AUROBINDO
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Lamivudine/Zidovudine Tablets USP 150 mg/300 mg Co-Packaged with Abacavir Tablets USP 300 mg

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use lamivudine/zidovudine tablets USP 150 mg/300 mg co-packaged with abacavir tablets USP 300 mg safely and effectively. See full prescribing information for lamivudine/zidovudine tablets USP 150 mg/300 mg co-packaged with abacavir tablets USP 300 mg.

Lamivudine/Zidovudine Tablets USP 150 mg/300 mg Co-Packaged with Abacavir Tablets USP 300 mg

WARNING: HEMATOLOGIC TOXICITY, LACTIC ACIDOSIS, EXACERBATIONS OF HEPATITIS B AND RISKS OF HYPERSENSITIVITY REACTIONS

See full prescribing information for complete boxed warning.

- **Hematologic toxicity including neutropenia and anemia have been associated with the use of zidovudine, one of the components of lamivudine and zidovudine. (5.1)**
- **Symptomatic myopathy associated with prolonged use of zidovudine. (5.2)**
- **Lactic acidosis and hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues including zidovudine and abacavir. (5.3)**
- **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 lamivudine and zidovudine. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.4)**
- **Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate. (5.5)**
- **Hypersensitivity to abacavir is a multi-organ clinical syndrome. Following a hypersensitivity reaction to abacavir, NEVER restart abacavir sulfate or any other abacavir-containing product. (5.5)**

--------INDICATIONS AND USAGE--------

Lamivudine/Zidovudine Tablets USP 150 mg/300 mg Co-Packaged with Abacavir Tablets USP 300 mg are nucleoside analogues, indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. (1)

--------DOSAGE AND ADMINISTRATION--------

- A medication guide and warning card should be dispensed with each new prescription and refill. (2)
- Adults and Adolescents weighing ≥40 kg: 1 tablet twice daily. The recommended oral dose of abacavir tablet for adults adolescents weighing ≥40 kg is 600 mg daily, administered as either 300 mg twice daily or 600 mg once daily. (2.1)
- Pediatrics: should not be used in pediatric patients <12 years of age or in pediatric patients weighing < 40 kg. (2.2)

--------DOSAGE FORMS AND STRENGTHS--------

Tablets: Scored lamivudine/zidovudine 150 mg/300 mg, and scored abacavir 300 mg (3)

--------CONTRAINDICATIONS--------

Lamivudine/Zidovudine Tablets Co-Packaged with Abacavir Tablets are contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the product. (4)

--------WARNINGS AND PRECAUTIONS--------

- See boxed warning for information about the following: Hematologic toxicity, symptomatic myopathy, lactic acidosis and severe hepatomegaly, and severe acute exacerbations of hepatitis B. (5.1, 5.2, 5.3, 5.4)
- Hypersensitivity: Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate and other abacavir-containing products. Read full prescribing information section 5.1 before prescribing abacavir sulfate. (5.5)
- Lamivudine/Zidovudine Tablets Co-Packaged with Abacavir Tablets should not be administered with other lamivudine- or zidovudine-containing products or emtricitabine-containing products. (5.6)
- Hepatic decompensation, some fatal, has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy and interferon alfa with/without ribavirin. Discontinue lamivudine and zidovudine as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.7)
- Exacerbation of anemia has been reported in HIV-1/HCV co-infected patients receiving ribavirin and zidovudine. Coadministration of ribavirin and zidovudine is not advised. (5.7)
- Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue treatment as clinically appropriate. (5.8)
- Immune reconstitution syndrome and redistribution/accumulation of body fat have been reported in patients treated with combination antiretroviral therapy. (5.9, 5.10)

--------ADVERSE REACTIONS--------

- Most commonly reported adverse reactions (incidence ≥10% in adult and ≥5% pediatric HIV-1 clinical studies of combination lamivudine/zidovudine tablets co-packaged with abacavir tablets were headache, nausea, malaise and fatigue, nasal signs and symptoms, diarrhea, and ear/nose/throat infections, cough. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aurobindo Pharma USA, Inc. at 1-866-850-2876 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

--------DRUG INTERACTIONS--------

- Concomitant use with the following drugs should be avoided: Stavudine, zalcitabine, doxorubicin. (7.1, 7.2)
- Bone marrow suppressive/cytotoxic agents: May increase the hematologic toxicity of zidovudine. (7.3)
- Ethanol: Decreases elimination of abacavir. (7.6)
- Methadone: An increased methadone dose may be required in a small number of patients. (7.7)

--------USE IN SPECIFIC POPULATIONS--------

- Pregnancy: Physicians are encouraged to register patients in the Antiretroviral Pregnancy Registry by calling 1-800-258-4263. (8.1)
- Nursing Mothers: HIV-1 infected mothers in the United States should not breastfeed to avoid potential postnatal transmission of HIV-1. (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Issued: September 2013

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: HEMATOLOGIC TOXICITY, LACTIC ACIDOSIS, EXACERBATIONS OF HEPATITIS B AND RISKS OF HYPERSENSITIVITY REACTIONS

Hematologic Toxicity: Zidovudine, one of the 2 active ingredients in lamivudine and zidovudine tablets, has been associated with hematologic toxicity including neutropenia and severe anemia, particularly in patients with advanced HIV disease *[see Warnings and Precautions (5.1)]*.

Lactic Acidosis and Severe Hepatomegaly: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including lamivudine, zidovudine, abacavir sulfate and other antiretrovirals. *[see Warnings and Precautions (5.3)]*.

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 HIV-1 and have discontinued lamivudine. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue lamivudine and are co-infected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.4)]*.

Hypersensitivity Reactions: Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate. Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups: (1) fever, (2) rash, (3) gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain), (4) constitutional (including generalized malaise, fatigue, or achiness), and (5) respiratory (including dyspnea, cough, or pharyngitis). Discontinue lamivudine/zidovudine tablets co-packaged with abacavir tablets if hypersensitivity cannot be ruled out, even when other diagnoses are possible.

Following a hypersensitivity reaction to abacavir, never restart any abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.

Reintroduction of any abacavir-containing product, even in patients who have no identified history or unrecognized symptoms of hypersensitivity to abacavir therapy, can result in serious or fatal hypersensitivity reactions. Such reactions can occur within hours *[see Warnings and Precautions (5.5)]*.

1 INDICATIONS AND USAGE

Lamivudine/Zidovudine Tablets USP 150 mg/300 mg Co-Packaged with Abacavir Tablets USP 300 mg, is for patients > 12 years of age and those weighing > 40 kg for the treatment of HIV infection, alone or in combination with other antiretroviral agents.

Additional important information on the use of lamivudine/zidovudine tablets USP 150 mg/300 mg co-packaged with abacavir tablets USP 300 mg for the treatment of HIV infection:

- Lamivudine/Zidovudine Tablets USP 150 mg/300 mg Co-Packaged with Abacavir Tablets USP 300 mg are one of multiple products containing abacavir. Before starting lamivudine/zidovudine tablets USP 150 mg/300 mg co-packaged with abacavir tablets USP 300 mg,review medical history for prior exposure to any abacavir-containing product in order to avoid reintroduction in a patient with a history of hypersensitivity to abacavir *[see Warnings and Precautions (5.5), Adverse Reactions (6)]*.
- Limited data exist on the use of a regimen of lamivudine, zidovudine, and abacavir alone in patients with higher baseline viral load levels (>100,000 copies/mL, *see Clinical Studies (14.1)*).

2 DOSAGE AND ADMINISTRATION

- A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill.

2.1 Adults and Adolescents Weighing ≥40 kg

The recommended oral dose of lamivudine and zidovudine tablets for adults and adolescents (≥12 years of age) weighing ≥40 kg is one tablet (containing 150 mg of lamivudine and 300 mg of zidovudine) twice daily with or without food.

The recommended oral dose of abacavir tablets for adults and adolescents (≥12 years of age) weighing ≥40 kg is 600 mg daily, administered as 300 mg twice daily with or without food.

2.2 Pediatric Patients

The lamivudine/zidovudine tablets co-packaged with abacavir tablets should not be used in pediatric patients <12 years of age or in pediatric patients weighing < 40 kg.

2.3 Patients with Hepatic and Renal Impairment

The lamivudine/zidovudine tablets co-packaged with abacavir tablets are not recommended for patients with impaired renal function (creatinine clearance <50 mL/min) or impaired hepatic function.

3 DOSAGE FORMS AND STRENGTHS

Lamivudine and Zidovudine Tablets, containing 150 mg lamivudine and 300 mg zidovudine, are white to off-white, modified capsule shaped, biconvex, film-coated tablets with deep breakline in between 'C' and '60' on one side and deep breakline on the other side.

Abacavir Tablets, containing abacavir sulfate equivalent to 300 mg abacavir, are yellow colored, biconvex, capsule shaped, coated tablet, debossed with 'D' and '88' on either side of the score line on one side and plain with a score line on other side. They are packaged as follows:

Co-package: A carton containing 60 lamivudine/zidovudine tablets 150 mg/300 mg co-packaged with 60 abacavir tablets 300 mg in six blister cards. Each blister card contains five co-packages with perforation in between and each co-package contains two lamivudine/ zidovudine tablets 150 mg/300 mg and two abacavir tablets 300 mg.

4 CONTRAINDICATIONS

Lamivudine/Zidovudine Tablets Co-packaged with Abacavir Tablets are contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the product.

Following a hypersensitivity reaction to abacavir, NEVER restart lamivudine/zidovudine tablets co-packaged with abacavir tablets or any other abacavir-containing product. Fatal rechallenge reactions have been associated with readministration of abacavir to patients with a prior history of a hypersensitivity reaction to abacavir *[see Warnings and Precautions (5.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hemotologic Toxicity/Bone Marrow Suppression

The major toxicities of zidovudine are neutropenia and anemia. The frequency and severity of these toxicities are greater in patients with more advanced disease and in those who initiate therapy later in the course of infection. Lamivudine/zidovudine tablets co-packaged with abacavir sulfate should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count <1,000 cells/mm^3 or hemoglobin <9.5 g/dL *[see Adverse Reactions (6.1)]*.

