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, AND EXACERBATIONS OF HEPATITIS B
See full prescribing information for complete boxed warning.

Hypersensitivity Reactions
- **Serious and sometimes fatal hypersensitivity reactions have occurred with abacavir-containing products. (5.1)**
- **Hypersensitivity to abacavir is a multi-organ clinical syndrome. (5.1)**
- **Patients who carry the HLA-B*5701 allele are at a higher risk of experiencing a hypersensitivity reaction to abacavir. (5.1)**
- **TRIUMEQ is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients. (4)**
- **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 TRIUMEQ, NEVER restart TRIUMEQ or any other abacavir-containing product. (5.1)**

Exacerbations of Hepatitis B
- **Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine, a component of TRIUMEQ. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.2)**

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

Boxed Warning	05/2018
Indications and Usage (1)	11/2017
Dosage and Administration, Pregnancy Testing before Initiation of TRIUMEQ (2.2)	09/2018
Dosage and Administration, Recommended Dosage (2.3)	11/2017
Warnings and Precautions, Hepatotoxicity (5.4)	11/2017
Warnings and Precautions, Lactic Acidosis and Severe Hepatomegaly with Steatosis (5.5)	05/2018
Warnings and Precautions, Embryo-Fetal Toxicity (5.6)	09/2018
Warnings and Precautions, Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions (5.7)	11/2017
Warnings and Precautions, Related Products that are Not Recommended (previous 5.8)	Removed - 11/2017
Warnings and Precautions, Fat Redistribution (previous 5.9)	Removed 05/2018
Warnings and Precautions, Myocardial Infarction (5.10)	05/2018

---------- 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 in adults and in pediatric patients weighing at least 40 kg. (1)

Limitations of Use:
- 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).
- Pregnancy Testing: Perform pregnancy testing before initiation of TRIUMEQ in adolescents and adults of childbearing potential. (2.2, 5.6)
- Adults and pediatric patients weighing at least 40 kg: One tablet daily. May be taken with or without food. (2.3)
- If dosing with certain UGT1A or CYP3A inducers, 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. (2.4)
- Because TRIUMEQ is a fixed-dose tablet and cannot be dose adjusted, TRIUMEQ is not recommended in patients requiring dosage adjustment or patients with hepatic impairment. (2.5, 4)

---------- 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)
- Prior hypersensitivity reaction to abacavir, dolutegravir, or lamivudine. (4)
- Coadministration with dofetilide. (4)
- Moderate or severe hepatic impairment. (4, 8.7)

---------- WARNINGS AND PRECAUTIONS ----------
- Hepatotoxicity has been reported in patients receiving a dolutegravir-containing regimen. Monitoring for hepatotoxicity is recommended. (5.4)
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. (5.5)
- Embryo-fetal toxicity may occur when used at the time of conception and in early pregnancy. Avoid use of TRIUMEQ at the time of conception through the first trimester of pregnancy due to the risk of neural tube defects. Advise adolescents and adults of childbearing potential to use effective contraception. (2.2, 5.6, 8.1, 8.3)
- 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. (5.8)
- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. (5.9)

---------- 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: Avoid use of TRIUMEQ at the time of conception through the first trimester due to the risk of neural tube defects. (2.2, 5.6, 8.1)
- Lactation: Breastfeeding is not recommended due to the potential for HIV-1 transmission. (8.2)
- Females and males of reproductive potential: Pregnancy testing and contraception are recommended in adolescents and adults of childbearing potential. (8.3)
- Pediatrics: Not recommended for patients weighing less than 40 kg. (8.4)
- 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.

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FULL PRESCRIBING INFORMATION

WARNING: HYPERSENSITIVITY REACTIONS, AND EXACERBATIONS OF HEPATITIS B

Hypersensitivity Reactions

Serious and sometimes fatal hypersensitivity reactions, with multiple organ involvement, have occurred with abacavir, a component of TRIUMEQ (abacavir, dolutegravir, and lamivudine). 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)]*.

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

Following a hypersensitivity reaction to TRIUMEQ, NEVER restart TRIUMEQ or any other abacavir-containing product because more severe symptoms, including death can occur within hours. Similar severe reactions have also occurred rarely following the

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reintroduction of abacavir-containing products in patients who have no history of abacavir hypersensitivity *[see Warnings and Precautions (5.1)]*.

<u>Exacerbations of Hepatitis B</u>

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. 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 (5.2)]*.

1 INDICATIONS AND USAGE

TRIUMEQ is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and in pediatric patients weighing at least 40 kg.

<u>Limitations of Use:</u>

- 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 TIVICAY (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 Pregnancy Testing before Initiation of TRIUMEQ

Perform pregnancy testing before initiation of TRIUMEQ in adolescents and adults of childbearing potential *[see Warnings and Precautions (5.6), Use in Specific Populations (8.1, 8.3)]*.

2.3 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 and in pediatric patients weighing at least 40 kg is one tablet once daily orally with or without food.

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2.4 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, carbamazepine, 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.

2.5 Not Recommended Due to Lack of Dosage Adjustment

Because TRIUMEQ is a fixed-dose tablet and cannot be dose adjusted, TRIUMEQ is not recommended in:

- patients with creatinine clearance less than 50 mL per minute *[see Use in Specific Populations (8.6)]*.
- patients with mild hepatic impairment. TRIUMEQ is contraindicated in patients with moderate or severe hepatic impairment *[see Contraindications (4), Use in Specific Populations (8.7)]*.

3 DOSAGE FORMS AND STRENGTHS

TRIUMEQ tablets are purple, biconvex, oval, and debossed with “572 Tri” 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 prior hypersensitivity reaction to abacavir, 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)]*.

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5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

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

Abacavir

Serious and sometimes fatal hypersensitivity reactions have occurred with abacavir-containing regimens. See full prescribing information for ZIAGEN (abacavir).

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

Due to the potential for severe, serious, and possibly fatal hypersensitivity reactions with abacavir:

- All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with TRIUMEQ or reinitiation of therapy with TRIUMEQ, unless patients have a previously documented HLA-B*5701 allele assessment.
- TRIUMEQ is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients.
- 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.
- To reduce the risk of a life-threatening hypersensitivity reaction, regardless of HLA-B*5701 status, discontinue TRIUMEQ immediately if a hypersensitivity reaction is suspected, even when other diagnoses are possible (e.g., acute onset respiratory diseases such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions to other medications). Clinical status, including liver chemistries, should be monitored and appropriate therapy initiated.
- If a hypersensitivity reaction cannot be ruled out, do not restart TRIUMEQ or any other abacavir-containing products because more severe symptoms, which may include life-

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threatening hypotension and death, can occur within hours.

