CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205551Orig1s000

<u>LABELING</u>

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

TRIUMEQ (abacavir, dolutegravir, and lamivudine) tablets, for oral use
Initial U.S. Approval: 2014

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

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 TRIUMEQ as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B*5701 status, permanently discontinue TRIUMEQ if hypersensitivity cannot be ruled out, even when other diagnoses are possible. (5.1)**
- **Following a hypersensitivity reaction to abacavir, NEVER restart TRIUMEQ 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 TRIUMEQ. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.3)**

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

TRIUMEQ, a combination of dolutegravir (integrase strand transfer inhibitor [INSTI]), abacavir, and lamivudine (both nucleoside analogue reverse transcriptase inhibitors) is indicated for the treatment of HIV-1 infection. (1)

Limitations of Use:

- TRIUMEQ alone is not recommended for use in patients with current or past history of resistance to any components of TRIUMEQ. (12.4)
- TRIUMEQ alone is not recommended in patients with resistance-associated integrase substitutions or clinically suspected integrase strand transfer inhibitor resistance because the dose of dolutegravir in TRIUMEQ is insufficient in these subpopulations. See the dolutegravir prescribing information. (1)

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

- Before initiating TRIUMEQ, screen for the HLA-B*5701 allele because TRIUMEQ contains abacavir. (2.1).
- Adults: One tablet daily. May be taken with or without food. (2.2)
- Dosing with certain concomitant medications: If efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin are coadministered, then the recommended dolutegravir dosage regimen is 50 mg twice daily. An additional 50-mg dose of dolutegravir, separated by 12 hours from TRIUMEQ, should be taken. (2.3)

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

Tablets: 600 mg of abacavir, 50 mg of dolutegravir, and 300 mg of lamivudine. (3)

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

- Presence of HLA-B*5701 allele. (4)
- Previous hypersensitivity reaction to abacavir, dolutegravir, or lamivudine. (4)
- Coadministration with dofetilide. (4)
- Moderate or severe hepatic impairment. (4, 8.7)

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

- Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of TRIUMEQ. Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with TRIUMEQ is recommended in patients with underlying hepatic disease such as hepatitis B or C. (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 TRIUMEQ as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.4)
- Immune reconstitution syndrome and redistribution/accumulation of body fat have been reported in patients treated with combination antiretroviral therapy. (5.5, 5.6)
- Administration of TRIUMEQ is not recommended in patients receiving other products containing abacavir or lamivudine. (5.8)

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

The most commonly reported adverse reactions of at least moderate intensity and incidence at least 2% (in those receiving TRIUMEQ) were insomnia, headache, and fatigue. (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----------

Coadministration of TRIUMEQ with other drugs can alter the concentration of other drugs and other drugs may alter the concentrations of TRIUMEQ. The potential drug-drug interactions must be considered prior to and during therapy. (4, 7, 12.3)

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

- Pregnancy: TRIUMEQ should be used during pregnancy only if the potential benefit justifies the potential risk. (8.1)
- Nursing mothers: Breastfeeding is not recommended due to the potential for HIV transmission. (8.3)
- TRIUMEQ is not recommended in patients with creatinine clearance less than 50 mL per min. (8.6)
- If a dose reduction of abacavir, a component of TRIUMEQ, is required for patients with mild hepatic impairment, then the individual components should be used. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, AND EXACERBATIONS OF HEPATITIS B
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Screening for HLA-B*5701 Allele Prior to Starting TRIUMEQ
2.2 Recommended Dosage
2.3 Dosage Recommendation with Certain Concomitant Medications
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity Reaction
5.2 Lactic Acidosis and Severe Hepatomegaly with Steatosis
5.3 Patients with Hepatitis B or C Virus Co-infection
5.4 Use with Interferon- and Ribavirin-based Regimens
5.5 Immune Reconstitution Syndrome
5.6 Fat Redistribution
5.7 Myocardial Infarction
5.8 Related Products that are Not Recommended
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Effect of Dolutegravir on the Phamacokinetics of Other Agents
7.2 Effect of Other Agents on the Pharmacokinetics of Dolutegravir
7.3 Established and Other Potentially Significant Drug Interactions
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

8.6 Patients with Impaired Renal Function
8.7 Patients with Impaired Hepatic Function
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 Adult Subjects
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
*****Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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

Hypersensitivity Reactions

Serious and sometimes fatal hypersensitivity reactions, with multiple organ involvement, have been associated with abacavir, a component of TRIUMEQ®. Patients who carry the HLA-B*5701 allele are at a higher risk of a hypersensitivity reaction to abacavir; although, hypersensitivity reactions have occurred in patients who do not carry the HLA-B*5701 allele *[see Warnings and Precautions (5.1)]*.

All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with TRIUMEQ or reinitiation of therapy with TRIUMEQ unless patients have had an HLA-B*5701 allele assessment. Discontinue TRIUMEQ if a hypersensitivity reaction is suspected. TRIUMEQ is contraindicated in patients who have the HLA-B*5701 allele or in patients with a prior hypersensitivity reaction to abacavir *[see Contraindications (4), Warnings and Precautions (5.1)]*. Reintroduction of TRIUMEQ or any other abacavir-containing product can result in life-threatening or fatal hypersensitivity reactions, even in patients who have no history of hypersensitivity to abacavir therapy. 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. Discontinue TRIUMEQ if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur *[see Warnings and Precautions (5.2)]*.

Exacerbations of Hepatitis B

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

TRIUMEQ is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection.

Limitations of Use:

- TRIUMEQ alone is not recommended for use in patients with current or past history of resistance to any components of TRIUMEQ *[see Microbiology (12.4)]*.
- TRIUMEQ alone is not recommended in patients with resistance-associated integrase substitutions or clinically suspected integrase strand transfer inhibitor resistance because the dose of dolutegravir in TRIUMEQ is insufficient in these subpopulations. See full prescribing information for dolutegravir.

2 DOSAGE AND ADMINISTRATION

2.1 Screening for HLA-B*5701 Allele Prior to Starting TRIUMEQ

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

2.2 Recommended Dosage

TRIUMEQ is a fixed-dose combination product containing 600 mg of abacavir, 50 mg of dolutegravir, and 300 mg of lamivudine. The recommended dosage regimen of TRIUMEQ in adults is one tablet once daily orally with or without food.

2.3 Dosage Recommendation with Certain Concomitant Medications

The dolutegravir dose (50 mg) in TRIUMEQ is insufficient when coadministered with medications listed in Table 1 that may decrease dolutegravir concentrations; the following dolutegravir dosage regimen is recommended.

Table 1. Dosing Recommendations for TRIUMEQ with Coadministered Medications

Coadministered Drug	Dosing Recommendation
Efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin	The recommended dolutegravir dosage regimen is 50 mg twice daily. An additional dolutegravir 50-mg tablet, separated by 12 hours from TRIUMEQ, should be taken.

3 DOSAGE FORMS AND STRENGTHS

TRIUMEQ tablets are purple, biconvex, oval, and debossed with “572 Trı” on one side. Each film-coated tablet contains abacavir sulfate equivalent to 600 mg of abacavir, dolutegravir sodium equivalent to 50 mg of dolutegravir, and 300 mg of lamivudine *[see Description (11)]*.

4 CONTRAINDICATIONS

TRIUMEQ is contraindicated in patients:

- who have the HLA-B*5701 allele *[see Warnings and Precautions (5.1)]*.
- with previous hypersensitivity reaction to abacavir. Before starting TRIUMEQ, review medical history for prior exposure to any abacavir-containing product. NEVER restart

TRIUMEQ or any other abacavir-containing product following a hypersensitivity reaction to abacavir, regardless of HLA-B*5701 status *[see Warnings and Precautions (5.1)]*.

- with previous hypersensitivity reaction to dolutegravir *[see Warnings and Precautions (5.1)]* or lamivudine.
- receiving dofetilide, due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events with concomitant use of dolutegravir *[see Drug Interactions (7)]*.
- with moderate or severe hepatic impairment *[see Use in Specific Populations (8.7)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reaction

Hypersensitivity reactions have been reported with the use of abacavir or dolutegravir, components of TRIUMEQ.

Abacavir: Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir-containing regimens. See full prescribing information for ZIAGEN® (abacavir). Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with abacavir or reinitiation of abacavir therapy unless HLA-B*5701 information is available. Do not treat HLA-B*5701-positive patients with an abacavir-containing regimen *[see Contraindications (4)]*.

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 TRIUMEQ if hypersensitivity cannot be ruled out, even when other diagnoses are possible.

Symptoms indicating a multi-organ clinical syndrome usually appear within the first 6 weeks of treatment with abacavir (median time to onset was 9 days), although the reaction may occur at any time during therapy. The reaction is typically characterized by the presentation of key signs or symptoms 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); (5) respiratory (including dyspnea, cough, or pharyngitis).

Other signs and symptoms of hypersensitivity include lethargy, headache, myolysis, edema, abnormal chest x-ray findings (predominantly infiltrates, which can be localized), arthralgia, 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 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 Abacavir Hypersensitivity: Discontinue TRIUMEQ as soon as a hypersensitivity reaction is suspected. To minimize the risk of a life-threatening hypersensitivity reaction, permanently discontinue TRIUMEQ 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 TRIUMEQ 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 TRIUMEQ has been discontinued for reasons other than symptoms of a hypersensitivity reaction, and if reinitiation of TRIUMEQ or any other abacavir-containing product is under consideration, carefully evaluate the reason for discontinuation of TRIUMEQ to ensure that the patient did not have symptoms of a hypersensitivity reaction.

If hypersensitivity cannot be ruled out, DO NOT reintroduce TRIUMEQ or any other abacavir-containing product.

