HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EPZICOM safely and effectively. See full prescribing information for EPZICOM.

EPZICOM (abacavir sulfate and lamivudine) Tablets, for oral use

Initial U.S. Approval: 2004

WARNING: RISK OF HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, AND EXACERBATIONS OF HEPATITIS

See full prescribing information for complete boxed warning.

- **Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir-containing products. (5.1)**
- **Hypersensitivity to abacavir is a multi-organ clinical syndrome. (5.1)**
- **Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. (5.1)**
- **Discontinue EPZICOM as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B*5701 status, permanently discontinue EPZICOM if hypersensitivity cannot be ruled out, even when other diagnoses are possible. (5.1)**
- **Following a hypersensitivity reaction to abacavir, NEVER restart EPZICOM or any other abacavir-containing product. (5.1)**
- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. (5.2)**
- **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 EPZICOM. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.3)**

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2)	05/2012
Warnings and Precautions, Hypersensitivity Reaction (5.1)	05/2012
Warnings and Precautions, Immune Reconstitution Syndrome (5.5)	11/2011

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

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

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

- A medication guide and warning card should be dispensed with each new prescription and refill. (2)
- Adults: One tablet daily. (2.1)
- Do not prescribe for patients requiring a dosage adjustment or patients with hepatic impairment. (2.2)

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

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

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

- Previously demonstrated hypersensitivity to abacavir or any other component of the product. (4, 5.1)
- Hepatic impairment. (4)

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

- See boxed warning for information about the following: hypersensitivity reactions, lactic acidosis and severe hepatomegaly, and severe acute exacerbations of hepatitis B. (5.1, 5.2, 5.3)
- Hepatic decompensation, some fatal, has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy and interferon alfa with or without ribavirin. Discontinue EPZICOM as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.4)
- Immune reconstitution syndrome (5.5) and redistribution/accumulation of body fat have been reported in patients treated with combination antiretroviral therapy. (5.6)
- EPZICOM should not be administered with other lamivudine- or zidovudine-containing products or emtricitabine-containing products. (5.8)

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

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

To report SUSPECTED ADVERSE REACTIONS, contact ViiV Healthcare at 1-877-844-8872 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Ethanol: Decreases elimination of abacavir. (7.2)
- Methadone: An increased methadone dose may be required in a small number of patients. (7.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: RISK OF HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, AND EXACERBATIONS OF HEPATITIS B

Hypersensitivity Reactions: Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate, a component of EPZICOM® (abacavir sulfate and lamivudine) Tablets.

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 EPZICOM as soon as a hypersensitivity reaction is suspected.

Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, screening for the HLA-B*5701 allele is recommended; this approach has been found to decrease the risk of hypersensitivity reaction. Screening is also recommended prior to reinitiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. HLA-B*5701-negative patients may develop a suspected hypersensitivity reaction to abacavir; however, this occurs significantly less frequently than in HLA-B*5701-positive patients.

Regardless of HLA-B*5701 status, permanently discontinue EPZICOM if hypersensitivity cannot be ruled out, even when other diagnoses are possible.

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

Reintroduction of EPZICOM or any other abacavir-containing product, even in patients who have no identified history or unrecognized symptoms of hypersensitivity to abacavir therapy, can result in serious or fatal hypersensitivity reactions. Such reactions can occur within hours *[see Warnings and Precautions (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 abacavir, lamivudine, and other antiretrovirals *[see Warnings and Precautions (5.2)]*.

Exacerbations of Hepatitis B: Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine, which is one component of EPZICOM. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue

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

1 INDICATIONS AND USAGE

EPZICOM Tablets, in combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection.

Additional important information on the use of EPZICOM for treatment of HIV-1 infection:

- EPZICOM is one of multiple products containing abacavir. Before starting EPZICOM, 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 (5.1), Adverse Reactions (6)]*.
- As part of a triple-drug regimen, EPZICOM Tablets are recommended for use with antiretroviral agents from different pharmacological classes and not with other nucleoside/nucleotide reverse transcriptase inhibitors.

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.
- EPZICOM can be taken with or without food.

2.1 Adult Patients

The recommended oral dose of EPZICOM for adults is one tablet daily, in combination with other antiretroviral agents.

2.2 Dosage Adjustment

Because it is a fixed-dose combination, EPZICOM should not be prescribed for:

- patients requiring dosage adjustment such as those with creatinine clearance <50 mL/min,
- patients with hepatic impairment.

Use of EPIVIR® (lamivudine) Oral Solution or Tablets and ZIAGEN® (abacavir sulfate) Oral Solution may be considered.

3 DOSAGE FORMS AND STRENGTHS

EPZICOM Tablets contain 600 mg of abacavir as abacavir sulfate and 300 mg of lamivudine. The tablets are modified capsule-shaped, orange, film-coated, and debossed with "GS FC2" on one side with no markings on the reverse side.

4 CONTRAINDICATIONS

EPZICOM Tablets are contraindicated in patients with:

- previously demonstrated hypersensitivity to abacavir or to any other component of the product. NEVER restart EPZICOM or any other abacavir-containing product following a

hypersensitivity reaction to abacavir, regardless of HLA-B*5701 status *[see Warnings and Precautions (5.1), Adverse Reactions (6)]*.

- hepatic impairment *[see Use in Specific Populations (8.7)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reaction

Serious and sometimes fatal hypersensitivity reactions have been associated with EPZICOM and other abacavir-containing products. Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, screening for the HLA-B*5701 allele is recommended; this approach has been found to decrease the risk of a hypersensitivity reaction. Screening is also recommended prior to reinitiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. For HLA-B*5701-positive patients, treatment with an abacavir-containing regimen is not recommended and should be considered only with close medical supervision and under exceptional circumstances when the potential benefit outweighs the risk.

HLA-B*5701-negative patients may develop a hypersensitivity reaction to abacavir; however, this occurs significantly less frequently than in HLA-B*5701-positive patients. Regardless of HLA-B*5701 status, permanently discontinue EPZICOM 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.