- 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.
- If a hypersensitivity reaction is ruled out, patients may restart TRIUMEQ. Rarely, patients who have stopped abacavir for reasons other than symptoms of hypersensitivity have also experienced life-threatening reactions within hours of reinitiating abacavir therapy. Therefore, reintroduction of TRIUMEQ, or any other abacavir-containing product, is recommended only if medical care can be readily accessed.
- A Medication Guide and Warning Card that provide information about recognition of abacavir hypersensitivity reactions should be dispensed with each new prescription and refill.

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 Posttreatment Exacerbations of Hepatitis in Patients with Hepatitis B Co-infection

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.

5.3 Emergence of Lamivudine-Resistant HBV

Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in subjects dually infected with HIV-1 and HBV. Emergence of hepatitis B virus variants associated with resistance to lamivudine has been reported in HIV-1-infected subjects who have

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received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus. See full prescribing information for EPIVIR-HBV (lamivudine).

5.4 Hepatotoxicity

Hepatic adverse events have been reported in patients receiving a dolutegravir-containing regimen *[see Adverse Reactions (6.1)]*. 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)]*. 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. Cases of hepatic toxicity including elevated serum liver biochemistries, hepatitis, and acute liver failure have also been reported in patients receiving a dolutegravir-containing regimen who had no pre-existing hepatic disease or other identifiable risk factors. Drug-induced liver injury leading to liver transplant has been reported with TRIUMEQ. Monitoring for hepatotoxicity is recommended.

5.5 Lactic Acidosis and Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues, including abacavir and lamivudine (components of TRIUMEQ). A majority of these cases have been in women. Female sex and obesity may be risk factors for the development of lactic acidosis and severe hepatomegaly with steatosis in patients treated with antiretroviral nucleoside analogues. 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.

5.6 Embryo-Fetal Toxicity

Preliminary data from an observational study showed that dolutegravir, a component of TRIUMEQ, was associated with increased risk of neural tube defects when administered at the time of conception and in early pregnancy. As there is limited understanding of reported types of neural tube defects associated with dolutegravir use and because the date of conception may not be determined with precision, avoid use of TRIUMEQ at the time of conception through the first trimester of pregnancy *[see Use in Specific Populations (8.1)]*.

If there are plans to become pregnant or if pregnancy is confirmed within the first trimester while on TRIUMEQ, if possible, switch to an alternative regimen.

Perform pregnancy testing before initiation of TRIUMEQ in adolescents and adults of childbearing potential to exclude use of TRIUMEQ during the first trimester of pregnancy *[see Dosage and Administration (2.2)]*.

Advise adolescents and adults of childbearing potential to consistently use effective contraception *[see Use in Specific Populations (8.1, 8.3)]*.

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5.7 Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

The concomitant use of TRIUMEQ and other drugs may result in known or potentially significant drug interactions, some of which may lead to *[see Contraindications (4), Drug Interactions (7.3)]*:

- Loss of therapeutic effect of TRIUMEQ and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs.

See Table 5 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with TRIUMEQ; review concomitant medications during therapy with TRIUMEQ; and monitor for the adverse reactions associated with the concomitant drugs.

5.8 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).

5.9 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.

5.10 Myocardial Infarction

Several prospective, observational, epidemiological studies have reported an association with the use of abacavir and the risk of myocardial infarction (MI). Meta-analyses of randomized, controlled clinical trials have observed no excess risk of MI in abacavir-treated subjects as compared with control subjects. To date, there is no established biological mechanism to explain a potential increase in risk. In totality, the available data from the observational studies and from controlled clinical trials show inconsistency; therefore, evidence for a causal relationship between abacavir and the risk of MI is inconclusive.

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

6 ADVERSE REACTIONS

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

- Serious and sometimes fatal hypersensitivity reaction *[see Boxed Warning, Warnings and Precautions (5.1)]*.
- Exacerbations of hepatitis B *[see Boxed Warning, Warnings and Precautions (5.3)]*.
- Hepatotoxicity *[see Warnings and Precautions (5.4)]*.
- Lactic acidosis and severe hepatomegaly with steatosis *[see Warnings and Precautions (5.5)]*.
- Hepatic decompensation in patients co-infected with HIV-1 and Hepatitis C *[see Warnings and Precautions (5.8)]*.
- Immune reconstitution syndrome *[see Warnings and Precautions (5.9)]*.
- Myocardial infarction *[see Warnings and Precautions (5.10)]*.

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.

Clinical Trials in Adults

Serious and Fatal Abacavir-Associated Hypersensitivity Reactions: In clinical trials, serious and sometimes fatal hypersensitivity reactions have occurred with abacavir, a component of TRIUMEQ *[see Boxed Warning, Warnings and Precautions (5.1)]*. These reactions have been characterized by 2 or more of the following signs or symptoms: (1) fever; (2) rash; (3) gastrointestinal symptoms (including nausea, vomiting, diarrhea, or abdominal pain); (4) constitutional symptoms (including generalized malaise, fatigue, or achiness); (5) respiratory symptoms (including dyspnea, cough, or pharyngitis). Almost all abacavir hypersensitivity reactions include fever and/or rash as part of the syndrome.

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

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erythema multiforme. Laboratory abnormalities included elevated liver chemistries, elevated creatine phosphokinase, elevated creatinine, and lymphopenia and abnormal chest x-ray findings (predominantly infiltrates, which were localized).

Serious Dolutegravir Hypersensitivity Reactions: In clinical trials, hypersensitivity reactions have occurred with dolutegravir, a component of TRIUMEQ *[see Warnings and Precautions (5.1)]*. These hypersensitivity reactions have been characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury.

Additional Treatment-Emergent Adverse Drug Reactions (ADRs) with Use of TRIUMEQ: 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 and lamivudine (EPZICOM) once daily (n = 414) or fixed-dose efavirenz/emtricitabine/tenofovir (ATRIPLA) once daily (n = 419) (study treatment was blinded through Week 96 and open-label from Week 96 through Week 144). Through 144 weeks, the rate of adverse events leading to discontinuation was 4% in subjects receiving TIVICAY + EPZICOM and 14% 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 144 Analysis)

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

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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 System Disorders: Somnolence.

Psychiatric Disorders: Suicidal ideation, attempt, behavior, or completion. These events were observed primarily in subjects with a pre-existing history of depression or other psychiatric illness. Nightmare and sleep disorder.

Renal and Urinary Disorders: Renal impairment.

Skin and Subcutaneous Tissue Disorders: Pruritus.