If symptoms consistent with abacavir 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 TRIUMEQ or any other abacavir-containing product and that reintroduction of TRIUMEQ 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.

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.

Dolutegravir: Hypersensitivity reactions have been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. The events were reported in less than 1% of subjects receiving TIVICAY® in Phase 3 clinical trials. Discontinue TRIUMEQ and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters or peeling of the skin, oral blisters or lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, difficulty breathing). Clinical status, including liver aminotransferases, should be monitored and appropriate therapy initiated. Delay in stopping treatment with TRIUMEQ or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction.

Clinically, it is not possible to determine whether a hypersensitivity reaction with TRIUMEQ would be caused by abacavir or dolutegravir. Therefore, never restart TRIUMEQ or any other abacavir- or dolutegravir-containing product in patients who have stopped therapy with TRIUMEQ due to a hypersensitivity 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 and other antiretrovirals. See full prescribing information for ZIAGEN (abacavir) and EPIVIR® (lamivudine). Treatment with TRIUMEQ should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

5.3 Patients with Hepatitis B or C Virus Co-infection

Effects on Serum Liver Biochemistries: Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of TRIUMEQ *[see Adverse Reactions (6.1)]*. See full prescribing information for TIVICAY (dolutegravir). In some cases the elevations in transaminases were consistent with immune reconstitution syndrome or hepatitis B reactivation particularly in the setting where anti-hepatitis therapy was withdrawn. Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with TRIUMEQ are recommended in patients with underlying hepatic disease such as hepatitis B or C.

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

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

5.4 Use with Interferon- and Ribavirin-based Regimens

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

5.5 Immune Reconstitution Syndrome

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

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

5.6 Fat Redistribution

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

5.7 Myocardial Infarction

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

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

5.8 Related Products that are Not Recommended

TRIUMEQ contains fixed doses of an INSTI (dolutegravir) and 2 nucleoside analogue reverse transcriptase inhibitors (abacavir and lamivudine); concomitant administration of TRIUMEQ with other products containing abacavir or lamivudine is not recommended.

6 ADVERSE REACTIONS

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

- Serious and sometimes fatal hypersensitivity reaction *[see Boxed Warning, Warnings and Precautions (5.1)]*.
- Lactic acidosis and severe hepatomegaly *[see Boxed Warning, Warnings and Precautions (5.2)]*.
- Effects on serum liver biochemistries in patients with hepatitis B or C co-infection *[see Warnings and Precautions (5.3)]*.
- 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 with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Treatment-Emergent Adverse Drug Reactions (ADRs): The safety assessment of TRIUMEQ is primarily based on the analyses of data from a randomized, international, multicenter, double-blind, active-controlled trial, SINGLE (ING114467) and supported by data in treatment-experienced, INSTI-naïve subjects from SAILING (ING111762) and by data from other treatment-naïve trials. See full prescribing information for TIVICAY.

Treatment-Naïve Subjects: In SINGLE, 833 adult subjects were randomized and received at least one dose of either dolutegravir (TIVICAY) 50 mg with fixed-dose abacavir sulfate and lamivudine (EPZICOM®) once daily (n = 414) or fixed-dose efavirenz/emtricitabine/tenofovir (ATRIPLA®) once daily (n = 419). Through 96 weeks, the rate of adverse events leading to discontinuation was 3% in subjects receiving TIVICAY + EPZICOM and 12% in subjects receiving ATRIPLA once daily.

Treatment-emergent ADRs of moderate to severe intensity observed in at least 2% of subjects in either treatment arm of SINGLE are provided in Table 2.

Table 2. Treatment-Emergent Adverse Drug Reactions of at Least Moderate Intensity (Grades 2 to 4) and at Least 2% Frequency in Treatment-naïve Subjects in SINGLE (Week 96 Analysis)

Adverse Reaction	TIVICAY + EPZICOM Once Daily (N = 414)	ATRIPLA Once Daily (N = 419)
Psychiatric		
Insomnia	3%	2%
Depression	1%	2%
Abnormal dreams	<1%	2%
Nervous System		
Dizziness	<1%	5%
Headache	2%	2%
Gastrointestinal		
Nausea	<1%	3%
Diarrhea	<1%	2%

Adverse Reaction	TIVICAY + EPZICOM Once Daily (N = 414)	ATRIPLA Once Daily (N = 419)
General Disorders		
Fatigue	2%	2%
Skin and Subcutaneous Tissue		
Rash[a]	<1%	6%
Ear and Labyrinth		
Vertigo	0	2%

[a] Includes pooled terms: rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, and drug eruption.

Treatment-experienced Subjects: SAILING is an international, double-blind trial in INSTI-naïve, antiretroviral treatment-experienced adult subjects. Subjects were randomized and received either TIVICAY 50 mg once daily or raltegravir 400 mg twice daily with investigator-selected background regimen consisting of up to 2 agents, including at least one fully active agent. At 48 weeks, the rate of adverse events leading to discontinuation was consistent with that seen in the overall treatment-naïve patient population. See full prescribing information for TIVICAY.

The ADRs observed in the subset of subjects who received TIVICAY + EPZICOM were generally consistent with those seen in the overall treatment-naïve patient population.

Less Common Adverse Reactions Observed in Clinical Trials: The following adverse reactions occurred in less than 2% of treatment-naïve or treatment-experienced subjects in any one trial. These events have been included because of their seriousness and/or assessment of potential causal relationship.

Gastrointestinal Disorders: Abdominal pain, abdominal distention, abdominal discomfort, dyspepsia, flatulence, gastroesophageal reflux disease, upper abdominal pain, vomiting.

General Disorders: Fever, lethargy.

Hepatobiliary Disorders: Hepatitis.

Metabolism and Nutrition Disorders: Anorexia, hypertriglyceridemia.

Musculoskeletal Disorders: Arthralgia, myositis.

Nervous: Somnolence.

Psychiatric: Nightmare and sleep disorder.

Renal and Urinary Disorders: Renal impairment.

Skin and Subcutaneous Tissue Disorders: Pruritus.

Laboratory Abnormalities: *Treatment-Naïve Subjects:* Selected laboratory abnormalities (Grades 2 to 4) with a worsening grade from baseline and representing the worst-grade toxicity in at least 2% of subjects in SINGLE are presented in Table 3. The mean change from baseline observed for selected lipid values is presented in Table 4.

Table 3. Selected Laboratory Abnormalities (Grades 2 to 4) in Treatment-naïve Subjects in SINGLE (Week 96 Analysis)

Laboratory Abnormality	TIVICAY + EPZICOM Once Daily (N = 414)	ATRIPLA Once Daily (N = 419)
ALT		
Grade 2 (>2.5-5.0 x ULN)	2%	5%
Grade 3 to 4 (>5.0 x ULN)	<1%	<1%
AST		
Grade 2 (>2.5-5.0 x ULN)	3%	3%
Grade 3 to 4 (>5.0 x ULN)	<1%	3%
Creatine kinase		
Grade 2 (6.0-9.9 x ULN)	4%	1%
Grade 3 to 4 (≥10.0 x ULN)	5%	7%
Hyperglycemia		
Grade 2 (126-250 mg/dL)	7%	5%
Grade 3 (>250 mg/dL)	2%	<1%
Lipase		
Grade 2 (>1.5-3.0 x ULN)	9%	9%
Grade 3 to 4 (>3.0 ULN)	4%	3%
Total neutrophils		
Grade 2 (0.75-0.99 x 10^9)	3%	5%
Grade 3 to 4 (<0.75 x 10^9)	2%	3%

ULN = Upper limit of normal.

Table 4. Mean Change from Baseline in Fasted Lipid Values in Treatment-naïve Subjects in SINGLE (Week 96 Analysis[a])

Lipid	TIVICAY + EPZICOM Once Daily (N = 414)	ATRIPLA Once Daily (N = 419)
Cholesterol (mg/dL)	23.2	28.0
HDL cholesterol (mg/dL)	5.2	7.4
LDL cholesterol (mg/dL)	14.5	18.0
Triglycerides (mg/dL)	17.2	17.4

[a] Subjects on lipid-lowering agents at baseline were excluded from these analyses (TIVICAY n = 30 and ATRIPLA n = 27). Fifty-five subjects initiated a lipid-lowering agent post-baseline; their last fasted on-treatment values (prior to starting the agent) were used regardless if they discontinued the agent (SINGLE: TIVICAY n = 25 and ATRIPLA: n = 30).

Treatment-experienced Subjects: Laboratory abnormalities observed in SAILING were generally similar compared with observations seen in the treatment-naïve trials.

Hepatitis C Virus Co-infection: In SINGLE, the pivotal Phase 3 trial, subjects with hepatitis C virus co-infection were permitted to enroll provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal; subjects with hepatitis B co-infection were excluded. Overall, the safety profile in subjects with hepatitis C virus co-infection was similar to that observed in subjects without hepatitis C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis C virus co-infection for both treatment groups. Grades 2 to 4 ALT abnormalities in hepatitis C co-infected compared with HIV mono-infected subjects receiving TRIUMEQ were observed in 15% and 2% (vs. 24% and 4% of subjects treated with ATRIPLA), respectively *[see Warnings and Precautions (5.3)]*. See also full prescribing information for TIVICAY.

Changes in Serum Creatinine: Dolutegravir has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function *[see Clinical Pharmacology (12.2)]*. Increases in serum creatinine occurred within the first 4 weeks of treatment and remained stable through 24 to 96 weeks. In SINGLE, a mean change from baseline of 0.14 mg per dL (range: -0.32 mg per dL to 0.59 mg per dL) was observed after 96 weeks of treatment. Creatinine increases were similar in treatment-experienced subjects.

