HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DOLUTEGRAVIR and LAMIVUDINE TABLETS safely and effectively. See full prescribing information for DOLUTEGRAVIR and LAMIVUDINE TABLETS.

DOLUTEGRAVIR and LAMIVUDINE tablets, for oral use
Initial U.S. Approval: 2019

WARNING: PATIENTS CO-INFECTED WITH HEPATITIS B VIRUS (HBV) AND HUMAN IMMUNODEFICIENCY VIRUS (HIV-1): EMERGENCE OF LAMIVUDINE-RESISTANT HBV AND EXACERBATIONS OF HBV

See full prescribing information for complete boxed warning.

All patients with HIV-1 should be tested for the presence of HBV prior to or when initiating dolutegravir and lamivudine tablets. Emergence of lamivudine-resistant HBV variants associated with lamivudine-containing antiretroviral regimens has been reported. If dolutegravir and lamivudine tablets is used in patients co-infected with HIV-1 and HBV, additional treatment should be considered for appropriate treatment of chronic HBV; otherwise, consider an alternative regimen.

Severe acute exacerbations of HBV have been reported in patients who are co-infected with HIV-1 and HBV and have discontinued lamivudine, a component of dolutegravir and lamivudine tablets. Closely monitor hepatic function in these patients and, if appropriate, initiate anti-HBV treatment. (5.1)

----------INDICATIONS AND USAGE----------
Dolutegravir and lamivudine tablet, a two-drug combination of dolutegravir (integrase strand transfer inhibitor [INSTI]) and lamivudine (nucleoside analogue reverse transcriptase inhibitor [NRTI]) is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults with no antiretroviral treatment history and with no known substitutions associated with resistance to the individual components of dolutegravir and lamivudine tablet. (1)

----------DOSAGE AND ADMINISTRATION----------
- Prior to or when initiating dolutegravir and lamivudine tablets, test patients for HBV infection. (2.1)
- Pregnancy Testing: Perform pregnancy testing before initiation of dolutegravir and lamivudine tablets in individuals of childbearing potential. (2.1, 5.4)
- One tablet taken orally once daily with or without food. (2.2)
- The dolutegravir dose (50 mg) in dolutegravir and lamivudine tablets is insufficient when coadministered with carbamazepine or rifampin. If dolutegravir and lamivudine tablet is coadministered with carbamazepine or rifampin, take one tablet of dolutegravir and lamivudine once daily, followed by an additional dolutegravir 50-mg tablet, approximately 12 hours from the dose of dolutegravir and lamivudine tablets. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 50 mg of dolutegravir and 300 mg of lamivudine. (3)

----------CONTRAINDICATIONS----------
- Prior hypersensitivity reaction to dolutegravir or lamivudine. (4)
- Coadministration with dofetilide. (4)

----------WARNINGS AND PRECAUTIONS----------
- Hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury, have been reported with dolutegravir. Discontinue dolutegravir and lamivudine tablets immediately if signs or symptoms of hypersensitivity reactions develop, as a delay in stopping treatment may result in a life-threatening reaction. (5.2)
- Hepatotoxicity has been reported in patients receiving a dolutegravir-containing regimen. Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with dolutegravir and lamivudine tablets. Monitoring for hepatotoxicity is recommended. (5.3)
- Embryo-fetal toxicity may occur when used at the time of conception and in early pregnancy. Avoid use of dolutegravir and lamivudine tablets at the time of conception through the first trimester of pregnancy due to the risk of neural tube defects. Advise individuals of childbearing potential to use effective contraception. (2.1, 5.4, 8.1, 8.3)
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. (5.5)
- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. (5.7)

----------ADVERSE REACTIONS----------
The most common adverse reactions (all grades) observed in ≥2% (in those receiving dolutegravir and lamivudine) were headache, diarrhea, nausea, insomnia, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Cipla Ltd at 1-866-604-3268 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Dolutegravir and lamivudine tablet is a complete regimen for the treatment of HIV-1 infection; therefore, coadministration with other antiretroviral drugs for the treatment of HIV-1 infection is not recommended. (7.1)
- Refer to the full prescribing information for important drug interactions with dolutegravir and lamivudine tablets. (4, 5.6, 7)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Avoid use of dolutegravir and lamivudine tablets at the time of conception through the first trimester due to the risk of neural tube defects. (2.1, 5.4, 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 individuals of childbearing potential. (8.3)
- Renal Impairment: Dolutegravir and lamivudine tablet is not recommended in patients with creatinine clearance less than 50 mL/min. (8.6)
- Hepatic Impairment: Dolutegravir and lamivudine tablet is not recommended in patients with severe hepatic impairment (Child-Pugh Score C). (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Patient Information.

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FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: PATIENTS CO-INFECTED WITH HEPATITIS B VIRUS (HBV) AND HUMAN IMMUNODEFICIENCY VIRUS (HIV-1): EMERGENCE OF LAMIVUDINE-RESISTANT HBV AND EXACERBATIONS OF HBV

All patients with HIV-1 should be tested for the presence of HBV prior to or when initiating dolutegravir and lamivudine tablets. Emergence of lamivudine-resistant HBV variants associated with lamivudine-containing antiretroviral regimens has been reported. If dolutegravir and lamivudine tablet is used in patients co-infected with HIV-1 and HBV, additional treatment should be considered for appropriate treatment of chronic HBV; otherwise, consider an alternative regimen.

Severe acute exacerbations of HBV have been reported in patients who are co-infected with HIV-1 and HBV and have discontinued lamivudine, a component of dolutegravir and lamivudine tablets. Closely monitor hepatic function in these patients and, if appropriate, initiate anti-HBV treatment *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

Dolutegravir and lamivudine tablet is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults with no antiretroviral treatment history and with no known substitutions associated with resistance to the individual components of dolutegravir and lamivudine tablet.

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to or When Initiating Treatment with Dolutegravir and Lamivudine Tablets

Prior to or when initiating dolutegravir and lamivudine tablets, test patients for HBV infection *[see Warnings and Precautions (5.1)]*.

Perform pregnancy testing before initiation of dolutegravir and lamivudine tablets in individuals of childbearing potential *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)]*.

2.2 Recommended Dosage

Dolutegravir and lamivudine tablet is a fixed-dose combination product containing 50 mg of dolutegravir and 300 mg of lamivudine. The recommended dosage regimen of dolutegravir and lamivudine in adults is one tablet taken orally once daily with or without food *[see Clinical Pharmacology (12.3)]*.

