavir and lamivudine has not been evaluated*:*

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.

Pediatric Patients

Abacavir and Lamivudine

The pharmacokinetic data for abacavir and lamivudine following administration of ABAMUNE-L Tablets in pediatric subjects weighing 25 kg and above are limited. 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 ABAMUNE-L Tablets. Refer to the lamivudine and abacavir USPI for pharmacokinetic information on the individual products in pediatric patients

Geriatric Patients

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

Male and Female Patients

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.

Racial Groups

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.

Drug Interaction Studies

The drug interactions described are based on trials conducted with abacavir or lamivudine as single entities; no drug interaction trials have been conducted with **ABAMUNE-L Tablets**.

Effect of Abacavir and Lamivudine on the Pharmacokinetics of Other Agents

Abacavir and lamivudine do not inhibit or induce CYP enzymes (such as CYP3A4, CYP2C9, or CYP2D6); therefore, it is unlikely that clinically significant drug interactions will occur with drugs metabolized through these pathways. Based on *in vitro* study results, abacavir and lamivudine at therapeutic drug exposures are not expected to affect the pharmacokinetics of drugs that are substrates of the following transporters: organic anion transporter polypeptide (OATP)1B1/3, breast cancer resistance protein (BCRP) or P-glycoprotein (P-gp), organic cation transporter (OCT)1, OCT2,

OCT3 (lamivudine only), or multidrug and toxic extrusion protein (MATE)1 and MATE2-K.

Effect of Other Agents on the Pharmacokinetics of Abacavir or Lamivudine

Abacavir and lamivudine are not significantly metabolized by cytochrome P450 enzymes; therefore, CYP enzyme inhibitors or inducers are not expected to affect their concentrations. *In vitro*, abacavir is not a substrate of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, MATE1, MATE2-K, multidrug resistance-associated protein 2 (MRP2) or MRP4; therefore, drugs that modulate these transporters are not expected to affect abacavir plasma concentrations. Abacavir is a substrate of BCRP and P-gp *in vitro*; however, considering its absolute bioavailability (83%), modulators of these transporters are unlikely to result in a clinically relevant impact on abacavir concentrations.

Lamivudine is a substrate of MATE1, MATE2-K, and OCT2 *in vitro*. Trimethoprim (an inhibitor of these drug transporters) has been shown to increase lamivudine plasma concentrations. This interaction is not considered clinically significant as no dose adjustment of lamivudine is needed.

Lamivudine is a substrate of P-gp and BCRP; however, considering its absolute bioavailability (87%), it is unlikely that these transporters play a significant role in the absorption of lamivudine. Therefore, coadministration of drugs that are inhibitors of these efflux transporters is unlikely to affect the disposition and elimination of lamivudine.

Abacavir: Lamivudine and/or Zidovudine

Fifteen HIV-1-infected subjects were enrolled in a crossover-designed drug 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.

Lamivudine: Zidovudine:

No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-1-infected adult subjects given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg every 12 h).

Other Interactions

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

Interferon Alfa: There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in a trial of 19 healthy male subjects.

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%). The addition of methadone has no clinically significant effect on the pharmacokinetic properties of abacavir.

Ribavirin: In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n

= 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected subjects.

Sorbitol (Excipient): Lamivudine and sorbitol solutions were coadministered to 16 healthy adult subjects in an open-label, randomized-sequence, 4-period, crossover trial. Each subject received a single 300-mg dose of lamivudine oral solution alone or coadministered with a single dose of 3.2 grams, 10.2 grams, or 13.4 grams of sorbitol in solution. Coadministration of lamivudine with sorbitol resulted in dose-dependent decreases of 20%, 39%, and 44% in the AUC(0-24); 14%, 32%, and 36% in the $AUC_{(\infty)}$; and 28%, 52%, and 55% in the C_{max}; of lamivudine, respectively.

The effects of other coadministered drugs on abacavir or lamivudine are provided in Table 3.

Table 3. Effect of co-administered drugs on abacavir or lamivudine

Coadministered Drug and Dose	**Drug and Dose**	**n**	**Concentrations of Abacavir or Lamivudine**		**Concentration of Coadministered Drug**
			AUC	**Variability**	
Ethanol 0.7 g/kg	Abacavir Single 600 mg	24	41 %	90% CI: 35% to 48%	« a
Nelfinavir 750 mg every 8 h x 7 to 10 days	Lamivudine Single 150 mg	11	10%	95% CI: 1% to 20%	«
Trimethoprim 160 mg/ Sulfamethoxazole 800 mg daily x 5 days	Lamivudine Single 300 mg	14	43%	90% CI: 32% to 55%	«

 = Increase; « = No significant change; AUC = Area under the concentration versus time curve; CI = Confidence interval.