Zidovudine-related hematologic toxicities appear related to pretreatment bone marrow reserve and to dose and duration of therapy. In patients with poor bone marrow reserve, particularly in patients with advanced symptomatic HIV disease, frequent monitoring of hematologic indices is recommended to detect serious anemia or neutropenia. In patients who experience hematologic toxicity reduction in hemoglobin may occur as early as 2 to 4 weeks, and neutropenia usually occurs after 6 to 8 weeks. If anemia or neutropenia develops discontinuation of lamivudine/zidovudine tablets co-packaged with abacavir tablets and/or transfusion may be warranted. Dose adjustments for zidovudine are not recommended for hematologic toxicities because the dosage form and strength of the zidovudine component of the tablets are not appropriate for dose adjustments *[see Dosage and Administration (2.1)]*. Instead, dose interruption, dose discontinuation and/or blood transfusions may be warranted to manage serious anemia.

Frequent blood counts are strongly recommended in patients with advanced HIV disease who are treated with lamivudine/zidovudine tablets co-packaged with abacavir tablets. For HIV-infected individuals and patients with asymptomatic or early HIV disease, periodic blood counts are recommended.

For patients requiring discontinuation of zidovudine treatment due to hematological toxicity (ies), treatment with lamivudine/zidovudine tablets co-packaged with abacavir tablets should be discontinued.

5.2 Myopathy

Myopathy and myositis, with pathological changes similar to that produced by HIV disease, have been associated with prolonged use of zidovudine, and therefore may occur with therapy with lamivudine and zidovudine.

5.3 Lactic Acidosis/Hepatomegaly With Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir, lamivudine, zidovudine, and other antiretrovirals. A majority of these cases have been in women. Although relative rates of lactic acidosis have not been assessed in prospective well-controlled trials, longitudinal cohort and retrospective studies suggest that this is infrequent event may be more often associated with antiretroviral combinations containing zidovudine. Female gender, obesity and prolonged nucleoside exposure may be risk factors. Fatal lactic acidosis has been reported in pregnant women who received the combination of zidovudine and didanosine with other antiretroviral agents. The combination of zidovudine and didanosine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk *[see Use in Specific Populations (8.1)]* Particular caution should be exercised when administering lamivudine/zidovudine tablets co-packaged with abacavir tablets to any patient with known risk factors for liver disease; however, cases of lactic acidosis have also been reported in patients with no known risk factors. Generalized fatigue, digestive symptoms (nausea, vomiting, abdominal pain, and sudden unexplained weight loss); respiratory symptoms (tachypnea and dyspnea); or neurologic symptoms (including motor weakness) might be indicative of lactic acidosis development.

An increased risk of hepatotoxicity may occur in patients treated with zidovudine in combination with didanosine and hydroyurea compared to when zidovudine is used alone. Deaths attributed to hepatotoxicity have occurred in patients receiving this combination. Patients treated with this combination should be closely monitored for signs of liver toxicity.

Treatment with lamivudine/zidovudine tablets co-packaged with abacavir 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).

5.4 Patients With HIV-1 and Hepatitis B Virus Co-infection

Posttreatment Exacerbations of Hepatitis: In clinical trials in non-HIV-infected patients treated with lamivudine for chronic hepatitis B, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence of hepatitis B viral DNA (HBV DNA). Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from postmarketing experience after changes from lamivudine-containing HIV treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV and HBV. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters the course of posttreatment exacerbations of hepatitis.

5.5 Hypersensitivity Reaction

Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir-containing products. To minimize the risk of a life-threatening hypersensitivity reaction, permanently discontinue lamivudine/zidovudine tablets co-packaged with abacavir tablets if hypersensitivity cannot be ruled out, even when other diagnoses are possible. Important information on signs and symptoms of hypersensitivity, as well as clinical management, is presented below.

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

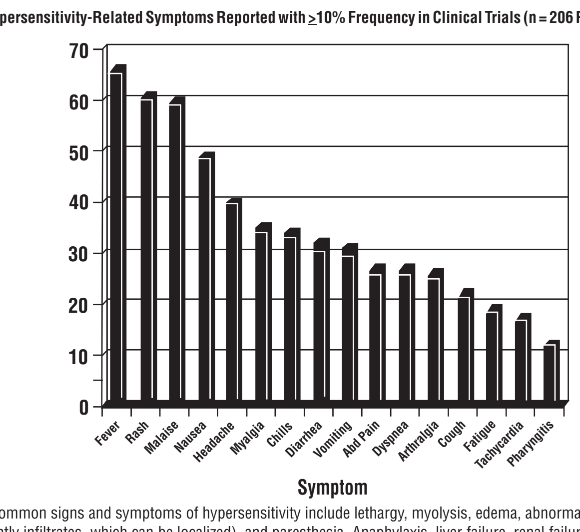
Group 1: Fever
Group 2: Rash
Group 3: Gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain)
Group 4: Constitutional (including generalized malaise, fatigue, or achiness)
Group 5: Respiratory (including dyspnea, cough, or pharyngitis).

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

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

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

Figure 1: Hypersensitivity-Related Symptoms Reported with ≥10% Frequency in Clinical Trials (n = 206 Patients)



Symptom

Other less common signs and symptoms of hypersensitivity include lethargy, myolysis, edema, abnormal chest x-ray findings (predominantly infiltrates, which can be localized), and paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure, and death have occurred in association with hypersensitivity reactions.

Physical findings associated with hypersensitivity to abacavir in some patients include lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and rash. The rash usually appears maculopapular or urticarial, but may be variable in appearance. There have been reports of erythema multiforme. Hypersensitivity reactions have occurred without rash.

Laboratory abnormalities associated with hypersensitivity to abacavir in some patients include elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, and lymphopenia.

Clinical Management of Hypersensitivity: Discontinue lamivudine/zidovudine tablets co-packaged with abacavir tablets as soon as a hypersensitivity reaction is suspected. To minimize the risk of a life-threatening hypersensitivity reaction, permanently discontinue lamivudine/zidovudine tablets co-packaged with abacavir tablets if hypersensitivity cannot be ruled out, even when other diagnoses are possible (e.g., acute onset respiratory diseases such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions to other medications).

Following a hypersensitivity reaction to abacavir, NEVER restart lamivudine/zidovudine tablets co-packaged with abacavir tablets or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.

When therapy with abacavir sulfate has been discontinued for reasons other than symptoms of a hypersensitivity reaction, and if reinitiation of abacavir is under consideration, carefully evaluate the reason for discontinuation to ensure that the patient did not have symptoms of a hypersensitivity reaction. If hypersensitivity cannot be ruled out, DO NOT reintroduce abacavir. If symptoms consistent with hypersensitivity are not identified, reintroduction can be undertaken with continued monitoring for symptoms of a hypersensitivity reaction. Make patients aware that a hypersensitivity reaction can occur with reintroduction of abacavir and that abacavir reintroduction needs to be undertaken only if medical care can be readily accessed by the patient or others.

5.6 Use With Other, Lamivudine-, Zidovudine-, and/or Abacavir-Containing Products

Lamivudine/Zidovudine Tablets Co-Packaged with Abacavir Tablets contain 3 nucleoside analogues: abacavir, lamivudine, and zidovudine and should not be administered concomitantly with other abacavir, lamivudine, zidovudine containing products including the combination drugs: COMBIVIR® (lamivudine and zidovudine), EPZICOM® (abacavir sulfate and lamivudine) tablets, TRIZIVIR® (abacavir sulfate, lamivudine, and zidovudine) tablets or emtricitabine-containing products, including ATRIPLA® (efavirenz, emtricitabine, and tenofovir), EMTRIVA® (emtricitabine), TRUVADA® (emtricitabine and tenofovir) or COMPLERA™ (rilpivirine/emtricitabine/tenofovir).

Lamivudine/Zidovudine Tablets Co-Packaged with Abacavir Tablets should not be prescribed for adolescents who weigh less than 40 kg or other patients requiring dosage adjustment.

The complete prescribing information for all agents being considered for use with lamivudine/zidovudine tablets co-packaged with abacavir tablets should be consulted before combination therapy with lamivudine/zidovudine tablets co-packaged with abacavir tablets is initiated.

5.7 Use With Interferon- and Ribavirin-Based Regimens

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine and zidovudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) interaction was seen when ribavirin was coadministered with lamivudine or zidovudine in HIV-1/HCV co-infected patients *[see Clinical Pharmacology (12.3)]*, hepatic decompensation (some fatal) has occurred in HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and lamivudine and zidovudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation, neutropenia, and anemia. Discontinuation of lamivudine and zidovudine 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 > 6) (see the complete prescribing information for interferon and ribavirin).

Exacerbation of anemia has been reported in HIV/HCV co-infected patients receiving ribavirin and zidovudine. Coadministration of ribavirin and zidovudine is not advised.

5.8 Pancreatitis

In pediatric patients with a history of prior antiretroviral exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, lamivudine should be used with caution. Treatment with lamivudine/zidovudine tablets co-packaged with abacavir tablets should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur *[see Adverse Reactions (6.1)]*.

5.9 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including lamivudine, abacavir and zidovudine. 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.

5.10 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.

6 ADVERSE REACTIONS

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

- Hematologic toxicity, including neutropenia and anemia *[see Boxed Warning, Warnings and Precautions (5.1)]*.
- Symptomatic myopathy *[see Boxed Warning, Warnings and Precautions (5.2)]*.
- Lactic acidosis and hepatomegaly with steatosis *[see Boxed Warning, Warnings and Precautions (5.3)]*.
- Acute exacerbations of hepatitis B *[see Boxed Warning, Warnings and Precautions (5.4)]*.
- Serious and sometimes fatal hypersensitivity reaction. In one study, once-daily dosing of abacavir was associated with more severe hypersensitivity reactions *[see Boxed Warning, Warnings and Precautions (5.5)]*.
- Exacerbation of anemia in HIV/HCV co-infected patients receiving ribavirin and zidovudine *[see Warnings and Precautions (5.7)]*.
- Pancreatitis *[see Warnings and Precautions (5.8)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a ≥5% frequency during therapy with abacavir 300 mg twice daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily compared with indinavir 800 mg 3 times daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily from CNA3005 are listed in Table 3.