Abacavir Sulfate and Lamivudine: Laboratory abnormalities observed in clinical trials of ZIAGEN (in combination with other antiretroviral treatment) were anemia, neutropenia, liver function test abnormalities, and elevations of CPK, blood glucose, and triglycerides. Additional laboratory abnormalities observed in clinical trials of EPIVIR (in combination with other antiretroviral treatment) were thrombocytopenia and elevated levels of bilirubin, amylase, and lipase.

6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postmarketing use. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Abacavir and/or Lamivudine:

Digestive: Stomatitis.

Gastrointestinal: Pancreatitis.

General: Weakness.

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

Hypersensitivity: Sensitization reactions (including anaphylaxis), urticaria.

Metabolism and Nutrition Disorders: Hyperlactemia.

Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.

Nervous: Paresthesia, peripheral neuropathy, seizures.

Respiratory: Abnormal breath sounds/wheezing.

Skin: Alopecia, erythema multiforme. 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.

7 DRUG INTERACTIONS

7.1 Effect of Dolutegravir on the Pharmacokinetics of Other Agents

In vitro, dolutegravir inhibited the renal organic cation transporters, OCT2 (IC_{50} = 1.93 μM) and multidrug and toxin extrusion transporter (MATE) 1 (IC_{50} = 6.34 μM). In vivo, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2 and potentially MATE1. Dolutegravir may increase plasma concentrations of drugs eliminated via OCT2 or MATE1 (dofetilide and metformin) *[see Contraindications (4), Drug Interactions (7.3)]*.

In vitro, dolutegravir inhibited the basolateral renal transporters, organic anion transporter (OAT) 1 (IC_{50} = 2.12 μM) and OAT3 (IC_{50} = 1.97 μM). However, in vivo, dolutegravir did not alter the plasma concentrations of tenofovir or para-amino hippurate, substrates of OAT1 and OAT3.

In vitro, dolutegravir did not inhibit (IC_{50} greater than 50 μM) the following: cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, UGT1A1, UGT2B7, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, or multidrug resistance protein (MRP)2, or MRP4. In vitro, dolutegravir did not induce CYP1A2, CYP2B6, CYP3A4. Based on these data and the results of drug interaction trials, dolutegravir is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters.

In drug interaction trials, dolutegravir did not have a clinically relevant effect on the pharmacokinetics of the following drugs: tenofovir, methadone, midazolam, rilpivirine, and oral contraceptives containing norgestimate and ethinyl estradiol. Using cross-study comparisons to historical pharmacokinetic data for each interacting drug, dolutegravir did not appear to affect the pharmacokinetics of the following drugs: atazanavir, darunavir, efavirenz, etravirine, fosamprenavir, lopinavir, ritonavir, and telaprevir.

7.2 Effect of Other Agents on the Pharmacokinetics of Dolutegravir

Dolutegravir is metabolized by UGT1A1 with some contribution from CYP3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, BCRP, and P-gp in vitro. Drugs that induce those enzymes and transporters may decrease dolutegravir plasma concentrations and reduce the therapeutic effect of dolutegravir.

Coadministration of dolutegravir and other drugs that inhibit these enzymes may increase dolutegravir plasma concentrations.

Etravirine significantly reduced plasma concentrations of dolutegravir, but the effect of etravirine was mitigated by coadministration of lopinavir/ritonavir or darunavir/ritonavir, and is expected to be mitigated by atazanavir/ritonavir (Table 5) *[see Drug Interactions (7.3), Clinical Pharmacology (12.3)]*.

Darunavir/ritonavir, lopinavir/ritonavir, rilpivirine, tenofovir, boceprevir, telaprevir, prednisone, rifabutin, and omeprazole had no clinically significant effect on the pharmacokinetics of dolutegravir.

7.3 Established and Other Potentially Significant Drug Interactions

There were no drug-drug interaction trials conducted with the abacavir, dolutegravir, and lamivudine fixed-dose combination tablets.

Information regarding potential drug interactions with dolutegravir (Table 5) and abacavir are provided below. These recommendations are based on either drug interaction trials or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy. *[See Clinical Pharmacology (12.3).]*

Table 5. Established and Other Potentially Significant Drug Interactions for Dolutegravir: Alterations in Dose May Be Recommended Based on Drug Interaction Trials or Predicted Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
HIV-1 Antiviral Agents		
Non-nucleoside reverse transcriptase inhibitor: Etravirine[a]	↓Dolutegravir	Use of TRIUMEQ with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir is not recommended.
Non-nucleoside reverse transcriptase inhibitor: Efavirenz[a]	↓Dolutegravir	Adjust dolutegravir dose to 50 mg twice daily. An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from TRIUMEQ.
Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓Dolutegravir	Avoid coadministration with TRIUMEQ because there are insufficient data to make dosing recommendations.
Protease inhibitor: Fosamprenavir/ritonavir[a] Tipranavir/ritonavir[a]	↓Dolutegravir	Adjust dolutegravir dose to 50 mg twice daily. An additional dolutegravir 50-mg dose should be taken, separated by 12 hours from TRIUMEQ.
Other Agents		
Oxcarbazepine	↓Dolutegravir	Avoid coadministration with TRIUMEQ

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
Phenytoin Phenobarbital Carbamazepine St. John's wort (*Hypericum perforatum*)		because there are insufficient data to make dosing recommendations.
Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing antacids[a] or laxatives Sucralfate Buffered medications	↓Dolutegravir	Administer TRIUMEQ 2 hours before or 6 hours after taking medications containing polyvalent cations.
Oral calcium and iron supplements, including multivitamins containing calcium or iron[a]	↓Dolutegravir	Administer TRIUMEQ 2 hours before or 6 hours after taking supplements containing calcium or iron. Alternatively, TRIUMEQ and supplements containing calcium or iron can be taken together with food.
Metformin	↑Metformin	Consider metformin dose reductions when coadministered with TRIUMEQ.
Rifampin[a]	↓Dolutegravir	Adjust dolutegravir dose to 50 mg twice daily. An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from TRIUMEQ.

[a] *See Clinical Pharmacology (12.3) Table 9 for magnitude of interaction.*

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)]*.

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 abacavir 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. The addition of methadone had no clinically significant effect on the pharmacokinetic properties of abacavir.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no adequate and well-controlled trials in pregnant women. Reproduction studies with the components of TRIUMEQ have been performed in animals (see Dolutegravir, Abacavir, and Lamivudine sections below). Animal reproduction studies are not always predictive of human response. TRIUMEQ should be used during pregnancy only if the potential benefit outweigh the risks.

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

Animal Data: *Dolutegravir:* Reproduction studies performed in rats and rabbits at doses up to 50 times the human dose of 50 mg once daily have revealed no evidence of impaired fertility or harm to the fetus due to dolutegravir.

Oral administration of dolutegravir to pregnant rats at doses up to 1,000 mg per kg daily, approximately 50 times the 50-mg once-daily human clinical exposure based on AUC, from days 6 to 17 of gestation did not elicit maternal toxicity, developmental toxicity, or teratogenicity.

Oral administration of dolutegravir to pregnant rabbits at doses up to 1,000 mg per kg daily, approximately 0.74 times the 50-mg once-daily human clinical exposure based on AUC, from days 6 to 18 of gestation did not elicit developmental toxicity or teratogenicity. In rabbits, maternal toxicity (decreased food consumption, scant/no feces/urine, suppressed body weight gain) was observed at 1,000 mg per kg.

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 28 times the human exposure for a dose of 600 mg 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 7 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 32 times the human exposure for a dose of 300 mg. 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 plasma levels up to 32 times those in humans.

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, instruct **mothers not to breastfeed**.

Dolutegravir: Studies in lactating rats and their offspring indicate that dolutegravir was present in rat milk. It is not known whether dolutegravir is excreted in human breast milk.

Abacavir: Abacavir is excreted in the milk of lactating rats.

Lamivudine: Lamivudine is excreted in human breast milk.

8.4 Pediatric Use

Safety and effectiveness of TRIUMEQ in pediatric patients have not been established *[see Clinical Pharmacology (12.3)]*.

8.5 Geriatric Use

Clinical trials of abacavir, dolutegravir, or lamivudine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of TRIUMEQ in elderly patient reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Clinical Pharmacology (12.3)]*.

8.6 Patients with Impaired Renal Function

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

8.7 Patients with Impaired Hepatic Function

TRIUMEQ is a fixed-dose combination and the dosage of the individual components cannot be adjusted. If a dose reduction of abacavir, a component of TRIUMEQ, is required for patients with mild hepatic impairment (Child-Pugh Score A), then the individual components should be used *[see Clinical Pharmacology (12.3)]*.

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

10 OVERDOSAGE

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

Dolutegravir: As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

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

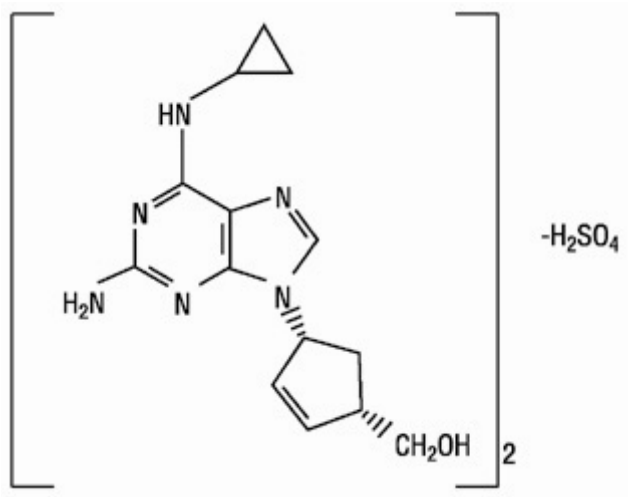
Lamivudine: Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event. If overdose occurs, the patient should be monitored, and standard supportive treatment applied as required.