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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 144 Analysis)

Laboratory Abnormality	TIVICAY + EPZICOM Once Daily (n = 414)	ATRIPLA Once Daily (n = 419)
ALT		
Grade 2 (>2.5-5.0 x ULN)	3%	5%
Grade 3 to 4 (>5.0 x ULN)	1%	<1%
AST		
Grade 2 (>2.5-5.0 x ULN)	3%	4%
Grade 3 to 4 (>5.0 x ULN)	1%	3%
Creatine kinase		
Grade 2 (6.0-9.9 x ULN)	5%	3%
Grade 3 to 4 (≥10.0 x ULN)	7%	8%
Hyperglycemia		
Grade 2 (126-250 mg/dL)	9%	6%
Grade 3 (>250 mg/dL)	2%	<1%
Lipase		
Grade 2 (>1.5-3.0 x ULN)	11%	11%
Grade 3 to 4 (>3.0 ULN)	5%	4%
Total neutrophils		
Grade 2 (0.75-0.99 x 10^9)	4%	5%
Grade 3 to 4 (<0.75 x 10^9)	3%	3%

ULN = Upper limit of normal.

Table 4. Mean Change from Baseline in Fasted Lipid Values in Treatment-Naïve Subjects in SINGLE (Week 144 Analysis[a])

Lipid	TIVICAY + EPZICOM Once Daily (n = 414)	ATRIPLA Once Daily (n = 419)
Cholesterol (mg/dL)	24.0	26.7
HDL cholesterol (mg/dL)	5.4	7.2
LDL cholesterol (mg/dL)	16.0	14.6
Triglycerides (mg/dL)	13.6	31.9

[a] Subjects on lipid-lowering agents at baseline were excluded from these analyses (TIVICAY + EPZICOM: n = 30 and ATRIPLA n = 27). Seventy-two subjects initiated a lipid-

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lowering agent post-baseline; their last fasted on-treatment values (prior to starting the agent) were used regardless if they discontinued the agent (TIVICAY + EPZICOM: n = 36 and ATRIPLA: n = 36).

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) (Week 96 analysis), respectively *[see Warnings and Precautions (5.2)]*. 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 144 weeks. In SINGLE, a mean change from baseline of 0.14 mg per dL (range: -0.25 mg per dL to 0.81 mg per dL) was observed after 144 weeks of treatment. Creatinine increases were similar in treatment-experienced subjects.

Abacavir 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.

Clinical Trials Experience in Pediatric Subjects

Abacavir and Lamivudine: The safety of once-daily compared with twice-daily dosing of abacavir and lamivudine, administered as either single products or as EPZICOM, was assessed in the ARROW trial (n = 336). Primary safety assessment in the ARROW (COL105677) trial was based on Grade 3 and Grade 4 adverse events. One event of Grade 4 hepatitis in the once-daily cohort was considered as uncertain causality by the investigator and all other Grade 3 or 4 adverse events were considered not related by the investigator. No additional safety issues were identified in pediatric subjects compared with historical data in adults.

Dolutegravir: IMPAACT P1093 is a 48-week multicenter, open-label, non-comparative trial of approximately 160 HIV-1-infected pediatric subjects aged 4 weeks to less than 18 years, of

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which, 23 treatment-experienced, INSTI-naïve subjects aged 12 to less than 18 years were enrolled *[see Use in Specific Populations (8.4), Clinical Studies (14.2)]*.

The ADR profile was similar to that for adults. Grade 2 ADRs reported by more than one subject were decreased neutrophil count (n = 2). No Grade 3 or 4 ADRs were reported. No ADRs led to discontinuation. The Grade 3 laboratory abnormalities reported in 1 subject each were elevated total bilirubin, elevated lipase, and decreased white blood cell count. There was one Grade 4 decreased neutrophil count. The changes in mean serum creatinine were similar to those observed in adults.

6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postmarketing use with one or more of the components of TRIUMEQ. 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.

<u>Blood and Lymphatic Systems</u>

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

<u>Digestive</u>

Stomatitis.

<u>Gastrointestinal</u>

Pancreatitis.

<u>General</u>

Weakness.

<u>Hepatobiliary Disorders</u>

Acute liver failure, liver transplant.

<u>Hypersensitivity</u>

Sensitization reactions (including anaphylaxis), urticaria *[see Warnings and Precautions (5.1), Adverse Reactions (6.1)]*.

<u>Investigations</u>

Weight increased.

<u>Metabolism and Nutrition Disorders</u>

Hyperlactemia.

<u>Musculoskeletal</u>

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CPK elevation, muscle weakness, myalgia, rhabdomyolysis.

Nervous

Paresthesia, peripheral neuropathy, seizures.

Psychiatric

Anxiety.

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 *[see Adverse Reactions (6.1)]*.

7 DRUG INTERACTIONS

7.1 Effect of Dolutegravir on the Pharmacokinetics of Other Agents

In vitro, dolutegravir inhibited the renal organic cation transporters (OCT)2 (IC_{50} = 1.93 microM) and multidrug and toxin extrusion transporter (MATE)1 (IC_{50} = 6.34 microM). 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 microM) and OAT3 (IC_{50} = 1.97 microM). 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 microM) the following: cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate (UDP)-glucuronosyl transferase (UGT)1A1, 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.

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In drug interaction trials, dolutegravir did not have a clinically relevant effect on the pharmacokinetics of the following drugs: daclatasvir, 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 boceprevir.

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)]*.

In vitro, dolutegravir was not a substrate of OATP1B1 or OATP1B3.

Darunavir/ritonavir, lopinavir/ritonavir, rilpivirine, tenofovir, boceprevir, daclatasvir, 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 the individual components of TRIUMEQ 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 Contraindications (4), Clinical Pharmacology (12.3).]*

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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		
Antiarrhythmic: Dofetilide	↑Dofetilide	Coadministration is contraindicated with TRIUMEQ *[see Contraindications (4)]*.
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		
Carbamazepine[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.
Oxcarbazepine Phenytoin Phenobarbital St. John's wort (*Hypericum perforatum*)	↓Dolutegravir	Avoid coadministration with TRIUMEQ because there are insufficient data to make dosing recommendations.
Medications containing polyvalent cations (e.g., Mg or Al):	↓Dolutegravir	Administer TRIUMEQ 2 hours before or 6 hours after taking medications containing polyvalent cations.

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Cation-containing antacids[a] or laxatives Sucralfate Buffered medications		
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[a]	↑Metformin	With concomitant use, limit the total daily dose of metformin to 1,000 mg either when starting metformin or TRIUMEQ. When stopping TRIUMEQ, the metformin dose may require an adjustment. Monitoring of blood glucose when initiating concomitant use and after withdrawal of TRIUMEQ is recommended.
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 8 or Table 9 for magnitude of interaction.*

Methadone

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.