2.3 Recommended Dosage with Certain Coadministered Drugs

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

Table 1. Dosing Recommendations for Dolutegravir and Lamivudine Tablets with Coadministered Drugs

Coadministered Drug	Dosing Recommendation
Carbamazepine, rifampin	An additional dolutegravir 50-mg tablet, separated by 12 hours from dolutegravir and lamivudine tablets, should be taken.

2.4 Not Recommended in Patients with Renal Impairment

Because dolutegravir and lamivudine tablet is a fixed-dose tablet and cannot be dose adjusted, dolutegravir and lamivudine tablet is not recommended in patients with creatinine clearance less than 50 mL per minute *[see Use in Specific Populations (8.6)]*.

2.5 Not Recommended in Patients with Severe Hepatic Impairment

Dolutegravir and lamivudine tablet is not recommended in patients with severe hepatic impairment (Child-Pugh Score C) *[see Use in Specific Populations (8.7)]*.

3 DOSAGE FORMS AND STRENGTHS

Dolutegravir and lamivudine tablets are gray colored capsule shaped biconvex film coated tablet debossed with "C" on one side and plain on other side. Each tablet contains 50 mg of dolutegravir and 300 mg of lamivudine.

4 CONTRAINDICATIONS

Dolutegravir and lamivudine tablet is contraindicated in patients:

- with prior hypersensitivity reaction to dolutegravir *[see Warnings and Precautions (5.2)]* or lamivudine.
- receiving dofetilide, due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events *[see Drug Interactions (7.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Patients Co-infected with HIV-1 and HBV: Emergence of Lamivudine-Resistant HBV and the Risk of Posttreatment Exacerbations of HBV

All patients with HIV-1 should be tested for the presence of HBV prior to or when initiating dolutegravir and lamivudine tablets.

<u>Emergence of Lamivudine-Resistant HBV</u>

Safety and efficacy of lamivudine have not been established for treatment of chronic HBV in subjects dually infected with HIV-1 and HBV. Emergence of HBV variants associated with resistance to lamivudine has been reported in HIV-1–infected subjects who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with HBV. If a decision is made to administer dolutegravir and lamivudine tablets to patients co-infected with HIV-1 and HBV, additional

treatment should be considered for appropriate treatment of chronic HBV; otherwise, consider an alternative regimen.

Severe Acute Exacerbations of HBV in Patients Co-infected with HIV-1 and HBV

Severe acute exacerbations of HBV have been reported in patients who are co-infected with HIV-1 and HBV and have discontinued products containing lamivudine, and may occur with discontinuation of dolutegravir and lamivudine tablets. Patients who are co-infected with HIV-1 and HBV who discontinue dolutegravir and lamivudine tablets should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with dolutegravir and lamivudine tablets. If appropriate, initiation of anti-HBV therapy may be warranted, especially in patients with advanced liver disease or cirrhosis, since posttreatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

5.2 Hypersensitivity Reactions

Hypersensitivity reactions have been reported with the use of dolutegravir, a component of dolutegravir and lamivudine tablets, and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. These events were reported in <1% of subjects receiving dolutegravir in Phase 3 clinical trials.

Discontinue dolutegravir and lamivudine tablets 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 dolutegravir and lamivudine tablets or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction *[see Contraindications (4)]*.

5.3 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 dolutegravir and lamivudine tablets *[see Adverse Reactions (6.1)]*. In some cases, the elevations in transaminases were consistent with immune reconstitution syndrome or HBV 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 (abacavir, dolutegravir, and lamivudine). Monitoring for hepatotoxicity is recommended.

5.4 Embryo-Fetal Toxicity

Preliminary data from an observational study showed that dolutegravir, a component of dolutegravir and lamivudine tablets, 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 dolutegravir and lamivudine tablets 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 dolutegravir and lamivudine tablets, if possible, switch to an alternative regimen.

Perform pregnancy testing before initiation of dolutegravir and lamivudine tablets in individuals of childbearing potential to exclude use of dolutegravir and lamivudine tablets during the first trimester of pregnancy *[see Dosage and Administration (2.1)]*.

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

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 lamivudine (a component of dolutegravir and lamivudine tablets). 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. Monitor closely when administering dolutegravir and lamivudine tablets to any patient with known risk factors for liver disease. Treatment with dolutegravir and lamivudine tablets should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity, which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations.

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

The coadministration of dolutegravir and lamivudine tablet and other drugs may result in known or potentially significant drug interactions, some of which may lead to *[see Contraindications (4), Drug Interactions (7.4)]*:

- Loss of therapeutic effect of dolutegravir and lamivudine tablets and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of coadministered 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 dolutegravir and lamivudine tablets; review coadministered drugs during therapy with dolutegravir and lamivudine tablets; and monitor for the adverse reactions associated with the coadministered drugs.

5.7 Immune Reconstitution Syndrome

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

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

6 ADVERSE REACTIONS

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

- Patients co-infected with HIV-1 and HBV *[see Warnings and Precautions (5.1)]*.
- Hypersensitivity reactions *[see Warnings and Precautions (5.2)]*.
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*.
- Lactic acidosis and severe hepatomegaly with steatosis *[see Warnings and Precautions (5.5)]*.
- Immune reconstitution syndrome *[see Warnings and Precautions (5.7)]*.

6.1 Clinical Trials Experience

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

The safety assessment of dolutegravir and lamivudine tablets in HIV-1–infected adults with no antiretroviral treatment history and with a plasma viral load ≤500,000 HIV-1 RNA copies/mL at the screening visit, is based on the pooled primary Week 48 analyses of data from 2 identical, multicenter, double-blind, controlled trials, GEMINI-1 and GEMINI-2. A total of 1,433 HIV-1–infected adults with no antiretroviral treatment history were randomized to dolutegravir (TIVICAY) 50 mg plus lamivudine (EPIVIR) 300 mg, as a complete regimen once daily, or TIVICAY 50 mg plus fixed-dose combination tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) (TRUVADA), administered once daily.

The rates of adverse events leading to discontinuation in the pooled analysis were 2% of subjects in both treatment arms. The most common adverse events leading to discontinuation were psychiatric disorders: <1% of subjects in both treatment arms.

Adverse reactions (all grades) observed in at least 2% of subjects in either treatment arm of the Week 48 pooled analysis from GEMINI-1 and GEMINI-2 trials are provided in Table 2.

The adverse reactions observed for TIVICAY plus EPIVIR in the Week 48 analysis of the pooled data from GEMINI-1 and GEMINI-2 were generally consistent with the adverse reaction profiles and severities for the individual components when administered with other antiretroviral agents.