11 DESCRIPTION

TRIUMEQ: TRIUMEQ contains an INSTI (dolutegravir) and 2 nucleoside analogues (abacavir and lamivudine) with inhibitory activity against HIV.

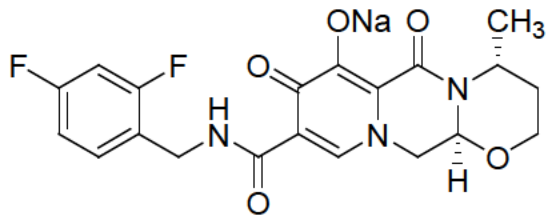
Each film-coated tablet contains abacavir sulfate equivalent to 600 mg of abacavir, dolutegravir sodium equivalent to 50 mg of dolutegravir, and 300 mg of lamivudine. TRIUMEQ tablets are purple, biconvex, oval, debossed with “572 Trı” on one side and contain the inactive ingredients D-mannitol, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate. The tablet film-coating (OPADRY® II Purple 85F90057) contains the inactive ingredients iron oxide black, iron oxide red, macrogol/PEG, polyvinyl alcohol–part hydrolyzed, talc, and titanium oxide.

Abacavir: 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). It has a molecular formula of $(C_{14}H_{18}N_6O)_2 \bullet H_2SO_4$ and a molecular weight of 670.76 g per mol. It has the following structural formula:



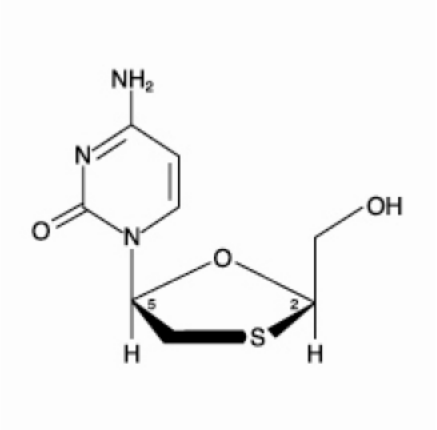
Abacavir sulfate is a white to off-white solid and is soluble in water.

Dolutegravir: The chemical name of dolutegravir sodium is sodium (4*R*,12a*S*)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazin-7-olate. The empirical formula is $C_{20}H_{18}F_2N_3NaO_5$ and the molecular weight is 441.36 g per mol. It has the following structural formula:



Dolutegravir sodium is a white to light yellow powder and is slightly soluble in water.

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



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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

TRIUMEQ is an HIV-1 antiviral agent *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Effects on Electrocardiogram: A thorough QT trial has been conducted for dolutegravir. Neither the effects of abacavir nor lamivudine as single entities or the combination of abacavir, dolutegravir, and lamivudine on the QT interval have been evaluated.

In a randomized, placebo-controlled, cross-over trial, 42 healthy subjects received single-dose oral administrations of placebo, dolutegravir 250-mg suspension (exposures approximately 3–fold of the 50-mg once-daily dose at steady state), and moxifloxacin 400 mg (active control) in random sequence. After baseline and placebo adjustment, the maximum mean QTc change based on Fridericia correction method (QTcF) for dolutegravir was 2.4 msec (1-sided 95% upper CI: 4.9 msec). Dolutegravir did not prolong the QTc interval over 24 hours postdose.

Effects on Renal Function: The effect of dolutegravir on renal function was evaluated in an open-label, randomized, 3-arm, parallel, placebo-controlled trial in healthy subjects (n = 37) who received dolutegravir 50 mg once daily (n = 12), dolutegravir 50 mg twice daily

(n = 13), or placebo once daily (n = 12) for 14 days. A decrease in creatinine clearance, as determined by 24-hour urine collection, was observed with both doses of dolutegravir after 14 days of treatment in subjects who received 50 mg once daily (9% decrease) and 50 mg twice daily (13% decrease). Neither dose of dolutegravir had a significant effect on the actual glomerular filtration rate (determined by the clearance of probe drug, iohexol) or effective renal plasma flow (determined by the clearance of probe drug, para-amino hippurate) compared with the placebo.

12.3 Pharmacokinetics

Pharmacokinetics in Adults: One TRIUMEQ tablet was bioequivalent to one dolutegravir (TIVICAY) tablet (50 mg) plus one abacavir and lamivudine fixed-dose combination tablet (EPZICOM) under fasted conditions in healthy subjects (n = 62).

Abacavir: Following oral administration, abacavir is rapidly absorbed and extensively distributed. After oral administration of a single dose of 600 mg of abacavir in 20 subjects, C_{max} was 4.26 ± 1.19 mcg per mL (mean ± SD) and AUC_{∞} was 11.95 ± 2.51 mcg•hour per mL. Binding of abacavir to human plasma proteins is approximately 50% and was independent of concentration. Total blood and plasma drug-related radioactivity concentrations are identical, demonstrating that abacavir readily distributes into erythrocytes. The primary routes of elimination of abacavir are metabolism by alcohol dehydrogenase to form the 5′-carboxylic acid and glucuronyl transferase to form the 5′-glucuronide. In single-dose trials, the observed elimination half-life ($t_{½}$) was 1.54 ± 0.63 hours. After intravenous administration, total clearance was 0.80 ± 0.24 L per hour per kg (mean ± SD).

Dolutegravir: Following oral administration of dolutegravir, peak plasma concentrations were observed 2 to 3 hours postdose. With once-daily dosing, pharmacokinetic steady state is achieved within approximately 5 days with average accumulation ratios for AUC, C_{max}, and $C_{24\,h}$ ranging from 1.2 to 1.5. Dolutegravir is a P-glycoprotein substrate in vitro. The absolute bioavailability of dolutegravir has not been established. Dolutegravir is highly bound (greater than or equal to 98.9%) to human plasma proteins based on in vivo data and binding is independent of plasma concentration of dolutegravir. The apparent volume of distribution (Vd/F) following 50-mg once-daily administration is estimated at 17.4 L based on a population pharmacokinetic analysis.

Dolutegravir is primarily metabolized via UGT1A1 with some contribution from CYP3A. After a single oral dose of [^{14}C] dolutegravir, 53% of the total oral dose is excreted unchanged in the feces. Thirty-one percent of the total oral dose is excreted in the urine, represented by an ether glucuronide of dolutegravir (18.9% of total dose), a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose), and its hydrolytic N-dealkylation product (3.6% of total dose). Renal elimination of unchanged drug was less than 1% of the dose. Dolutegravir has a terminal half-life of approximately 14 hours and an apparent clearance (CL/F) of 1.0 L per hour based on population pharmacokinetic analyses.

The pharmacokinetic properties of dolutegravir have been evaluated in healthy adult subjects and HIV-1–infected adult subjects. Exposure to dolutegravir was generally similar between healthy subjects and HIV-1–infected subjects.

Table 6. Dolutegravir Steady-state Pharmacokinetic Parameter Estimates in HIV-1–Infected Adults

Parameter	50 mg Once Daily Geometric Mean (%CV)
$AUC_{(0-24)}$ (mcg•h/mL)	53.6 (27)
C_{max} (mcg/mL)	3.67 (20)
C_{min} (mcg/mL)	1.11 (46)

Cerebrospinal Fluid (CSF): In 11 treatment-naïve subjects on dolutegravir 50 mg daily plus abacavir/lamivudine, the median dolutegravir concentration in CSF was 18 ng per mL (range: 4 ng per mL to 23.2 ng per mL) 2 to 6 hours postdose after 2 weeks of treatment. The clinical relevance of this finding has not been established.

Lamivudine: Following oral administration, lamivudine is rapidly absorbed and extensively distributed. After multiple-dose oral administration of lamivudine 300 mg once daily for 7 days to 60 healthy subjects, steady-state C_{max} ($C_{max,ss}$) was 2.04 ± 0.54 mcg per mL (mean ± SD) and the 24-hour steady-state AUC ($AUC_{24,ss}$) was 8.87 ± 1.83 mcg•hour per mL. Binding to plasma protein is low. Approximately 70% of an intravenous dose of lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours). In most single-dose trials in HIV-1–infected subjects, HBV-infected subjects, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{½}$) ranged from 5 to 7 hours. In HIV-1–infected subjects, total clearance was 398.5 ± 69.1 mL per min (mean ± SD).

Effect of Food on Oral Absorption: TRIUMEQ may be taken with or without food. Overall, when compared with fasted conditions, administration of TRIUMEQ to healthy adult subjects with a high-fat meal (53% fat, 869 calories) resulted in decreased C_{max} for abacavir and increased C_{max} and AUC for dolutegravir. Lamivudine exposures were not affected by food. With a high-fat meal, the C_{max} of abacavir decreased 23% and the C_{max} and AUC of dolutegravir increased 37% and 48%, respectively.

Special Populations: *Renal Impairment:* The effect of renal impairment on the combination of abacavir, dolutegravir, and lamivudine has not been evaluated.

Abacavir: The pharmacokinetic properties of abacavir have not been determined in patients with impaired renal function.

Dolutegravir: In a trial comparing 8 subjects with severe renal impairment (CrCl less than 30 mL per min) with 8 matched healthy controls, AUC, C_{max}, and C_{24} of dolutegravir were decreased by 40%, 23%, and 43%, respectively, compared with those in matched healthy

subjects. The cause of this decrease is unknown. Population pharmacokinetic analysis indicated that mild and moderate renal impairment had no clinically relevant effect on the exposure of dolutegravir.