Sorbitol

Lamivudine: Coadministration of single doses of lamivudine and sorbitol resulted in a sorbitol dose-dependent reduction in lamivudine exposures. When possible, avoid use of sorbitol-containing medicines with lamivudine-containing medicines *[see Clinical Pharmacology (12.3)]*.

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8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

Preliminary data from an observational study has identified a possible increased risk of neural tube defects when dolutegravir, a component of TRIUMEQ, is administered at the time of conception compared with non-dolutegravir-containing antiretroviral regimens. As defects related to closure of the neural tube occur from conception through the first 6 weeks of gestation, embryos exposed to dolutegravir from the time of conception through the first 6 weeks of gestation are at potential risk. In addition, 2 of the 4 birth defects (encephalocele and iniencephaly), which have been observed with dolutegravir use, although often termed neural tube defects, may occur post-neural tube closure, the time period of which may be later than 6 weeks of gestation, but within the first trimester. Due to the limited understanding of the types of reported neural tube defects associated with dolutegravir use and because the date of conception may not be determined with precision, avoid use of TRIUMEQ at the time of conception through the first trimester of pregnancy. No neural tube defects have been reported in infants born to mothers who have started dolutegravir after the first trimester of pregnancy *(see Data)*.

If there are plans to become pregnant or if pregnancy is confirmed while on TRIUMEQ during the first trimester, if possible, switch to an alternative regimen. Advise pregnant adolescents and adults of the potential risk to the embryo exposed to TRIUMEQ from the time of conception through the first trimester of pregnancy.

There are insufficient human data on the use of TRIUMEQ during pregnancy to definitively assess a drug-associated risk for birth defects and miscarriage. The background risk for major birth defects for the indicated population is unknown. In the U.S. general population, the estimated background rate for major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with dolutegravir at systemic exposures (AUC) less than (rabbits) and approximately 50 times (rats) the exposure in humans at the recommended human dose (RHD) *(see Data)*. Oral administration of abacavir to pregnant rats during organogenesis resulted in fetal malformations and other embryonic and fetal toxicities at exposures 35 times the human exposure (AUC) at the RHD. No adverse developmental effects were observed following oral administration of abacavir to pregnant rabbits during organogenesis at exposures approximately 9 times the human exposure (AUC) at the RHD. Oral administration of lamivudine to pregnant rabbits during organogenesis

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resulted in embryolethality at a human exposure (AUC) similar to the RHD; however, no adverse development effects were observed with oral administration of lamivudine to pregnant rats during organogenesis at plasma concentrations (C_{max}) 35 times the RHD *(see Data).*

Data

Human Data: Dolutegravir: As of May 2018, in an ongoing birth outcome surveillance study in Botswana, there have been 4 cases of neural tube defects reported out of 426 births (0.94%) to mothers who were exposed to dolutegravir-containing regimens at the time of conception. In comparison, the neural tube defect prevalence rates were 0.12% (14/11,300) in the non-dolutegravir arm and 0.09% (61/66,057) in the HIV-uninfected arm. Four cases reported with dolutegravir included one case each of encephalocele, anencephaly, myelomeningocele, and iniencephaly. No infant born to a woman who started dolutegravir during pregnancy had a neural tube defect (n = 2,812).

Data analyzed to date from other sources including the APR, clinical trials, and postmarketing data are insufficient to address the risk of neural tube defects with dolutegravir.

Abacavir: Based on prospective reports to the APR of over 2,000 exposures to abacavir during pregnancy resulting in live births (including over 1,000 exposed in the first trimester), there was no difference between the overall risk of birth defects for abacavir compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of defects in live births was 2.9% (95% CI: 2.0% to 4.1%) following first trimester exposure to abacavir-containing regimens and 2.7% (95% CI: 1.9% to 3.7%) following second/third trimester exposure to abacavir-containing regimens.

Abacavir has been shown to cross the placenta and concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery *[see Clinical Pharmacology (12.3)]*.

Lamivudine: Based on prospective reports to the APR of over 11,000 exposures to lamivudine during pregnancy resulting in live births (including over 4,500 exposed in the first trimester), there was no difference between the overall risk of birth defects for lamivudine compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of birth defects in live births was 3.1% (95% CI: 2.6% to 3.6%) following first trimester exposure to lamivudine-containing regimens and 2.8% (95% CI: 2.5%, 3.3%) following second/third trimester exposure to lamivudine-containing regimens.

Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical trials conducted in South Africa. The trials assessed pharmacokinetics in 16 women at 36 weeks' gestation using 150 mg lamivudine twice daily with zidovudine, 10 women at 38 weeks' gestation using 150 mg lamivudine twice daily with zidovudine, and 10 women at 38 weeks' gestation using lamivudine 300 mg twice daily without other antiretrovirals. These trials were not designed or powered to provide efficacy information. Lamivudine concentrations were generally similar in maternal,

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neonatal, and umbilical cord serum samples. In a subset of subjects, amniotic fluid specimens were collected following natural rupture of membranes and confirmed that lamivudine crosses the placenta in humans. Based on limited data at delivery, median (range) amniotic fluid concentrations of lamivudine were 3.9 (1.2 to 12.8)–fold greater compared with paired maternal serum concentration (n = 8).

Animal Data: Dolutegravir: Dolutegravir was administered orally to pregnant rats and rabbits (up to 1,000 mg per kg per day) on gestation Days 6 to 17 and 6 to 18, respectively, and to rats on gestation Day 6 to lactation/post-partum Day 20. No adverse effects on embryo-fetal (rats and rabbits) or pre/post-natal (rats) development were observed up to the highest dose tested. During organogenesis, systemic exposures (AUC) to dolutegravir in rabbits were less than the exposure in humans at the RHD and in rats were approximately 50 times the exposure in humans at the RHD. In the rat pre/post-natal development study, decreased body weight of the developing offspring was observed during lactation at a maternally toxic dose (approximately 50 times human exposure at the RHD).

Abacavir: Abacavir was administered orally to pregnant rats (at 100, 300, and 1,000 mg per kg per day) and rabbits (at 125, 350, or 700 mg per kg per day) during organogenesis (on gestation Days 6 through 17 and 6 through 20, respectively). Fetal malformations (increased incidences of fetal anasarca and skeletal malformations) or developmental toxicity (decreased fetal body weight and crown-rump length) were observed in rats at doses up to 1,000 mg per kg per day, resulting in exposures approximately 35 times the human exposure (AUC) at the RHD. No developmental effects were observed in rats at 100 mg per kg per day, resulting in exposures (AUC) 3.5 times the human exposure at the recommended daily dose. In a fertility and early embryo-fetal development study conducted in rats (at 60, 160, or 500 mg per kg per day), embryonic and fetal toxicities (increased resorptions, decreased fetal body weights) or toxicities to the offspring (increased incidence of stillbirth and lower body weights) occurred at doses up to 500 mg per kg per day. No developmental effects were observed in rats at 60 mg per kg per day, resulting in exposures (AUC) approximately 4 times the human exposure at the RHD. Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. In pregnant rabbits, no developmental toxicities and no increases in fetal malformations occurred at up to the highest dose evaluated, resulting in exposures (AUC) approximately 9 times the human exposure at the RHD.