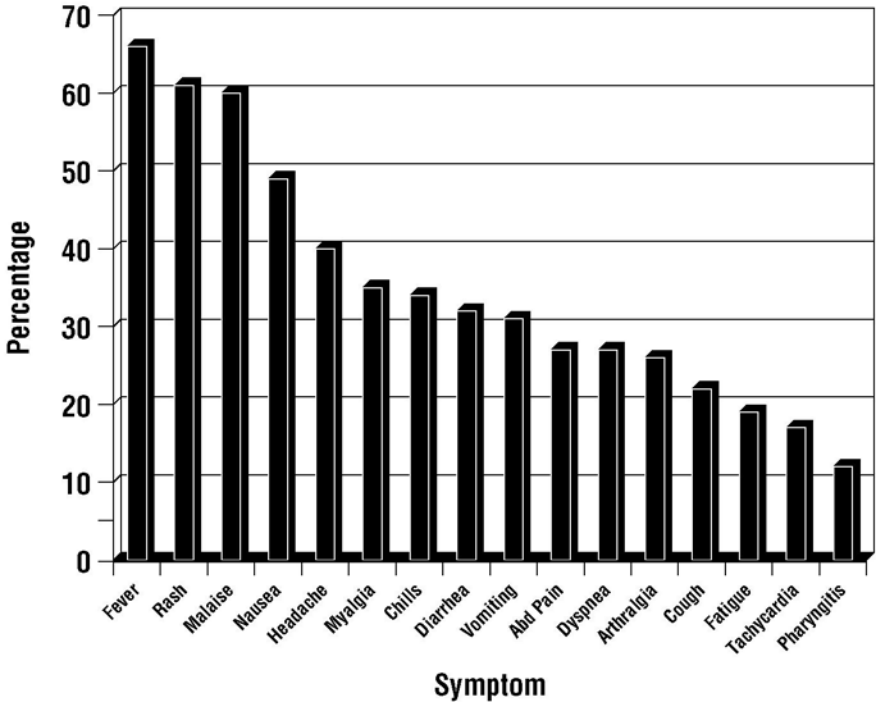
Signs and Symptoms of Hypersensitivity: Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups.

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 subjects (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 subjects reported symptoms from 2 or more of the 5 groups listed above.

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



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. In one trial, 4 subjects (11%) receiving ZIAGEN 600 mg once daily experienced hypotension with a hypersensitivity reaction compared with 0 subjects receiving ZIAGEN 300 mg twice daily.

Physical findings associated with hypersensitivity to abacavir in some subjects 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 subjects include elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, and lymphopenia.

Clinical Management of Hypersensitivity: Discontinue EPZICOM as soon as a hypersensitivity reaction is suspected. To minimize the risk of a life-threatening hypersensitivity reaction, permanently discontinue EPZICOM 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 EPZICOM 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 EPZICOM has been discontinued for reasons other than symptoms of a hypersensitivity reaction, and if reinitiation of EPZICOM or any other abacavir-containing product is under consideration, carefully evaluate the reason for discontinuation of EPZICOM to ensure that the patient did not have symptoms of a hypersensitivity reaction. If the patient is of unknown HLA-B*5701 status, screening for the allele is recommended prior to reinitiation of EPZICOM.

If hypersensitivity cannot be ruled out, DO NOT reintroduce EPZICOM or any other abacavir-containing product. Even in the absence of the HLA-B*5701 allele, it is important to permanently discontinue abacavir and not rechallenge with abacavir if a hypersensitivity reaction cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

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 EPZICOM or any other abacavir-containing product and that reintroduction of EPZICOM or introduction of any other abacavir-containing product needs to be undertaken only if medical care can be readily accessed by the patient or others.

Risk Factor: *HLA-B*5701 Allele:* Trials have shown that carriage of the HLA-B*5701 allele is associated with a significantly increased risk of a hypersensitivity reaction to abacavir.

CNA106030 (PREDICT-1), a randomized, double-blind trial, evaluated the clinical utility of prospective HLA-B*5701 screening on the incidence of abacavir hypersensitivity reaction in abacavir-naive HIV-1-infected adults (n = 1,650). In this trial, use of pre-therapy screening for the HLA-B*5701 allele and exclusion of subjects with this allele reduced the incidence of clinically suspected abacavir hypersensitivity reactions from 7.8% (66/847) to 3.4% (27/803). Based on this trial, it is estimated that 61% of patients with the HLA-B*5701 allele will develop a clinically suspected hypersensitivity reaction during the course of abacavir treatment compared with 4% of patients who do not have the HLA-B*5701 allele.

Screening for carriage of the HLA-B*5701 allele is recommended prior to initiating treatment with abacavir. Screening is also recommended prior to reinitiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. For HLA-B*5701-positive patients, initiating or reinitiating treatment with an abacavir-containing regimen is not recommended and should be considered only with close medical supervision and under exceptional circumstances where potential benefit outweighs the risk.

Skin patch testing is used as a research tool and should not be used to aid in the clinical diagnosis of abacavir hypersensitivity.

In any patient treated with abacavir, the clinical diagnosis of hypersensitivity reaction must remain the basis of clinical decision-making. Even in the absence of the HLA-B*5701 allele, it is important to permanently discontinue abacavir and not rechallenge with abacavir if a

hypersensitivity reaction cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

5.2 Lactic Acidosis and Severe Hepatomegaly With Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir and lamivudine and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering EPZICOM to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with EPZICOM should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

5.3 Patients With HIV-1 and Hepatitis B Virus Co-Infection

Posttreatment Exacerbations of Hepatitis: In clinical trials in non-HIV-1-infected subjects treated with lamivudine for chronic HBV, 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 HBV DNA. Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from post-marketing experience after changes from lamivudine-containing HIV-1 treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV-1 and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. 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.