Table 1. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2 to 4, ≥5% Frequency) in Therapy-Naive Adults (CNA3005) Through 48 Weeks of Treatment

Adverse Reaction	Abacavir plus Lamivudine/Zidovudine (n = 262)	Indinavir plus Lamivudine/Zidovudine (n = 264)
Nausea	19%	17%
Headache	13%	9%
Malaise and fatigue	12%	12%
Nausea and vomiting	10%	10%
Hypersensitivity reaction	8%	2%
Diarrhea	7%	5%
Fever and/or chills	6%	3%
Depressive disorders	6%	4%
Musculoskeletal pain	5%	7%
Skin rashes	5%	4%
Ear/nose/throat infections	5%	4%
Viral respiratory infections	5%	5%
Anxiety	5%	3%
Renal sign/symptoms	<1%	5%
Pain (non-site-specific)	<1%	5%

Five patients receiving abacavir in study CNA3005 experienced worsening of pre-existing depression compared to none in the indinavir arm. The background rates of pre-existing depression were similar in the 2 treatment arms.

Laboratory Abnormalities: Laboratory abnormalities in study CNA3005 are listed in Table 4.

Table 2. Treatment-Emergent Laboratory Abnormalities (Grades 3 to 4) in Study CNA3005

Grade 3/4 Laboratory Abnormalities	Number of Subjects by Treatment Group	
	Abacavir plus Lamivudine/Zidovudine (n = 262)	Indinavir plus Lamivudine/Zidovudine (n = 264)
Elevated CPK (>4 x ULN)	18 (7%)	18 (7%)
ALT (>5 x ULN)	16 (6%)	16 (6%)
Neutropenia (<750/mm^3)	13 (5%)	13 (5%)
Hypertriglyceridemia (>750 mg/dL)	5 (2%)	3 (1%)
Hyperamylasemia (>2 x ULN)	5 (2%)	1 (<1%)
Hyperglycemia (>13.9 mmol/L)	2 (<1%)	2 (<1%)
Anemia (Hgb ≤6.9 g/dL)	0 (0%)	3 (1%)

ULN = Upper limit of normal.
ANC = Absolute neutrophil count.
n = Number of patients assessed.

6.2 Postmarketing Experience

The following events have been identified during post-approval use of abacavir, lamivudine, zidovudine, and/or combinations of these drug products. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to lamivudine, zidovudine, abacavir and/or the combination products containing two or more of these components.

Abacavir: 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, Zidovudine, and/or Abacavir:

Body as a Whole: Back pain, chest pain, flu-like syndrome, generalized pain, redistribution/accumulation of body fat *[see Warnings and Precautions (5.10)]*.

Cardiovascular: Cardiomyopathy, syncope.

Digestive: Stomatitis.

Endocrine and Metabolic: Gynecomastia, hyperglycemia.

Eye: Macular edema.

Gastrointestinal: Oral mucosal pigmentation, stomatitis, constipation, flatulence.

General: Vasculitis, weakness, sensitization reactions including anaphylaxis, and angioedema.

Hemic and Lymphatic: Anemia, (including pure red cell aplasia and anemias progressing on therapy), hemolytic anemia, leukopenia, lymphadenopathy, splenomegaly.

Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis, pancreatitis, posttreatment exacerbation of hepatitis B *[see Warnings and Precautions (5.3, 5.8)]*.

Hypersensitivity: Sensitization reactions (including anaphylaxis), urticaria.

Musculoskeletal: Muscle weakness, CPK elevation, muscle spasm, myopathy, myositis with pathologic change, (similar to that produced by HIV) rhabdomyolysis.

Nervous: Paresthesia, peripheral neuropathy, seizures.

Respiratory: Abnormal breath sounds/wheezing.

Skin: Alopecia, erythema multiforme, Stevens-Johnson syndrome, pruritis, rash, toxic epidermal necrolysis, sweat, urticaria.

Special Senses: Amblyopia, hearing loss, photophobia, taste perversion.

Urogenital: Urinary frequency, urinary hesitancy.

7 DRUG INTERACTIONS

No clinically significant changes to pharmacokinetic parameters were observed for abacavir, lamivudine or zidovudine when administered together.

7.1 Antiretroviral Agents

Lamivudine: *Zalcitabine:* may inhibit the intracellular phosphorylation of one another. Therefore, use of combination product in combination with zalcitabine is not recommended.

Lamivudine is predominantly eliminated in the urine by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system (e.g., trimethoprim).

Zidovudine: *Stavudine:* Concomitant use of the combination product with stavudine should be avoided since an antagonistic relationship with zidovudine has been demonstrated *in vitro*.

7.2 Doxorubicin

Zidovudine: Concomitant use of lamivudine, zidovudine and abacavir with doxorubicin should be avoided since an antagonistic relationship with zidovudine has been demonstrated *in vitro*.

7.3 Hematologic/Bone Marrow Suppressive/Cytotoxic Agents

Zidovudine: Coadministration of ganciclovir, interferon alfa, ribavirin, and other bone marrow suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine.

7.4 Interferon- and Ribavirin-Based Regimens

No evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV/HCV virologic suppression) was seen when ribavirin was co-administered with the components of lamivudine and zidovudine. However, HIV/HCV co-infected patients who were administered zidovudine, in combination with pegylated interferon and ribavirin developed severe neutropenia (ANC <500) and severe anemia (hemoglobin <8 g/dL) more frequently than similar patients not receiving zidovudine (neutropenia 15% vs. 9%, anemia 5% vs. 1%) *[see Warnings and Precautions (5.7), Clinical Pharmacology (12.3)]*.

7.5 Trimethoprim/Sulfamethoxazole (TMP/SMX)

Trimethoprim (TMP) 160 mg/sulfamethoxazole (SMX) 800 mg once daily has been shown to increase lamivudine exposure (AUC) by 44%. No change in dose of either drug is recommended. The effect of higher doses of TMP/SMX on lamivudine pharmacokinetics has not been investigated *[see clinical Pharmacology (12.3)]*. No data are available regarding the potential for interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

7.6 Ethanol

Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol decreases the elimination of abacavir causing an increase in overall exposure *[see Clinical Pharmacology (12.3)]*.

7.7 Methadone

The addition of methadone has no clinically significant effect on the pharmacokinetic properties of abacavir. In a study of 11 HIV-1-infected patients receiving methadone-maintenance therapy with 600 mg of abacavir sulfate 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 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies of lamivudine and zidovudine in pregnant women. Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. Animal reproduction studies performed with lamivudine, zidovudine and abacavir showed increased embryotoxicity and fetal malformations, and increased embryolethality. Lamivudine/Zidovudine Tablets Co-Packaged with Abacavir Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to lamivudine and zidovudine and other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV infection. Because of both the potential for HIV transmission and serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving lamivudine, zidovudine and abcavir.

Lamivudine and zidovudine are excreted in human breast milk; abacavir and lamivudine are secreted into the milk of lactating rats. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving lamivudine/zidovudine tablets co-packaged with abacavir tablets.

8.4 Pediatric Use

Adjustment of the dose of lamivudine/zidovudine tablets co-packaged with abacavir tablets are not possible; therefore, these products are not recommended for patients <12 years of age or those who weigh <40 kg.

8.5 Geriatric Use

Clinical studies of abacavir, lamivudine, and zidovudine did not include sufficient numbers of patient's aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Lamivudine/Zidovudine Tablets Co-Packaged with Abacavir Tablets are not recommended for patients with impaired renal function (i.e., creatinine clearance <50 mL/min.

8.6 Renal Impairment

Reduction of the dosages of lamivudine/zidovudine tablets co-packaged with abacavir tablets are recommended for patients with impaired renal function. Patients with creatinine clearance less than 50 mL/min should not receive lamivudine/zidovudine tablets co-packaged with abacavir tablets because it is a fixed-dose combination that cannot be adjusted.

8.7 Hepatic Impairment

A reduction in the daily dose of zidovudine may be necessary in patients with mild to moderate impaired hepatic function or liver cirrhosis. Lamivudine/Zidovudine Tablets Co-Packaged with Abacavir Tablets are not recommended for patients with impaired hepatic function because it is a fixed-dose combination that cannot be adjusted.

10 OVERDOSAGE

Lamivudine: One case of an adult ingesting 6 grams of lamivudine was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. 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.

Zidovudine: Acute overdoses of zidovudine have been reported in pediatric patients and adults. These involved exposures up to 50 grams. The only consistent findings were nausea and vomiting. Other reported occurrences included headache, dizziness, drowsiness, lethargy, confusion, and 1 report of a grand mal seizure. Hematologic changes were transient. All patients recovered. Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine, while elimination of its primary metabolite, 3'-azido-3'-deoxy-5'-*O*-*β*-*D*-glucopyranuronosylthymidine (GZDV), is enhanced.

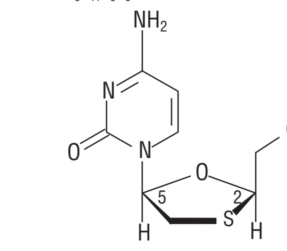
Abacavir: There is no known antidote for abacavir sulfate. It is not known whether abacavir can be removed by peritoneal dialysis or hemodialysis.

11 DESCRIPTION

Lamivudine and Zidovudine: Lamivudine and Zidovudine tablets USP are combination tablets containing lamivudine and zidovudine. Lamivudine (EPIVIR) and zidovudine (RETROVIR, azidothymidine, AZT, or ZDV) are synthetic nucleoside analogues with activity against HIV-1.

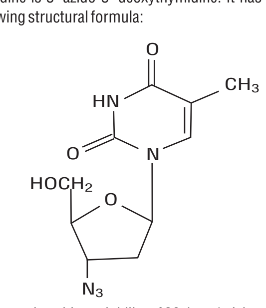
Lamivudine and Zidovudine tablets USP are for oral administration. Each film-coated tablet contains 150 mg of lamivudine, 300 mg of zidovudine, as active ingredients and the inactive ingredients colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

Lamivudine: The chemical name of lamivudine is (2R,cis)-4-amino-l-(2-hydroxymethyl-l,3-oxathiolan-5-yl)-(lH)-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. It has the following structural formula:



Lamivudine USP is a white to off-white solid with a solubility of approximately 70 mg/mL in water at 20°C.