Lamivudine: Lamivudine was administered orally to pregnant rats (at 90, 600, and 4,000 mg per kg per day) and rabbits (at 90, 300 and 1,000 mg per kg per day and at 15, 40, and 90 mg per kg per day) during organogenesis (on gestation Days 7 through 16 [rat] and 8 through 20 [rabbit]). No evidence of fetal malformations due to lamivudine was observed in rats and rabbits at doses producing plasma concentrations (C_{max}) approximately 35 times higher than human exposure at the recommended daily dose. Evidence of early embryolethality was seen in the rabbit at systemic exposures (AUC) similar to those observed in humans, but there was no indication of this effect in the rat at plasma concentrations (C_{max}) 35 times higher than human

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exposure at the recommended daily dose. Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. In the fertility/pre- and postnatal development study in rats, lamivudine was administered orally at doses of 180, 900, and 4,000 mg per kg per day (from prior to mating through postnatal Day 20). In the study, development of the offspring, including fertility and reproductive performance, were not affected by the maternal administration of lamivudine.

8.2 Lactation

Risk Summary

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

Abacavir and lamivudine are present in human milk. When administered to lactating rats, dolutegravir was present in milk *(see Data).* There is no information on the effects of TRIUMEQ or its components on the breastfed infant or the effects of the drug on milk production.

Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving TRIUMEQ.

Data

Animal Data: Dolutegravir was the primary drug-related component excreted into the milk of lactating rats following a single oral dose of 50 mg per kg on lactation Day 10, with milk concentrations of up to approximately 1.3 times that of maternal plasma concentrations observed 8 hours postdose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Perform pregnancy testing in adolescents and adults of childbearing potential before initiation of TRIUMEQ.

Contraception

Adolescents and adults of childbearing potential should avoid use of TRIUMEQ at the time of conception through the first trimester of pregnancy because of the potential risk of neural tube defects *[see Use in Specific Populations (8.1)]*.

Advise adolescents and adults of childbearing potential who are taking TRIUMEQ to consistently use effective contraception.

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8.4 Pediatric Use

The clinical data supporting use of TRIUMEQ in HIV-1 infected pediatric patients weighing at least 40 kg is derived from the following previously conducted pediatric trials using the individual components of TRIUMEQ:

- The safety and efficacy of once-daily abacavir and lamivudine were established with a randomized, multicenter trial (ARROW [COL105677]) in HIV-1–infected, treatment-naïve subjects aged 3 months to 17 years with a first-line regimen containing abacavir and lamivudine, using either the combination of EPIVIR and ZIAGEN or EPZICOM *[see Adverse Reactions (6.2), Clinical Studies (14.2)]*.
- The safety and antiviral activity (efficacy) of dolutegravir was established through a 48-week, open-label, multicenter, dose-finding clinical trial (IMPAACT P1093), in which treatment-experienced, INSTI-naïve, HIV-1–infected subjects aged 6 to less than 18 years were treated with dolutegravir (TIVICAY) plus optimized background therapy *[see Adverse Reactions (6.2), Clinical Pharmacology (12.3), Clinical Studies (14.2)]*.

TRIUMEQ is a fixed-dose combination tablet which cannot be adjusted for patients weighing less than 40 kg *[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 patients 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 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 *[see Contraindications (4)]*.

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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.

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 Sulfate

The chemical name of abacavir sulfate is *(*1*S*,*cis)*-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1). 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:

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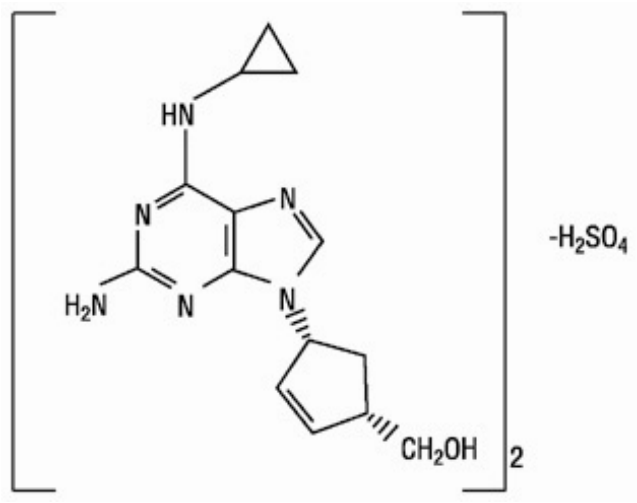
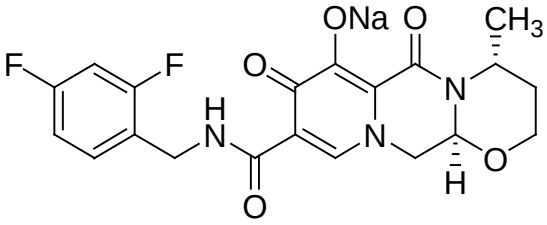


Abacavir sulfate is a white to off-white solid and is soluble in water.

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:

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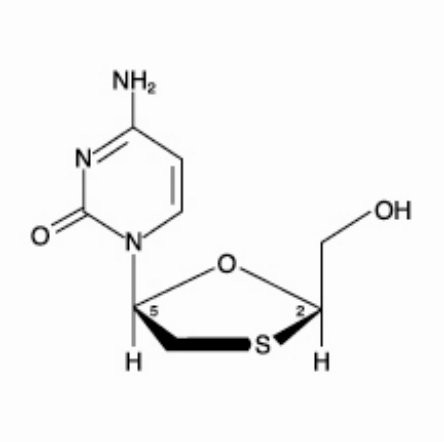

Lamivudine is a white to off-white crystalline solid and is soluble in water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

TRIUMEQ is an HIV-1 antiretroviral 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.

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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-gp 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.

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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.

Specific Populations

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

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

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Pediatric Patients: The pharmacokinetics for the individual components of TRIUMEQ (abacavir, dolutegravir, and lamivudine) have been evaluated in pediatric subjects.