Lamivudine: The pharmacokinetic properties of lamivudine have been determined in a small group of HIV-1–infected adults with impaired renal function (Table 7).

Table 7. Pharmacokinetic Parameters (Mean ± SD) After a Single 300-mg Oral Dose of Lamivudine in 3 Groups of Adults with Varying Degrees of Renal Function

Parameter	Creatinine Clearance Criterion (Number of Subjects)		
	>60 mL/min (n = 6)	**10-30 mL/min (n = 4)**	**<10 mL/min (n = 6)**
Creatinine clearance (mL/min)	111 ± 14	28 ± 8	6 ± 2
C_{max} (mcg/mL)	2.6 ± 0.5	3.6 ± 0.8	5.8 ± 1.2
AUC∞ (mcg•h/mL)	11.0 ± 1.7	48.0 ± 19	157 ± 74
Cl/F (mL/min)	464 ± 76	114 ± 34	36 ± 11

Hepatic Impairment: The effect of hepatic impairment on the combination of abacavir, dolutegravir, and lamivudine has not been evaluated.

Abacavir: The pharmacokinetics of abacavir have been studied in subjects with mild hepatic impairment (Child-Pugh score 5 to 6). Results showed that there was a mean increase of 89% in the abacavir AUC and an increase of 58% in the half-life of abacavir after a single dose of 600 mg of abacavir. The AUCs of the metabolites were not modified by mild liver disease; however, the rates of formation and elimination of the metabolites were decreased. The safety, efficacy, and pharmacokinetics of abacavir have not been studied in patients with moderate or severe hepatic impairment.

Dolutegravir: In a trial comparing 8 subjects with moderate hepatic impairment (Child- Pugh Score B) with 8 matched healthy controls, exposure of dolutegravir from a single 50-mg dose was similar between the 2 groups. The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir has not been studied.

Lamivudine: The pharmacokinetic properties of lamivudine have been determined in adults with impaired hepatic function. Pharmacokinetic parameters were not altered by diminishing hepatic function. Safety and efficacy of lamivudine have not been established in the presence of decompensated liver disease.

Pediatric Patients: The pharmacokinetics of the combination of abacavir, dolutegravir, and lamivudine in pediatric subjects have not been established.

Geriatric Patients: Population analyses using pooled pharmacokinetic data from adult trials indicated age had no clinically relevant effect on the pharmacokinetics of dolutegravir. The

pharmacokinetics of abacavir or lamivudine have not been studied in subjects older than 65 years.

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

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

Drug Interactions: The drug interaction trials described were conducted with dolutegravir, abacavir, and/or lamivudine as single entities; no drug interaction trials have been conducted using the combination of abacavir, dolutegravir, and lamivudine. No clinically significant drug interactions are expected between dolutegravir, abacavir, and lamivudine.

Dosing recommendations as a result of established and other potentially significant drug-drug interactions with dolutegravir or abacavir are provided in Section 7.3 *[see Drug Interactions (7)]*.

Table 8. Summary of Effect of Dolutegravir on the Pharmacokinetics of Coadministered Drugs

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug with/without Dolutegravir No Effect = 1.00		
			C_{max}	AUC	C_{τ} or C_{24}
Ethinyl estradiol 0.035 mg	50 mg twice daily	15	0.99 (0.91 to 1.08)	1.03 (0.96 to 1.11)	1.02 (0.93 to 1.11)
Methadone 16 to 150 mg	50 mg twice daily	11	1.00 (0. 94 to 1.06)	0.98 (0.91 to 1.06)	0.99 (0.91 to 1.07)
Midazolam 3 mg	25 mg once daily	10	–	0.95 (0.79 to 1.15)	–
Norelgestromin 0.25 mg	50 mg twice daily	15	0.89 (0.82 to 0.97)	0.98 (0.91 to 1.04)	0.93 (0.85 to 1.03)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.10 (0.99 to 1.22)	1.06 (0.98 to 1.16)	1.21 (1.07 to 1.38)
Tenofovir disoproxil fumarate 300 mg once daily	50 mg once daily	15	1.09 (0.97 to 1.23)	1.12 (1.01 to 1.24)	1.19 (1.04 to 1.35)

Table 9. Summary of Effect of Coadministered Drugs on the Pharmacokinetics of Dolutegravir

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00		
			C_{max}	AUC	C_{τ} or C_{24}
Atazanavir 400 mg once daily	30 mg once daily	12	1.50 (1.40 to 1.59)	1.91 (1.80 to 2.03)	2.80 (2.52 to 3.11)
Atazanavir/ritonavir 300/100 mg once daily	30 mg once daily	12	1.34 (1.25 to 1.42)	1.62 (1.50 to 1.74)	2.21 (1.97 to 2.47)
Tenofovir 300 mg once daily	50 mg once daily	15	0.97 (0.87 to 1.08)	1.01 (0.91 to 1.11)	0.92 (0.82 to 1.04)
Darunavir/ritonavir 600/100 mg twice daily	30 mg once daily	15	0.89 (0.83 to 0.97)	0.78 (0.72 to 0.85)	0.62 (0.56 to 0.69)
Efavirenz 600 mg once daily	50 mg once daily	12	0.61 (0.51 to 0.73)	0.43 (0.35 to 0.54)	0.25 (0.18 to 0.34)
Etravirine 200 mg twice daily	50 mg once daily	16	0.48 (0.43 to 0.54)	0.29 (0.26 to 0.34)	0.12 (0.09 to 0.16)
Etravirine + darunavir/ritonavir 200 mg + 600/100 mg twice daily	50 mg once daily	9	0.88 (0.78 to 1.00)	0.75 (0.69 to 0.81)	0.63 (0.52 to 0.76)
Etravirine + lopinavir/ritonavir 200 mg + 400/100 mg twice daily	50 mg once daily	8	1.07 (1.02 to 1.13)	1.11 (1.02 to 1.20)	1.28 (1.13 to 1.45)
Fosamprenavir/ritonavir 700 mg /100 mg twice daily	50 mg once daily	12	0.76 (0.63 to 0.92)	0.65 (0.54 to 0.78)	0.51 (0.41 to 0.63)
Lopinavir/ritonavir 400/100 mg twice daily	30 mg once daily	15	1.00 (0.94 to 1.07)	0.97 (0.91 to 1.04)	0.94 (0.85 to 1.05)
Antacid (Maalox®) simultaneous administration	50 mg single dose	16	0.28 (0.23 to 0.33)	0.26 (0.22 to 0.32)	0.26 (0.21 to 0.31)
Antacid (Maalox®) 2 h after dolutegravir	50 mg single dose	16	0.82 (0.69 to 0.98)	0.74 (0.62 to 0.90)	0.70 (0.58 to 0.85)
Calcium carbonate 1,200 mg simultaneous administration (fasted)	50 mg single dose	12	0.63 (0.50 to 0.81)	0.61 (0.47 to 0.80)	0.61 (0.47 to 0.80)
Calcium carbonate 1,200 mg simultaneous administration (fed)	50 mg single dose	11	1.07 (0.83 to 1.38)	1.09 (0.84 to 1.43)	1.08 (0.81 to 1.42)

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00		
			C_{max}	AUC	C_{τ} or C_{24}
Calcium carbonate 1,200 mg 2 h after dolutegravir	50 mg single dose	11	1.00 (0.78 to 1.29)	0.94 (0.72 to 1.23)	0.90 (0.68 to 1.19)
Ferrous fuarate 324 mg simultaneous administration (fasted)	50 mg single dose	11	0.43 (0.35 to 0.52)	0.46 (0.38 to 0.56)	0.44 (0.36 to 0.54)
Ferrous fuarate 324 mg simultaneous administration (fed)	50 mg single dose	11	1.03 (0.84 to 1.26)	0.98 (0.81 to 1.20)	1.00 (0.81 to 1.23)
Ferrous fuarate 324 mg 2 h after dolutegravir	50 mg single dose	10	0.99 (0.81 to 1.21)	0.95 (0.77 to 1.15)	0.92 (0.74 to 1.13)
Multivitamin (One-A-Day®) simultaneous administration	50 mg single dose	16	0.65 (0.54 to 0.77)	0.67 (0.55 to 0.81)	0.68 (0.56 to 0.82)
Omeprazole 40 mg once daily	50 mg single dose	12	0.92 (0.75 to 1.11)	0.97 (0.78 to 1.20)	0.95 (0.75 to 1.21)
Prednisone 60 mg once daily with taper	50 mg once daily	12	1.06 (0.99 to 1.14)	1.11 (1.03 to 1.20)	1.17 (1.06 to 1.28)
Rifampin[a] 600 mg once daily	50 mg twice daily	11	0.57 (0.49 to 0.65)	0.46 (0.38 to 0.55)	0.28 (0.23 to 0.34)
Rifampin[b] 600 mg once daily	50 mg twice daily	11	1.18 (1.03 to 1.37)	1.33 (1.15 to 1.53)	1.22 (1.01 to 1.48)
Rifabutin 300 mg once daily	50 mg once daily	9	1.16 (0.98 to 1.37)	0.95 (0.82 to 1.10)	0.70 (0.57 to 0.87)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.13 (1.06 to 1.21)	1.12 (1.05 to 1.19)	1.22 (1.15 to 1.30)
Tipranavir/ritonavir 500/200 mg twice daily	50 mg once daily	14	0.54 (0.50 to 0.57)	0.41 (0.38 to 0.44)	0.24 (0.21 to 0.27)
Telaprevir 750 mg every 8 hours	50 mg once daily	15	1.18 (1.11 to 1.26)	1.25 (1.19 to 1.31)	1.40 (1.29 to 1.51)
Boceprevir 800 mg every 8 hours	50 mg once daily	13	1.05 (0.96 to 1.15)	1.07 (0.95 to 1.20)	1.08 (0.91 to 1.28)

[a] Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg twice daily.