Zidovudine: The chemical name of zidovudine is 3'-azido-3'-deoxythymidine. It has a molecular formula of $C_{10}H_{13}N_5O_4$ and a molecular weight of 267.24. It has the following structural formula:

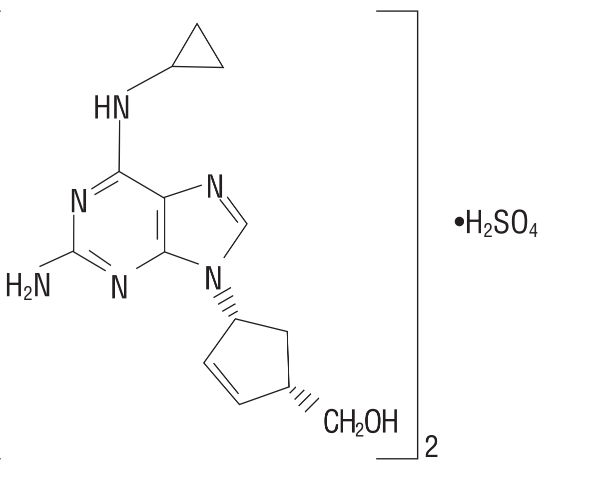


Zidovudine USP is a white to light yellowish powder with a solubility of 20.1 mg/mL in water at 25°C.

Abacavir Tablets USP: Abacavir tablets USP are for oral administration. Each tablet contains abacavir sulfate USP equivalent to 300 mg of abacavir as active ingredient and the following inactive ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablets are coated with a film that is made of hypromellose, iron oxide yellow, polysorbate 80, titanium dioxide, and triacetin.

In vivo, abacavir sulfate dissociates to its free base, abacavir. All dosages for abacavir sulfate are expressed in terms of abacavir.

Abacavir sulfate is a synthetic carbocyclic nucleoside analogue with inhibitory activity against HIV-1. The chemical name of abacavir sulfate is (1*S*,*cis*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-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 $(C_{14}H_{18}N_6O)_2 \cdot H_2SO_4$ and a molecular weight of 670.76 daltons. It has the following structural formula:



Abacavir sulfate USP is a white to off-white powder with a solubility of approximately 77 mg/mL in distilled water at 25°C. It has an octanol/water (pH 7.1 to 7.3) partition coefficient (log *P*) of approximately 1.2 at 25°C.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lamivudine, Zidovudine and Abacavir are antiviral agents *[see Clinical Pharmacology (12.4)]*.

12.3 Pharmacokinetics

Aurobindo Combination Tablets containing lamivudine 150 mg and zidovudine 300 mg are bioequivalent to COMBIVIR® tablets (lamivudine 150 mg, zidovudine 300 mg; GlaxoSmithKline, Research Triangle Park, NC 27709) when administered as a single dose to healthy volunteers under fasting conditions and under fed conditions (high fat, high calorie meal). Aurobindo tablets containing 300 mg abacavir sulfate are bioequivalent to ZIAGEN® tablets (abacavir sulfate 300 mg; GlaxoSmithKline, Research Triangle Park, NC 27709) when administered as a single dose to healthy volunteers under fasting conditions and under fed conditions (high fat, high calorie meal).
Pharmacokinetics in Adults: *Lamivudine and Zidovudine:* One lamivudine and zidovudine tablet was bioequivalent to 1 EPIVIR tablet (150 mg) plus 1 RETROVIR tablet (300 mg) following single-dose administration to fasting healthy subjects (n = 24).

Lamivudine: The pharmacokinetic properties of lamivudine in fasting patients are summarized in Table 3. Following oral administration, lamivudine is rapidly absorbed and extensively distributed. 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). Serum concentrations of this metabolite have not been determined.

Zidovudine: The pharmacokinetic properties of zidovudine in fasting patients are summarized in Table 3. Following oral administration, zidovudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low. Zidovudine is

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⬆ DETACH BEFORE DISPENSING

MEDICATION GUIDE
Lamivudine/Zidovudine Tablets USP 150 mg/300 mg Co-Packaged with Abacavir Tablets USP 300 mg

Read this Medication Guide before you start taking abacavir tablets and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment. Be sure to carry your abacavir tablets Warning Card with you at all times.

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

1. **Serious allergic reaction (hypersensitivity reaction).** Abacavir tablets contain abacavir (also contained in EPZICOM® and TRIZIVIR®). Patients taking abacavir tablets may have a serious allergic reaction (hypersensitivity reaction) that can cause death. 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 tablets, call your healthcare provider right away to find out if you should stop taking abacavir 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 tablets because of an allergic reaction, never take abacavir sulfate or any other abacavir-containing medicine (EPZICOM and TRIZIVIR) again. If you take abacavir sulfate 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 tablets for any other reason, even for a few days, and you are not allergic to abacavir tablets, talk with your healthcare provider before taking them again. Taking abacavir tablets again can cause a serious allergic or life-threatening reaction, even if you never had an allergic reaction to them before.

If your healthcare provider tells you that you can take abacavir tablets again, start taking them when you are around medical help or people who can call a healthcare provider if you need one.

2. **Lactic Acidosis (buildup of acid in the blood). Some human immunodeficiency virus (HIV) medicines, including abacavir tablets, can cause a rare but serious condition called lactic acidosis. Lactic acidosis is a serious medical emergency that can cause death and must be treated in the hospital.**

Call your healthcare provider right away if you get any of the following signs or symptoms of lactic acidosis:

- you feel very weak or tired
- you have unusual (not normal) muscle pain
- you have trouble breathing
- you have stomach pain with nausea and vomiting
- you feel cold, especially in your arms and legs
- you feel dizzy or light-headed
- you have a fast or irregular heartbeat

3. **Serious liver problems. Some people who have taken medicines like abacavir tablets have developed serious liver problems called hepatotoxicity, with liver enlargement (hepatomegaly) and fat in the liver (steatosis). Hepatomegaly with steatosis is a serious medical emergency that can cause death.**

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)
- your urine turns dark
- your bowel movements (stools) turn light in color
- you don't feel like eating food for several days or longer
- you feel sick to your stomach (nausea)
- you have lower stomach area (abdominal) pain

You may be more likely to get lactic acidosis or serious liver problems if you are female, very overweight, or have been taking nucleoside analogue medicines for a long time.

- Muscle weakness (myopathy). Zidovudine, one of the medicines in lamivudine/zidovudine tablets co-packaged with abacavir tablets, can cause muscle weakness. This can be a serious problem.
- Worsening of hepatitis B virus (HBV) infection. Patients with HBV infection who take lamivudine, one of the medicines in lamivudine/zidovudine tablets co-packaged with abacavir tablets, and then stop it, may get "flare-ups" of their hepatitis. "Flare-up" is when the disease suddenly returns in a worse way than before. If you have HBV infection, your doctor should closely monitor your liver function for several months after stopping lamivudine. You may need to take anti-HBV medicines.

What are abacavir tablets?

Abacavir sulfate one of the medications in lamivudine/zidovudine tablets co-packaged with abacavir tablets. Abacavir tablets are a prescription medicine used to treat HIV infection. Abacavir sulfate and lamivudine and zidovudine tablets are called nucleoside analogue reverse transcriptase inhibitors (NRTIs). Abacavir tablets are always used with other anti-HIV medicines. When used in combination with these other medicines, abacavir tablets help lower the amount of HIV in your blood.
Different combinations of medicines are used to treat HIV infection. You and your doctor should discuss which combination of medicines is best for you.

- **Lamivudine/Zidovudine Tablets Co-Packaged with Abacavir Tablets do not cure HIV infection or AIDS.** We do not know if taking lamivudine/zidovudine tablets co-packaged with abacavir tablets will help you live longer or have fewer of the medical problems that people get with HIV or AIDS. It is very important that you see your doctor regularly while you are taking lamivudine/zidovudine tablets co-packaged with abacavir tablets.
- **Lamivudine/Zidovudine Tablets Co-Packaged with Abacavir Tablets do not lower the risk of passing HIV to other people through sexual contact, sharing needles, or being exposed to your blood.** For your health and the health of others, it is important to always practice safe sex by using latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood. Never use or share dirty needles.
- It is very important that you see your doctor regularly while you are taking abacavir tablets.

Who should not take lamivudine/zidovudine tablets co-packaged with abacavir tablets?

Do not take lamivudine/zidovudine tablets co-packaged with abacavir tablets if you:

- are allergic to abacavir or any of the ingredients in abacavir tablets. See the end of this Medication Guide for a complete list of ingredients in abacavir tablets.
- have certain liver problems.

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

Before you take abacavir tablets, tell your healthcare provider if you:

- have hepatitis B virus infection or have other liver problems.
- have heart problems, smoke, or have diseases that increase your risk of heart disease such as high blood pressure, high cholesterol, or diabetes.
- are pregnant or plan to become pregnant. It is

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Black

eliminated primarily by hepatic metabolism. The major metabolite of zidovudine is GZDV. GZDV area under the curve (AUC) is about 3-fold greater than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 14% and 74% of the dose following oral administration, respectively. A second metabolite, 3'-amino-3'-deoxythymidine (AMT), has been identified in plasma. The AMT AUC was one-fifth of the zidovudine AUC.

Abacavir: Following oral administration, abacavir is rapidly absorbed and extensively distributed. Binding of abacavir to human plasma proteins is approximately 50%. Binding of abacavir to plasma proteins was independent of concentration. Total blood and plasma drug-related radioactivity concentrations are identical, demonstrating that abacavir readily distributes into 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.

In humans, abacavir, lamivudine, and zidovudine are not significantly metabolized by cytochrome P450 enzymes.

The pharmacokinetic properties of abacavir, lamivudine, and zidovudine in fasting patients are summarized in Table 3.

Table 3. Pharmacokinetic Parameters* for Abacavir, Lamivudine, and Zidovudine in Adults

Parameter	Abacavir		Lamivudine		Zidovudine	
Oral bioavailability (%)	86 ± 25	n = 6	86 ± 16	n = 12	64 ± 10	n = 5
Apparent volume of distribution (L/kg)	0.86 ± 0.15	n = 6	1.3 ± 0.4	n = 20	1.6 ± 0.6	n = 8
Systemic clearance (L/hr/kg)	0.8 ± 0.24	n = 6	0.33 ± 0.06	n = 20	1.6 ± 0.6	n = 6
Renal clearance (L/hr/kg)	.007 ± .008	n = 6	0.22 ± 0.06	n = 20	0.34 ± 0.05	n = 9
Elimination half-life (hr)†	1.45 ± 0.32	n = 20	5 to 7		0.5 to 3	

*Data presented as mean ± standard deviation except where noted.
†Approximate range.