Emergence of Lamivudine-Resistant HBV: Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in subjects dually infected with HIV-1 and HBV. In non–HIV-1-infected subjects treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected and has been associated with diminished treatment response (see full prescribing information for EPIVIR-HBV® [lamivudine] Tablets and Oral Solution for additional information). Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-1-infected subjects who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

5.4 Use With Interferon- and Ribavirin-Based Regimens

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

5.5 Immune Reconstitution Syndrome

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

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

5.6 Fat Redistribution

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

5.7 Myocardial Infarction

In a published prospective, observational, epidemiological trial designed to investigate the rate of myocardial infarction in patients on combination antiretroviral therapy, the use of abacavir within the previous 6 months was correlated with an increased risk of myocardial infarction (MI).[1] In a sponsor-conducted pooled analysis of clinical trials, no excess risk of MI was observed in abacavir-treated subjects as compared with control subjects. In totality, the available data from the observational cohort and from clinical trials are inconclusive.

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

5.8 Use With Other Abacavir-, Lamivudine-, and/or Emtricitabine-Containing Products

EPZICOM contains fixed doses of 2 nucleoside analogues, abacavir and lamivudine, and should not be administered concomitantly with other abacavir-containing and/or lamivudine-containing products, including ZIAGEN (abacavir sulfate) Tablets and Oral Solution, EPIVIR (lamivudine) Tablets and Oral Solution, EPIVIR-HBV® (lamivudine) Tablets and Oral Solution, COMBIVIR® (lamivudine and zidovudine) Tablets, or TRIZIVIR® (abacavir sulfate, lamivudine, and zidovudine) Tablets; or emtricitabine-containing products, including ATRIPLA® (efavirenz/emtricitabine/tenofovir disoproxil fumarate) Tablets, EMTRIVA® (emtricitabine) Capsules and Oral Solution, TRUVADA® (emtricitabine/tenofovir disoproxil fumarate) Tablets, or COMPLERA™ (emtricitabine/rilpivirine/tenofovir disoproxil fumarate) Tablets.

The complete prescribing information for all agents being considered for use with EPZICOM should be consulted before combination therapy with EPZICOM is initiated.

6 ADVERSE REACTIONS

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

- Serious and sometimes fatal hypersensitivity reaction. In one trial, once-daily dosing of abacavir was associated with more severe hypersensitivity reactions *[see Boxed Warning, Warnings and Precautions (5.1)]*.
- Lactic acidosis and severe hepatomegaly *[see Boxed Warning, Warnings and Precautions (5.2)]*.
- Acute exacerbations of hepatitis B *[see Boxed Warning, Warnings and Precautions (5.3)]*.
- Hepatic decompensation in patients co-infected with HIV-1 and Hepatitis C *[see Warnings and Precautions (5.4)]*.
- Immune reconstitution syndrome *[see Warnings and Precautions (5.5)]*.
- Fat redistribution *[see Warnings and Precautions (5.6)]*.
- Myocardial infarction *[see Warnings and Precautions (5.7)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Therapy-Naive Adults: Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a ≥5% frequency during therapy with ZIAGEN 600 mg once daily or ZIAGEN 300 mg twice daily, both in combination with lamivudine 300 mg once daily and efavirenz 600 mg once daily, are listed in Table 1.

Table 1. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Naive Adults (CNA30021) Through 48 Weeks of Treatment

Adverse Event	ZIAGEN 600 mg q.d. plus EPIVIR plus Efavirenz (n = 384)	ZIAGEN 300 mg b.i.d. plus EPIVIR plus Efavirenz (n = 386)
Drug hypersensitivity[a,b]	9%	7%
Insomnia	7%	9%
Depression/Depressed mood	7%	7%
Headache/Migraine	7%	6%
Fatigue/Malaise	6%	8%
Dizziness/Vertigo	6%	6%
Nausea	5%	6%
Diarrhea[a]	5%	6%
Rash	5%	5%
Pyrexia	5%	3%
Abdominal pain/gastritis	4%	5%
Abnormal dreams	4%	5%
Anxiety	3%	5%

[a] Subjects receiving ZIAGEN 600 mg once daily, experienced a significantly higher incidence of severe drug hypersensitivity reactions and severe diarrhea compared with subjects who received ZIAGEN 300 mg twice daily. Five percent (5%) of subjects receiving ZIAGEN 600 mg once daily had severe drug hypersensitivity reactions compared with 2% of subjects receiving ZIAGEN 300 mg twice daily. Two percent (2%) of subjects receiving ZIAGEN 600 mg once daily had severe diarrhea while none of the subjects receiving ZIAGEN 300 mg twice daily had this event.

[b] CNA30024 was a multi-center, double-blind, controlled trial in which 649 HIV-1-infected, therapy-naive adults were randomized and received either ZIAGEN (300 mg twice daily), EPIVIR (150 mg twice daily), and efavirenz (600 mg once daily); or zidovudine (300 mg twice daily), EPIVIR (150 mg twice daily), and efavirenz (600 mg once daily). CNA30024 used double-blind ascertainment of suspected hypersensitivity reactions. During the blinded portion of the trial, suspected hypersensitivity to abacavir was reported by investigators in 9% of 324 subjects in the abacavir group and 3% of 325 subjects in the zidovudine group.

Laboratory Abnormalities: Laboratory abnormalities observed in clinical trials of ZIAGEN were anemia, neutropenia, liver function test abnormalities, and elevations of CPK, blood glucose, and triglycerides. Additional laboratory abnormalities observed in clinical trials of EPIVIR were thrombocytopenia and elevated levels of bilirubin, amylase, and lipase.

The frequencies of treatment-emergent laboratory abnormalities were comparable between treatment groups in CNA30021.

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

6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following reactions have been identified during postmarketing use of abacavir, lamivudine, and/or EPZICOM. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These reactions have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to abacavir, lamivudine, and/or EPZICOM.

