Abacavir and Lamivudine Tablets USP 600 mg/300 mg

2042002

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

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

**ABACAVIR and LAMIVUDINE tablets, for oral use**

**Initial U.S. Approval: 2004** **POM Schedule: S2/NS2/PP**

**WARNING: HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, and EXACERBATIONS OF HEPATITIS B**
**See full prescribing information for complete boxed warning.**

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

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

**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, a component of abacavir and lamivudine tablets. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.3)**

**RECENT MAJOR CHANGES**

Warnings and Precautions, Related Products that are Not Recommended (5.8) — Removed 03/2017

**INDICATIONS AND USAGE**

Abacavir and Lamivudine tablets, are a combination of abacavir and lamivudine, both nucleoside analogue HIV-1 reverse transcriptase inhibitors, is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. (1)

**DOSAGE AND ADMINISTRATION**
- Before initiating abacavir and lamivudine tablets, screen for the HLA-B*5701 allele because abacavir and lamivudine tablets contains abacavir. (2.1)
- Adults: One tablet orally once daily. (2.2)
- Pediatric patients weighing at least 25 kg: One tablet daily. (2.3)
- Because abacavir and lamivudine is a fixed-dose tablet and cannot be dose adjusted, abacavir and lamivudine tablets is not recommended in patients requiring dosage adjustment or patients with hepatic impairment. (2.4, 4)

**DOSAGE FORMS AND STRENGTHS**

Tablets: 600 mg of abacavir and 300 mg of lamivudine. (3)

**CONTRAINDICATIONS**
- Presence of HLA-B*5701 allele. (4)
- Prior hypersensitivity reaction to abacavir or lamivudine. (4)
- Moderate or severe hepatic impairment. (4, 8.7)

**WARNINGS AND PRECAUTIONS**
- Hepatic decompensation, some fatal, has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy and interferon alfa with or without ribavirin. Discontinue abacavir and lamivudine as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.4)
- Immune reconstitution syndrome and redistribution/accumulation of body fat have been reported in patients treated with combination antiretroviral therapy. (5.5, 5.6)

**ADVERSE REACTIONS**

The most commonly reported adverse reactions of at least moderate intensity (incidence greater than 5%) in an adult HIV-1 clinical trial were drug hypersensitivity, insomnia, depression/depressed mood, headache/migraine, fatigue/malaise, dizziness/vertigo, nausea, and diarrhea. (6.1)

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

**USE IN SPECIFIC POPULATIONS**
- Lactation: Women infected with HIV should be instructed not to breastfeed due to potential for HIV transmission. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 03/2017

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**FULL PRESCRIBING INFORMATION**

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

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

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

**Lactic Acidosis and Severe Hepatomegaly with Steatosis**

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

**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 abacavir and lamivudine tablets. 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 tablets and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.3)]*.**

**1 INDICATIONS AND USAGE**

Abacavir and Lamivudine tablets, in combination with other antiretroviral agents, are indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection.

**2 DOSAGE AND ADMINISTRATION**

**2.1 Screening for HLA-B*5701 Allele Prior to Starting Abacavir and Lamivudine Tablets**

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

**2.2 Recommended Dosage for Adult Patients**

The recommended dosage of abacavir and lamivudine tablets for adults is one tablet taken orally once daily, in combination with other antiretroviral agents, with or without food.

**2.3 Recommended Dosage for Pediatric Patients**

The recommended oral dose of abacavir and lamivudine tablets for pediatric patients weighing at least 25 kg is one tablet daily in combination with other antiretroviral agents *[see Clinical Studies (14.2)]*. Before prescribing abacavir and lamivudine tablets, pediatric patients should be assessed for the ability to swallow tablets.

**2.4 Not Recommended Due to Lack of Dosage Adjustment**

Because Abacavir and Lamivudine is a fixed-dose tablet and cannot be dose adjusted, Abacavir and Lamivudine tablets are not recommended for:
- patients with creatinine clearance less than 50 mL per minute *[see Use in Specific Populations (8.6)]*.
- patients with mild hepatic impairment. Abacavir and Lamivudine tablets are contraindicated in patients with moderate or severe hepatic impairment *[see Contraindications (4), Use in Specific Populations (8.7)]*.

Use of EPIVIR® (lamivudine) oral solution or tablets and ZIAGEN® (abacavir) oral solution may be considered.

**3 DOSAGE FORMS AND STRENGTHS**

Abacavir and Lamivudine tablets, USP contain 600 mg of abacavir as abacavir sulfate USP and 300 mg of lamivudine USP. The tablets are orange, modified capsule shaped, biconvex, film-coated tablets de-bossed with 'H' on one side and 'A1' on other side.

**4 CONTRAINDICATIONS**

Abacavir and Lamivudine tablets are contraindicated in patients:
- who have the HLA-B*5701 allele *[see Warnings and Precautions (5.1)]*.
- with prior hypersensitivity reaction to abacavir *[see Warnings and Precautions (5.1)]* or lamivudine.
- with moderate or severe hepatic impairment *[see Use in Specific Populations (8.7)]*.

**5 WARNINGS AND PRECAUTIONS**

**5.1 Hypersensitivity Reactions**

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

Due to the potential for severe, serious, and possibly fatal hypersensitivity reactions with abacavir:
- All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with abacavir and lamivudine or reinitiation of therapy with abacavir and lamivudine, unless patients have a previously documented HLA-B*5701 allele assessment.
- Abacavir and Lamivudine tablets are contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients.
- Before starting abacavir and lamivudine tablet, review medical history for prior exposure to any abacavir-containing product. NEVER restart abacavir and lamivudine 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 abacavir and lamivudine 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 abacavir and lamivudine 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 abacavir and lamivudine tablet. 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 and lamivudine tablets or any other abacavir-containing product is recommended only if medical care can be readily accessed.
- A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill.