Table 2. Adverse Reactions (All Grades) Reported in ≥2% of Subjects in Any Treatment Group in Adults with No Antiretroviral Treatment History in GEMINI-1 and GEMINI-2 (Week 48 Pooled Analysis)

Adverse Reaction	TIVICAY plus EPIVIR (n = 716)	TIVICAY plus TRUVADA (n = 717)
Headache[a]	3%	4%
Nausea	2%	5%
Diarrhea	2%	3%
Insomnia	2%	3%
Fatigue[b]	2%	2%
Dizziness	1%	2%

[a] The only adverse reaction of Grade 2 or greater occurring in ≥1% of subjects treated with TIVICAY plus EPIVIR was headache (1%).
[b] Fatigue: includes fatigue, asthenia, and malaise.

Less Common Adverse Reactions

The following adverse reactions occurred in <2% of subjects receiving dolutegravir plus lamivudine or are from studies described in the prescribing information of the individual components, TIVICAY (dolutegravir) and EPIVIR (lamivudine). Some events have been included because of their seriousness and assessment of potential causal relationship.

Blood and Lymphatic Systems Disorders: Anemia, neutropenia, thrombocytopenia.

Gastrointestinal Disorders: Abdominal discomfort, abdominal pain, flatulence, upper abdominal pain, vomiting.

General: Fever.

Hepatobiliary Disorders: Hepatitis.

Immune System Disorders: Hypersensitivity, immune reconstitution syndrome.

Musculoskeletal Disorders: Myositis.

Nervous System Disorders: Somnolence.

Psychiatric Disorders: Anxiety, abnormal dreams, depression. Suicidal ideation, attempt, behavior, or completion; these events were observed primarily in subjects with a pre-existing history of depression or other psychiatric illness.

Renal and Urinary Disorders: Renal impairment.

Skin and Subcutaneous Tissue Disorders: Pruritus, rash.

Laboratory Abnormalities

Selected laboratory abnormalities with a worsening grade from baseline and representing the worst-grade toxicity in ≥2% of subjects 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; Week 48 Pooled Analyses) in GEMINI-1 and GEMINI-2 Trials

Laboratory Parameter Preferred Term	TIVICAY plus EPIVIR (n = 716)	TIVICAY plus TRUVADA (n = 717)
ALT		
Grade 2 (>2.5-5.0 x ULN)	2%	3%
Grade 3 to 4 (>5.0 x ULN)	3%	3%
AST		
Grade 2 (>2.5-5.0 x ULN)	3%	3%
Grade 3 to 4 (>5.0 x ULN)	2%	3%
Total Bilirubin		
Grade 2 (1.6-2.5 x ULN)	1%	2%
Grade 3 to 4 (>2.5 x ULN)	<1%	<1%
Creatine kinase		

Grade 2 (6.0-9.9 x ULN)	4%	3%
Grade 3 to 4 (≥10.0 x ULN)	4%	5%
Hyperglycemia		
Grade 2 (126-250 mg/dL)	7%	4%
Grade 3 to 4 (>250 mg/dL)	<1%	<1%
Hypophosphatemia (Phosphate)		
Grade 2 (1.4 to <2.0 mg/dL)	7%	8%
Grade 3 to 4 (<1.4 mg/dL)	<1%	<1%
Lipase		
Grade 2 (>1.5-3.0 x ULN)	5%	5%
Grade 3 to 4 (>3.0 x ULN)	<1%	3%

ULN = Upper limit of normal.

Table 4. Mean Change from Baseline in Fasted Lipid Values (Week 48 Pooled Analyses[a]) in GEMINI-1 and GEMINI-2 Trials

Laboratory Parameter Preferred Term	TIVICAY plus EPIVIR (n = 716)	TIVICAY plus TRUVADA (n = 717)
Cholesterol (mg/dL)	13.3	-6.9
HDL cholesterol (mg/dL)	5.6	0.8
LDL cholesterol (mg/dL)	7.5	-6.3
Triglycerides (mg/dL)	3.7	-6.9
Total cholesterol/HDL cholesterol ratio	-0.1	-0.3

[a] Subjects on lipid-lowering agents at baseline are excluded (TIVICAY plus EPIVIR, n = 29; TIVICAY plus TRUVADA, n = 23). Lipid last observation carried forward data were used such that the last available fasted, on-treatment lipid value prior to the initiation of a lipid-lowering agent is used in place of future observed values. A total of 23 and 13 subjects receiving TIVICAY plus EPIVIR and TIVICAY plus TRUVADA, respectively, initiated lipid-lowering agents post-baseline.

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 in both arms and remained stable through 48 weeks. A mean change from baseline of 0.116 mg/dL and 0.154 mg/dL was observed after 48 weeks of treatment with TIVICAY plus EPIVIR and TIVICAY plus TRUVADA, respectively. These changes are not considered to be clinically relevant.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing experience in patients receiving a dolutegravir- or lamivudine-containing regimen. Because postmarketing 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.

Body as a Whole

Redistribution/accumulation of body fat.

Endocrine and Metabolic

Hyperglycemia.

General

Weakness.

Hemic and Lymphatic

Anemia (including pure red cell aplasia and severe anemias progressing on therapy).

Hepatic and Pancreatic

Lactic acidosis and hepatic steatosis *[see Warnings and Precautions (5.5)]*, pancreatitis, posttreatment exacerbations of HBV *[see Warnings and Precautions (5.1)]*.

Hepatobiliary Disorders

Acute liver failure, hepatotoxicity.

Hypersensitivity

Anaphylaxis, urticaria.

Investigations

Weight increased.

Musculoskeletal

Arthralgia, CPK elevation, muscle weakness, myalgia, rhabdomyolysis.

Nervous System

Paresthesia, peripheral neuropathy.

Skin

Alopecia.

7 DRUG INTERACTIONS

7.1 Coadministration with Other Antiretroviral Drugs

Dolutegravir and lamivudine tablet is a complete regimen for the treatment of HIV-1 infection; therefore, coadministration with other antiretroviral drugs for the treatment of HIV-1 infection is not recommended *[see Indications and Usage (1)]*. Information regarding potential drug-drug interactions with other antiretroviral drugs is not provided *[see Contraindications (4), Warnings and Precautions (5.6), Clinical Pharmacology (12.3)]*.

7.2 Potential for Dolutegravir and Lamivudine Tablets to Affect Other Drugs

Dolutegravir, a component of dolutegravir and lamivudine tablets, inhibits the renal organic cation transporters (OCT)2 and multidrug and toxin extrusion transporter (MATE)1; thus, it may increase plasma concentrations of drugs eliminated via OCT2 or MATE1 such as dofetilide and metformin *[see Contraindications (4), Drug Interactions (7.4), Clinical Pharmacology (12.3)]*.