Abacavir:

Cardiovascular: Myocardial infarction.

Skin: Suspected Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients receiving abacavir primarily in combination with medications known to be associated with SJS and TEN, respectively. Because of the overlap of clinical signs and symptoms between hypersensitivity to abacavir and SJS and TEN, and the possibility of multiple drug sensitivities in some patients, abacavir should be discontinued and not restarted in such cases.

There have also been reports of erythema multiforme with abacavir use.

Abacavir and Lamivudine:

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

Digestive: Stomatitis.

Endocrine and Metabolic: Hyperglycemia.

General: Weakness.

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

Hepatic: Lactic acidosis and hepatic steatosis *[see Warnings and Precautions (5.2)]*, posttreatment exacerbation of hepatitis B *[see Warnings and Precautions (5.3)]*.

Hypersensitivity: Sensitization reactions (including anaphylaxis), urticaria.

Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.

Nervous: Paresthesia, peripheral neuropathy, seizures.

Respiratory: Abnormal breath sounds/wheezing.

Skin: Alopecia, erythema multiforme, Stevens-Johnson syndrome.

7 DRUG INTERACTIONS

- No drug interaction trials have been conducted using EPZICOM Tablets *[see Clinical Pharmacology (12.3)]*.

7.1 Ethanol

Abacavir: 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)]*.

7.2 Interferon- and Ribavirin-Based Regimens

Lamivudine: Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected subjects, hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected subjects receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.3)]*.

7.3 Methadone

Abacavir: The addition of methadone has no clinically significant effect on the pharmacokinetic properties of abacavir. In a trial of 11 HIV-1-infected subjects receiving methadone-maintenance therapy with 600 mg of ZIAGEN twice daily (twice the currently recommended dose), oral methadone clearance increased *[see Clinical Pharmacology (12.3)]*. This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients.

7.4 Trimethoprim/Sulfamethoxazole (TMP/SMX)

Lamivudine: No change in dose of either drug is recommended *[see Clinical Pharmacology (12.3)]*. There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used to treat PCP.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

EPZICOM: Pregnancy Category C. There are no adequate and well-controlled studies of EPZICOM in pregnant women. Reproduction studies with abacavir and lamivudine have been performed in animals (see Abacavir and Lamivudine sections below). EPZICOM should be used during pregnancy only if the potential benefits outweigh the risks.

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.

Lamivudine: Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. Reproduction studies with orally administered lamivudine have been

performed in rats and rabbits at doses producing plasma levels up to approximately 35 times that for the recommended 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.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to EPZICOM or 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-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

Abacavir: Abacavir is secreted into the milk of lactating rats.

Lamivudine: Lamivudine is excreted in human breast milk and into the milk of lactating rats.

Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving EPZICOM.

8.4 Pediatric Use

Safety and effectiveness of EPZICOM in pediatric patients have not been established. EPZICOM is not recommended for use in patients younger than 18 years because it cannot be dose adjusted.

8.5 Geriatric Use

Clinical studies of abacavir and lamivudine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, 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 *[see Dosage and Administration (2.2), Use in Specific Populations (8.6, 8.7)]*.

8.6 Patients With Impaired Renal Function

EPZICOM is not recommended for patients with impaired renal function (creatinine clearance <50 mL/min) because EPZICOM is a fixed-dose combination and the dosage of the individual components cannot be adjusted.

8.7 Patients With Impaired Hepatic Function

EPZICOM is contraindicated for patients with hepatic impairment because EPZICOM is a fixed-dose combination and the dosage of the individual components cannot be adjusted.

10 OVERDOSAGE

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

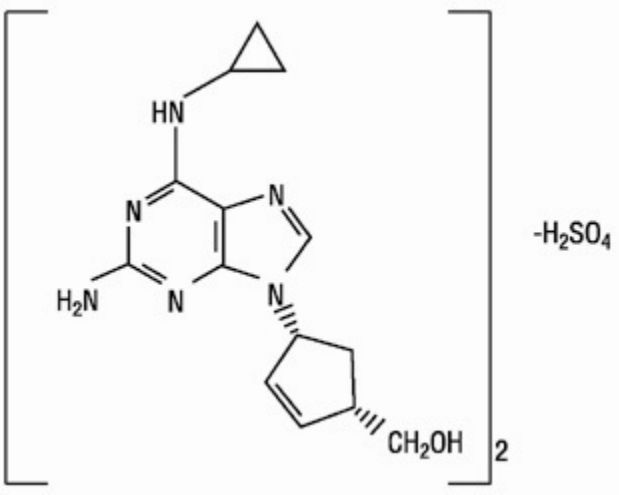
Lamivudine: One case of an adult ingesting 6 grams of lamivudine was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. It is not known whether lamivudine can be removed by peritoneal dialysis or hemodialysis.

11 DESCRIPTION

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

EPZICOM Tablets are for oral administration. Each orange, film-coated tablet contains the active ingredients 600 mg of abacavir as abacavir sulfate and 300 mg of lamivudine, and the inactive ingredients magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablets are coated with a film (OPADRY® orange YS-1-13065-A) that is made of FD&C Yellow No. 6, hypromellose, polyethylene glycol 400, polysorbate 80, and titanium dioxide.

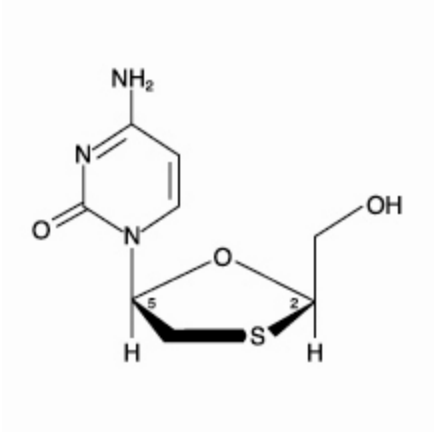
Abacavir Sulfate: The chemical name of abacavir sulfate is *(1S,cis)*-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1). Abacavir sulfate is the enantiomer with *1S, 4R* absolute configuration on the cyclopentene ring. It has a molecular formula of $(C_{14}H_{18}N_6O)_2 \bullet H_2SO_4$ and a molecular weight of 670.76 daltons. It has the following structural formula:



Abacavir sulfate is a white to off-white solid with a solubility of approximately 77 mg/mL in distilled water at 25°C.