**5.2 Lactic Acidosis and Severe Hepatomegaly with Steatosis**

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues and other antiretrovirals. See full prescribing information for ZIAGEN (abacavir) and EPIVIR (lamivudine). Treatment with abacavir and lamivudine 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).

**5.3 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 EPIVIR (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 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 EPIVIR (lamivudine).

**5.4 Use with Interferon- and Ribavirin-Based Regimens**

Patients receiving interferon alfa with or without ribavirin and abacavir and lamivudine tablets should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. See full prescribing information for EPIVIR (lamivudine). Discontinuation of abacavir and lamivudine tablets 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 full prescribing information for interferon and ribavirin).

**5.5 Immune Reconstitution Syndrome**

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including abacavir and lamivudine tablets. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as Mycobacterium avium infection, cytomegalovirus, Pneumocystis jirovecii pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

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

**5.6 Fat Redistribution**

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

**5.7 Myocardial Infarction**

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

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

**6 ADVERSE REACTIONS**

The following adverse reactions are discussed in other sections of the labeling:
- Serious and sometimes fatal hypersensitivity reactions *[see Boxed Warning, Warnings and Precautions (5.1)]*.
- Lactic acidosis and severe hepatomegaly with steatosis *[see Boxed Warning, Warnings and Precautions (5.2)]*.
- Exacerbations of hepatitis B *[see Boxed Warning, Warnings and Precautions (5.3)]*.
- Hepatic decompensation in patients co-infected with HIV-1 and Hepatitis C *[see Warnings and Precautions (5.4)]*.
- Immune reconstitution syndrome *[see Warnings and Precautions (5.5)]*.
- Fat redistribution *[see Warnings and Precautions (5.6)]*.
- Myocardial infarction *[see Warnings and Precautions (5.7)]*

**6.1 Clinical Trials Experience in Adult Subjects**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in 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 and lamivudine tablets *[see Boxed Warning, Warnings and Precautions (5.1)]*. These reactions have been characterized by 2 or more of the following signs or symptoms: (1) fever; (2) rash; (3) gastrointestinal symptoms (including nausea, vomiting, diarrhea, or abdominal pain); (4) constitutional symptoms (including generalized malaise, fatigue, or achiness); (5) respiratory symptoms (including dyspnea, cough, or pharyngitis). Almost all abacavir hypersensitivity reactions include fever and/or rash as part of the syndrome.

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

x-ray findings (predominantly infiltrates, which were localized).

Additional Adverse Reactions with Use of Abacavir and Lamivudine Tablets:

*Therapy-Naive Adults:* Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with greater than or equal to 5% frequency during therapy with ZIAGEN 600 mg once daily or ZIAGEN 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 to 4, Greater than or Equal to 5% Frequency) in Therapy-Naive Adults (CNA30021) through 48 Weeks of Treatment**

| Adverse Event | ZIAGEN 600 mg q.d. plus EPIVIR plus Efavirenz (n = 384) | ZIAGEN 300 mg b.i.d. plus EPIVIR 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 ZIAGEN 600 mg once daily, experienced a significantly higher incidence of severe drug hypersensitivity reactions and severe diarrhea compared with subjects who received ZIAGEN 300 mg twice daily. Five percent (5%) of subjects receiving ZIAGEN 600 mg once daily had severe drug hypersensitivity reactions compared with 2% of subjects receiving ZIAGEN 300 mg twice daily. Two percent (2%) of subjects receiving ZIAGEN 600 mg once daily had severe diarrhea while none of the subjects receiving ZIAGEN 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 ZIAGEN (300 mg twice daily), EPIVIR (150 mg twice daily), and efavirenz (600 mg once daily); or zidovudine (300 mg twice daily), EPIVIR (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 ZIAGEN were anemia, neutropenia, liver function test abnormalities, and elevations of CPK, blood glucose, and triglycerides. Additional laboratory abnormalities observed in clinical trials of EPIVIR 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.

**6.2 Clinical Trials Experience in Pediatric Subjects**

The safety of once-daily compared with twice-daily dosing of abacavir and lamivudine, administered as either single products or as abacavir and lamivudine tablets, was assessed in the ARROW trial (n = 336). Primary safety assessment in the ARROW (COL105677) trial was based on Grade 3 and Grade 4 adverse events. The frequency of Grade 3 and 4 adverse events was similar among subjects randomized to once-daily dosing compared with subjects randomized to twice-daily dosing. One event of Grade 4 hepatitis in the once-daily cohort was considered as uncertain causality by the investigator and all other Grade 3 or 4 adverse events were considered not related by the investigator. No additional safety issues were identified in pediatric subjects receiving abacavir and lamivudine once-daily compared with historical data in adults *[see Adverse Reactions (6.1)]*.

**6.3 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 Adverse Reactions (6.1)]*.

Abacavir and Lamivudine

*Body as a Whole:* Redistribution/accumulation of body fat *[see Warnings and Precautions (5.6)]*.

*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 (5.2)]*, posttreatment exacerbations of hepatitis B *[see Warnings and Precautions (5.3)]*.

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.

**7 DRUG INTERACTIONS**

**7.1 Methadone**

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

**8 USES IN SPECIFIC POPULATIONS**

**8.1 Pregnancy: *Teratogenic Effects:***

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to abacavir and lamivudine during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

Available data from the APR show no difference in the overall risk of birth defects for abacavir or lamivudine compared with the background rate for birth defects of 2.7% in the Metropolitan Atlanta Congenital Defects Program (MACDP) reference population *[see Data]*. 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 (Cmax) 35 times the recommended clinical dose *[see Data]*.

Data

*Human Data:* Abacavir: Based on prospective reports to the 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 U.S. 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 *[see Clinical Pharmacology (12.3)]*.

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 (Cmax) 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 (Cmax) 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 gestation Day 6 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.