Effect of Food on Absorption of Lamivudine/Zidovudine Tablets Co-Packaged with Abacavir Tablets: Lamivudine/Zidovudine Tablets Co-Packaged with Abacavir Tablets can be administered with or without food. The extent of lamivudine and zidovudine absorption (AUC) following administration of lamivudine/zidovudine tablets with food was similar when compared to exposure following administration to fasting healthy subjects. The extent of abacavir absorption (AUC) following administration of abacavir tablets with food was similar when compared to exposure following administration to fasting subjects.

Special Populations:

Pregnancy: [See Use in Specific Populations (8.1).]

Pediatric patients: Lamivudine/Zidovudine Tablets Co-Packaged with Abacavir Tablets are not recommended for patients <12 years of age or those who weigh <40 kg, because dose adjustment is not possible for the lamivudine/zidovudine tablets.

Nursing Mothers: [See Use in Specific Populations (8.3).]

Geriatric Patients: The pharmacokinetics of lamivudine, zidovudine and abacavir has not been studied in patients over 65 years of age.

Gender and Race:

Lamivudine and Zidovudine Tablets: A pharmacokinetic study in healthy male (n = 12) and female (n = 12) subjects showed no gender differences in zidovudine exposure (AUC_{∞}) or lamivudine (AUC_{∞}) normalized for body weight.

Lamivudine: There is no significant gender or racial differences in lamivudine pharmacokinetics.

Zidovudine: A pharmacokinetic study in healthy male (n = 12) and female (n = 12) subjects showed no differences in zidovudine exposure (AUC) when a single dose of zidovudine was administered as the 300-mg zidovudine tablet.

Abacavir: A population pharmacokinetic analysis in HIV-infected male (n = 304) and female (n = 67) patients showed no gender differences in abacavir AUC normalized for lean body weight. There are no significant differences between Blacks and Caucasians in abacavir pharmacokinetics.

Drug Interactions: *[See Drug Interactions (7).]*

The drug interactions described are based on studies conducted with the individual nucleoside analogues. In humans, lamivudine, zidovudine and abacavir are not significantly metabolized by cytochrome P450 enzymes; therefore, it is unlikely that clinically significant drug interactions will occur with drugs metabolized through these pathways.

Lamivudine Plus Zidovudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q 12 hr). Other coadministered drugs may alter either lamivudine or zidovudine blood concentrations (Table 2) but dose modification of either are not warranted.

Lamivudine

Lamivudine and trimethoprim/sulfamethoxazole (TMP/SMX) were coadministered to 14 HIV-positive patients in a single-center, open-label, randomized, crossover study. Each patient received treatment with a single 300-mg dose of lamivudine and TMP 160 mg/SMX 800 mg once a day for 5 days with concomitant administration of lamivudine 300 mg with the fifth dose in a crossover design. Coadministration of TMP/SMX with lamivudine resulted in an increase of 44% ± 23% (mean ± SD) in lamivudine AUC_{∞}, a decrease of 29% ± 13% in lamivudine oral clearance, and a decrease of 30% ± 36% in lamivudine renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by coadministration with lamivudine.

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of lamivudine in combination with zalcitabine is not recommended. There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in a study of 19 healthy male subjects.

Zidovudine: See Table 4 and **PRECAUTIONS: Drug Interactions.**

Abacavir: Due to the common metabolic pathways of abacavir and zidovudine via glucuronyl transferase, 15 HIV-infected patients were enrolled in a crossover study 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.

In a study of 11 HIV-infected patients receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of abacavir twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI 6% to 42%). This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients.

Table 4. Effect of Coadministered Drugs on Lamivudine, Zidovudine and Abacavir AUC*

Note: ROUTINE DOSE MODIFICATION OF ABACAVIR, LAMIVUDINE, ZIDOVUDINE AND ABACAVIR ARE NOT WARRANTED WITH COADMINISTRATION OF THE FOLLOWING DRUGS.

Drugs That May Alter Lamivudine Blood Concentrations					
Coadministered Drug and Dose	**Lamivudine Dose**	**n**	**Lamivudine Concentrations**		**Concentration of Coadministered Drug**
			AUC	**Variability**	
Nelfinavir 750 mg q 8 h x 7 to 10 days	Single 150 mg	11	↑ 10%	95% CI: 1% to 20%	↔
Trimethoprim 160 mg/ Sulfamethoxazole 800 mg daily x 5 days	Single 300 mg	14	↑ 43%	90% CI: 32% to 55%	↔
Drugs That May Alter Zidovudine Blood Concentrations					
Coadministered Drug and Dose	**Lamivudine Dose**	**n**	**Lamivudine Concentrations**		**Concentration of Coadministered Drug**
			AUC	**Variability**	
Atovaquone 750 mg q 12 h With food	200 mg q 8 h	14	↑ 31%	Range 23% to 78%†	↔
Fluconazole 400 mg daily	200 mg q 8 h	12	↑ 74%	95% CI: 54% to 98%	Not Reported
Methadone 30 to 90 mg daily	200 mg q 4 h	9	↑ 43%	Range 16% to 64%†	↔
Nelfinavir 750 mg q 8 h x 7 to 10 days	Single 200 mg	11	↓ 35%	Range 28% to 41%	↔
Probenecid 500 mg q 6 h x 2 days	2 mg/kg q 8 h x 3 days	3	↑ 106%	Range 100% to 170%†	Not Assessed
Ritonavir 300 mg q 6 h x 4 days	200 mg q 8 h x 4 days	9	↓ 25%	95% CI: 15% to 34%	↔
Valproic acid 250 mg or 500 mg q 8 h x 4 days	100 mg q 8 h x 4 days	6	↑ 80%	Range 64% to 130%†	Not Assessed
Drugs That May Alter Abacavir Blood Concentrations					
Coadministered Drug and Dose	**Lamivudine Dose**	**n**	**Lamivudine Concentrations**		**Concentration of Coadministered Drug**
			AUC	**Variability**	
Ethanol 0.7 g/kg	single 600mg	24	↑ 41%	90% CI: 35% to 48%	↔

↑ = Increase; ↓ = Decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; CI = confidence interval.

*See **PRECAUTIONS: Drug Interactions** for additional information on drug interactions.
†Estimated range of percent difference.

12.4 Microbiology

Mechanism of Action: *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 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue. 3TC-TP is a weak inhibitor of cellular DNA polymerases α, β, γ.

Zidovudine: Zidovudine is a synthetic nucleoside analogue of the naturally occurring nucleoside, thymidine, in which the 3'-hydroxy (-OH) group is replaced by an azido (-N3) group. Intracellularly, zidovudine is phosphorylated to its active 5'-triphosphate metabolite, zidovudine triphosphate (ZDV-TP). The principal mode of action of ZDV-TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue. ZDV-TP is a weak inhibitor of the cellular DNA polymerases α and γ and has been reported to be incorporated into the DNA of cells in culture.

Abacavir is a carbocyclic synthetic nucleoside analogue. Abacavir is converted by cellular enzymes to the active metabolite, carbovir triphosphate (CBV-TP), an analogue of deoxyguanosine-5′-triphosphate (dGTP). CBV-TP inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation into viral DNA. The lack of a 3′-OH group in the incorporated nucleotide analogue prevents the formation of the 5′ to 3′ phosphodiester linkage essential for DNA chain elongation, and therefore, the viral DNA growth is terminated. CBV-TP is a weak inhibitor of cellular DNA polymerases α, β, and γ.

Antiviral Activity: *Lamivudine Plus Zidovudine:* In HIV-1-infected MT-4 cells, lamivudine in combination with zidovudine at various ratios exhibited synergistic antiretroviral activity.

Lamivudine: In vitro activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes). IC_{50} and IC_{90} values (50% and 90% inhibitory concentrations) for lamivudine were 0.0006 mcg/mL to 0.034 mcg/mL and 0.015 to 0.321 mcg/mL, respectively. Lamivudine had anti–HIV-1 activity in all acute virus-cell infections tested. In HIV-1-infected MT-4 cells, lamivudine in combination with zidovudine at various ratios exhibited synergistic antiretroviral activity.

Zidovudine: In vitro activity of zidovudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes). The IC_{50} and IC_{90} values for zidovudine were 0.003 to 0.013 mcg/mL and 0.03 to 0.13 mcg/mL, respectively. Zidovudine had anti–HIV-1 activity in all acute virus-cell infections tested. However, zidovudine activity was substantially less in chronically infected cell lines. In cell culture drug combination studies with zidovudine, interferon-alpha demonstrated additive activity and zalcitabine, didanosine, saquinavir, indinavir, ritonavir, nevirapine, nelfinavir, efavirenz, and delavirdine demonstrated additive to synergistic activity.

Abacavir: The *in vitro* anti–HIV-1 activity of abacavir was evaluated against a T-cell tropic laboratory strain HIV-1$_{IIIB}$ in lymphoblastic cell lines, a monocyte/macrophage tropic laboratory strain HIV-1$_{BaL}$ in primary monocytes/macrophages, and clinical isolates in peripheral blood mononuclear cells. The concentration of drug necessary to inhibit viral replication by 50 percent (IC_{50}) ranged from 3.7 to 5.8 μM (1 μM = 0.28 mcg/mL) and 0.07 to 1 μM against HIV-1$_{IIIB}$ and HIV-1$_{BaL}$, respectively, and was 0.26 ± 0.18 μM against 8 clinical isolates. The IC_{50} values of abacavir against different HIV-1 clades (A-G) ranged from 0.0015 to 1.05 μM, and against HIV-2 isolates, from 0.024 to 0.49 μM. Abacavir had synergistic activity *in vitro* in combination with the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, and the protease inhibitor (PI) amprenavir; and additive activity in combination with the NRTIs didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine. Ribavirin (50 μM) had no effect on the *in vitro* anti–HIV-1 activity of abacavir.