[b] Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg once daily.

Abacavir or Lamivudine: The drug interactions described are based on trials conducted with abacavir or lamivudine as single entities.

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

Methadone: In a trial of 11 HIV-1-infected subjects receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of abacavir twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI: 6% to 42%) *[see Drug Interactions (7.3)]*.

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)]*.

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

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

The effects of other coadministered drugs on abacavir or lamivudine are provided in Table 10.

Table 10. Effect of Coadministered Drugs on Abacavir or Lamivudine

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

↑ = Increase; ↔ = no significant change; AUC = area under the concentration versus time curve; CI = confidence interval.
[a] The drug-drug interaction was only evaluated in males.

12.4 Microbiology

Mechanism of Action: *Dolutegravir:* Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration which is essential for the HIV replication cycle. Strand transfer biochemical assays using purified recombinant HIV-1 integrase and pre-processed substrate DNA resulted in IC_{50} values of 2.7 nM and 12.6 nM.

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

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

Antiviral Activity in Cell Culture: *Dolutegravir:* Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean concentration of drug necessary to effect viral replication by 50 percent (EC_{50}) values of 0.5 nM (0.21 ng per mL) to 2.1 nM (0.85 ng per mL) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells. Dolutegravir exhibited antiviral activity against 13 clinically diverse clade B isolates with a median EC_{50} value of 0.54 nM (range: 0.41 to 0.60 nM) in a viral susceptibility assay using the integrase coding region from clinical isolates. Dolutegravir demonstrated antiviral activity in cell culture against a panel of HIV-1 clinical isolates with median EC_{50} values of 0.18 nM (n = 3, range: 0.09 to 0.5 nM), 0.08 nM (n = 5, range: 0.05 to 2.14 nM) 0.12 nM (n = 4, range: 0.05 to 0.51 nM), 0.17 nM (n = 3, range: 0.16 to 0.35 nM), 0.24 nM (n = 3, range: 0.09 to 0.32 nM), 0.17 nM (range: 0.07 to 0.44 nM), 0.2 nM (n = 3, range: 0.02 to 0.87 nM), and 0.42 nM (n = 3, range: 0.41 to 1.79 nM) for clades A, B, C, D, E, F, and G, and group O viruses, respectively. Dolutegravir EC_{50} values against three HIV-2 clinical isolates in PBMC assays ranged from 0.09 nM to 0.61 nM.

Abacavir: The antiviral activity of abacavir against HIV-1 was assessed in a number of cell lines including in primary monocytes/macrophages and PBMCs. EC_{50} values ranged from 3.7 to 5.8 μM (1 μM = 0.28 mcg per mL) and 0.07 to 1.0 μM against $HIV\text{-}1_{IIIB}$ and $HIV\text{-}1_{BaL}$, respectively, and was 0.26 ± 0.18 μM against 8 clinical isolates. The median EC_{50} values of abacavir were 344 nM (range: 14.8 to 676 nM), 16.9 nM (range: 5.9 to 27.9 nM), 8.1 nM (range: 1.5 to 16.7 nM), 356 nM (range: 35.7 to 396 nM), 105 nM (range: 28.1 to 168 nM), 47.6 nM (range: 5.2 to 200 nM), 51.4 nM (range: 7.1 to 177 nM), and 282 nM (range: 22.4 to 598 nM)

against HIV-1 clades A-G and group O viruses (n = 3 except n = 2 for clade B), respectively. The EC_{50} values against HIV-2 isolates (n = 4), ranged from 0.024 to 0.49 μM.

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

Antiviral Activity in Combination with Other Antiviral Agents: Neither dolutegravir, abacavir, nor lamivudine were antagonistic to all tested anti-HIV agents. See full prescribing information for ZIAGEN (abacavir), TIVICAY (dolutegravir), and EPIVIR (lamivudine).

Resistance in Cell Culture: *Dolutegravir:* Dolutegravir-resistant viruses were selected in cell culture starting from different wild-type HIV-1 strains and clades. Amino acid substitutions E92Q, G118R, S153F or Y, G193E or R263K emerged in different passages and conferred decreased susceptibility to dolutegravir of up to 4-fold.

Abacavir and Lamivudine: HIV-1 isolates with reduced susceptibility to the combination of abacavir and lamivudine have been selected in cell culture with amino acid substitutions M184V/I, K65R, L74V, and Y115F in HIV-1 RT. Substitution at M184I or V causes high-level resistance to lamivudine and approximately 2-fold decreased susceptibility to abacavir. Substitutions K65R, L74M, or Y115F with M184I or V conferred a 7-fold to 8-fold reduction in abacavir susceptibility, and combinations of three substitutions were required to confer more than an 8-fold reduction in susceptibility.

Resistance in Clinical Subjects: *Dolutegravir:* No subjects in the treatment arm receiving dolutegravir + EPZICOM of SINGLE (treatment-naïve trial) had a detectable decrease in susceptibility to dolutegravir or background NRTIs in the resistance analysis subset (n = 9 with HIV-1 RNA greater than 400 copies per mL at failure or last visit through Week 96 and having resistance data). One subject in SINGLE with 275 copies per mL HIV-1 RNA had a treatment-emergent integrase substitution (E157Q/P) detected at Week 24, but no corresponding decrease in dolutegravir susceptibility. No treatment-emergent genotypic resistance to abacavir and lamivudine, components of TRIUMEQ, was observed in the arm receiving dolutegravir + EPZICOM in the SINGLE trial.

Cross Resistance: *Dolutegravir:* The single INSTI-resistance substitutions T66K, I151L, and S153Y conferred a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.3-fold to 3.6-fold from reference). Combinations of multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148, and substitutions at E138/G140/Q148 showed a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.5-fold to 21-fold from reference). In HIV-2 mutants, combinations of substitutions A153G/N155H/S163G and E92Q/T97A/N155H/S163D conferred 4-fold decreases

in dolutegravir susceptibility, and E92Q/N155H and G140S/Q148R showed 8.5-fold and 17-fold decreases in dolutegravir susceptibility, respectively.

Abacavir and Lamivudine: Cross-resistance has been observed among NRTIs. 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: *Dolutegravir:* Two-year carcinogenicity studies in mice and rats were conducted with dolutegravir. Mice were administered doses of up to 500 mg per kg, and rats were administered doses of up to 50 mg per kg. In mice, no significant increases in the incidence of drug-related neoplasms were observed at the highest doses tested, resulting in dolutegravir AUC exposures approximately 26-fold higher than those in humans at the recommended dose of 50 mg once daily. In rats, no increases in the incidence of drug-related neoplasms were observed at the highest dose tested, resulting in dolutegravir AUC exposures 17-fold and 30-fold higher in males and females, respectively, than those in humans at the recommended dose of 50 mg once daily.

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 7 to 28 times the human exposure at the recommended dose of 600 mg.

Lamivudine: Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 12 times (mice) and 57 times (rats) the human exposures at the recommended dose of 300 mg.

Mutagenicity: *Dolutegravir:* Dolutegravir was not genotoxic in the bacterial reverse mutation assay, mouse lymphoma assay, or in the in vivo rodent micronucleus assay.

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: Dolutegravir, abacavir, or lamivudine did not affect male or female fertility in rats at doses associated with exposures approximately 44, 9, or 112 times (respectively) higher than the exposures in humans at the doses of 50 mg, 600 mg, and 300 mg (respectively).

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 21 times the expected systemic exposure in humans at a dose of 600 mg. The clinical relevance of this finding has not been determined.

14 CLINICAL STUDIES

14.1 Adult Subjects

The efficacy of TRIUMEQ is supported by data from a randomized, controlled trial in antiretroviral treatment-naïve subjects, SINGLE (ING114467) and other trials in treatment-naïve subjects. See full prescribing information for TIVICAY. The efficacy of dolutegravir, in combination with at least two active background regimens in treatment-experienced, INSTI-naïve subjects is supported by data from SAILING (ING111762) (refer to the prescribing information for TIVICAY).

Treatment-naïve Subjects: In SINGLE, 833 subjects were randomized and received at least 1 dose of either TIVICAY 50 mg once daily with fixed-dose abacavir and lamivudine (EPZICOM) or fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate (ATRIPLA). At baseline, the median age of subjects was 35 years, 16% female, 32% non-white, 7% had hepatitis C co-infection (hepatitis B virus co-infection was excluded), 4% were CDC Class C (AIDS), 32% had HIV-1 RNA greater than 100,000 copies per mL, and 53% had CD4+ cell count less than 350 cells per mm^3; these characteristics were similar between treatment groups. Week 96 outcomes for SINGLE are provided in Table 11.

Table 11. Virologic Outcomes of Randomized Treatment in SINGLE at 96 Weeks (Snapshot Algorithm)

	TIVICAY + EPZICOM Once Daily (N = 414)	**ATRIPLA Once Daily (N = 419)**
HIV-1 RNA <50 copies/mL	80%	72%
Treatment difference[a]	8.0% (95% CI: 2.3%, 13.8%)	
Virologic nonresponse[b]	7%	8%
No virologic data	12%	20%

Reasons		
Discontinued study/study drug due to adverse event or death[c]	3%	11%
Discontinued study/study drug for other reasons[d]	9%	8%
Missing data during window but on study	<1%	0
Proportion (%) of Subjects with HIV-1 RNA <50 copies/mL by Baseline Category		
Plasma viral load (copies/mL)[e]		
≤100,000	85%	73%
>100,000	71%	72%
Gender		
Male	81%	75%
Female	76%	56%
Race		
White	79%	77%
African-American/African Heritage/Other	83%	62%

[a] Adjusted for pre-specified stratification factors.