7.3 Potential for Other Drugs to Affect the Components of Dolutegravir and Lamivudine Tablets

Dolutegravir is metabolized by uridine diphosphate (UDP)-glucuronosyl transferase (UGT)1A1 with some contribution from cytochrome P450 (CYP)3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, breast cancer resistance protein (BCRP), and P-glycoprotein (P-gp) *in vitro*. Drugs that induce those enzymes and transporters may decrease dolutegravir plasma concentrations and reduce the therapeutic effect of dolutegravir and lamivudine tablets *[see Drug Interactions (7.4), Clinical Pharmacology (12.3)]*. Coadministration of dolutegravir and lamivudine tablets and other drugs that inhibit these enzymes may increase dolutegravir plasma concentrations.

Coadministration of dolutegravir with polyvalent cation-containing products may lead to decreased absorption of dolutegravir *[see Drug Interactions (7.4), Clinical Pharmacology (12.3)]*.

7.4 Established and Other Potentially Significant Drug Interactions

No drug interaction studies were conducted with dolutegravir and lamivudine tablets. The drug interactions described are based on studies conducted with dolutegravir or lamivudine when administered alone *[see Clinical Pharmacology (12.3)]*. Information regarding potential drug interactions with dolutegravir and lamivudine tablets are provided in Table 5. 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)]*.

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

Coadministered Drug Class: Drug Name	Effect on Concentration	Clinical Comment
Antiarrhythmic: Dofetilide	↑Dofetilide	Coadministration is contraindicated with dolutegravir and lamivudine tablets *[see Contraindications (4)]*.
Anticonvulsant: Carbamazepine[a]	↓Dolutegravir	An additional dolutegravir 50-mg dose should be taken, separated by 12 hours from dolutegravir and lamivudine tablets *[see Dosage and Administration (2.3)]*.
Anticonvulsants: Oxcarbazepine Phenytoin Phenobarbital	↓Dolutegravir	Avoid coadministration with dolutegravir and lamivudine tablets because there are insufficient data to make dosing recommendations.
Antidiabetic: Metformin[a]	↑Metformin	Refer to the prescribing information of metformin for assessing the benefit and risk of concomitant use of dolutegravir and lamivudine tablets and metformin.
Antimycobacterial:	↓Dolutegravir	An additional 50-mg dose of dolutegravir

Rifampin[a]		should be taken, separated by 12 hours from dolutegravir and lamivudine tablets *[see Dosage and Administration (2.3)]*.
Herbal Product: St. John's wort (*Hypericum perforatum*)	↓Dolutegravir	Avoid coadministration with dolutegravir and lamivudine tablets because there are insufficient data to make dosing recommendations.
Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing antacids[a] or laxatives Sucralfate Buffered medications	↓Dolutegravir	Administer dolutegravir and lamivudine tablets 2 hours before or 6 hours after taking medications containing polyvalent cations.
Oral calcium and iron supplements, including multivitamins containing calcium or iron[a]	↓Dolutegravir	When taken with food, dolutegravir and lamivudine tablets and supplements or multivitamins containing calcium or iron can be taken at the same time. Under fasting conditions, dolutegravir and lamivudine tablets should be taken 2 hours before or 6 hours after taking supplements containing calcium or iron.
Sorbitol[a]	↓Lamivudine	When possible, avoid use of sorbitol-containing medicines with dolutegravir and lamivudine tablets.

↑ = Increase, ↓ = Decrease.
[a] *See Clinical Pharmacology (12.3) Table 8 or Table 9 for magnitude of interaction.*

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 dolutegravir and lamivudine tablets 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 have identified a possible increased risk of neural tube defects when dolutegravir, a component of dolutegravir and lamivudine tablets, 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) that 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 dolutegravir and lamivudine tablets 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 dolutegravir and lamivudine tablets during the first trimester, if possible, switch to an alternative regimen. Advise pregnant individuals of the potential risk to the embryo exposed to dolutegravir and lamivudine tablets from the time of conception through the first trimester of pregnancy.

There are insufficient human data on the use of dolutegravir and lamivudine tablets 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 50 times (rats) the exposure in humans at the recommended human dose (RHD) *(see Data)*. Oral administration of lamivudine to pregnant rabbits during organogenesis resulted in embryolethality at systemic exposure (AUC) similar to the RHD; however, no adverse developmental 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.

Lamivudine: Based on prospective reports to the APR of over 12,000 exposures to lamivudine during pregnancy resulting in live births (including over 5,000 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 defects in live births was 3.0% (95% CI: 2.6% to 3.5%) following first trimester exposure to lamivudine-containing regimens and 2.9% (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 lamivudine 150 mg twice daily with zidovudine, 10 women at 38 weeks' gestation using lamivudine 150 mg twice daily with zidovudine, and 10 women at 38 weeks' gestation using lamivudine 300 mg twice daily without other antiretrovirals. These trials were not designed or powered to provide efficacy information. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, amniotic fluid specimens were collected following natural rupture of membranes and confirmed that lamivudine crosses the placenta in humans. Based on limited data at delivery, median (range) amniotic fluid concentrations of lamivudine were 3.9-fold (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/kg/day) on Gestation Days 6 to 17 and 6 to 18, respectively, and also to rats on Gestation Day 6 to Lactation/Postpartum Day 20. No adverse effects on embryo-fetal (rats and rabbits) or pre/postnatal (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/postnatal 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).

Lamivudine: Lamivudine was administered orally to pregnant rats (at 90, 600, and 4,000 mg/kg/day) and rabbits (at 90, 300 and 1,000 mg/kg/day and at 15, 40, and 90 mg/kg/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 RHD. 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 exposure at the RHD. 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/kg/day (from prior to mating through Postnatal Day 20). In the study, development of the offspring, including fertility and reproductive performance, was 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.

Lamivudine, a component of dolutegravir and lamivudine tablets, is present in human milk. It is not known whether dolutegravir, a component of dolutegravir and lamivudine tablets, is present in human milk. When administered to lactating rats, dolutegravir was present in milk *(see Data)*. There is no information on the effects of dolutegravir and lamivudine tablet or the components of dolutegravir and lamivudine tablet on the breastfed infant or the effects of the drugs 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 dolutegravir and lamivudine tablets.

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/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 individuals of childbearing potential before initiation of dolutegravir and lamivudine tablets.

Contraception

Individuals of childbearing potential should avoid use of dolutegravir and lamivudine tablets 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 individuals of childbearing potential who are taking dolutegravir and lamivudine tablets to consistently use effective contraception.