Resistance: *Lamivudine Plus Zidovudine Administered As Separate Formulations:* In patients receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most patients became phenotypically and genotypically resistant to lamivudine within 12 weeks. In some patients harboring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine plus zidovudine delayed the emergence of amino acid substitutions conferring resistance to zidovudine.

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients after prolonged lamivudine and zidovudine therapy. Dual resistance required the presence of multiple amino acid substitutions, the most essential of which may be G333E. The incidence of dual resistance and the duration of combination therapy required before dual resistance occurs are unknown.

Lamivudine: Lamivudine-resistant isolates of HIV-1 have been selected in cell culture and have also been recovered from patients treated with lamivudine or lamivudine plus zidovudine. Genotypic analysis of isolates selected in cell culture and recovered from lamivudine-treated patients showed that the resistance was due to a specific amino acid substitution in the HIV-1 reverse transcriptase at codon 184 changing the methionine to either isoleucine or valine (MI84V/I).

Mutations in the HBV polymerase YMDD motif have been associated with reduced susceptibility of HBV to lamivudine *in vitro*. In studies of non-HIV-infected patients with chronic hepatitis B, HBV isolates with YMDD mutations were detected in some patients who received lamivudine daily for 6 months or more, and were associated with evidence of diminished treatment response; similar HBV mutants have been reported in HIV-infected patients who received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus

Zidovudine: HIV isolates with reduced susceptibility to zidovudine have been selected in cell culture and were also recovered from patients treated with zidovudine. Genotypic analyses of the isolates selected in cell culture and recovered from zidovudine-treated patients showed substitutions in the HIV-1 RT gene resulting in 6 amino acid substitutions (M41L, D67N, K70R, L210W, T215Y or F, and K219Q) that confer zidovudine resistance. In general, higher levels of resistance were associated with greater number of amino acid substitutions.

Abacavir: Genotypic analysis of isolates selected *in vitro* and recovered from abacavir-treated patients demonstrated that amino acid substitutions K65R, L74V, Y115F, and M184V/I in RT contributed to abacavir resistance. In a study of subjects receiving abacavir once or twice daily in combination with lamivudine and efavirenz once daily, 39% (7/18) of the isolates from patients who experienced virologic failure in the abacavir once-daily arm had a >2.5-fold decrease in abacavir susceptibility with a median-fold decrease of 1.3 (range 0.5 to 11) compared with 29% (5/17) of the failure isolates in the twice-daily arm with a median-fold decrease of 0.92 (range 0.7 to 13).

Cross-Resistance: Cross-resistance has been observed among NRTIs.

Lamivudine Plus Zidovudine: Cross-resistance between lamivudine and zidovudine has not been reported. In some patients treated with lamivudine alone or in combination with zidovudine, isolates have emerged with a substitution at codon 184, which confers resistance to lamivudine. Cross-resistance to abacavir, didanosine, tenofovir, and zalcitabine has been observed in some patients harboring lamivudine-resistant HIV-1 isolates. In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple drugs, including lamivudine, have emerged (see under Zidovudine below).

Lamivudine: Lamivudine-resistant HIV-1 mutants were cross resistant to didanosine (ddI) and zalcitabine (ddC). In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

In one clinical study comparing an antiretroviral regimen containing once daily lamivudine to a regimen containing twice daily lamivudine, 53/554 (10%) patients were identified as virological failures (plasma HIV-1 RNA level 400 copies/mL) by Week 48. Of the 53 failures 28 had been randomized to lamivudine once-daily and 25 to lamivudine twice-daily. Genotypic analysis of on-therapy isolates from patients 22 patients in the lamivudine twice-daily treatment group showed:

- isolates from 1/22 patients contained treatment-emergent zidovudine resistance mutations (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E)
- isolates from 7/22 contained treatment-emergent efavirenz resistance mutations (L100I, K101E, K103N, V108I, or Y181C)
- isolates from 5/22 contained treatment-emergent lamivudine resistance mutations (M184I or M184V)

Phenotypic analysis of baseline-matched on-therapy HIV-1 isolates from 13 patients receiving lamivudine twice daily showed:

- isolates from all 13 patients were susceptible to zidovudine
- isolates from 3/13 patients exhibited a 21- to 342-fold decrease in susceptibility to efavirenz
- isolates from 4/13 patients exhibited a 29- to 159-fold decrease in susceptibility to lamivudine

Zidovudine: The potential for cross-resistance between HIV reverse transcriptase inhibitors and protease inhibitors is low because of the different enzyme targets involved. Combination therapy with zidovudine plus zalcitabine or didanosine does not appear to prevent the emergence of zidovudine-resistant isolates. Combination therapy with zidovudine plus lamivudine delayed the emergence of mutations conferring resistance to zidovudine. In some patients harboring zidovudine-resistant virus, combination therapy with zidovudine plus lamivudine restored phenotypic sensitivity to zidovudine by 12 weeks of treatment.

HIV isolates with multidrug resistance to zidovudine, didanosine, zalcitabine, stavudine, and lamivudine were recovered from a small number of patients treated for ≥1 year with zidovudine plus didanosine or zidovudine plus zalcitabine. The pattern of genotypic resistant mutations with such combination therapies was different (Ala62→Val, Val75→Ile, Phe77→Leu, Phe116→Tyr, and Gln151→Met) from the pattern with zidovudine monotherapy, with the 151 mutation being most commonly associated with multidrug resistance. The mutation at codon 151 in combination with the mutations at 62, 75, 77, and 116 results in a virus with reduced susceptibility to zidovudine, didanosine, zalcitabine, stavudine, and lamivudine.

Multiple-drug resistance has been observed in 2 of 39 (5%) patients receiving zidovudine and didanosine combination therapy for 2 years.

Abacavir: Isolates containing abacavir resistance-associated mutations, namely, K65R, L74V, Y115F, and M184V, exhibited cross-resistance to didanosine, emtricitabine, lamivudine, tenofovir, and zalcitabine *in vitro* and in patients. The K65R mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine; the L74V mutation can confer resistance to abacavir, didanosine, and zalcitabine; and the M184V mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, and zalcitabine. An increasing number of thymidine analogue mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219E/R/H/Q/N) is associated with a progressive reduction in abacavir susceptibility.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity:

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) those observed in humans at the recommended therapeutic dose for HIV infection.

Zidovudine: Zidovudine was administered orally at 3 dosage levels to separate groups of mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60, and 120 mg/kg/day in mice and 80, 220, and 600 mg/kg/day in rats. The doses in mice were reduced to 20, 30, and 40 mg/kg/day after day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg/kg/day on day 91 and then to 300 mg/kg/day on day 279.

In mice, 7 late-appearing (after 19 months) vaginal neoplasms (5 nonmetastasizing squamous cell carcinomas, 1 squamous cell papilloma, and 1 squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of a middle-dose animal. No vaginal tumors were found at the lowest dose.

In rats, 2 late appearing (after 20 months), nonmetastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle dose in rats. No other drug-related tumors were observed in either sex of either species.

At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 3 times (mouse) and 24 times (rat) the estimated human exposure at the recommended therapeutic dose of 100 mg every 4 hours.

Two transplacental carcinogenicity studies were conducted in mice. One study administered zidovudine at doses of 20 mg/kg/day or 40 mg/kg/day from gestation day 10 through parturition and lactation with dosing continuing in offspring for 24 months postnatally. The doses of zidovudine employed in this study produced zidovudine exposures approximately 3 times the estimated human exposure at recommended doses. After 24 months at the highest dose, an increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in either gender. These findings are consistent with results of the standard oral carcinogenicity study in mice, as described earlier. A second study administered zidovudine at maximum tolerated doses of 12.5 mg/day or 25 mg/day (~1,000 mg/kg nonpregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from days 12 through 18 of gestation. There was an increase in the number of tumors in the lung, liver, and female reproductive tracts in the offspring of mice receiving the higher dose level of zidovudine. It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

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.

Mutagenicity:

Lamivudine: Lamivudine was negative in a microbial mutagenicity screen, 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. It was mutagenic in an L5178Y/$TK^{+/-}$ mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes.

Zidovudine: Zidovudine was mutagenic in an L5178Y/$TK^{+/-}$ mouse lymphoma assay, positive in an *in vitro* cell transformation assay, clastogenic in a cytogenetic assay using cultured human lymphocytes, and positive in mouse and rat micronucleus tests after repeated doses. It was negative in a cytogenetic study in rats given a single dose.

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/$TK^{+/-}$ 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.

Impairment of Fertility:

Lamivudine: In a study of reproductive performance, lamivudine, administered to male and female rats at doses up to 130 times the usual adult dose based on body surface area considerations, revealed no evidence of impaired fertility (judged by conception rates) and no effect on the survival, growth, and development to weaning of the offspring.

Zidovudine: Zidovudine, administered to male and female rats at doses up to 7 times the usual adult dose based on body surface area considerations, had no effect on fertility judged by conception rates.

Abacavir: Abacavir had no adverse effects on the mating performance or fertility of male and female rats at a dose approximately 8 times the human exposure at the recommended dose based on body surface area comparisons.

13.2 Reproductive and Developmental Toxicology Studies

Lamivudine: Reproduction studies have been performed in rats and rabbits at orally administered doses up to 4,000 mg/kg/day and 1,000 mg/kg/day, respectively, producing plasma levels up to approximately 35 times that for the adult HIV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryolethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 35 times those in humans. Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta.

In 2 clinical studies conducted in South Africa, pharmacokinetic measurements were performed on samples from pregnant women who received lamivudine beginning at week 38 of gestation (10 women who received 150 mg twice daily in combination with zidovudine and 10 who received lamivudine 300 mg twice daily without other antiretrovirals) or beginning at week 36 of gestation (16 women who received lamivudine 150 mg twice daily in combination with zidovudine). These studies were not designed or powered to provide efficacy information.

Lamivudine pharmacokinetics in the pregnant women were similar to those obtained following birth and in non-pregnant adults. Lamivudine concentrations were generally similar in maternal, neonatal, and cord serum samples. In a subset of subjects from whom amniotic fluid specimens were obtained following natural rupture of membranes, amniotic fluid concentrations of lamivudine ranged from 1.2 to 2.5 mcg/mL (150 mg twice daily) and 2.1 to 5.2 mcg/mL (300 mg twice daily) and were typically greater than 2 times the maternal serum levels.