Dolutegravir: The pharmacokinetics of dolutegravir in HIV-1–infected children (n = 14) weighing at least 40 kg were similar to those observed in HIV-1–infected adults who received dolutegravir 50 mg once daily (Table 7) *[see Clinical Studies (14.2)]*.

Table 7. Dolutegravir Steady-State Pharmacokinetic Parameters in Pediatric Subjects

Weight (n)	Dose of TIVICAY	Dolutegravir Pharmacokinetic Parameter Estimates Geometric Mean (%CV)		
		C_{max} (mcg/mL)	$AUC_{(0-24)}$ (mcg.h/mL)	C_{24} (mcg/mL)
≥40 kg (n = 14)	50 mg once daily	3.89 (43)	50.1 (53)	0.99 (66)

Abacavir and Lamivudine: The pharmacokinetic data for abacavir and lamivudine once daily following administration of EPZICOM in pediatric subjects weighing at least 40 kg are limited. The dosing recommendations in this population are based on the safety and efficacy established in a controlled trial conducted using either the combination of EPIVIR and ZIAGEN or EPZICOM. Refer to the prescribing information for EPIVIR and ZIAGEN for pharmacokinetic information on the individual products in pediatric patients *[see Dosage and Administration (2.2), Clinical Studies (14.2)]*.

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.

Male and Female Patients: 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.

Racial Groups: 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 Interaction Studies

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.

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Dosing recommendations as a result of established and other potentially significant drug-drug interactions with the individual components of TRIUMEQ 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}
Daclatasvir 60 mg once daily	50 mg once daily	12	1.03 (0.84 to 1.25)	0.98 (0.83 to 1.15)	1.06 (0.88 to 1.29)
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)
Metformin 500 mg twice daily	50 mg once daily	15[a]	1.66 (1.53 to 1.81)	1.79 (1.65 to 1.93)	_
Metformin 500 mg twice daily	50 mg twice daily	15[a]	2.11 (1.91 to 2.33)	2.45 (2.25 to 2.66)	_
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)

[a] The number of subjects represents the maximum number of subjects that were evaluated.

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)

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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)
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)
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)
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)
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)
Boceprevir 800 mg every 8 h	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)
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)
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)
Carbamazepine 300 mg twice daily	50 mg once daily	16[c]	0.67 (0.61 to 0.73)	0.51 (0.48 to 0.55)	0.27 (0.24 to 0.31)
Daclatasvir 60 mg once daily	50 mg once daily	12	1.29 (1.07 to 1.57)	1.33 (1.11 to 1.59)	1.45 (1.25 to 1.68)

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Ferrous fumarate 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 fumarate 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 fumarate 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)

[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.

[c] The number of subjects represents the maximum number of subjects that were evaluated.

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

Effect of Abacavir and Lamivudine on the Pharmacokinetics of Other Agents: Abacavir and lamivudine do not inhibit or induce CYP enzymes (such as CYP3A4, CYP2C9, or CYP2D6). Based on in vitro study results, abacavir and lamivudine at therapeutic drug exposures are not expected to affect the pharmacokinetics of drugs that are substrates of the following transporters: OATP1B1/3, BCRP or P-gp, OCT1, OCT2, OCT3 (lamivudine only), or MATE1 and MATE2-K.

Effect of Other Agents on the Pharmacokinetics of Abacavir or Lamivudine: In vitro, abacavir is not a substrate of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, MATE1, MATE2-K, MRP2 or MRP4; therefore, drugs that modulate these transporters are not expected to affect abacavir plasma concentrations. Abacavir is a substrate of BCRP and P-gp in vitro; however, considering its absolute bioavailability (83%), modulators of these transporters are unlikely to result in a clinically relevant impact on abacavir concentrations.

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

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

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

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

Methadone: In a trial of 11 HIV-1-infected subjects receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of abacavir twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI: 6% to 42%) *[see Drug Interactions (7.3)]*. The addition of methadone has no clinically significant effect on the pharmacokinetic properties of abacavir.

Ribavirin: In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected subjects *[see Warnings and Precautions (5.8)]*.

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

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.

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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 hours).

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.

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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 microM (1 microM = 0.28 mcg per mL) and 0.07 to 1.0 microM against HIV-1_{IIIB} and HIV-1_{BaL}, respectively, and the mean EC_{50} value was 0.26 ± 0.18 microM against 8 clinical isolates. The median EC_{50} values of abacavir were 344 nM (range: 14.8 to 676 nM), 16.9 nM (range: 5.9 to 27.9 nM), 8.1 nM (range: 1.5 to 16.7 nM), 356 nM (range: 35.7 to 396 nM), 105 nM (range: 28.1 to 168 nM), 47.6 nM (range: 5.2 to 200 nM), 51.4 nM (range: 7.1 to 177 nM), and 282 nM (range: 22.4 to 598 nM) against HIV-1 clades A-G and group O viruses (n = 3 except n = 2 for clade B), respectively. The EC_{50} values against HIV-2 isolates (n = 4), ranged from 0.024 to 0.49 microM.

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

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).

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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 K65R, L74V, Y115F, and M184V/I in HIV-1 RT. M184V or I substitutions resulted in high-level resistance to lamivudine and approximately 2-fold decrease in susceptibility to abacavir. Substitutions K65R, L74M, or Y115F with M184V or I conferred a 7- to 8-fold reduction in abacavir susceptibility, and combinations of three substitutions were required to confer more than an 8-fold reduction in susceptibility.

Resistance in Clinical Subjects

Dolutegravir: No subjects in the treatment arm receiving dolutegravir + EPZICOM in SINGLE (treatment-naïve trial) had a detectable decrease in susceptibility to dolutegravir or background NRTIs in the resistance analysis subset (n = 11 with HIV-1 RNA greater than 400 copies per mL at failure or last visit and having resistance data). Two virologic failure subjects in SINGLE had treatment-emergent G/D/E193D and G193G/E integrase substitutions at Week 84 and Week 108, respectively, and 1 subject with 275 copies per mL HIV-1 RNA had a treatment-emergent Q157Q/P integrase substitution detected at Week 24. None of these subjects had a 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 through Week 144.

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 a K65R substitution with or without an M184V/I substitution, viruses with L74V plus the M184V/I substitution, and viruses with thymidine analog mutation (TAM) substitutions (M41L, D67N,

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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,

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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 (double-blind through 96 weeks and open-label phase from 96 to 144 weeks) in antiretroviral treatment-naïve subjects, SINGLE (ING114467, NCT01263015) 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, NCT01231516) (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 144 (open-label-phase analysis which followed the Week 96 double-blind phase) outcomes for SINGLE are provided in Table 11.