8.4 Pediatric Use

The safety and efficacy of dolutegravir and lamivudine tablets have not been established in pediatric patients.

8.5 Geriatric Use

Clinical trials of dolutegravir and lamivudine tablets 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 dolutegravir and lamivudine tablets in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

Dolutegravir and lamivudine tablet is not recommended for patients with creatinine clearance <50 mL/min because dolutegravir and lamivudine tablet is a fixed-dose combination and the dosage of the individual components cannot be adjusted. If a dose reduction of lamivudine, a component of dolutegravir and lamivudine tablets, is required for patients with creatinine clearance <50 mL/min, then the individual components should be used.

8.7 Hepatic Impairment

No dosage adjustment of dolutegravir and lamivudine tablet is necessary in patients with mild or moderate hepatic impairment (Child-Pugh Score A or B). Dolutegravir has not been studied in patients with severe hepatic impairment (Child-Pugh Score C); therefore, dolutegravir and lamivudine tablet is not recommended for patients with severe hepatic impairment.

10 OVERDOSAGE

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

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.

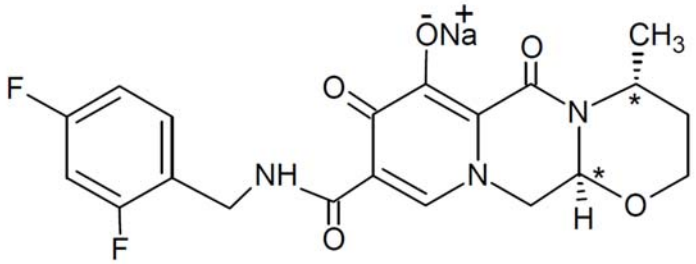
11 DESCRIPTION

Dolutegravir and lamivudine tablet is a fixed-dose combination tablet containing dolutegravir (as dolutegravir sodium), an INSTI, and lamivudine (also known as 3TC), an NRTI.

Dolutegravir and lamivudine tablets are for oral administration. Each film-coated tablet contains the active ingredients 50 mg of dolutegravir (equivalent to 52.620 mg dolutegravir sodium) and 300 mg of lamivudine and the inactive ingredients colloidal silicon dioxide, mannitol, microcrystalline cellulose, povidone PVPK 30, purified water, sodium starch glycolate, sodium stearyl fumarate. The tablet film-coating contains the inactive ingredients ferrosoferric oxide, hypromellose, macrogol, polysorbate 80, titanium dioxide.

Dolutegravir

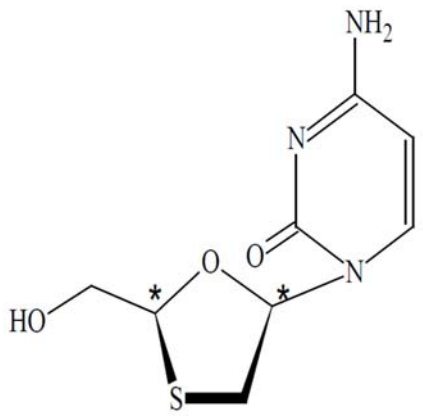
The chemical name of dolutegravir sodium is sodium (4*R*,12a*S*)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazin-7-olate. The empirical formula is $C_{20}H_{18}F_2N_3NaO_5$ and the molecular weight is 441.36 g/mol.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



Dolutegravir sodium is an off-white to pale yellow powder and is very slightly soluble in dimethylformamide, dimethyl sulfoxide, methanol and practically insoluble 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/mol. It has the following structural formula:



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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dolutegravir and lamivudine tablet is a fixed-dose combination of the HIV-1 antiretroviral agents, dolutegravir and lamivudine *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of combination therapy as dolutegravir and lamivudine tablet or lamivudine given alone on the QT interval has not been studied. At a 250-mg suspension dose (exposures approximately 3–fold that of the 50-mg once-daily dose at steady state), dolutegravir given alone did not prolong the QTc interval to any clinically relevant extent.

Effects of Dolutegravir on Renal Function

No clinically significant dolutegravir exposure-response relationship on the glomerular filtration rate or effective renal plasma flow was observed. 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.

12.3 Pharmacokinetics

The C_{max}, C_{trough}, and AUC_{tau} parameters of the components of dolutegravir and lamivudine tablets are provided in Table 6.

Table 6. Multiple-Dose Pharmacokinetic Parameters of the Components of Dolutegravir and Lamivudine Tablets

Parameter Mean (%CV)	Dolutegravir[a]	Lamivudine[b]
C_{max} (mcg/mL)	3.67 (20%)	2.04 (26%)

C_{trough} (mcg/mL)	1.11 (46%)	0.042 (38%)
AUC_{tau} (mcg/h/mL)	53.6 (27%)	8.87 (21%)

[a] Based on dolutegravir 50-mg once-daily dosage administered to antiretroviral (ART) treatment-naive adults.
[b] Based on lamivudine 300-mg once-daily dosage administered to healthy subjects.
C_{max} = Maximum concentration; C_{trough} = Lowest concentration before administration of the next dose;
AUC_{tau} = Area under the concentration-time curve integrated across the dosing interval.

The absorption, distribution, and elimination pharmacokinetic parameters of the components of dolutegravir and lamivudine tablets are provided in Table 7.

Table 7. Pharmacokinetic Properties of the Components of Dolutegravir and Lamivudine Tablets

Pharmacokinetic Parameters	Dolutegravir	Lamivudine
Absorption		
T_{max} (h), median[a]	2.5	1
Effect of Food		
High-fat meal[b] (relative to fasting)	No clinically significant differences in the pharmacokinetics of either component (after administration of dolutegravir and lamivudine tablets) were observed[c]	
Distribution		
Plasma protein binding[d]	Approximately 99%	36%
Blood-to-plasma ratio	0.44 - 0.54	1.1 - 1.2
Elimination		
$t_{1/2}$ (h)	Approximately 14	13 - 19
Metabolism		
Metabolic pathways	UGT1A1 (primary) CYP3A (minor)	Not significantly metabolized
Excretion		
Major route of elimination	Metabolism	Renal, by OCT system
Urine (unchanged)	31% (<1%)[e]	Approximately 70%[f]
Feces (unchanged)	64% (53%)[e]	–

[a] After administration of dolutegravir and lamivudine tablets (fasted state).
[b] High-fat meal is approximately 900 kcal, 56% fat.
[c] The geometric mean (90% confidence interval) AUC ratio (fed/fasted) of dolutegravir and lamivudine is 1.33 (1.18, 1.48) and 0.91 (0.87, 0.96), respectively.
[d] Based on *in vitro* data.
[e] Based on single-dose, mass balance study of radiolabeled dolutegravir.
[f] Based on 24-hour urine collection obtained after oral or IV administration.
T_{max} = Time to maximum concentration (C_{max}); $t_{1/2}$ = Elimination half-life.