**8.2 Lactation**

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. 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) serious adverse reactions in a breastfed infant, instruct mothers not to breastfeed if they are receiving abacavir and lamivudine tablets.

**8.4 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 EPIVIR and ZIAGEN or abacavir and lamivudine tablets *[see Dosage and Administration (2.3), Adverse Reactions (6.2), Clinical Studies (14.2)]*.

In pediatric patients weighing less than 25 kg, use of abacavir and lamivudine as single products is recommended to achieve appropriate dosing.

**8.5 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 and lamivudine tablets 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 (2.4), Use in Specific Populations (8.6, 8.7)]*.

**8.6 Patients with Impaired Renal Function**

Abacavir and Lamivudine tablets are not recommended for patients with creatinine clearance less than 50 mL per min because abacavir and lamivudine tablets are a fixed-dose combination and the dosage of the individual components cannot be adjusted. If a dose reduction of lamivudine, a component of abacavir and lamivudine tablets, is required for patients with creatinine clearance less than 50 mL per min, then the individual components should be used *[see Clinical Pharmacology (12.3)]*.

**8.7 Patients with Impaired Hepatic Function**

Abacavir and Lamivudine tablet 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 and lamivudine tablets, is required for patients with mild hepatic impairment (Child-Pugh Class A), then the individual components should be used *[see Clinical Pharmacology (12.3)]*.

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 and lamivudine tablets are contraindicated in these patients *[see Contraindications (4)]*.

**10 OVERDOSAGE**

There is no known specific treatment for overdose with abacavir and lamivudine 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.

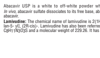
**Lamivudine:** Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event.

**11 DESCRIPTION**

**Abacavir and Lamivudine Tablets, USP:** Abacavir and Lamivudine tablets, USP contain the following 2 synthetic nucleoside analogues: abacavir sulfate USP (ZIAGEN, also a component of TRIZIVIR) and lamivudine USP (also known as EPIVIR or 3TC) with inhibitory activity against HIV-1.

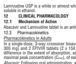
Abacavir and Lamivudine tablets, USP are for oral administration. Each orange film-coated tablet contains 600 mg of abacavir as abacavir sulfate USP and 300 mg of lamivudine USP. The inactive ingredients are colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose and sodium starch glycolate. The tablets are coated with opadry orange which contains FD & C Yellow #6/Sunset Yellow FCF Aluminum lake, hypromellose, polyethylene glycol, polysorbate 80 and titanium dioxide.

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



Abacavir USP is a white to off-white powder which is soluble in water and slightly soluble in methanol. *In vivo*, abacavir sulfate dissociates to its free base, abacavir. All dosages for abacavir sulfate are expressed in terms of abacavir.

**Lamivudine:** The chemical name of lamivudine is 2(1H) - Pyrimidinone, 4-amino-1- [2- (hydroxymethyl)-1, 3-oxathiolan-5- yl], (2R-cis)-. Lamivudine has also been referred to as (-)-2',3'-deoxy-3'-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.26. It has the following structural formula:



Lamivudine USP is a white or almost white powder which is soluble in water, sparingly soluble in methanol and slightly soluble in ethanol.

**12 CLINICAL PHARMACOLOGY**

**12.1 Mechanism of Action**

Abacavir and Lamivudine tablet is an antiretroviral agent *[see Microbiology (12.4)]*.

12.3 Pharmacokinetics

Pharmacokinetics in Adults

In a single-dose, 3-way crossover bioavailability trial of 1 abacavir and lamivudine tablet versus 2 ZIAGEN tablets (2 x 300 mg) and 2 EPIVIR 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 per mL (mean ± SD) and $AUC_{\infty}$ 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 Parameters[a] 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) | .007 ± .0008 | 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 and Lamivudine:

Abacavir and Lamivudine 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 AUClast, $AUC_{\infty}$, and Cmax for lamivudine. Food did not alter the extent of systemic exposure to abacavir ($AUC_{\infty}$), 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.

Specific Populations

*Renal Impairment:* Abacavir and Lamivudine: The effect of renal impairment on the combination of abacavir and lamivudine has not been evaluated (see the U.S. prescribing information for the individual abacavir and lamivudine components).

Hepatic Impairment: Abacavir and Lamivudine: The effect of hepatic impairment on the combination of abacavir and lamivudine has not been evaluated (see the U.S. prescribing information for the individual abacavir and lamivudine components).

*Pregnancy:* 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 abacavir and lamivudine 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 EPIVIR and ZIAGEN or abacavir and lamivudine tablets. Refer to the EPIVIR and ZIAGEN USPI for pharmacokinetic information on the individual products in pediatric patients *[see Dosage and Administration (2.3), Adverse Reactions (6.1), Clinical Studies (14.2)]*.

*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.

Drug Interactions

The drug interactions described are based on trials conducted with abacavir or lamivudine as single entities; no drug interaction trials have been conducted with abacavir and lamivudine.

*Cytochrome P450 Enzymes:* In humans, abacavir and lamivudine are not significantly metabolized by cytochrome P450 enzymes nor do they inhibit or induce this enzyme system; therefore, it is unlikely that clinically significant drug interactions will occur with drugs metabolized through these pathways.

*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.

*Methadone:* In a trial of 11 HIV-1-infected subjects receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of ZIAGEN twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI: 6% to 42%) *[see Drug Interactions (7)]*. 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 *[see Warnings and Precautions (5.4)]*.

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

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

**Table 3. Effect of Coadministered Drugs on Abacavir or Lamivudine**

| Coadministered Drug and Dose | Drug and Dose | n | Concentrations of Abacavir or Lamivudine: AUC | Concentrations of Abacavir or Lamivudine: Variability | Concentration of Coadministered Drug |
|---|---|---|---|---|---|
| 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.