Zidovudine: Oral teratology studies in the rat and in the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal toxicity as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one-half of the daily dose) in rats 66 to 226 times, and in rabbits 12 to 87 times, mean steady-state peak human plasma concentrations (after one-sixth of the daily dose) achieved with the recommended daily dose (100 mg every 4 hours). In an *in vitro* experiment with fertilized mouse oocytes, zidovudine exposure resulted in a dose-dependent reduction in blastocyst formation. In an additional teratology study in rats, a dose of 3,000 mg/kg/day (very near the oral median lethal dose in rats of 3,683 mg/kg) caused marked maternal toxicity and an increase in the incidence of fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations. (Estimated AUC in rats at this dose level was 300 times the daily AUC in humans given 600 mg/day.) No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg/day or less.

A randomized, double blind, placebo-controlled trial was conducted in HIV-infected pregnant women to determine the utility of zidovudine for the prevention of maternal-fetal HIV-transmission. Congenital abnormalities occurred with similar frequency between neonates born to mothers who received zidovudine and neonates born to mothers who received placebo. Abnormalities were either problems in embryogenesis (prior to 14 weeks) or were recognized on ultrasound before or immediately after initiation of study drug.

Abacavir: Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. Fetal malformations (increased incidences of fetal anasarca and skeletal malformations) and developmental toxicity (depressed fetal body weight and reduced crown-rump length) were observed in rats at a dose which produced 35 times the human exposure, based on AUC. Embryonic and fetal toxicities (increased resorptions, decreased fetal body weights) and toxicities to the offspring (increased incidence of stillbirth and lower body weights) occurred at half of the above-mentioned dose in separate fertility studies conducted in rats. In the rabbit, no developmental toxicity and no increases in fetal malformations occurred at doses that produced 8.5 times the human exposure at the recommended dose based on AUC.

14 CLINICAL STUDIES

14.1 Adults

CNA3005 was a multicenter, double-blind, controlled study in which 562 HIV-infected, therapy-naive adults were randomized to receive either abacavir (300 mg twice daily) plus (lamivudine 150 mg/zidovudine 300 mg twice daily), or indinavir (800 mg 3 times a day) plus lamivudine 150 mg/zidovudine 300 mg twice daily. The study was stratified at randomization by pre-entry plasma HIV-1 RNA 10,000 to 100,000 copies/mL and plasma HIV-1 RNA >100,000 copies/mL. Study participants were male (87%), Caucasian (73%), Black (15%), and Hispanic (9%). At baseline the median age was 36 years, the median pretreatment CD4+ cell count was 360 cells/mm3, and median plasma HIV-1 RNA was 4.8 log10 copies/mL. Proportions of patients with plasma HIV-1 RNA <400 copies/mL (using Roche Amplicor HIV-1 MONITOR Test) through 48 weeks of treatment are summarized in Table 5.

Table 5. Outcomes of Randomized Treatment Through Week 48 (CNA3005)

Outcome	Abacavir plus Lamivudine, Zidovudine (n = 262)	Indinavir plus Lamivudine, Zidovudine (n = 265)
Responder*	49%	50%
Virologic failure†	31%	28%
Discontinued due to adverse reactions	10%	12%
Discontinued due to other reasons‡	11%	10%

*Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL.
†Includes viral rebound and failure to achieve confirmed <400 copies/mL by Week 48.
‡Includes consent withdrawn, lost to follow up, protocol violations, those with missing data, clinical progression, and other.

Treatment response by plasma HIV-1 RNA strata is shown in Table 6.

Table 6. Proportions of Responders Through Week 48 By Screening PlasmaHIV-1 RNA Levels (CNA3005)

Screening HIV-1 RNA (copies/mL)	Abacavir plus Lamivudine, Zidovudine (n = 262)		Indinavir plus Lamivudine, Zidovudine (n = 265)	
	<400 copies/mL	n	<400 copies/mL	n
≥10,000 -≤100,000	50%	166	48%	165
>100,000	48%	96	52%	100

In subjects with baseline viral load >100,000 copies/mL, percentages of patients with HIV-1 RNA levels <50 copies/mL were 31% in the group receiving abacavir vs. 45% in the group receiving indinavir.

Through Week 48, an overall mean increase in CD4+ cell count of about 150 cells/mm^3 was observed in both treatment arms. **Through Week 48, 9 subjects (3.4%) in the group receiving abacavir sulfate (6 CDC classification C events and 3 deaths) and 3 subjects (1.5%) in the group receiving indinavir (2 CDC classification C events and 1 death) experienced clinical disease progression.**

14.2 Prevention of Maternal-Fetal HIV-1 Transmission

The utility of zidovudine alone for the prevention of maternal-fetal HIV-1 transmission was demonstrated in a randomized, double-blind, placebo-controlled trial conducted in HIV-1-infected pregnant women with CD4+ cell counts of 200 to 1,818 cells/mm^3 (median in the treated group: 560 cells/mm3) who had little or no previous exposure to zidovudine. Oral zidovudine was initiated between 14 and 34 weeks of gestation (median 11 weeks of therapy) followed by IV administration of zidovudine during labor and delivery. Following birth, neonates received oral zidovudine syrup for 6 weeks. The study showed a statistically significant difference in the incidence of HIV-1 infection in the neonates (based on viral culture from peripheral blood) between the group receiving zidovudine and the group receiving placebo. Of 363 neonates evaluated in the study, the estimated risk of HIV-1 infection was 7.8% in the group receiving zidovudine and 24.9% in the placebo group, a relative reduction in transmission risk of 68.7%. Zidovudine was well tolerated by mothers and infants. There was no difference in pregnancy-related adverse events between the treatment groups.

16 HOW SUPPLIED/STORAGE AND HANDLING

Lamivudine and Zidovudine Tablets USP, containing 150 mg lamivudine and 300 mg zidovudine, are white to off-white, modified capsule shaped, biconvex, film-coated tablets with deep breakline in between 'C' and '60' on one side and deep breakline on the other side.

Abacavir Tablets USP, containing abacavir sulfate equivalent to 300 mg abacavir, are yellow colored, biconvex, capsule shaped, coated tablet, debossed with 'D' and '88' on either side of the score line on one side and plain with a score line on other side. They are packaged as follows:

Co-package: A carton containing 60 lamivudine/zidovudine tablets USP 150 mg/300 mg co-packaged with 60 abacavir tablets USP 300 mg in six blister cards. Each blister card contains five co-packages with perforation in between and each co-package contains two lamivudine/ zidovudine tablets USP 150 mg/300 mg and two abacavir tablets USP 300 mg.

30 co-packages NDC 65862-114-08

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Store in a safe place out of the reach of children.

17 PATIENT COUNSELING INFORMATION

17.1 Advice for the Patient

Neutropenia and Anemia: Patients should be informed that the important toxicities associated with zidovudine are neutropenia and/or anemia. They should be told of the extreme importance of having their blood counts followed closely while on therapy, especially for patients with advanced HIV-1 disease *[see Boxed Warning, Warnings and Precautions (5.1)]*.

Myopathy: Patients should be informed that myopathy and myositis with pathological changes, similar to that produced by HIV-1 disease, have been associated with prolonged use of zidovudine *[see Warnings and Precautions (5.2)]*.

Lactic Acidosis/Hepatomegaly: Patients should be informed that some HIV medicines, including lamivudine, zidovudine and abacavir can cause a rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly) *[see Warnings and Precautions (5.3)]*.

HIV-1/HBV Co-Infection: Patients co-infected with HIV-1 and HBV should be informed that deterioration of liver disease has occurred in some cases when treatment with lamivudine was discontinued. Patients should be advised to discuss any changes in regimen with their physician *[see Warnings and Precautions (5.4)]*.

Hypersensitivity Reaction: 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 sulfate, and encourage the patient to read the Medication Guide and Warning Card every time to obtain any new information that may be present about abacavir sulfate. (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 Medication Guide]*.
- that if they develop symptoms consistent with a hypersensitivity reaction they should call their doctor right away to determine if they should stop taking abacavir sulfate.
- that a hypersensitivity reaction can worsen and lead to hospitalization or death if abacavir sulfate is not immediately discontinued.
- that in one study, more severe hypersensitivity reactions were seen when abacavir sulfate was dosed 600 mg once daily.
- to not restart abacavir sulfate 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 a hypersensitivity reaction is usually reversible if it is detected promptly and abacavir sulfate is stopped right away.
- that if they have interrupted abacavir sulfate 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 sulfate or any other abacavir-containing product without medical consultation and that restarting abacavir needs to be undertaken only if medical care can be readily accessed by the patient or others.
- abacavir sulfate should not be coadministered with EPZICOM® (abacavir sulfate and lamivudine) tablets or TRIZIVIR® (abacavir sulfate, lamivudine, and zidovudine) tablets.

Use With Other Lamivudine-, Zidovudine-, and/or Emtricitabine-Containing Products:
Lamivudine/Zidovudine Tablets Co-Packaged with Abacavir Tablets should not be coadministered with drugs containing abacavir, lamivudine, and zidovudine including: COMBIVIR® (lamivudine and zidovudine), EPZICOM® (abacavir sulfate and lamivudine) tablets, TRIZIVIR® (abacavir sulfate, lamivudine, and zidovudine) tablets or emtricitabine-containing products, including ATRIPLA® (efavirenz, emtricitabine, and tenofovir), EMTRIVA® (emtricitabine), TRUVADA® (emtricitabine and tenofovir) or COMPLERA™ (rilpivirine/emtricitabine/tenofovir) *[see Warnings and Precautions (5.6)]*.

HIV-1/HCV Co-Infection: Patients with HIV-1/HCV co-infection should be informed 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)]*.

Redistribution/Accumulation of Body Fat: Patients should be informed 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 (5.10)]*.

Information About HIV-1 Infection: Lamivudine/Zidovudine Tablets Co-Packaged with Abacavir Tablets are not a cure for HIV infection. Patients should be advised of the importance of taking lamivudine/zidovudine tablets co-packaged with abacavir tablets on a regular dosing schedule as prescribed and to avoid missing doses.

Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** Lamivudine and zidovudine are excreted in human breast milk. Mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

Patients should be informed to take all HIV medications exactly as prescribed.