Specific Populations

No clinically significant differences in the pharmacokinetics of the components of dolutegravir and lamivudine tablet were observed based on age, sex, or race. Pharmacokinetic data for dolutegravir and lamivudine in subjects aged 65 years and older are limited. The effect of renal or hepatic impairment on the pharmacokinetics of dolutegravir and lamivudine tablet is unknown.

Drug Interaction Studies

Clinical Studies: No drug interaction studies were conducted with dolutegravir and lamivudine tablets. The drug interaction studies described below were conducted with dolutegravir or lamivudine when used alone. Table 8 summarizes the effects of dolutegravir on the pharmacokinetics of coadministered drugs.

Table 9 summarizes the effect of other drugs on the pharmacokinetics of dolutegravir when used alone and Table 10 summarizes the effect of sorbitol on the pharmacokinetics of lamivudine when used alone.

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

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug with/without Dolutegravir No Effect = 1.00		
		C_{max}	AUC	C_{tau} or C_{24}
Daclatasvir 60 mg once daily	50 mg once daily	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	0.99 (0.91 to 1.08)	1.03 (0.96 to 1.11)	1.02 (0.93 to 1.11)
Grazoprevir 200 mg once daily	50 mg single dose	0.64 (0.44, 0.93)	0.81 (0.67, 0.97)	0.86 (0.79, 0.93)
Metformin[a] 500 mg twice daily	50 mg once daily	1.66 (1.53 to 1.81)	1.79 (1.65 to 1.93)	_
Metformin[a] 500 mg twice daily	50 mg twice daily	2.11 (1.91 to 2.33)	2.45 (2.25 to 2.66)	_
Methadone 16 to 150 mg	50 mg twice daily	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	_	0.95 (0.79 to 1.15)	_
Norelgestromin[b] 0.25 mg	50 mg twice daily	0.89 (0.82 to 0.97)	0.98 (0.91 to 1.04)	0.93 (0.85 to 1.03)
Sofosbuvir 400 mg once daily Metabolite (GS-331007)	50 mg once daily	0.88 (0.80, 0.98) 1.01 (0.93, 1.10)	0.92 (0.85, 0.99) 0.99 (0.97, 1.01)	NA 0.99 (0.97, 1.01)
Velpatasvir 100 mg once daily	50 mg once daily	0.94 (0.86, 1.02)	0.91 (0.84, 0.98)	0.88 (0.82, 0.94)

[a] OCT2 or MATE1 substrate.
[b] Norelgestromin is the active metabolite of norgestimate.

No clinically significant differences in the pharmacokinetics of tenofovir (organic anion transporter [OAT]1 and OAT3 substrates) or para-amino hippurate (OAT1 and OAT3 substrates) were observed when coadministered with dolutegravir.

No clinically significant differences in the pharmacokinetics of trimethoprim/sulfamethoxazole were observed when coadministered with lamivudine.

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

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00		
		C_{max}	AUC	$C_{\tau au}$ or C_{24}
Antacid (MAALOX) simultaneous administration	50-mg single dose	0.28 (0.23 to 0.33)	0.26 (0.22 to 0.32)	0.26 (0.21 to 0.31)
Antacid (MAALOX)	50-mg single dose	0.82	0.74	0.70

2 h after dolutegravir		(0.69 to 0.98)	(0.62 to 0.90)	(0.58 to 0.85)
Calcium carbonate 1,200 mg simultaneous administration (fasted)	50-mg single dose	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	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	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	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	1.29 (1.07 to 1.57)	1.33 (1.11 to 1.59)	1.45 (1.25 to 1.68)
Ferrous fumarate 324 mg simultaneous administration (fasted)	50-mg single dose	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	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	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	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	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	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	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	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	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.

Table 10. Effect of Sorbitol on the Pharmacokinetics of Lamivudine

Coadministered Drug and Dose[a]		Lamivudine Pharmacokinetic Parameters (% Decreased)		
		C_{max}	AUC_{0-24}	AUC_{inf}
Sorbitol (Excipient)	3.2 grams	28%	20%	14%
	10.2 grams	52%	39%	32%
	13.4 grams	55%	44%	36%

[a] Coadministered with a single dose of lamivudine 300 mg.
C_{max} = Maximum concentration; $AUC_{(0-24)}$ = Area under the concentration-time curve integrated from time of administration to 24 hours; $AUC_{(inf)}$ = Area under the concentration-time curve from the time of administration to infinity.

No clinically significant differences in the pharmacokinetics of lamivudine were observed when coadministered with trimethoprim (MATE1, MATE2-K, and OCT2 inhibitor)/sulfamethoxazole, interferon alfa, or ribavirin.

In Vitro Studies Where Drug Interaction Potential Was Not Further Evaluated Clinically: Dolutegravir: Dolutegravir does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A. Dolutegravir does not induce CYP1A2, CYP2B6, or CYP3A4.

Dolutegravir is a substrate of UGT1A3 and UGT1A9. Dolutegravir does not inhibit UGT1A1 or UGT2B7.

Dolutegravir is a substrate of BCRP and P-gp. Dolutegravir does not inhibit P-gp, BCRP, bile salt export pump (BSEP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, multidrug resistance protein (MRP)2, or MRP4. Dolutegravir is not a substrate of OATP1B1 or OATP1B3.

Lamivudine: Lamivudine is a substrate of P-gp and BCRP. Lamivudine does not inhibit OATP1B1/3, BCRP, P-gp, MATE1, MATE2-K, OCT1, OCT2, or OCT3.

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.

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

Antiviral Activity in Cell Culture

Dolutegravir: Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean concentrations of drug necessary to effect viral replication by 50 percent (EC_{50}) values of 0.5 nM (0.21 ng/mL) to 2.1 nM (0.85 ng/mL) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells.

Dolutegravir exhibited antiviral activity against 13 clinically diverse clade B isolates with a mean EC_{50} value of 0.52 nM in a viral integrase 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 (3 in each group of M [clades A-G], and 3 in group O) with EC_{50} values ranging from 0.02 nM to 2.14 nM for HIV-1. Dolutegravir EC_{50} values against three HIV-2 clinical isolates in PBMC assays ranged from 0.09 nM to 0.61 nM.