**12.4 Microbiology**

Mechanism of Action

*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). $EC_{50}$ values ranged from 3.7 to 5.8 microM (1 microM = 0.28 mcg per mL) and 0.07 to 1 microM against HIV-1IIIB and HIV-1BaL, 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-1clades 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 to 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 ZIAGEN (abacavir) and EPIVIR (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.

Resistance

HIV-1 isolates with reduced susceptibility to the combination of abacavir and lamivudine have been selected in cell culture with amino acid substitutions K65R, L74V, Y115F, and M184V/I emerging in HIV-1 RT. M184V or I substitutions resulted in high-level resistance to lamivudine and an approximately 2-fold decrease in susceptibility to abacavir. Substitutions K65R, L74M, or Y115F with M184V or I conferred a 7- to 8-fold reduction in abacavir susceptibility, and combinations of three substitutions were required to confer more than an 8-fold reduction in susceptibility.

Cross-Resistance:

Cross-resistance has been observed among nucleoside reverse transcriptase inhibitors (NRTIs). The combination of abacavir/lamivudine has demonstrated decreased susceptibility to viruses with a K65R substitution with or without an M184V/I substitution, viruses with L74V plus the M184V/I substitution, and viruses with thymidine analog mutation substitutions (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219E/R/H/Q/N) plus M184V. An increasing number of TAMs is associated with a progressive reduction in abacavir susceptibility.

**13 NONCLINICAL TOXICOLOGY**

**13.1 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 ($C_{max}$) in humans at the dose of 300 mg.

**13.2 Animal Toxicology and/or Pharmacology**

Myocardial degeneration was found in mice and rats following administration of abacavir for 2 years. The systemic exposures were equivalent to 7 to 24 times the expected systemic exposure in humans at a dose of 600 mg. The clinical relevance of this finding has not been determined.

**14 CLINICAL STUDIES**

**14.1 Adults**

One abacavir and lamivudine tablet given once daily is an alternative regimen to EPIVIR tablets 300 mg once daily plus ZIAGEN tablets 2 x 300 mg once daily as a component of antiretroviral therapy.

The following trial was conducted with the individual components of abacavir and lamivudine tablets.

Therapy-Naive Adults

CNA30021 was an international, multicenter, double-blind, controlled trial in which 770 HIV-1-infected, therapy-naive adults were randomized and received either ZIAGEN 600 mg once daily or ZIAGEN 300 mg twice daily, both in combination with EPIVIR 300 mg once daily and efavirenz 600 mg once daily. The double-blind treatment duration was at least 48 weeks. Trial participants had a mean age of 37 years; were male (81%), white (54%), black (27%), and American Hispanic (15%). The median baseline CD4+ cell count was 262 cells per mm³ (range: 21 to 918 cells per mm³) and the median baseline plasma HIV-1 RNA was 4.89 $log_{10}$ copies per mL (range: 2.60 to 6.99 $log_{10}$ copies per mL).

The outcomes of randomized treatment are provided in Table 4.

**Table 4. Outcomes of Randomized Treatment through Week 48 (CNA30021)**

| Outcome | ZIAGEN 600 mg q.d. plus EPIVIR plus Efavirenz (n = 384) | ZIAGEN 300 mg b.i.d. plus EPIVIR plus Efavirenz (n = 386) |
|---|---|---|
| Responder[a] | 64% (71%) | 65% (72%) |
| Virologic failure[b] | 11% (5%) | 11% (5%) |
| Discontinued due to adverse reactions | 13% | 11% |
| Discontinued due to other reasons[c] | 11% | 13% |

a Subjects achieved and maintained confirmed HIV-1 RNA less than 50 copies per mL (less than 400 copies per mL) through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR® standard test version 1).

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

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

After 48 weeks of therapy, the median CD4+ cell count increases from baseline were 188 cells per mm³ in the group receiving ZIAGEN 600 mg once daily and 200 cells per mm³ in the group receiving ZIAGEN 300 mg twice daily. Through Week 48, 6 subjects (2%) in the group receiving ZIAGEN 600 mg once daily (4 CDC classification C events and 2 deaths) and 10 subjects (3%) in the group receiving ZIAGEN 300 mg twice daily (7 CDC classification C events and 3 deaths) experienced clinical disease progression. None of the deaths were attributed to trial medications.

**14.2 Pediatric Subjects**

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

Of the 1,206 original ARROW subjects, 669 participated in Randomization 3. Subjects randomized to receive once-daily dosing (n = 336) and who weighed at least 25 kg received abacavir 600 mg and lamivudine 300 mg, as either the single entities or as abacavir and lamivudine tablets.

The proportions of subjects with HIV-1 RNA less than 80 copies per mL through 96 weeks are shown in Table 5. The differences between virologic responses in the two treatment arms were comparable across baseline characteristics for gender and age.

Table 5. Virologic Outcome of Randomized Treatment at Week 96[a] (ARROW Randomization 3)

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

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

b Risk difference (95% CI) of response rate is -2.4% (-9% to 5%) at Week 96.

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

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

**16 HOW SUPPLIED/STORAGE AND HANDLING**

Abacavir and Lamivudine is available as tablets. Each film coated tablet contains 600 mg of abacavir as abacavir sulfate USP and 300 mg of lamivudine USP. Abacavir and Lamivudine tablets, USP are orange, modified capsule shaped, biconvex, film-coated tablets debossed with 'H' on one side and 'A1' on other side. They are packaged as follows:

Bottles of 30 Tablets NDC 68554-5138-0

Store below 30°C

**17 PATIENT COUNSELING INFORMATION**

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

Hypersensitivity Reactions:

Inform patients:
- that a Medication Guide and Warning Card summarizing the symptoms of the abacavir hypersensitivity reaction and other product information will be dispensed by the pharmacist with each new prescription and refill of abacavir and lamivudine tablets, and instruct the patient to read the Medication Guide and Warning Card every time to obtain any new information that may be present about abacavir and lamivudine tablets. The complete text of the Medication Guide is reprinted at the end of this document.
- to carry the Warning Card with them.
- how to identify a hypersensitivity reaction *[see Warnings and Precautions (5.1), Medication Guide]*.
- that if they develop symptoms consistent with a hypersensitivity reaction they should call their healthcare provider right away to determine if they should stop taking abacavir and lamivudine tablets.
- that a hypersensitivity reaction can worsen and lead to hospitalization or death if abacavir and lamivudine tablets are not immediately discontinued.
- to not restart abacavir and lamivudine tablets or any other abacavir-containing product following a hypersensitivity reaction because more severe symptoms can occur within hours and may include life-threatening hypotension and death.
- that if they have a hypersensitivity reaction, they should dispose of any unused abacavir and lamivudine tablets to avoid restarting abacavir.
- that a hypersensitivity reaction is usually reversible if it is detected promptly and abacavir and lamivudine tablets are stopped right away.
- that if they have interrupted abacavir and lamivudine tablets for reasons other than symptoms of hypersensitivity (for example, those who have an interruption in drug supply), a serious or fatal hypersensitivity reaction may occur with reintroduction of abacavir.
- to not restart abacavir and lamivudine tablets or any other abacavir-containing product without medical consultation and only if medical care can be readily accessed by the patient or others.

Lactic Acidosis/Hepatomegaly with Steatosis

Advise patients that lactic acidosis and severe hepatomegaly with steatosis have been reported with use of nucleoside analogues and other antiretrovirals. Advise patients to stop taking abacavir and lamivudine tablets if they develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity *[see Warnings and Precautions (5.2)]*.

Patients with Hepatitis B or C Co-infection

Advise patients co-infected with HIV-1 and HBV that worsening of liver disease has occurred in some cases when treatment with lamivudine was discontinued. Advise patients to discuss any changes in regimen with their physician *[see Warnings and Precautions (5.3)]*.

Inform patients with HIV-1/HCV co-infection that hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin *[see Warnings and Precautions (5.4)]*.

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any signs and symptoms of infection as inflammation from previous infection may occur soon after combination antiretroviral therapy, including when abacavir and lamivudine tablets is started *[see Warnings and Precautions (5.5)]*.

Redistribution/Accumulation of Body Fat

Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time *[see Warnings and Precautions (5.6)]*.

Pregnancy Registry

Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to abacavir and lamivudine tablets during pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk *[see Use in Specific Populations (8.2)]*.

Missed Dose

Instruct patients that if they miss a dose of abacavir and lamivudine tablets, to take it as soon as they remember. Advise patients not to double their next dose or take more than the prescribed dose *[see Dosage and Administration (2)]*.

Availability of Medication Guide

Instruct patients to read the Medication Guide before starting abacavir and lamivudine tablets and to re-read it each time the preparation is renewed. Instruct patients to inform their physician or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.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Category of Distribution: Prescription preparation

Pharmacological Classification: 7.13 Antivirals

Zimbabwe Reg. No.: 2015/7.13/5083

Date of publication: 29-06-2015 (Botswana); 11-08-2016 (Namibia); 14-09-2015 (Zimbabwe).

Revised: 03/2017


Manufactured by:
**HETERO LABS LIMITED**
Unit-V, TSIIC SEZ, Polepally Village,
Jadcherla Mandal, Mahaboob Nagar - 509 301,
Telangana, India.


**MEDICATION GUIDE**
**Abacavir and Lamivudine**
**tablets USP 600 mg/300 mg**

**What is the most important information I should know about abacavir and lamivudine tablets?**

**Abacavir and Lamivudine can cause serious side effects, including:**
- **Serious allergic reactions (hypersensitivity reaction)** that can cause death have happened with abacavir and lamivudine 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 abacavir and lamivudine tablets, call your healthcare provider right away to find out if you should stop taking abacavir and lamivudine 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 abacavir and lamivudine tablets because of an allergic reaction, never take abacavir and lamivudine tablets or any other abacavir-containing medicine (TRIUMEQ®, TRIZIVIR®, or ZIAGEN®) again.**
- If you have an allergic reaction, dispose of any unused abacavir and lamivudine tablets tablets. Ask your pharmacist how to properly dispose of medicines.
- If you take abacavir and lamivudine 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 abacavir and lamivudine tablets for any other reason, even for a few days, and you are not allergic to abacavir and lamivudine tablets, talk with your healthcare provider before taking it again. Taking abacavir and lamivudine 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 abacavir and lamivudine tablets again, start taking it when you are around medical help or people who can call a healthcare provider if you need one.**
- **Build-up of acid in your blood (lactic acidosis).** Lactic acidosis can happen in some people who take abacavir and lamivudine 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 abacavir and lamivudine 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:**

**You may be more likely to get lactic acidosis or serious liver problems if you are female, very overweight (obese), or have been taking nucleoside analogue medicines for a long time.**
- your skin or the white part of your eyes turns yellow (jaundice)- loss of appetite for several days or longer
- dark or "tea-colored" urine- nausea
- light-colored stools (bowel movements)- pain, aching, or tenderness on the right side of your stomach area
- **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 abacavir and lamivudine 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 abacavir and lamivudine tablets. Refill your prescription or talk to your healthcare provider before your abacavir and lamivudine tablets is all gone.
- Do not stop abacavir and lamivudine tablets without first talking to your healthcare provider. If you stop taking abacavir and lamivudine 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 abacavir and lamivudine tablets and become harder to treat (resistant).
- **Use with interferon and ribavirin-based regimens.** Worsening of liver disease that has caused death has happened in people infected with both HIV-1 and hepatitis C virus who are taking antiretroviral medicines and are also being treated for hepatitis C with interferon with or without ribavirin. If you are taking abacavir and lamivudine tablets and interferon with or without ribavirin tell your healthcare provider if you have any new symptoms.