[a] The drug-drug interaction was only evaluated in males.

Nonclinical Properties

Animal toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

Abacavir

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.

Lamivudine

Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) the human exposures at the recommended dose of 300 mg.

Mutagenicity

Abacavir

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.

Lamivudine

Lamivudine was mutagenic in an L5178Y mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was not mutagenic in a microbial mutagenicity assay, in an *in vitro* cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver.

Impairment of Fertility

Abacavir

Abacavir did not affect male or female fertility in rats at a dose associated with exposures (AUC) approximately 3.3 times (male) or 4.1 times (female) those in humans at the clinically recommended dose.

Lamivudine

Lamivudine did not affect male or female fertility in rats at doses up to 4,000 mg per kg per day, associated with concentrations approximately 42 times (male) or 63 times (female) higher than the concentrations (Cmax) in humans at the dose of 300 mg.

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 at a dose of 600 mg. The clinical relevance of this finding has not been determined.

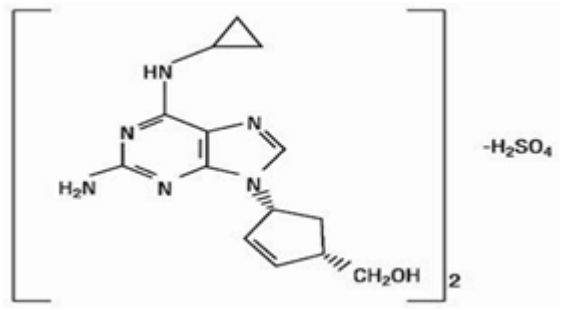
Description

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

ABAMUNE-L tablets are for oral administration.

Abacavir Sulfate

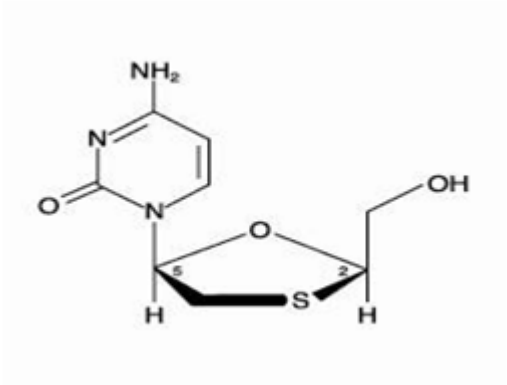
The chemical name of abacavir sulfate is *(1S,cis)*-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9 yl]--
-cyclopentene-1-methanol sulfate (salt) (2:1). Abacavir sulfate is the enantiomer with *1S*, *4R* absolute configuration on the cyclopentene ring. It has a molecular formula of(C14H18N6O)2●H2SO4 and a molecular weight of 670.76 g
per mol. It has the following structuralformula



Abacavir sulfate is a white to off-white solid and is soluble in water. In vivo, abacavir sulfate dissociates to its free base, abacavir. Dosages are expressed in terms of abacavir.

Lamivudine

The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl) (1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2¢,3¢-dideoxy, 3¢-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.3 g per mol. It has the following structural formula



Lamivudine is a white to off-white crystalline solid and is soluble in water.

Pharmaceutical Particulars

Incompatibilities

Not applicable.

Shelf-life

As on the pack.

Packaging Information

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

Storage and Handling Instructions

Store below 30°C. Protected from moisture.

Patient Counseling Information

What is the most important information I should know about ABAMUNE-L Tablets?

ABAMUNE-L Tablets can cause serious side effects, including:

- Serious allergic reactions (hypersensitivity reaction) that can cause death have happened with **ABAMUNE-L Tablets** 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 ABAMUNE-L Tablets, call your healthcare provider right away to find out if you should stop taking ABAMUNE-L Tablets.

	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 **ABAMUNE-L Tablets** because of an allergic reaction, never take **ABAMUNE-L Tablets** (abacavir and lamivudine) or any other abacavir-containing medicine again.