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

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



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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

EPZICOM is an antiviral agent *[see Clinical Pharmacology (12.4)]*.

12.3 Pharmacokinetics

Pharmacokinetics in Adults: *EPZICOM:* In a single-dose, 3-way crossover bioavailability trial of 1 EPZICOM Tablet versus 2 ZIAGEN Tablets (2 x 300 mg) and 2 EPIVIR Tablets (2 x 150 mg) administered simultaneously in healthy subjects (n = 25), there was no difference in the extent of absorption, as measured by the area under the plasma concentration-time curve (AUC) and maximal peak concentration (C_{max}), of each component.

Abacavir: Following oral administration, abacavir is rapidly absorbed and extensively distributed. After oral administration of a single dose of 600 mg of abacavir in 20 subjects, C_{max} was 4.26 ± 1.19 mcg/mL (mean ± SD) and AUC_{∞} was 11.95 ± 2.51 mcg•hr/mL. Binding of abacavir to human plasma proteins is approximately 50% and was independent of concentration. Total blood and plasma drug-related radioactivity concentrations are identical, demonstrating that abacavir readily distributes into erythrocytes. The primary routes of elimination of abacavir are metabolism by alcohol dehydrogenase to form the 5′-carboxylic acid and glucuronyl transferase to form the 5′-glucuronide.

Lamivudine: Following oral administration, lamivudine is rapidly absorbed and extensively distributed. After multiple-dose oral administration of lamivudine 300 mg once daily for 7 days to 60 healthy subjects, steady-state C_{max} ($C_{max,ss}$) was 2.04 ± 0.54 mcg/mL (mean ± SD) and the 24-hour steady-state AUC ($AUC_{24,ss}$) was 8.87 ± 1.83 mcg•hr/mL. Binding to plasma protein is low. Approximately 70% of an intravenous dose of lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours).

The steady-state pharmacokinetic properties of the EPIVIR 300-mg tablet once daily for 7 days compared with the EPIVIR 150-mg tablet twice daily for 7 days were assessed in a

crossover trial in 60 healthy subjects. EPIVIR 300 mg once daily resulted in lamivudine exposures that were similar to EPIVIR 150 mg twice daily with respect to plasma $AUC_{24,ss}$; however, $C_{max,ss}$ was 66% higher and the trough value was 53% lower compared with the 150-mg twice-daily regimen. Intracellular lamivudine triphosphate exposures in peripheral blood mononuclear cells were also similar with respect to $AUC_{24,ss}$ and $C_{max24,ss}$; however, trough values were lower compared with the 150-mg twice-daily regimen. Inter-subject variability was greater for intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough concentrations. The clinical significance of observed differences for both plasma lamivudine concentrations and intracellular lamivudine triphosphate concentrations is not known.

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

The pharmacokinetic properties of abacavir and lamivudine in fasting subjects are summarized in Table 2.

Table 2. Pharmacokinetic Parameters[a] for Abacavir and Lamivudine in Adults

Parameter	Abacavir		Lamivudine	
Oral bioavailability (%)	86 ± 25	n = 6	86 ± 16	n = 12
Apparent volume of distribution (L/kg)	0.86 ± 0.15	n = 6	1.3 ± 0.4	n = 20
Systemic clearance (L/hr/kg)	0.80 ± 0.24	n = 6	0.33 ± 0.06	n = 20
Renal clearance (L/hr/kg)	.007 ± .008	n = 6	0.22 ± 0.06	n = 20
Elimination half-life (hr)	1.45 ± 0.32	n = 20	5 to 7[b]	

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

[b] Approximate range.

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

Special Populations: *Renal Impairment: EPZICOM:* Because lamivudine requires dose adjustment in the presence of renal insufficiency, EPZICOM is not recommended for use in patients with creatinine clearance <50 mL/min *[see Dosage and Administration (2.2)]*.

Hepatic Impairment: EPZICOM: EPZICOM is contraindicated for patients with hepatic impairment because EPZICOM is a fixed-dose combination and the dosage of the individual components cannot be adjusted. Abacavir is contraindicated in patients with moderate to severe hepatic impairment, and dose reduction is required in patients with mild hepatic impairment.

Pregnancy: See Use in Specific Populations (8.1).

Abacavir and Lamivudine: No data are available on the pharmacokinetics of abacavir or lamivudine during pregnancy.

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

Abacavir: No data are available on the pharmacokinetics of abacavir in nursing mothers.

Lamivudine: Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

Pediatric Patients: EPZICOM: The pharmacokinetics of EPZICOM in pediatric subjects are under investigation. There are insufficient data at this time to recommend a dose.

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

Gender: Abacavir: A population pharmacokinetic analysis in HIV-1-infected male (n = 304) and female (n = 67) subjects showed no gender differences in abacavir AUC normalized for lean body weight.

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

Race: Abacavir: There are no significant differences between blacks and Caucasians in abacavir pharmacokinetics.

Lamivudine: There are no significant racial differences in lamivudine pharmacokinetics.

Drug Interactions: The drug interactions described are based on trials conducted with the individual nucleoside analogues. In humans, abacavir and lamivudine are not significantly metabolized by cytochrome P450 enzymes nor do they inhibit or induce this enzyme system; therefore, it is unlikely that clinically significant drug interactions will occur with drugs metabolized through these pathways.