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 3 to 15,000 nM (1 nM = 230 ng/mL). The EC_{50} values of lamivudine against different HIV-1 clades (A-G) and group O viruses ranged from 1 to 120 nM, and against HIV-2 isolates from 3 to 120 nM in PBMCs.

Antiviral Activity in Combination with Other Antiviral Agents

Neither dolutegravir nor lamivudine were antagonistic to all tested anti-HIV agents.

Resistance

Cell Culture: Dolutegravir: Dolutegravir-resistant viruses were selected in cell culture starting from different wild-type HIV-1 strains and clades. Amino acid substitutions emerged in different passages; the substitution G118R emergence conferred decreased susceptibility to dolutegravir of 10-fold, while substitutions E92Q, S153F or Y, G193E, or R263K conferred decreased susceptibility to dolutegravir of up to 4-fold.

Lamivudine: HIV-1 resistance to lamivudine involves the development of a M184V or M184I amino acid change close to the active site of the viral RT. This variant arises both in cell culture and in HIV-1–infected patients treated with lamivudine-containing antiretroviral therapy. Substitutions M184V or I confer high-level resistance to lamivudine.

Clinical Subjects: At Week 48, none of the 6 subjects in the dolutegravir plus lamivudine group or the 4 subjects in the dolutegravir plus TDF/FTC group who met the protocol-defined confirmed virologic withdrawal criteria across the pooled GEMINI-1 and GEMINI-2 trials had emergent INSTI- or NRTI-resistance substitutions.

Cross-Resistance

Dolutegravir: The susceptibility of dolutegravir was tested against 60 INSTI-resistant site-directed mutant HIV-1 viruses (28 with single substitutions and 32 with 2 or more substitutions). The single INSTI-resistance substitutions T66K, I151L, and S153Y conferred a >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 >2-fold decrease in dolutegravir susceptibility (range: 2.5-fold to 21-fold from reference).

Lamivudine: Cross-resistance conferred by the M184V or I RT has been observed within the NRTI class of antiretroviral agents. The M184V or I substitution confers resistance to emtricitabine and to abacavir, which selects M184V or I plus additional RT substitutions K65R, L74V, and Y115F. Zidovudine maintains its antiretroviral activities against lamivudine-resistant HIV-1. Abacavir and tenofovir maintain antiretroviral activity against lamivudine-resistant HIV-1 harboring only the M184V or I substitution.

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/kg, and rats were administered doses of up to 50 mg/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 times higher than those in humans at the recommended dose. In rats, no increases in the incidence of drug-related neoplasms were observed at the highest dose tested, resulting in dolutegravir AUC exposures 17 times higher than those in humans at the recommended dose.

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

recommended dose.

Mutagenicity

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

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

Impairment of Fertility

Dolutegravir or lamivudine did not affect male or female fertility in rats at doses associated with exposures approximately 44 or 112 times, respectively, higher than the exposures in humans at the recommended dose.

14 CLINICAL STUDIES

14.1 Clinical Trials in Adult Subjects

The efficacy of dolutegravir and lamivudine tablets is supported by data from 2 randomized, double-blind, controlled trials (GEMINI-1 [NCT02831673] and GEMINI-2 [NCT02831764]) in HIV–1-infected adults with no antiretroviral treatment history.

GEMINI-1 and GEMINI-2 are identical 148-week, Phase 3, randomized, multicenter, parallel-group, non-inferiority trials. A total of 1,433 HIV-1–infected adults with no antiretroviral treatment history received treatment in the trials. Subjects were enrolled with a screening plasma HIV-1 RNA of 1,000 to ≤500,000 copies/mL and without evidence of major resistance-associated mutations or evidence of HBV infection. Subjects were randomized to receive a 2-drug regimen of TIVICAY 50 mg plus EPIVIR 300 mg administered once daily or TIVICAY 50 mg plus fixed-dose TRUVADA administered once daily. The primary efficacy endpoint for each GEMINI trial was the proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Week 48 (Snapshot algorithm) who were randomized and treated.

At baseline, in the pooled analysis, the median age of subjects was 33 years, 15% female, 68% white, 9% were CDC Stage 3 (AIDS), the median plasma HIV-1 RNA was 4.4 $\log_{10}$ copies/mL, 20% had HIV-1 RNA >100,000 copies/mL, the median $CD4^+$ cell count was 432 cells/mm^3, and 8% had $CD4^+$ cell count ≤200 cells/mm^3; these characteristics were similar between trials and treatment arms within each trial.

The primary endpoint and other outcomes (including outcomes by key baseline covariates) for the pooled GEMINI-1 and GEMINI-2 trials are shown in Table 11. The results of the pooled analysis are consistent with the results from the individual trials, for which the primary endpoint (difference in proportion <50 copies/mL plasma HIV-1 RNA at Week 48 based on the Snapshot algorithm for TIVICAY plus EPIVIR versus TIVICAY plus TRUVADA) was met. The adjusted difference was -2.6 (95% CI: -6.7; 1.5) for GEMINI-1 and -0.7 (95% CI: -4.3; 2.9) for GEMINI-2 with a prespecified non-inferiority margin of 10%. At Week 48, no subjects had any detectable treatment-emergent substitutions associated with resistance to dolutegravir or NRTIs.

Table 11. Pooled Virologic Outcomes of Randomized Treatment of HIV-1–Infected Adults with No Antiretroviral Treatment History in GEMINI-1 and GEMINI-2 Trials at Week 48 (Snapshot Algorithm)

Virologic Outcomes	GEMINI-1 and GEMINI-2 Pooled Data	
	TIVICAY plus EPIVIR (n = 716)	**TIVICAY plus TRUVADA (n = 717)**
HIV-1 RNA <50 copies/mL	91%	93%
Treatment Difference[a]	-1.7% (95% CI: -4.4%, 1.1%)	
Virologic nonresponse	3%	2%
Reasons		
Data in window not <50 copies/mL	1%	<1%
Discontinued for lack of efficacy	<1%	<1%
Discontinued for other reasons and ≥50 copies/mL	<1%	<1%
Change in ART	<1%	<1%
No virologic data at Week 48 window	6%	5%
Reasons		
Discontinued trial due to adverse event or death	1%	2%
Discontinued trial for other reasons	4%	3%
Missing data during window but on trial	<1%	0%
Proportion (%) of Subjects with HIV-1 RNA <50 copies/mL by Baseline Category		
	% (n/N)	**% (n/N)**
Plasma Viral Load (copies/mL)		
≤100,000	91% (526/576)	94% (531/564)
>100,000	92% (129/140)	90% (138/153)
$CD4^+$ (cells/mm^3)		
≤200	79% (50/63)	93% (51/55)
>200	93% (605/653)	93% (618/662)
Gender		
Male	92% (555/603)	94% (580/619)
Female	88% (100/113)	91% (89/98)
Race		
White	93% (447/480)	95% (471/497)
African-American/African Heritage	84% (83/99)	84% (64/76)
Asian	94% (67/71)	94% (68/72)
Other	88% (58/66)	92% (66/72)
Ethnicity		
Hispanic or Latino	90% (193/215)	93% (216/232)
Not Hispanic or Latino	92% (462/501)	93% (453/485)
Age (years)		
<50	92% (597/651)	94% (597/637)
≥50	89% (58/65)	90% (72/80)