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Manufactured for:
Aurobindo Pharma USA, Inc.
2400 Route 130 North
Dayton, NJ 08810

Manufactured by:
Aurobindo Pharma Limited
Hyderabad-500 072, India

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MEDICATION GUIDE

Lamivudine/Zidovudine Tablets USP 150 mg/300 mg
Co-Packaged with Abacavir Tablets USP 300 mg

Read this Medication Guide before you start taking abacavir tablets and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment. Be sure to carry your abacavir tablets Warning Card with you at all times.

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

1. Serious allergic reaction (hypersensitivity reaction). Abacavir tablets contain abacavir (also contained in EPZICOM® and TRIZIVIR®). Patients taking abacavir tablets may have a serious allergic reaction (hypersensitivity reaction) that can cause death. 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 tablets, call your healthcare provider right away to find out if you should stop taking abacavir 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 tablets because of an allergic reaction, never take abacavir sulfate or any other abacavir-containing medicine (EPZICOM and TRIZIVIR) again. If you take abacavir sulfate 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 tablets for any other reason, even for a few days, and you are not allergic to abacavir tablets, talk with your healthcare provider before taking them again. Taking abacavir tablets again can cause a serious allergic or life-threatening reaction, even if you never had an allergic reaction to them before.

   If your healthcare provider tells you that you can take abacavir tablets again, start taking them when you are around medical help or people who can call a healthcare provider if you need one.

2. **Lactic Acidosis (buildup of acid in the blood). Some human immunodeficiency virus (HIV) medicines, including abacavir tablets, can cause a rare but serious condition called lactic acidosis. Lactic acidosis is a serious medical emergency that can cause death and must be treated in the hospital.**

   Call your healthcare provider right away if you get any of the following signs or symptoms of lactic acidosis:
   - you feel very weak or tired
   - you have unusual (not normal) muscle pain
   - you have trouble breathing
   - you have stomach pain with nausea and vomiting
   - you feel cold, especially in your arms and legs
   - you feel dizzy or light-headed
   - you have a fast or irregular heartbeat

3. **Serious liver problems. Some people who have taken medicines like abacavir tablets have developed serious liver problems called hepatotoxicity, with liver enlargement (hepatomegaly) and fat in the liver (steatosis). Hepatomegaly with steatosis is a serious medical emergency that can cause death.**

   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)
   - your urine turns dark
   - your bowel movements (stools) turn light in color
   - you don't feel like eating food for several days or longer
   - you feel sick to your stomach (nausea)
   - you have lower stomach area (abdominal) pain

   You may be more likely to get lactic acidosis or serious liver problems if you are female, very overweight, or have been taking nucleoside analogue medicines for a long time.

- Muscle weakness (myopathy). Zidovudine, one of the medicines in lamivudine/zidovudine tablets co-packaged with abacavir tablets, can cause muscle weakness. This can be a serious problem.
- Worsening of hepatitis B virus (HBV) infection. Patients with HBV infection who take lamivudine, one of the medicines in lamivudine/zidovudine tablets co-packaged with abacavir tablets, and then stop it, may get "flare-ups" of their hepatitis. "Flare-up" is when the disease suddenly returns in a worse way than before. If you have HBV infection, your doctor should closely monitor your liver function for several months after stopping lamivudine. You may need to take anti-HBV medicines.

What are abacavir tablets?

Abacavir sulfate one of the medications in lamivudine/zidovudine tablets co-packaged with abacavir tablets. Abacavir tablets are a prescription medicine used to treat HIV infection. Abacavir sulfate and lamivudine and zidovudine tablets are called nucleoside analogue reverse transcriptase inhibitors (NRTIs). Abacavir tablets are always used with other anti-HIV medicines. When used in combination with these other medicines, abacavir tablets help lower the amount of HIV in your blood.

Different combinations of medicines are used to treat HIV infection. You and your doctor should discuss which combination of medicines is best for you.

- **Lamivudine/Zidovudine Tablets Co-Packaged with Abacavir Tablets do not cure HIV infection or AIDS.** We do not know if taking lamivudine/zidovudine tablets co-packaged with abacavir tablets will help you live longer or have fewer of the medical problems that people get with HIV or AIDS. It is very important that you see your doctor regularly while you are taking lamivudine/zidovudine tablets co-packaged with abacavir tablets.
- **Lamivudine/Zidovudine Tablets Co-Packaged with Abacavir Tablets do not lower the risk of passing HIV to other people through sexual contact, sharing needles, or being exposed to your blood.** For your health and the health of others, it is important to always practice safe sex by using latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood. Never use or share dirty needles.
- It is very important that you see your doctor regularly while you are taking abacavir tablets.

Who should not take lamivudine/zidovudine tablets co-packaged with abacavir tablets?

Do not take lamivudine/zidovudine tablets co-packaged with abacavir tablets if you:

- are allergic to abacavir or any of the ingredients in abacavir tablets. See the end of this Medication Guide for a complete list of ingredients in abacavir tablets.
- have certain liver problems.

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

Before you take abacavir tablets, tell your healthcare provider if you:

- have hepatitis B virus infection or have other liver problems.
- have heart problems, smoke, or have diseases that increase your risk of heart disease such as high blood pressure, high cholesterol, or diabetes.
- are pregnant or plan to become pregnant. It is not known if abacavir tablets will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
- **Pregnancy Registry.** If you take abacavir tablets while you are pregnant, talk to your healthcare provider about how you can take part in the Pregnancy Registry for abacavir tablets. The purpose of the Pregnancy Registry is to collect information about the health of you and your baby.
- **are breastfeeding or plan to breastfeed. Do not breastfeed.** We do not know if abacavir sulfate can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.
- **Tell your healthcare provider about all the medicines you take,** including prescription and nonprescription medicines, vitamins, and herbal supplements.

Especially tell your healthcare provider if you take:

- alcohol
- methadone
- trimethoprim (TMP/sulfamethoxazole)
- Ganciclovir
- interferon-alfa
- doxorubicin
- ribavirin
- any bone marrow suppressive medicines or cytotoxic medicines. Ask your doctor if you are not sure.
- any of the following anti-HIV medicines: Combivir® (lamivudine and zidovudine), Emtriva™ (emtricitabine), Epivir or Epivir-HBV® (lamivudine, 3TC), Epzicom

(abacavir sulfate and lamivudine), Hivid® (zalcitabine, ddC), Retrovir (zidovudine, AZT, or ZDV), Truvada® (emtricitabine and tenofovir), Zerit® (stavudine, d4T), or Ziagen® (abacavir sulfate).

How should I take lamivudine/zidovudine tablets co-packaged with abacavir tablets?

- Take abacavir tablets exactly as your healthcare provider tells you to take them.
  Abacavir tablets are taken by mouth as a tablet. The usual doses are 1 tablet twice a day along with Lamivudine and Zidovudine tablets. Do not skip doses.
- Abacavir tablets may be taken with or without food.
- If you miss a dose of lamivudine/zidovudine tablets co-packaged with abacavir tablets, take the missed dose right away. Then, take the next dose at the usual time. Do not skip doses.
- Do not let your abacavir tablets run out.
- Starting abacavir sulfate again can cause a serious allergic or life-threatening reaction, even if you never had an allergic reaction to it before. If you run out of abacavir sulfate even for a few days, you must ask your doctor if you can start abacavir sulfate again. If your doctor tells you that you can take abacavir sulfate again, start taking it when you are around medical help or people who can call a doctor if you need one.
- If you stop your anti-HIV medicines, even for a short time, the amount of virus in your blood may increase and the virus may become harder to treat. If you take too much abacavir sulfate, call your healthcare provider or poison control center or go to the nearest hospital emergency room right away.

What are the possible side effects of lamivudine/zidovudine tablets co-packaged with abacavir tablets?

- Abacavir tablets can cause serious side effects including allergic reactions, lactic acidosis, and liver problems. See **"What is the most important information I should know about abacavir tablets?"**
- **Lactic acidosis with liver enlargement (hepatomegaly) that can cause death.** See **"What is the most important information I should know about abacavir sulfate?"**
- **Changes in body fat (fat redistribution).** Changes in body fat (lipoatrophy or lipodystrophy) can happen in some people taking antiretroviral medicines including abacavir tablets.

  These changes may include:
- more fat in or around your trunk, upper back and neck (buffalo hump), breast, or chest loss of fat in your legs, arms, or face
- **Heart attack (myocardial infarction).** Some HIV medicines including abacavir tablets may increase your risk of heart attack.

The most common side effects of lamivudine/zidovudine tablets co-packaged with abacavir tablets in adults include:

- bad dreams or sleep problems
- nausea
- headache
- tiredness
- vomiting
- fever and chills
- loss of appetite

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 lamivudine/zidovudine tablets co-packaged with abacavir tablets. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store lamivudine/zidovudine tablets co-packaged with abacavir tablets?

- Store lamivudine/zidovudine tablets co-packaged with abacavir tablets at room temperature, between 20° to 25°C (68° to 77°F).
- Do not freeze abacavir tablets.
- **Keep lamivudine/zidovudine tablets co-packaged with abacavir tablets and all medicines out of the reach of children.**

General information for safe and effective use of lamivudine/zidovudine tablets co-packaged with abacavir tablets

Avoid doing things that can spread HIV-1 infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

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

This Medication Guide summarizes the most important information about abacavir tablets. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for the information that is written for healthcare professionals.

For more information call 1-866-850-2876.

What are the ingredients in abacavir tablets?

Lamivudine/Zidovudine Tablets:

Each film-coated tablet contains 150 mg of lamivudine, 300 mg of zidovudine as active ingredients, and the following inactive ingredients: colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate and titanium dioxide.

Abacavir Tablets:

Each tablet contains abacavir sulfate equivalent to 300 mg of abacavir as active ingredient and the following inactive ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The film-coating is made of hypromellose, polysorbate 80, iron oxide yellow, titanium dioxide, and triacetin.

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

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Manufactured for:
Aurobindo Pharma USA, Inc.
2400 Route 130 North
Dayton, NJ 08810

Manufactured by:
Aurobindo Pharma Limited
Hyderabad-500 072, India

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⬆ **DETACH BEFORE DISPENSING**

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Especially tell your healthcare provider if you take:

- alcohol
- methadone
- trimethoprim (TMP/sulfamethoxazole)
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