Abacavir: Lamivudine and Zidovudine: Fifteen HIV-1-infected subjects were enrolled in a crossover-designed drug interaction trial evaluating single doses of abacavir (600 mg), lamivudine (150 mg), and zidovudine (300 mg) alone or in combination. Analysis showed no clinically relevant changes in the pharmacokinetics of abacavir with the addition of lamivudine or zidovudine or the combination of lamivudine and zidovudine. Lamivudine exposure (AUC decreased 15%) and zidovudine exposure (AUC increased 10%) did not show clinically relevant changes with concurrent abacavir.

Methadone: In a trial of 11 HIV-1-infected subjects receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of ZIAGEN twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI: 6% to 42%) *[see Drug Interactions (7.4)]*.

Lamivudine: Zidovudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-1-infected adult subjects

given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q 12 hr).

Ribavirin: In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected subjects *[see Warnings and Precautions (5.4)]*.

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

Table 3. Effect of Coadministered Drugs on Abacavir and Lamivudine AUC

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

Drugs That May Alter Abacavir Blood Concentrations					
Coadministered Drug and Dose	**Abacavir Dose**	**n**	**Abacavir Concentrations**		**Concentration of Coadministered Drug**
			AUC	**Variability**	
Ethanol 0.7 g/kg	Single 600 mg	24	↑41%	90% CI: 35% to 48%	↔
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 hr 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%	↔

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

12.4 Microbiology

Mechanism of Action: *Abacavir:* Abacavir is a carbocyclic synthetic nucleoside analogue. Abacavir is converted by cellular enzymes to the active metabolite, carbovir triphosphate (CBV-TP), an analogue of deoxyguanosine-5′-triphosphate (dGTP). CBV-TP inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation into viral DNA. 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.

Lamivudine: Lamivudine is a synthetic nucleoside analogue. Intracellularly lamivudine is phosphorylated to its active 5′-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue. CBV-TP and 3TC-TP are weak inhibitors of cellular DNA polymerases α, β, and γ.

Antiviral Activity: *Abacavir:* The antiviral activity of abacavir against HIV-1 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 effect viral replication by 50 percent (EC_{50}) ranged from 3.7 to 5.8 μM (1 μM = 0.28 mcg/mL) and 0.07 to 1.0 μM against HIV-1_{IIIB} and HIV-1_{BaL}, respectively, and was 0.26 ± 0.18 μM against 8 clinical isolates. The EC_{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. Ribavirin (50 μM) had no effect on the anti–HIV-1 activity of abacavir in cell culture.

Lamivudine: The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. EC_{50} values were in the range of 0.003 to 15 μM (1 μM = 0.23 mcg/mL). HIV-1 from therapy-naive subjects with no amino acid substitutions associated with resistance gave median EC_{50} values of 0.429 μM (range: 0.200 to 2.007 μM) from Virco (n = 92 baseline samples from COLA40263) and 2.35 μM (1.37 to 3.68 μM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC_{50} values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120 μM, and against HIV-2 isolates from 0.003 to 0.120 μM in peripheral blood mononuclear cells. Ribavirin (50 μM) decreased the anti–HIV-1 activity of lamivudine by 3.5 fold in MT-4 cells.

The combination of abacavir and lamivudine has demonstrated antiviral activity in cell culture against non-subtype B isolates and HIV-2 isolates with equivalent antiviral activity as for subtype B isolates. Abacavir/lamivudine had additive to synergistic activity in cell culture in combination with the nucleoside reverse transcriptase inhibitors (NRTIs) emtricitabine, stavudine, tenofovir, zalcitabine, zidovudine; the non-nucleoside reverse transcriptase inhibitors (NNRTIs) delavirdine, efavirenz, nevirapine; the protease inhibitors (PIs) amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir; or the fusion inhibitor, enfuvirtide. Ribavirin, used in combination with interferon for the treatment of HCV infection, decreased the anti-HIV-1 potency of abacavir/lamivudine reproducibly by 2- to 6-fold in cell culture.

Resistance: HIV-1 isolates with reduced susceptibility to the combination of abacavir and lamivudine have been selected in cell culture and have also been obtained from subjects failing abacavir/lamivudine-containing regimens. Genotypic characterization of

abacavir/lamivudine-resistant viruses selected in cell culture identified amino acid substitutions M184V/I, K65R, L74V, and Y115F in HIV-1 RT.

Genotypic analysis of isolates selected in cell culture and recovered from abacavir-treated subjects demonstrated that amino acid substitutions K65R, L74V, Y115F, and M184V/I in HIV-1 RT contributed to abacavir resistance. Genotypic analysis of isolates selected in cell culture and recovered from lamivudine-treated subjects showed that the resistance was due to a specific amino acid substitution in HIV-1 RT at codon 184 changing the methionine to either isoleucine or valine (M184V/I). In a trial of therapy-naive adults receiving ZIAGEN 600 mg once daily (n = 384) or 300 mg twice daily (n = 386) in a background regimen of lamivudine 300 mg and efavirenz 600 mg once daily (CNA30021), the incidence of virologic failure at 48 weeks was similar between the 2 groups (11% in both arms). Genotypic (n = 38) and phenotypic analyses (n = 35) of virologic failure isolates from this trial showed that the RT substitutions that emerged during abacavir/lamivudine once-daily and twice-daily therapy were K65R, L74V, Y115F, and M184V/I. The abacavir- and lamivudine-associated resistance substitution M184V/I was the most commonly observed substitution in virologic failure isolates from subjects receiving abacavir/lamivudine once daily (56%, 10/18) and twice daily (40%, 8/20).

Thirty-nine percent (7/18) of the isolates from subjects 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). Fifty-six percent (10/18) of the virologic failure isolates in the once-daily abacavir group compared with 41% (7/17) of the failure isolates in the twice-daily abacavir group had a >2.5-fold decrease in lamivudine susceptibility with median-fold changes of 81 (range: 0.79 to >116) and 1.1 (range: 0.68 to >116) in the once-daily and twice-daily abacavir arms, respectively.