[a] Based on Cochran–Mantel–Haenszel-stratified analysis adjusting for the following baseline stratification factors: plasma HIV-1 RNA (≤100,000 copies/mL versus >100,000 copies/mL) and $CD4^+$ cell count (≤200 cells/mm^3 versus >200 cells/mm^3). Pooled analysis also stratified by trial. Assessed using a non-inferiority margin of 10%.

Virologic outcomes by baseline $CD4^+$ (cells/mm^3) in GEMINI-1 and GEMINI-2 are shown in Table 12. In both trials, lower response rates (HIV-1 RNA <50 copies/mL) were observed in subjects with baseline

$CD4^+$ ≤200 cells/mm^3. These findings were seen irrespective of baseline plasma HIV-1 RNA.

Table 12. Virologic Outcomes by Baseline $CD4^+$ in GEMINI-1 and GEMINI-2 Trials at Week 48 (Snapshot Algorithm)

	GEMINI-1		GEMINI-2	
	TIVICAY plus EPIVIR (n = 356)	**TIVICAY plus TRUVADA (n = 358)**	**TIVICAY plus EPIVIR (n = 360)**	**TIVICAY plus TRUVADA (n = 359)**
Proportion (%) of Subjects with HIV-1 RNA <50 copies/mL				
Baseline $CD4^+$ (cells/mm^3)				
≤200	81% (25/31)[a]	90% (26/29)	78% (25/32)[a]	96% (25/26)
>200	91% (295/325)	93% (306/329)	95% (310/328)	94% (312/333)

[a] With the exception of one subject treated with TIVICAY plus EPIVIR in GEMINI-1 who was withdrawn due to confirmed loss of virologic response, none of the subjects treated with TIVICAY plus EPIVIR who did not have HIV-1 RNA <50 copies/mL at Week 48 (based on Snapshot Algorithm) were discontinued for treatment-related reasons by Week 48. A subject in GEMINI-1 whose last HIV-1 RNA was 64,366 copies/mL was lost to follow-up.

The adjusted mean change from baseline in $CD4^+$ cell count based on the pooled analysis at Week 48 was 224 cells/mm^3 for the group receiving TIVICAY plus EPIVIR and 217 cells/mm^3 for the group receiving TIVICAY plus TRUVADA.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each dolutegravir and lamivudine tablet contains 50 mg of dolutegravir as dolutegravir sodium and 300 mg lamivudine and is a gray colored capsule shaped biconvex film coated tablet debossed with "C" on one side and plain on other side.

Bottle of 30 tablets with non child-resistant closure.
Bottle of 90 tablets with non child-resistant closure.

Store below 30°C (86°F).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Emergence of Lamivudine-Resistant HBV in Hepatitis B Co-infection

Advise all patients with HIV-1 to be tested for the presence of HBV prior to or when initiating dolutegravir and lamivudine tablets. Advise patients co-infected with HIV-1 and HBV that emergence of HBV variants associated with resistance to lamivudine has been reported in HIV-1–infected subjects who have received lamivudine-containing antiretroviral regimens. Advise patients co-infected with HIV-1 and HBV who are being treated with dolutegravir and lamivudine tablets to discuss with their healthcare provider if additional treatment should be considered for appropriate treatment of chronic HBV *[see Warnings and Precautions (5.1)]*.

Severe Acute Exacerbations of Hepatitis in Patients with HBV Co-infection

Advise all patients with HIV-1 to be tested for the presence of HBV prior to or when initiating dolutegravir and lamivudine tablets. 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 healthcare provider *[see Warnings and Precautions (5.1)]*.

Hypersensitivity Reactions

Advise patients to immediately contact their healthcare provider if they develop a rash. Instruct patients to immediately stop taking dolutegravir and lamivudine tablets and seek medical attention if they develop a rash associated with any of the following symptoms, as it may be a sign of a more serious reaction such as severe hypersensitivity: fever; generally ill feeling; extreme tiredness; muscle or joint aches; blisters or peeling of the skin; oral blisters or lesions; eye inflammation; facial swelling; swelling of the eyes, lips, tongue, or mouth; breathing difficulty; and/or signs and symptoms of liver problems (e.g., yellowing of the skin or whites of the eyes; dark or tea-colored urine; pale-colored stools or bowel movements; nausea; vomiting; loss of appetite; or pain, aching, or sensitivity on the right side below the ribs). Advise patients that if hypersensitivity occurs, they will be closely monitored, laboratory tests will be ordered, and appropriate therapy will be initiated *[see Warnings and Precautions (5.2)]*.

Hepatotoxicity

Inform patients that hepatotoxicity has been reported with dolutegravir, a component of dolutegravir and lamivudine tablets *[see Warnings and Precautions (5.3), Adverse Reactions (6.1)]*. Inform patients that monitoring for hepatotoxicity during therapy with dolutegravir and lamivudine tablet is recommended.

Embryo-Fetal Toxicity

Advise individuals of childbearing potential to avoid use of dolutegravir and lamivudine tablets at the time of conception through the first trimester of pregnancy. Advise individuals of childbearing potential to contact their healthcare provider if they plan to become pregnant, become pregnant, or if pregnancy is suspected during treatment with dolutegravir and lamivudine tablets *[see Warnings and Precaution (5.4)]*.

Advise individuals of childbearing potential taking dolutegravir and lamivudine tablets to consistently use effective contraception *[see Use in Specific Populations (8.1, 8.3)]*.

Lactic Acidosis/Hepatomegaly with Steatosis

Inform patients that some HIV medicines, including dolutegravir and lamivudine tablets, can cause a rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly) *[see Warnings and Precautions (5.5)]*.

Drug Interactions

Dolutegravir and lamivudine tablets 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), Warnings and Precautions (5.6), Drug Interactions (7)]*.

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 dolutegravir and lamivudine tablets, is started *[see Warnings and Precautions (5.7)]*.

Pregnancy Registry

Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes in those exposed to dolutegravir and lamivudine tablets 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)]*.

Missed Dose

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

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