**What is abacavir and lamivudine tablet?**

Abacavir and Lamivudine tablet 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). Abacavir and lamivudine tablet contains 2 prescription medicines, abacavir (ZIAGEN) and lamivudine (EPIVIR®).

Abacavir and lamivudine tablet should not be used in children weighing less than 55 pounds (25 kg).

**When used with other antiretroviral medicines to treat HIV-1 infection, abacavir and lamivudine tablet may help:**
- reduce the amount of HIV-1 in your blood. This is called "viral load".
- increase the number of CD4+ (T) cells in your blood, that help fight off other infections.

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

**Abacavir and lamivudine tablets 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 abacavir and lamivudine tablets?**

**Do not take abacavir and lamivudine 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 abacavir and lamivudine tablets.
- are allergic to abacavir or any of the ingredients in abacavir and lamivudine tablets. See the end of this Medication Guide for a complete list of ingredients in abacavir and lamivudine tablets.
- have liver problems.

**What should I tell my healthcare provider before taking abacavir and lamivudine tablets?**

**Before you take abacavir and lamivudine 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 abacavir and lamivudine 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-the counter medicines, vitamins, and herbal supplements.

Some medicines interact with abacavir and lamivudine 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 abacavir and lamivudine 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 abacavir and lamivudine 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 abacavir and lamivudine tablets?**
- **Take abacavir and lamivudine exactly as your healthcare provider tells you.**
- Do not change your dose or stop taking abacavir and lamivudine tablets without talking with your healthcare provider. If you miss a dose of abacavir and lamivudine tablet, take it as soon as you remember. Do not take 2 doses at the same time. If you are not sure about your dosing, call your healthcare provider.
- Stay under the care of a healthcare provider while taking abacavir and lamivudine tablets.
- Abacavir and lamivudine tablets may be taken with or without food.
- Tell your healthcare provider if your child has trouble swallowing abacavir and lamivudine tablets.
- Do not run out of abacavir and lamivudine 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 abacavir and lamivudine tablets, call your healthcare provider or go to the nearest hospital emergency room right away.

**What are the possible side effects of Abacavir and Lamivudine tablets?**
- **Abacavir and Lamivudine tablets can cause serious side effects including:**
- **See "What is the most important information I should know about abacavir and lamivudine tablets?"**
- **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 abacavir and lamivudine tablets.
- **Changes in body fat** can happen in people who take HIV-1 medicines. These changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the middle of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term health effects of these conditions are not known.
- **Heart attack (myocardial infarction).** Some HIV-1 medicines including abacavir and lamivudine tablets may increase your risk of heart attack.

**The most common side effects of abacavir and lamivudine 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.

These are not all the possible side effects of abacavir and lamivudine tablets. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects.

**How should I store abacavir and lamivudine tablets?**
- Store below 30°C

**Keep abacavir and lamivudine tablets and all medicines out of the reach of children.**

**General information for safe and effective use of abacavir and lamivudine tablets.**

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

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

**What are the ingredients in abacavir and lamivudine tablets?**

Active ingredients: abacavir USP and lamivudine USP

Inactive ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, sodium starch glycolate. The tablets are coated with opadry orange which contains FD & C Yellow #6/Sunset Yellow FCF Aluminum lake, hypromellose, polyethylene glycol, polysorbate 80, and titanium dioxide.


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

Revised: 03/2017

Size: 430 x 850 mm
Pharma Code: Front: 4149 & Back: 4150
Folding size: 33 x 33mm
Spec.: Printed on 31 GSM Bible paper, front & back side printing
Note: Pharma code position and Orientation are tentative, will be changed based on folding size.
No of Colours: 01 - Black

**DONNÉES ESSENTIELLES DE LA MONOGRAPHIE DU PRODUIT**

**Ces données essentielles ne contiennent pas toutes les informations nécessaires pour utiliser ABACAVIR et LAMIVUDINE COMPRIMÉS efficacement et en toute sécurité. Voir la monographie complète du produit ABACAVIR et LAMIVUDINE COMPRIMÉS.**

**ABACAVIR et LAMIVUDINE comprimés, voie orale**

**Première autorisation aux États-Unis : 2004** **POM Schedule: S2/NS2/PP**

**MISE EN GARDE : RÉACTIONS D'HYPERSENSIBILITÉ, ACIDOSE LACTIQUE, HÉPATOMÉGALIE SÉVÈRE ACCOMPAGNÉE DE STÉATOSE ET EXACERBATIONS DE L'HÉPATITE B**

***Voir la totalité de l'encadré de mise en garde dans la monographie complète du produit.***

**Réactions d'hypersensibilité**

- **Des réactions d'hypersensibilité graves, parfois fatales se sont produites avec des médicaments contenant de l'abacavir (5.1).**
- **L'hypersensibilité à l'abacavir est un syndrome clinique multiviscéral (5.1).**
- **Les patients porteurs de l'allèle HLA-B*5701 sont exposés à un risque plus élevé de réaction d'hypersensibilité à l'abacavir (5.1).**
- **Abacavir et lamivudine comprimés est contre-indiqué chez les patients ayant présenté une réaction d'hypersensibilité antérieure à l'abacavir et chez les patients porteurs de l'allèle HLA-B*5701 (4).**
- **Arrêter immédiatement Abacavir et lamivudine comprimés en cas de suspicion de réaction d'hypersensibilité. Arrêter définitivement Abacavir et lamivudine comprimés si une hypersensibilité ne peut être exclue, même lorsque d'autres diagnostics sont possibles et ce, quel que soit le statut HLA-B*5701 (5.1).**
- **Après une réaction d'hypersensibilité à Abacavir et lamivudine comprimés, ne JAMAIS reprendre le traitement par Abacavir et lamivudine comprimés ni par aucun autre médicament contenant de l'abacavir (5.1).**