Cross-Resistance: Cross-resistance has been observed among NRTIs. Viruses containing abacavir and lamivudine resistance-associated amino acid substitutions, namely, K65R, L74V, M184V, and Y115F, exhibit cross-resistance to didanosine, emtricitabine, lamivudine, tenofovir, and zalcitabine in cell culture and in subjects. The K65R substitution can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine; the L74V substitution can confer resistance to abacavir, didanosine, and zalcitabine; and the M184V substitution can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, and zalcitabine.

The combination of abacavir/lamivudine has demonstrated decreased susceptibility to viruses with the substitutions K65R with or without the M184V/I substitution, viruses with L74V plus the M184V/I substitution, and viruses with thymidine analog mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219 E/R/H/Q/N) plus M184V. An increasing number of TAMs is associated with a progressive reduction in abacavir susceptibility.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity: *Abacavir:* Abacavir was administered orally at 3 dosage levels to separate groups of mice and rats in 2-year carcinogenicity studies. Results showed an increase in the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver of female rats. In addition, non-malignant tumors also occurred in the liver and thyroid gland of female rats. These observations were made at systemic exposures in the range of 6 to 32 times the human exposure at the recommended dose.

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-1 infection.

It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Mutagenicity: *Abacavir:* Abacavir induced chromosomal aberrations both in the presence and absence of metabolic activation in an in vitro cytogenetic study in human lymphocytes. Abacavir was mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence of metabolic activation in an L5178Y mouse lymphoma assay. Abacavir was clastogenic in males and not clastogenic in females in an in vivo mouse bone marrow micronucleus assay. Abacavir was not mutagenic in bacterial mutagenicity assays in the presence and absence of metabolic activation.

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

Impairment of Fertility: Abacavir or lamivudine induced no adverse effects on the mating performance or fertility of male and female rats at doses producing systemic exposure levels approximately 8 or 130 times, respectively, higher than those in humans at the recommended dose based on body surface area comparisons.

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

EPZICOM: There have been no clinical trials conducted with EPZICOM. One EPZICOM Tablet given once daily is an alternative regimen to EPIVIR Tablets 300 mg once daily plus ZIAGEN Tablets 2 x 300 mg once daily as a component of antiretroviral therapy.

The following trial was conducted with the individual components of EPZICOM.

Therapy-Naive Adults: **CNA30021** was an international, multi-center, double-blind, controlled trial in which 770 HIV-1-infected, therapy-naive adults were randomized and received either ZIAGEN 600 mg once daily or ZIAGEN 300 mg twice daily, both in combination with EPIVIR 300 mg once daily and efavirenz 600 mg once daily. The double-blind treatment duration was at least 48 weeks. Trial participants had a mean age of 37 years; were male (81%), Caucasian (54%), black (27%), and American Hispanic (15%). The median baseline CD4+ cell count was 262 cells/mm^3 (range: 21 to 918 cells/mm^3) and the median baseline plasma HIV-1 RNA was 4.89 $\log_{10}$ copies/mL (range: 2.60 to 6.99 $\log_{10}$ copies/mL).

The outcomes of randomized treatment are provided in Table 4.

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

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

[a] Subjects achieved and maintained confirmed HIV-1 RNA <50 copies/mL (<400 copies/mL) through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR® standard test version 1.0).

[b] Includes viral rebound, failure to achieve confirmed <50 copies/mL (<400 copies/mL) by Week 48, and insufficient viral load response.

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

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

15 REFERENCES

1. Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group. *Lancet*. 2008;371 (9622):1417-1426.

16 HOW SUPPLIED/STORAGE AND HANDLING

EPZICOM is available as tablets. Each tablet contains 600 mg of abacavir as abacavir sulfate and 300 mg of lamivudine. The tablets are orange, film-coated, modified capsule-shaped, and debossed with GS FC2 on one side with no markings on the reverse side. They are packaged as follows:

Bottles of 30 Tablets (NDC 49702-206-13).

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

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 EPZICOM, and encourage the patient to read the Medication Guide and Warning Card every time to obtain any new information that may be present about EPZICOM. (The complete text of the Medication Guide is reprinted at the end of this document.)
- to carry the Warning Card with them.
- how to identify a hypersensitivity reaction *[see Warnings and Precautions (5.1), Medication Guide]*.
- that if they develop symptoms consistent with a hypersensitivity reaction they should call their doctor right away to determine if they should stop taking EPZICOM.
- that a hypersensitivity reaction can worsen and lead to hospitalization or death if EPZICOM is not immediately discontinued.
- that in one study, more severe hypersensitivity reactions were seen when ZIAGEN was dosed 600 mg once daily.
- to not restart EPZICOM 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 EPZICOM is stopped right away.
- that if they have interrupted EPZICOM 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 EPZICOM 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.
- EPZICOM should not be administered concomitantly with ATRIPLA, COMBIVIR, COMPLERA, EMTRIVA, EPIVIR, EPIVIR-HBV, TRIZIVIR, TRUVADA, or ZIAGEN.

Lactic Acidosis/Hepatomegaly: Inform patients that some HIV medicines, including EPZICOM, can cause a rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly) *[see Warnings and Precautions (5.2)]*.

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 (5.3)]*.

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

Information About HIV-1 Infection: EPZICOM is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using EPZICOM.

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 to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** Lamivudine is excreted in human breast milk. It is not known if abacavir 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.

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

Manufactured for

ViiV Healthcare
Research Triangle Park, NC 27709
by:

GlaxoSmithKline
Research Triangle Park, NC 27709

Lamivudine is manufactured under agreement from
Shire Pharmaceuticals Group plc
Basingstoke, UK

EPZ:PI

MEDICATION GUIDE

EPZICOM® (ep' zih com)

(abacavir sulfate and lamivudine)

Tablets

Read this Medication Guide before you start taking EPZICOM 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 EPZICOM Warning Card with you at all times.