[b] Includes subjects who discontinued prior to Week 96 for lack or loss of efficacy, and subjects who were HIV-1 RNA greater than or equal to 50 copies per mL in the Week 96 window.

[c] Includes subjects who discontinued due to an adverse event or death at any time point from Day 1 through the Week 96 window if this resulted in no virologic data on treatment during the Week 96 window.

[d] Other includes reasons such as withdrew consent, loss to follow-up, moved, and protocol deviation.

[e] The proportion of subjects who had no virologic data due to reasons such as withdrew consent, lost to follow-up, moved, and protocol deviation was 10% (TIVICAY + EPZICOM) and 6% (ATRIPLA) in the greater than 100,000–copies-per-mL-group and 8% and 9% (respectively) in the less than or equal to 100,000–copies-per-mL-group.

Treatment differences were maintained across baseline characteristics including CD4+ cell count, age, gender, and race. The adjusted mean changes in CD4+ cell counts from baseline were 325 cells per mm^3 in the group receiving TIVICAY + EPZICOM and 281 cells per mm^3 for the ATRIPLA group at 96 weeks. The adjusted difference between treatment arms and 95% CI was 44.0 cells per mm^3 (14.3 cells per mm^3, 73.6 cells per mm^3) (adjusted for pre-specified stratification factors: baseline HIV-1 RNA, baseline CD4+ cell count, and multiplicity).

Treatment-experienced: In SAILING, there were 715 subjects included in the efficacy and safety analyses (see full prescribing information for TIVICAY). At Week 48, 71% of subjects randomized to TIVICAY plus background regimen versus 64% of subjects randomized to raltegravir plus background regimen had HIV-1 RNA less than 50 copies per mL [treatment difference and 95% CI: 7.4% (0.7%, 14.2%)].

16 HOW SUPPLIED/STORAGE AND HANDLING

TRIUMEQ tablets, 600 mg of abacavir as abacavir sulfate, 50 mg of dolutegravir as dolutegravir sodium, and 300 mg lamivudine, are purple, oval, film-coated, biconvex tablets debossed with "572 Tri" on one side.

Bottle of 30 with child-resistant closure NDC 49702-231-13.

Store and dispense in the original package, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant.

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Drug Interactions: Do not coadminister TRIUMEQ with dofetilide (TIKOSYN®) because the interaction between dofetilide and dolutegravir can result in potentially life-threatening adverse events *[see Contraindications (4)]*. Patients should be advised to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products.

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 TRIUMEQ, and instruct the patient to read the Medication Guide and Warning Card every time to obtain any new information that may be present about TRIUMEQ. (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 TRIUMEQ.
- that a hypersensitivity reaction can worsen and lead to hospitalization or death if TRIUMEQ is not immediately discontinued.
- to not restart TRIUMEQ 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 TRIUMEQ is stopped right away.
- that if they have interrupted TRIUMEQ 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 TRIUMEQ or any other abacavir-containing product without medical consultation and only if medical care can be readily accessed by the patient or others.
- to not restart TRIUMEQ or any other dolutegravir-containing product following a hypersensitivity reaction to TRIUMEQ.

Inform patients that they should not take TRIUMEQ with ATRIPLA, COMBIVIR®, COMPLERA®, EMTRIVA®, EPIVIR, EPIVIR-HBV®, EPZICOM, STRIBILD®, TRIZIVIR, TRUVADA®, or ZIAGEN.

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

Patients with Hepatitis B or C Co-infection: Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of TRIUMEQ and advise patients to have laboratory testing before and during therapy *[see Warnings and Precautions (5.3)]*.

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

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

Immune Reconstitution Syndrome: In some patients with advanced HIV infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. Advise patients to inform their healthcare provider immediately of any symptoms of infection *[see Warnings and Precautions (5.5)]*.

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

Information About HIV-1 Infection: TRIUMEQ is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients must remain on continuous HIV therapy to control HIV-1infection and decrease HIV-related illness. Inform patients that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death.

Advise patients to remain under the care of a physician when using TRIUMEQ.

Advise patients to take all HIV medications exactly as prescribed.

Advise patients to avoid doing things that can spread HIV-1 infection to others.

Advise patients not to re-use or share needles or other injection equipment.

Advise patients not to share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.

Always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

Female patients should be advised not to breastfeed because it is not known if TRIUMEQ can be passed to your baby in your breast milk and whether it could harm your baby. Mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

Instruct patients to read the Medication Guide before starting TRIUMEQ and to reread it each time the prescription is renewed. Instruct patients to inform their physician or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.

Instruct patients that if they miss a dose, they should take it as soon as they remember. If they do not remember until it is within 4 hours of the time for the next dose, they should be instructed to skip the missed dose and go back to the regular schedule. Patients should not double their next dose or take more than the prescribed dose.

Instruct patients to store TRIUMEQ in the original package, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant.

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Manufactured for

ViiV Healthcare
Research Triangle Park, NC 27709
by:

GlaxoSmithKline
Research Triangle Park, NC 27709

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Shire Pharmaceuticals Group plc
Basingstoke, UK

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TRM:XPI

MEDICATION GUIDE

TRIUMEQ® (TRI-u-meck)
(abacavir, dolutegravir, and lamivudine)
Tablets

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

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

- **Serious allergic reaction (hypersensitivity reaction).** TRIUMEQ contains abacavir (also contained in EPZICOM®, TRIZIVIR®, and ZIAGEN®). Patients taking TRIUMEQ may have a serious allergic reaction (hypersensitivity reaction) that can cause death. Your risk of this allergic reaction to abacavir 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 TRIUMEQ, call your healthcare provider right away to find out if you should stop taking TRIUMEQ.

	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 TRIUMEQ because of an allergic reaction, never take TRIUMEQ or any other medicines that contain abacavir or dolutegravir

(EPZICOM, ZIAGEN, TRIZIVIR, or TIVICAY®) again. If you take TRIUMEQ 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 TRIUMEQ for any other reason, even for a few days, and you are not allergic to TRIUMEQ, talk with your healthcare provider before taking it again. Taking TRIUMEQ 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 TRIUMEQ again, start taking it when you are around medical help or people who can call a healthcare provider if you need one.

- **Build-up of acid in your blood (lactic acidosis).** Lactic acidosis can happen in some people who take TRIUMEQ. Lactic acidosis is a serious medical emergency that can lead to death.

  Lactic acidosis can be hard to identify early, because the symptoms could seem like symptoms of other health problems.
  Call your healthcare provider right away if you get the following symptoms that could be signs of lactic acidosis:

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

- **Severe liver problems**. Severe liver problems can happen in people who take TRIUMEQ. In some cases these severe liver problems can lead to death. Your liver may become large (hepatomegaly) and you may develop fat in your liver (steatosis).

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

  - your skin or the white part of your eyes turns yellow
  - dark “tea-colored” urine
  - light colored stools (bowel movements)
  - nausea
  - itching
  - stomach-area 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.

- **Worsening of hepatitis B virus in people who have HIV-1 infection.** If you have HIV-1 and hepatitis B virus infections, your hepatitis virus infection may get worse if you stop taking TRIUMEQ. To help avoid this: Take TRIUMEQ exactly as prescribed.
    - Do not run out of TRIUMEQ.
    - Do not stop TRIUMEQ without talking to your healthcare provider.
    - Your healthcare provider should monitor your health and do regular blood tests to check your liver for at least several months if you stop taking TRIUMEQ.
- **Resistant Hepatitis B Virus (HBV).** If you have HIV-1 and hepatitis B, the hepatitis B virus can change (mutate) during your treatment with TRIUMEQ and become harder to treat (resistant).
- **Use with interferon and ribavirin-based regimens.** Worsening of liver disease has happened in people infected with HIV-1 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 TRIUMEQ and interferon with or without ribavirin, tell your healthcare provider if you have any new symptoms.

What is TRIUMEQ?

TRIUMEQ is a prescription medicine used to treat HIV-1 (Human Immunodeficiency Virus-type 1) infection. TRIUMEQ contains 3 prescription medicines: abacavir (ZIAGEN), dolutegravir (TIVICAY), and lamivudine (EPIVIR®).

- TRIUMEQ is not for use by itself in people who have or have had resistance to abacavir, dolutegravir, or lamivudine.

It is not known if TRIUMEQ is safe and effective in children.

TRIUMEQ may help:

- reduce the amount of HIV-1 in your blood. This is called “viral load”.
- increase the number of white blood cells called CD4+ (T) cells in your blood, which help fight off other infections.

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

TRIUMEQ does not cure HIV-1 infection or AIDS. You must stay on continuous HIV-1 therapy to control HIV-1 infection and decrease HIV-related illnesses.

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

- Do not share or re-use 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 safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

Ask your healthcare provider if you have any questions about how to prevent passing HIV to other people.

Who should not take TRIUMEQ?

Do not take TRIUMEQ if you:

- have a certain type of gene variation called the HLA-B*5701 allele. Your healthcare provider will test you for this before prescribing treatment with TRIUMEQ.
- have ever had an allergic reaction to abacavir, dolutegravir, or lamivudine
- take dofetilide (TIKOSYN®). Taking TRIUMEQ and dofetilide (TIKOSYN) can cause side effects that may be life-threatening.
- have certain liver problems

What should I tell my healthcare provider before taking TRIUMEQ?