**Acidose lactique et hépatomégalie sévère accompagnée de stéatose**

- **Des cas d'acidose lactique et d'hépatomégalie sévère accompagnée de stéatose, y compris des cas fatals, ont été rapportés avec l'utilisation d'analogues nucléosidiques (5.2).**

**Exacerbations de l'hépatite B**

- **Des exacerbations aiguës sévères de l'hépatite B ont été décrites chez des patients co-infectés par le virus de l'hépatite B (VHB) et le virus de l'immunodéficience humaine (VIH-1) ayant arrêté leur traitement par la lamivudine, un composant d'Abacavir et lamivudine comprimés. Surveiller étroitement la fonction hépatique chez ces patients et, le cas échéant, instaurer un traitement anti-hépatite B (5.3).**

**MODIFICATIONS MAJEURES RÉCENTES**

Mises en garde et précautions d'emploi, Produits apparentés non recommandés (5.8) Retiré 03/2017

**INDICATIONS ET UTILISATION**

Abacavir et lamivudine comprimés est une combinaison d'abacavir et de lamivudine, deux inhibiteurs nucléosidiques de la transcriptase inverse du VIH-1, indiquée en association à d'autres médicaments antirétroviraux dans le traitement de l'infection par le VIH-1 (1).

**POSOLOGIE ET ADMINISTRATION**

- Avant d'instaurer Abacavir et lamivudine comprimés, rechercher la présence de l'allèle HLA-B*5701 car Abacavir et lamivudine comprimés contient de l'abacavir (2.1).
- Adultes : un comprimé par voie orale une fois/jour (2.2).
- Patients de pédiatrie pesant au moins 25 kg : un comprimé par jour (2.3).
- Dans la mesure où Abacavir et lamivudine comprimés est une combinaison à dose fixe dont la dose ne peut être ajustée, il n'est pas recommandé chez les patients nécessitant un ajustement de leur posologie ou chez les patients insuffisants hépatiques (2.4, 4).

**FORMES PHARMACEUTIQUES ET DOSAGES**

Comprimés : 600 mg d'abacavir et 300 mg de lamivudine (3).

**CONTRE-INDICATIONS**

- Présence de l'allèle HLA-B*5701 (4).
- Réaction d'hypersensibilité antérieure à l'abacavir ou à la lamivudine (4).
- Insuffisance hépatique modérée ou sévère (4, 8.7).

**MISES EN GARDE ET PRÉCAUTIONS D'EMPLOI**

- Une décompensation hépatique, parfois fatale, s'est produite chez des patients co-infectés par le VIH-1 et le virus de l'hépatite C (VHC) recevant un traitement antirétroviral combiné et de l'interféron alpha avec ou sans ribavirine. Arrêter le traitement par Abacavir et lamivudine si cela est justifié sur le plan médical et envisager une diminution de la posologie, voire l'arrêt du traitement par l'interféron alpha et/ou la ribavirine (5.4).
- Un syndrome inflammatoire de restauration immunitaire et une lipodystrophie ont été décrits chez des patients recevant un traitement antirétroviral combiné (5.5, 5.6).

**EFFETS INDÉSIRABLES**

Les effets indésirables les plus fréquemment signalés, d'intensité au moins modérée (incidence supérieure à 5 %) lors d'une étude clinique menée chez des adultes infectés par le VIH-1 étaient : hypersensibilité au médicament, insomnies, dépression/humeur dépressive, céphalées/migraine, fatigue/malaise, sensation vertigineuse/vertige, nausées et diarrhée (6.1).

**INTERACTIONS MÉDICAMENTEUSES**

- Méthadone : une dose plus forte de méthadone peut s'avérer nécessaire chez un petit nombre de patients (7.1).

**UTILISATION DANS LES POPULATIONS PARTICULIÈRES**

- Allaitement : les femmes infectées par le VIH doivent être informées de ne pas allaiter en raison du risque de transmission du VIH (8.2).

**Voir la rubrique 17 concernant les INFORMATIONS DESTINÉES AU CONSEIL DES PATIENTS ainsi que la notice.**

Révisée en : 03/2017

**MONOGRAPHIE COMPLÈTE DU PRODUIT : CONTENU***


**MISE EN GARDE : RÉACTIONS D'HYPERSENSIBILITÉ, ACIDOSE LACTIQUE, HÉPATOMÉGALIE SÉVÈRE ACCOMPAGNÉE DE STÉATOSE ET EXACERBATIONS DE L'HÉPATITE B**

1 **INDICATIONS ET UTILISATION**

2 **POSOLOGIE ET ADMINISTRATION**
- 2.1 Recherche de l'allèle HLA-B*5701 avant l'instauration du traitement par Abacavir et lamivudine comprimés
- 2.2 Posologie recommandée chez les patients adultes
- 2.3 Posologie recommandée chez les patients de pédiatrie
- 2.4 Non Recommandé en raison de l'impossibilité d'ajustement de la posologie

3 **FORMES PHARMACEUTIQUES ET DOSAGES**

4 **CONTRE-INDICATIONS**

5 **MISES EN GARDE ET PRÉCAUTIONS D'EMPLOI**
- 5.1 Réactions d'hypersensibilité
- 5.2 Acidose lactique et hépatomégalie sévère accompagnée de stéatose
- 5.3 Patients présentant une co-infection par le virus de l'hépatite B
- 5.4 Utilisation avec des traitements contenant de l'interféron et de la ribavirine
- 5.5 Syndrome inflammatoire de restauration immunitaire
- 5.6 Lipodystrophie
- 5.7 Infarctus du myocarde

6 **EFFETS INDÉSIRABLES**
- 6.1 Expérience issue des études cliniques chez des patients adultes
- 6.2 Expérience issue des études cliniques en pédiatrie
- 6.3 Données de pharmacovigilance

7 **INTERACTIONS MÉDICAMENTEUSES**
- 7.1 Méthadone

8 **UTILISATION DANS LES POPULATIONS PARTICULIÈRES**
- 8.1 Grossesse
- 8.2 Allaitement
- 8.4 Population pédiatrique
- 8.5 Sujets âgés
- 8.6 Patients insuffisants rénaux
- 8.7 Patients insuffisants hépatiques.