- If you have an allergic reaction, dispose of any unused **ABAMUNE-L Tablets**. Ask your pharmacist how to properly dispose of medicines.
- If you take **ABAMUNE-L Tablets** 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 **ABAMUNE-L Tablets** for any other reason, even for a few days, and you are not allergic to **ABAMUNE-L Tablets**, talk with your healthcare provider before taking it again. Taking **ABAMUNE-L Tablets** 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 **ABAMUNE-L Tablets** again, start taking it when you are around medical help or people who can call a healthcare provider if you need one.
- Worsening of hepatitis B virus in people who have HIV-1 infection. If you have HIV-1 and hepatitis B virus (HBV) infection, your HBV may get worse (flare-up) if you stop taking **ABAMUNE-L Tablets**. A “flare-up” is when your HBV infection suddenly returns in a worse way than before. Worsening liver disease can be serious and may lead to death
- Do not run out of **ABAMUNE-L Tablets**. Refill your prescription or talk to your healthcare provider before your **ABAMUNE-L Tablets** is all gone.
- Do not stop **ABAMUNE-L Tablets** without first talking to your healthcare provider.
- If you stop taking **ABAMUNE-L Tablets**, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your liver.

- Resistant Hepatitis B Virus (HBV). If you have HIV-1 and hepatitis B, the hepatitis B virus can change (mutate) during your treatment with **ABAMUNE-L Tablets** and become harder to treat (resistant).

What is ABAMUNE-L Tablets?

ABAMUNE-L Tablets 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). **ABAMUNE-L Tablets** contains 2 prescription medicines, abacavir and lamivudine.

ABAMUNE-L Tablets should not be used in children weighing less than 55 pounds (25 kg).

When used with other antiretroviral medicines to treat HIV-1 infection, **ABAMUNE-L Tablets** 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).

ABAMUNE-L 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.

Who should not take ABAMUNE-L Tablets?

Do not take **ABAMUNE-L Tablets** 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 **ABAMUNE-L Tablets**.
- are allergic to abacavir or any of the ingredients in **ABAMUNE-L Tablets**.
- have liver problems.

What should I tell my healthcare provider before taking ABAMUNE-L Tablets?

Before you take **ABAMUNE-L Tablets** tell your healthcare provider 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 kidney 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. 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 **ABAMUNE-L Tablets.**
- 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-thecounter medicines, vitamins, and herbal supplements.

Some medicines interact with **ABAMUNE-L Tablets**. 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 **ABAMUNE-L Tablets**. Do not start taking a new medicine without telling your healthcare provider. Your healthcare provider can tell you if it is safe to take **ABAMUNE-L Tablets** with other medicines.

Tell your healthcare provider if you take:

- any other medicine to treat HIV-1
- medicines to treat hepatitis viruses such as interferon or ribavirin
- methadone

How should I take ABAMUNE-L Tablets?

- Take **ABAMUNE-L Tablets** exactly as your healthcare provider tells you.
- Do not change your dose or stop taking **ABAMUNE-L Tablets** without talking with your healthcare provider. If you miss a dose of **ABAMUNE-L Tablets**, 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 **ABAMUNE-L Tablets**.
- **ABAMUNE-L Tablets** may be taken with or without food.
- Tell your healthcare provider if your child has trouble swallowing **ABAMUNE-L** tablets.
- Do not run out of **ABAMUNE-L Tablets**. The virus in your blood may increase and the virus may become harder to treat. When your supply starts to run low, get more from your healthcare provider or pharmacy
- If you take too much **ABAMUNE-L Tablets**, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of ABAMUNE-L Tablets?

ABAMUNE-L Tablets can cause serious side effects including:

- See “What is the most important information I should know about **ABAMUNE-L Tablets**?”
- Build-up of acid in your blood (lactic acidosis). Lactic acidosis can happen in some people who take **ABAMUNE-L Tablets**. 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 **ABAMUNE-L Tablets**. 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). Call your healthcare provider right away if you get any of the following signs or symptoms of liver problems:

- your skin or the white part of your eyes turns yellow (jaundice)
- dark or “tea-colored” urine
- 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 or very overweight (obese).

- Changes in your immune system (Immune Reconstitution Syndrome) can happen when you 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 symptoms after you start taking **ABAMUNE-L Tablets**.
- Heart attack (myocardial infarction). Some HIV-1 medicines including **ABAMUNE-L Tablets** may increase your risk of heart attack.

The most common side effects of **ABAMUNE-L Tablets** include:

- trouble sleeping
- depression
- headache
- tiredness
- dizziness
- nausea
- diarrhea
- rash
- fever

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

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 or you can report to Cipla Ltd on 1800 267 7779. By reporting side effects, you can help provide more information on the safety of this product

How should I store ABAMUNE-L Tablets?

Store below 30°C. Protect from moisture.

Details of Manufacturer

Mfg. By Cipla Ltd

Registered Office: Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg Lower Parel, Mumbai – 400 013, India

Details of Permission or Licence Number with Date

25-845 and 08.01.2018

Date of Revision

24/04/2020