Table 11. Virologic Outcomes of Randomized Treatment in SINGLE at 144 Weeks (Snapshot Algorithm)

	TIVICAY + EPZICOM Once Daily (n = 414)	**ATRIPLA Once Daily (n = 419)**
HIV-1 RNA <50 copies/mL	71%	63%
Treatment difference[a]	8.3% (95% CI: 2.0%, 14.6%)[d]	

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Virologic nonresponse	10%	7%
Data in window not <50 copies/mL	4%	<1%
Discontinued for lack of efficacy	3%	3%
Discontinued for other reasons while not suppressed	3%	4%
No virologic data	18%	30%
Reasons		
Discontinued study/study drug due to adverse event or death[b]	4%	14%
Discontinued study/study drug for other reasons[c]	12%	13%
Missing data during window but on study	2%	3%
Proportion (%) of Subjects with HIV-1 RNA <50 copies/mL by Baseline Category		
Plasma viral load (copies/mL)		
≤100,000	73%	64%
>100,000	69%	61%
Gender		
Male	72%	66%
Female	69%	48%
Race		
White	72%	71%
African-American/African Heritage/Other	71%	47%

[a] Adjusted for pre-specified stratification factors.

[b] Includes subjects who discontinued due to an adverse event or death at any time point if this resulted in no virologic data on treatment during the analysis window.

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

[d] The primary endpoint was assessed at Week 48 and the virologic success rate was 88% in the group receiving TIVICAY and 81% in the ATRIPLA group, with a treatment difference of 7.4% and 95% CI of (2.5%, 12.3%).

Treatment differences were maintained across baseline characteristics including baseline viral load, CD4+ cell count, age, gender, and race. The adjusted mean changes in CD4+ cell counts from baseline were 378 cells per mm^3 in the group receiving TIVICAY + EPZICOM and 332 cells per mm^3 for the ATRIPLA group at 144 weeks. The adjusted difference between treatment arms and 95% CI was 46.9 cells per mm^3 (15.6 cells per mm^3, 78.2 cells per mm^3) (adjusted for pre-specified stratification factors: baseline HIV-1 RNA, and baseline CD4+ cell count).

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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%]).

14.2 Pediatric Subjects

The efficacy of the individual components of TRIUMEQ for the treatment of HIV-1 infection was evaluated in pediatric patients enrolled in the IMPAACT P1093 trial (NCT01302847) or the ARROW trial (NCT02028676), as summarized below.

- Abacavir and lamivudine once daily, in combination with a third antiretroviral drug, were evaluated in a randomized, multicenter trial (ARROW) in HIV-1–infected, treatment-naïve subjects. Subjects randomized to once-daily dosing (n = 336) and who weighed at least 25 kg received abacavir 600 mg and lamivudine 300 mg, as either the single entities or as EPZICOM. At Week 96, 67% of subjects receiving abacavir and lamivudine once-daily in combination with a third antiretroviral drug, had HIV-1 RNA less than 80 copies per mL.
- Dolutegravir, in combination with other antiretroviral drugs was evaluated in treatment-experienced, INSTI-naïve, HIV-1–infected subjects aged 6 to less than 18 years in a 48-week open-label, multicenter, dose-finding clinical trial, IMPAACT P1093. Subjects aged 12 to less than 18 years were enrolled in Cohort I and subjects aged 6 to less than 12 years were enrolled in Cohort IIA. At 48 weeks, 61% (14/23) of subjects aged 12 to less than 18 years treated with TIVICAY once daily plus optimized background therapy achieved virologic response defined as HIV-1 RNA less than 50 copies per mL. Across both cohorts, virologic suppression at Week 48 was achieved in 67% (16/24) of subjects weighing at least 40 kg.

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).

<u>Drug Interactions</u>

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TRIUMEQ may interact with many drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John's wort *[see Contraindications (4), Drug Interactions (7)]*.

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 healthcare provider 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 if they have a hypersensitivity reaction, they should dispose of any unused TRIUMEQ to avoid restarting abacavir.
- 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.

Hepatotoxicity

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Inform patients that hepatotoxicity has been reported with dolutegravir, a component of TRIUMEQ *[see Warnings and Precautions (5.4), Adverse Reactions (6.1)]*. Inform patients that monitoring for hepatotoxicity during therapy with TRIUMEQ is recommended.

Posttreatment Exacerbations of Hepatitis in Patients with Hepatitis B Co-infection

Advise patients co-infected with HIV-1 and HBV that worsening of liver disease has occurred in some cases when treatment with lamivudine was discontinued. Advise patients to discuss any changes in regimen with their physician *[see Warnings and Precautions (5.2)]*.

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 Boxed Warning, Warnings and Precautions (5.5)]*.

Embryo-Fetal Toxicity

Advise adolescents and adults of childbearing potential to avoid use of TRIUMEQ at the time of conception through the first trimester of pregnancy. Advise adolescents and adults of childbearing potential to contact their healthcare provider if they plan to become pregnant, become pregnant, or if pregnancy is suspected during treatment with TRIUMEQ *[see Warnings and Precaution (5.6)]*.

Advise adolescents and adults of childbearing potential taking TRIUMEQ to consistently use effective contraception *[see Use in Specific Populations (8.1, 8.3)]*.

Use with Interferon- and Ribavirin-Based Regimens in Patients with Hepatitis C Co-infection

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 (5.8)]*.

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any signs and symptoms of infection as inflammation from previous infection may occur soon after combination antiretroviral therapy, including when TRIUMEQ is started *[see Warnings and Precautions (5.9)]*.

Pregnancy Registry

Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes in those exposed to TRIUMEQ during pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

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

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Missed Dose

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

Availability of Medication Guide

Instruct patients to read the Medication Guide before starting TRIUMEQ and to re-read 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.

Storage

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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Research Triangle Park, NC 27709

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MEDICATION GUIDE

TRIUMEQ (TRI-u-meck)

(abacavir, dolutegravir, and lamivudine tablets)

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

TRIUMEQ can cause serious side effects, including:

- **Serious allergic reactions (hypersensitivity reaction)** that can cause death have happened with TRIUMEQ and other abacavir-containing products. 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 (abacavir, dolutegravir and lamivudine) or any other medicine that contains abacavir or dolutegravir (EPZICOM, TIVICAY, TRIZIVIR, or ZIAGEN) again.

  - If you have an allergic reaction, dispose of any unused TRIUMEQ. Ask your pharmacist how to properly dispose of medicines.
  - 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.

- **Worsening of hepatitis B virus in people who have HIV-1 infection.** If you have Human Immunodeficiency Virus type 1 (HIV-1) and hepatitis B virus (HBV) infection, your HBV may get

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worse (flare-up) if you stop taking TRIUMEQ. A “flare-up” is when your HBV infection suddenly returns in a worse way than before. Worsening liver disease can be serious and may lead to death.