10 **SURDOSAGE**

11 **DESCRIPTION**

12 **PHARMACOLOGIE CLINIQUE**
- 12.1 Mécanisme d'action
- 12.3 Pharmacocinétique
- 12.4 Microbiologie

13 **TOXICOLOGIE NON CLINIQUE**
- 13.1 Cancérogenèse, mutagenèse, baisse de la fertilité
- 13.2 Toxicologie et/ou pharmacologie animale(s)

14 **ÉTUDES CLINIQUES**
- 14.1 Adultes
- 14.2 Population pédiatrique

16 **PRÉSENTATION/CONSERVATION ET MANIPULATION**

17 **INFORMATIONS DESTINÉES AU CONSEIL DES PATIENTS**


* Les rubriques ou sous-rubriques non renseignées de la monographie complète ne sont pas mentionnées.

**MONOGRAPHIE COMPLÈTE DU PRODUIT**

**MISE EN GARDE : RÉACTIONS D'HYPERSENSIBILITÉ, ACIDOSE LACTIQUE, HÉPATOMÉGALIE SÉVÈRE ACCOMPAGNÉE DE STÉATOSE ET EXACERBATIONS DE L'HÉPATITE B**

**Réactions d'hypersensibilité**

**Des réactions d'hypersensibilité graves, parfois fatales, comportant une atteinte multiviscérale, se sont produites avec l'abacavir, un composant d'Abacavir et lamivudine comprimés. Les patients porteurs de l'allèle HLA-B*5701 sont exposés à un risque plus élevé de réaction d'hypersensibilité à l'abacavir, bien que ces réactions d'hypersensibilité se soient produites chez des patients non porteurs de l'allèle HLA-B*5701 [*voir Mises en garde et précautions d'emploi (5.1)*]**

[illegible]

**NOTICE**
**Abacavir et lamivudine**
**comprimés**

**Quelles sont les informations les plus importantes à connaître à propos d'Abacavir et lamivudine comprimés ?**
**Abacavir et lamivudine peut provoquer des effets indésirables graves, dont :**

- **Des réactions allergiques graves (réactions d'hypersensibilité)** pouvant être mortelles, qui se sont produites avec Abacavir et lamivudine comprimés et d'autres médicaments contenant de l'abacavir. Le risque de réaction allergique est beaucoup plus élevé chez les patients porteurs d'une mutation génique appelée HLA-B*5701. Votre professionnel de santé peut déterminer par une analyse de sang si vous êtes porteur (-euse) de cette mutation génique.
  **Si vous présentez des symptômes d'au moins 2 des groupes suivants pendant la prise d'Abacavir et lamivudine comprimés, appelez immédiatement votre professionnel de santé afin de savoir si vous devez arrêter de prendre Abacavir et lamivudine comprimés.**

| | Symptôme(s) |
|---|---|
| Groupe 1 | Fièvre |
| Groupe 2 | Éruption cutanée |
| Groupe 3 | Nausées, vomissements, diarrhée, douleurs abdominales (au ventre) |
| Groupe 4 | Sensation de mal-être général, fatigue extrême ou douleurs |
| Groupe 5 | Essoufflement, toux, mal de gorge |

Une liste de ces symptômes figure sur la carte de mise en garde qui vous a été remise par votre pharmacien. **Ayez toujours cette carte de mise en garde sur vous.**

**Si vous arrêtez de prendre Abacavir et lamivudine comprimés en raison d'une réaction allergique, ne reprenez jamais Abacavir et lamivudine comprimés ni aucun autre médicament contenant de l'abacavir TRIUMEQ®, TRIZIVIR® ou ZIAGEN®).**

- Si vous présentez une réaction allergique, débarrassez-vous de tout comprimé non utilisé d'Abacavir et lamivudine comprimés. Demandez à votre pharmacien comment se débarrasser correctement des médicaments.
- Si vous reprenez Abacavir et lamivudine comprimés ou tout autre médicament contenant de l'abacavir après avoir présenté une réaction allergique, vous pourriez **en quelques heures** présenter des **symptômes mettant la vie en danger**, notamment une **pression artérielle très basse,** voire un **décès**.
- Si vous arrêtez Abacavir et lamivudine comprimés pour toute autre raison, même pendant quelques jours et si vous n'êtes pas allergique à Abacavir et lamivudine comprimés, parlez-en avec votre professionnel de santé avant de reprendre le traitement. La reprise du traitement par Abacavir et lamivudine comprimés peut provoquer une réaction allergique grave ou mettant la vie en danger, même si vous n'avez jamais présenté de réaction allergique à ce médicament auparavant.

**Si votre professionnel de santé vous dit que vous pouvez reprendre votre traitement par Abacavir et lamivudine comprimés, commencez à le prendre lorsque vous êtes à proximité d'une aide médicale ou d'une personne pouvant appeler un professionnel de santé le cas échéant.**

- **Une accumulation d'un acide dans le sang (acidose lactique).** L'acidose lactique peut survenir chez certaines personnes prenant Abacavir et lamivudine comprimés. L'acidose lactique est une urgence médicale grave pouvant entraîner la mort. **Appelez immédiatement votre professionnel de santé si vous présentez l'un des symptômes suivants qui pourrait être le signe d'une acidose lactique :**

- vous vous sentez très faible ou fatigué(e),
- vous avez froid, notamment aux bras et aux jambes,
- vous souffrez de douleurs musculaires inhabituelles (non normales),
- vous avez des vertiges ou des étourdissements,

[illegible]