What is the most important information I should know about EPZICOM?

1. **Serious allergic reaction (hypersensitivity reaction).** EPZICOM contains abacavir (also contained in ZIAGEN® and TRIZIVIR®). Patients taking EPZICOM 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 EPZICOM, call your healthcare provider right away to find out if you should stop taking EPZICOM.

	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 EPZICOM because of an allergic reaction, never take EPZICOM (abacavir sulfate and lamivudine) or any other abacavir-containing medicine (ZIAGEN and TRIZIVIR) again. If you take EPZICOM 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 EPZICOM for any other reason, even for a few days, and you are not allergic to EPZICOM, talk with your healthcare provider before taking it again. Taking EPZICOM again can cause a serious allergic or life-threatening reaction, even if you never had an allergic reaction to it before.

If your healthcare provider tells you that you can take EPZICOM again, start taking it 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 EPZICOM, 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 EPZICOM 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.

4. **Use with interferon and ribavirin-based regimens.** Worsening of liver disease (sometimes resulting in death) has occurred in patients infected with both HIV and hepatitis C virus who are taking anti-HIV medicines and are also being treated for hepatitis C with interferon with or without ribavirin. If you are taking EPZICOM as well as interferon with or without ribavirin and you experience side effects, be sure to tell your healthcare provider.
5. **If you have HIV and hepatitis B virus infection, your hepatitis B virus infection may get worse if you stop taking EPZICOM.**
   - Take EPZICOM exactly as prescribed.
   - Do not run out of EPZICOM.
   - Do not stop EPZICOM without talking to your healthcare provider.

Your healthcare provider should monitor your health and do regular blood tests to check your liver if you stop taking EPZICOM.

What is EPZICOM?

EPZICOM is a prescription medicine used to treat HIV infection. EPZICOM contains 2 medicines: abacavir (ZIAGEN) and lamivudine or 3TC (EPIVIR®). Both of these

medicines are called nucleoside analogue reverse transcriptase inhibitors (NRTIs). When used together, they help lower the amount of HIV in your blood.

- **EPZICOM does not cure HIV infection or AIDS.**
- It is not known if EPZICOM 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 healthcare provider regularly while you are taking EPZICOM.
- It is not known if EPZICOM is safe or effective in children under the age of 18.

Who should not take EPZICOM?

Do not take EPZICOM if you:

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

What should I tell my healthcare provider before taking EPZICOM?

Before you take EPZICOM tell your healthcare provider if you:

- **have been tested and know whether or not you have a particular gene variation called HLA-B*5701.**
- **have hepatitis B virus infection or have other liver problems.**
- **have kidney problems.**
- **have heart problems, smoke, or have diseases that increase your risk of heart disease such as high blood pressure, high cholesterol, or diabetes.**
- **are pregnant or plan to become pregnant.** It is not known if EPZICOM will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant.

  Pregnancy Registry. If you take EPZICOM while you are pregnant, talk to your healthcare provider about how you can take part in the Pregnancy Registry for EPZICOM. 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.** Lamivudine is excreted in human breast milk. We do not know if abacavir 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
- medicines used to treat hepatitis viruses such as interferon or ribavirin.
- methadone
- ATRIPLA® (efavirenz/emtricitabine/tenofovir disoproxil fumarate)
- COMBIVIR® (lamivudine and zidovudine)
- COMPLERA™ (emtricitabine/rilpivirine/tenofovir disoproxil fumarate)
- EMTRIVA® (emtricitabine)
- EPIVIR or EPIVIR-HBV® (lamivudine)
- TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine)
- TRUVADA® (emtricitabine/tenofovir disoproxil fumarate)
- ZIAGEN (abacavir sulfate)

Ask your healthcare provider if you are not sure if you take one of the medicines listed above.

EPZICOM may affect the way other medicines work, and other medicines may affect how EPZICOM works.

Know the medicines you take. Keep a list of your medicines with you to show to your healthcare provider and pharmacist when you get a new medicine.

How should I take EPZICOM?

- **Take EPZICOM exactly as your healthcare provider tells you to take it.**
- EPZICOM may be taken with or without food.
- Do not skip doses.
- **Do not let your EPZICOM run out.**

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 EPZICOM, 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 EPZICOM?

- **EPZICOM can cause serious side effects including allergic reactions, lactic acidosis, and liver problems. See "What is the most important information I should know about EPZICOM?"**

- **Changes in immune system (Immune Reconstitution Syndrome).** Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider if you start having new or worse symptoms of infection after you start taking EPZICOM.
- **Changes in body fat (fat redistribution).** Changes in body fat (lipoatrophy or lipodystrophy) can happen in some people taking antiretroviral medicines including EPZICOM.

  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 EPZICOM may increase your risk of heart attack.

The most common side effects of EPZICOM include:

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

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

These are not all the possible side effects of EPZICOM. 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 EPZICOM?

Store EPZICOM at 59°F to 86°F (15°C to 30°C).

Keep EPZICOM and all medicines out of the reach of children.

General information for safe and effective use of EPZICOM.

Avoid doing things that can spread HIV 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 EPZICOM for a condition for which it was not prescribed. Do not give EPZICOM to other people, even if they have the same symptoms that you have. It may harm them.

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

For more information go to www.EPZICOM.com or call 1-877-844-8872.

What are the ingredients in EPZICOM?

Active ingredients: abacavir sulfate and lamivudine

Inactive ingredients: magnesium stearate, microcrystalline cellulose, sodium starch glycolate, and OPADRY® orange YS-1-13065-A, a film coating made of FD&C Yellow No. 6, hypromellose, polyethylene glycol 400, polysorbate 80, and titanium dioxide.

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

Manufactured for:

ViiV Healthcare

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by:

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Lamivudine is manufactured under agreement from
Shire Pharmaceuticals Group plc
Basingstoke, UK

May 2012
EPZ:MG