Before you take TRIUMEQ, tell your healthcare provider if you:

- have been tested and know whether or not you have a particular gene variation called HLA-B*5701
- have or had liver problems, including hepatitis B or C virus infection
- have kidney problems
- have heart problems, smoke, or have diseases that increase your risk of heart disease such as high blood pressure, high cholesterol, or diabetes
- drink alcoholic beverages
- have any other medical condition
- are pregnant or plan to become pregnant. It is not known if TRIUMEQ will harm your unborn baby. Tell your healthcare provider if you become pregnant while taking TRIUMEQ.

Pregnancy Registry. There is a pregnancy registry for women who take antiviral medicines during pregnancy. The purpose of the registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.

- **are breastfeeding or plan to breastfeed. Do not breastfeed if you take TRIUMEQ.** You should not breastfeed because of the risk of passing HIV-1 to your baby. It is not known if abacavir or dolutegravir passes into your breast milk. Lamivudine can pass into your breast milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. TRIUMEQ may affect the way other medicines work, and other medicines may affect how TRIUMEQ works.

You should not take TRIUMEQ if you also take:

- abacavir (EPZICOM, TRIZIVIR, or ZIAGEN)
- lamivudine (COMBIVIR®, EPIVIR, EPIVIR-HBV®, EPZICOM, or TRIZIVIR)
- emtricitabine (EMTRIVA®, ATRIPLA®, COMPLERA®, STRIBILD®, TRUVADA®)

Tell your healthcare provider if you take:

- antacids, laxatives, or other medicines that contain aluminum, magnesium, sucralfate (CARAFATE®), or buffered medicines. TRIUMEQ should be taken at least 2 hours before or 6 hours after you take these medicines.
- anti-seizure medicines:
  - oxcarbazepine (TRILEPTAL®)
  - phenytoin (DILANTIN®, DILANTIN®-125, PHENYTEK®)
  - phenobarbital
  - carbamazepine (CARBATROL®, EQUETRO®, TEGRETOL®, TEGRETOL®-XR, TERIL®, EPITOL®)
- any other medicine to treat HIV-1
- iron or calcium supplements taken by mouth. Supplements containing calcium or iron may be taken at the same time with TRIUMEQ if taken with food. Otherwise, TRIUMEQ should be taken at least 2 hours before or 6 hours after you take these medicines.
- medicines used to treat hepatitis virus infections, such as interferon or ribavirin
- a medicine that contains metformin
- methadone
- rifampin (RIFATER®, RIFAMATE®, RIMACTANE®, RIFADIN®)
- St. John's wort (*Hypericum perforatum*)

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.

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

How should I take TRIUMEQ?

- **Take TRIUMEQ exactly as your healthcare provider tells you.**
- Do not change your dose or stop taking TRIUMEQ without talking with your healthcare provider.
- Stay under the care of a healthcare provider while taking TRIUMEQ.
- You can take TRIUMEQ with or without food.
- If you miss a dose of TRIUMEQ, take it as soon as you remember. If it is within 4 hours of your next dose, skip the missed dose and take the next dose at your regular time. Do not take 2 doses at the same time. If you are not sure about your dosing, call your healthcare provider.
- Do not run out of TRIUMEQ. The virus in your blood may become resistant to other HIV-1 medicines if TRIUMEQ is stopped for even a short time. When your supply starts to run low, get more from your healthcare provider or pharmacy.
- If you take too much TRIUMEQ, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of TRIUMEQ?

TRIUMEQ can cause serious side effects including:

- **See "What is the most important information I should know about TRIUMEQ?"**
- **Changes in liver tests**. People with a history of hepatitis B or C virus may have an increased risk of developing new or worsening changes in certain liver tests during treatment with TRIUMEQ. Your healthcare provider may do tests to check your liver function before and during treatment with TRIUMEQ.
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having new symptoms after starting your HIV-1 medicine.
- **Changes in body fat (fat redistribution)** can happen in people who take HIV-1 medicines. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the middle of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term health effects of these problems are not known.

- **Heart attack (myocardial infarction).** Some HIV medicines including TRIUMEQ may increase your risk of heart attack.

The most common side effects of TRIUMEQ include:

- trouble sleeping
- headache
- tiredness

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 TRIUMEQ. 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 TRIUMEQ?

- Store TRIUMEQ at room temperature between 68°F to 77°F (20°C to 25°C).
- Store TRIUMEQ in the original bottle.
- Keep the bottle of TRIUMEQ tightly closed and protect from moisture.
- The bottle of TRIUMEQ contains a desiccant packet to help keep your medicine dry (protect it from moisture). Keep the desiccant packet in the bottle. Do not remove the desiccant packet.

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

General information about the safe and effective use of TRIUMEQ

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TRIUMEQ for a condition for which it was not prescribed. Do not give TRIUMEQ 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 TRIUMEQ. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about TRIUMEQ that is written for health professionals.

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

What are the ingredients in TRIUMEQ?

Active ingredients: abacavir, dolutegravir, and lamivudine
Inactive ingredients: D-mannitol, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate. The tablet film-coating contains iron oxide

black, iron oxide red, macrogol/PEG, polyvinyl alcohol–part hydrolyzed, talc, and titanium oxide.

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

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

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EPIVIR-HBV is a registered trademark of the GSK group of companies.

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(Front of card)

WARNING CARD
TRIUMEQ® (abacavir, dolutegravir, and lamivudine) Tablets

Patients taking TRIUMEQ may have a serious allergic reaction (hypersensitivity reaction) that can cause death. If you get a symptom from 2 or more of the following groups while taking TRIUMEQ, call your doctor right away to determine if you should stop taking this medicine.

	Symptom(s)
Group 1	**Fever**
Group 2	**Rash**
Group 3	**Nausea, vomiting, diarrhea, or abdominal (stomach area) pain**
Group 4	**Generally ill feeling, extreme tiredness, or achiness**
Group 5	**Shortness of breath, cough, or sore throat**

Always carry this Warning Card with you to help recognize symptoms of this allergic reaction.

(Back of Card)

WARNING CARD
TRIUMEQ® (abacavir, dolutegravir, and lamivudine) Tablets

If you must stop treatment with TRIUMEQ because you have had an allergic reaction to abacavir, **NEVER** take TRIUMEQ or any other abacavir-containing medicine (ZIAGEN®, EPZICOM®, TRIZIVIR®) again. If you take TRIUMEQ or another 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**.

Please read the Medication Guide for additional information on TRIUMEQ.

August 2014 TRM:1WC

NDC 49702-231-13

Triumeq®

(abacavir, dolutegravir, and lamivudine)

600 mg / 50 mg / 300 mg

TABLETS

Notice to Authorized Dispenser:

Each time TRIUMEQ is dispensed, give the patient a Medication Guide and Warning Card from the carton.

Rx Only

30 Tablets

Each film-coated tablet contains abacavir sulfate equivalent to 600 mg of abacavir, dolutegravir sodium equivalent to 50 mg of dolutegravir, and 300 mg of lamivudine.

Store in original package at controlled room temperature of 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (See USP).

Keep bottle tightly closed; protect from moisture.

Do not remove desiccant.

See prescribing information for dosage information.

Manufactured for:

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ViiV Healthcare

ViiV Healthcare
RTP, NC 27709

by:

GlaxoSmithKline

GlaxoSmithKline
Research Triangle Park, NC 27709 (b) (4) Rev. 8/14

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NDC 49702-231-13

Triumeq®
(abacavir, dolutegravir, and lamivudine)
600 mg / 50 mg / 300 mg
TABLETS
30 Tablets

NDC 49702-231-13

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Store in original package at controlled room temperature of 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (See USP). Keep bottle tightly closed; protect from moisture. Do not remove desiccant.
Do not use if printed safety seal under cap is broken or missing.
See prescribing information for dosage information.

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Each time TRIUMEQ is dispensed, give the patient a Medication Guide and Warning Card from the carton.

Rx Only

30 Tablets

NDC 49702-231-13

Triumeq®
(abacavir, dolutegravir, and lamivudine)
600 mg / 50 mg / 300 mg
TABLETS

Lamivudine is manufactured under agreement from **Shire Pharmaceuticals Group plc,** Basingstoke, UK
Manufactured for:
ViiV Healthcare
Research Triangle Park, NC 27709
by:
GlaxoSmithKline
GlaxoSmithKline
Research Triangle Park, NC 27709
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Rev. 8/14

NDC 49702-231-13

Triumeq®
(abacavir, dolutegravir, and lamivudine)
600 mg / 50 mg / 300 mg
TABLETS

Rx Only

30 Tablets

Lamivudine is manufactured under agreement from **Shire Pharmaceuticals Group plc,** Basingstoke, UK
Manufactured for:
ViiV Healthcare
Research Triangle Park, NC 27709
by:
GlaxoSmithKline
GlaxoSmithKline
Research Triangle Park, NC 27709
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Carton Outside

WARNING CARD

TRIUMEQ® (abacavir, dolutegravir, and lamivudine) Tablets

Patients taking TRIUMEQ may have a serious allergic reaction (hypersensitivity reaction) that can cause death. If you have a symptom from 2 or more of the following groups while taking TRIUMEQ, call your doctor right away to determine if you should stop taking this medicine.

	Symptom(s)
Group 1	Fever
Group 2	Rash
Group 3	Nausea, vomiting, diarrhea, or abdominal (stomach area) pain
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WARNING CARD

TRIUMEQ® (abacavir, dolutegravir, and lamivudine) Tablets

If you have had a serious allergic reaction to abacavir, NEVER take TRIUMEQ or any other abacavir-containing medicine (ZIAGEN®, EPZICOM®, TRIZIVIR®) again. If you take TRIUMEQ or another 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**.

Please read the Medication Guide for additional information on TRIUMEQ.

August 2014 TRM.1WC 10000000118541

Carton Inside

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