- Do not run out of TRIUMEQ. Refill your prescription or talk to your healthcare provider before your TRIUMEQ is all gone.
- Do not stop TRIUMEQ without first talking to your healthcare provider.
- If you stop taking TRIUMEQ, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your liver.

- **Resistant Hepatitis B Virus (HBV).** If you have HIV-1 and hepatitis B, the hepatitis B virus can change (mutate) during your treatment with TRIUMEQ and become harder to treat (resistant).
- **Use with interferon and ribavirin-based regimens.** Worsening of liver disease that has caused death has happened in people infected with both HIV-1 and hepatitis C virus who were taking antiretroviral medicines and were 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 HIV-1 (Human Immunodeficiency Virus type 1) medicine used to treat HIV-1 infection in adults and children who weigh at least 88 pounds (40 kg).

HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

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 who weigh less than 88 pounds (40 kg).

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.
- are allergic to abacavir, dolutegravir, lamivudine, or any of the ingredients in TRIUMEQ. See the end of this Medication Guide for a complete list of ingredients in TRIUMEQ.
- take dofetilide (TIKOSYN). Taking TRIUMEQ and dofetilide (TIKOSYN) can cause serious side effects that may be serious or life-threatening.
- have certain liver problems.

Before you take TRIUMEQ, tell your healthcare provider about all of your medical conditions, including if you:

- have been tested and know whether or not you have a particular gene variation called HLA-B*5701.
- have or have had liver problems, including hepatitis B or C virus infection.
- have kidney problems.

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- have heart problems, smoke, or have diseases that increase your risk of heart disease such as high blood pressure, high cholesterol, or diabetes.
- drink alcohol or take medicines that contain alcohol.
- are pregnant or plan to become pregnant. One of the medicines in TRIUMEQ called dolutegravir may harm your unborn baby.
  - **You should not take TRIUMEQ at the time of becoming pregnant or during the first 12 weeks of pregnancy.** Your healthcare provider may change your medicine during this time in your pregnancy.
  - If you can become pregnant, your healthcare provider will perform a pregnancy test before you start treatment with TRIUMEQ.
  - If you can become pregnant, you should consistently use effective birth control (contraception) during treatment with TRIUMEQ.
  - Tell your healthcare provider right away if you are planning to become pregnant, you become pregnant, or think you may be pregnant during treatment with TRIUMEQ.

Pregnancy Registry. There is a pregnancy registry for individuals who take antiretroviral medicines, including TRIUMEQ, during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk with 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 if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  - Two of the medicines in TRIUMEQ (abacavir and lamivudine) pass into your breastmilk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some medicines interact with TRIUMEQ. Keep a list of your medicines to show your healthcare provider and pharmacist when you get a new medicine**.**

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with TRIUMEQ.
- **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take TRIUMEQ with other medicines.

How should I take TRIUMEQ?

- **Take TRIUMEQ exactly as your healthcare provider tells you to take it.**
- Do not change your dose or stop taking TRIUMEQ without talking with your healthcare provider.
- TRIUMEQ may be taken with or without food.
- If you take antacids, laxatives, or other medicines that contain aluminum, magnesium, or buffered medicines, TRIUMEQ should be taken at least 2 hours before or 6 hours after you take these medicines.

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- If you need to take iron or calcium supplements by mouth during treatment with TRIUMEQ:
  - If you take TRIUMEQ with food, you may take these supplements at the same time that you take TRIUMEQ.
  - If you do not take TRIUMEQ with food, take TRIUMEQ at least 2 hours before or 6 hours after you take these supplements.
- If you miss a dose of TRIUMEQ, take it as soon as you remember. Do not take 2 doses at the same time or take more than your healthcare provider tells you to take.
- Stay under the care of a healthcare provider during treatment with TRIUMEQ.
- Do not run out of TRIUMEQ. The virus in your blood may increase and the virus may become harder to treat. When your supply starts to run low, get more from your healthcare provider or pharmacy.
- If you take too much 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?"**
- **Serious liver problems can happen** in people who take TRIUMEQ. People with a history of hepatitis B or C virus may have an increased risk of developing new or worsening changes in certain liver function tests during treatment with TRIUMEQ. Liver problems including liver failure have also happened with TRIUMEQ in people without a history of liver disease or other risk factors. Liver failure resulting in liver transplant has also been reported with TRIUMEQ. Your healthcare provider may do blood tests to check your liver function. **Call your healthcare provider right away if you develop any of the signs or symptoms of liver problems listed below.**
  - your skin or the white part of your eyes turns yellow (jaundice)
  - dark or "tea-colored" urine
  - light colored stools (bowel movements)
  - loss of appetite
  - nausea or vomiting
  - pain, aching, or tenderness on the right side of your stomach area
- **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 cause death. **Call your healthcare provider right away if you get any of the following symptoms that could be signs of lactic acidosis:**
  - feel very weak or tired
  - unusual (not normal) muscle pain
  - trouble breathing
  - stomach pain with nausea and vomiting
  - feel cold, especially in your arms and legs
  - feel dizzy or lightheaded
  - have a fast or irregular heartbeat

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- **Lactic acidosis can also lead to serious liver problems,** which 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 signs or symptoms of liver problems which are listed above under "Serious liver problems". You may be more likely to get lactic acidosis or serious liver problems if you are female or very overweight (obese).**
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having new symptoms after you start taking TRIUMEQ.
- **Heart attack (myocardial infarction).** Some HIV-1 medicines including TRIUMEQ may increase your risk of heart attack.
- **The most common side effects of TRIUMEQ include:**
  - o trouble sleeping
  - o tiredness
  - o headache

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 it from moisture.
- The bottle of TRIUMEQ contains a desiccant packet to help keep your medicine dry (protect it from moisture). Do not remove the desiccant packet from the bottle.

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. You can ask your pharmacist or healthcare provider for information about TRIUMEQ that is written for health professionals.

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.

Tablet film-coating contains: iron oxide black, iron oxide red, macrogol/PEG, polyvinyl alcohol–part hydrolyzed, talc, and titanium oxide.

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Manufactured for:

ViiV Healthcare

Research Triangle Park, NC 27709

by:

GlaxoSmithKline

Research Triangle Park, NC 27709

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

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 09/2018

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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 healthcare provider right away to find out 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®, or TRIZIVIR®) again. If you have an allergic reaction, dispose of any unused TRIUMEQ. Ask your pharmacist how to properly dispose of medicines. 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.

03/2017 TRM:XWC