DOLUTEGRAVIR and LAMIVUDINE

20XXXXX

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 are 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)**

--- RECENT MAJOR CHANGES ---

Indications and Usage (1)	4/2024
Dosage and Administration (2.1, 2.2)	4/2024
Warnings and Precautions, Embryo Fetal Toxicity (5.4) Removed	4/2024

---INDICATIONS AND USAGE---

Dolutegravir and lamivudine tablets, 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 HIV-1 infection in adults and adolescents 12 years of age and older and weighing at least 25 kg with no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of dolutegravir and lamivudine tablets. (1)

---DOSAGE AND ADMINISTRATION ---

- Prior to or when initiating dolutegravir and lamivudine tablets, test patients for hepatitis B virus (HBV) infection. (2.1)
- 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 tablets are coadministered with carbamazepine or rifampin, take one tablet of dolutegravir and lamivudine tablets 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. Monitoring for hepatotoxicity is recommended. (5.3)
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. (5.4)
- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. (5.6)

---ADVERSE REACTIONS---

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

To report SUSPECTED ADVERSE REACTIONS, contact Hetero Labs Limited at 1-866-495-1995 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---DRUG INTERACTIONS---

- Dolutegravir and lamivudine 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. (4, 5.5, 7)

---USE IN SPECIFIC POPULATIONS---

- Renal impairment: Dolutegravir and lamivudine is not recommended in patients with creatinine clearance less than 30 mL/min. (8.6)
- Hepatic impairment: Dolutegravir and lamivudine is not recommended in patients with severe hepatic impairment (Child-Pugh Score C). (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 04/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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 tablets are 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 tablets are indicated as a complete regimen for the treatment of HIV-1 infection in adults and adolescents 12 years of age and older and weighing at least 25 kg with no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of dolutegravir and lamivudine tablets.

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)]*.

2.2 Recommended Dosage

Dolutegravir and lamivudine tablets are a fixed-dose combination product containing 50 mg of dolutegravir and 300 mg of lamivudine. The recommended dosage regimen of dolutegravir and lamivudine tablets in adults and adolescents 12 years of age and older and weighing at least 25 kg 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 are 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 tablet, should be taken.

2.4 Not Recommended in Patients with Renal Impairment

Because dolutegravir and lamivudine tablets are a fixed-dose tablet and cannot be dose adjusted, dolutegravir and lamivudine tablets are not recommended in patients with creatinine clearance less than 30 mL/min *[see Use in Specific Populations (8.6)]*.

2.5 Not Recommended in Patients with Severe Hepatic Impairment

Dolutegravir and lamivudine tablets are 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 white to off white colored, film coated, oval shaped bevel edged biconvex tablet debossed with 'D54' on one side and 'H' on another side. Each tablet contains 50 mg of dolutegravir and 300 mg of lamivudine USP.

4 CONTRAINDICATIONS

Dolutegravir and lamivudine tablets are 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.

Emergence of Lamivudine-Resistant HBV

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 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. Patients who are co-infected with HIV-1 and HBV who discontinue dolutegravir and lamivudine should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with dolutegravir and lamivudine. 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, 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 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 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 *[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 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). 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 to any patient with known risk factors for liver disease. Treatment with dolutegravir and lamivudine 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.

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

The coadministration of dolutegravir and lamivudine 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 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, review coadministered drugs during therapy with dolutegravir and lamivudine, and monitor for the adverse reactions associated with the coadministered drugs.

5.6 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including dolutegravir and lamivudine. 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 (5.4)]*
- Immune reconstitution syndrome *[see Warnings and Precautions (5.6)]*

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 with No Antiretroviral Treatment History

The safety assessment of dolutegravir and lamivudine 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 Week 144 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 received either 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 4% of subjects who received TIVICAY plus EPIVIR and 5% in subjects who received TIVICAY plus TRUVADA. The most common adverse events leading to discontinuation were psychiatric disorders: 2% of subjects who received TIVICAY plus EPIVIR and 1% in subjects who received TIVICAY plus TRUVADA.

Adverse reactions (all grades) observed in at least 2% of subjects in either treatment arm of the Week 144 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 144 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 144 Pooled Analysis)

Adverse Reaction	TIVICAY plus EPIVIR (n = 716)	TIVICAY plus TRUVADA (n = 717)
Headache	3%	4%
Nausea	2%	6%
Diarrhea	2%	3%
Insomnia	2%	3%
Fatigue[a]	2%	2%
Anxiety	2%	1%
Dizziness	1%	2%

[a] Fatigue: includes fatigue, asthenia, and malaise.

Adverse reactions of at least Grade 2 occurring in ≥1% of subjects treated with TIVICAY plus EPIVIR were headache, anxiety, suicidal ideation, and insomnia (all at 1%).

Less Common Adverse Reactions: The following adverse reactions (all grades) 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: 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.

Clinical Trials in Virologically Suppressed Adults

The safety of dolutegravir and lamivudine in virologically suppressed adults was based on Week 144 data from 740 subjects in a randomized, parallel-group, open-label, multicenter, non-inferiority controlled trial (TANGO). Subjects who were on a stable suppressive tenofovir alafenamide-based regimen (TBR) were randomized to receive dolutegravir and lamivudine once daily or continue with their TBR for up to 148 weeks; at Week 148, the subjects randomized to continue with their TBR were switched to dolutegravir and lamivudine once daily. All subjects are followed up to Week 200. Overall, the safety profile of dolutegravir and lamivudine in virologically suppressed adult subjects in the TANGO trial was similar to that of TIVICAY plus EPIVIR in subjects with no antiretroviral treatment history in the GEMINI trials *[see Clinical Studies (14.3)]*. Adverse reactions observed in at least 2% of subjects in the TANGO trial who were treated with dolutegravir and lamivudine were weight increased (3%) and insomnia (2%).

Laboratory Abnormalities

Selected laboratory abnormalities with a worsening grade from baseline and representing the worst-grade toxicity 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 144 Pooled Analyses) in GEMINI-1 and GEMINI-2 Trials

Laboratory Parameter Abnormality	TIVICAY plus EPIVIR (n = 716)	TIVICAY plus TRUVADA (n = 717)
Alanine aminotransferase (ALT)		
Grade 2 (2.5 to <5.0 x ULN)	4%	4%
Grade 3 to 4 (≥5.0 x ULN)	4%	3%
Aspartate aminotransferase (AST)		
Grade 2 (2.5 to <5.0 x ULN)	5%	5%
Grade 3 to 4 (≥5.0 x ULN)	3%	4%
Total bilirubin		
Grade 2 (1.6 to <2.6 x ULN)	3%	4%
Grade 3 to 4 (≥2.6 x ULN)	1%	1%
Creatine kinase		
Grade 2 (6.0 to <10 x ULN)	5%	5%
Grade 3 to 4 (≥10.0 x ULN)	8%	9%
Hyperglycemia (glucose)		
Grade 2 (126 to 250 mg/dL)	11%	8%
Grade 3 to 4 (>250 mg/dL)	1%	1%
Hypophosphatemia (phosphate)		
Grade 2 (1.4 to <2.0 mg/dL)	11%	12%
Grade 3 to 4 (<1.4 mg/dL)	1%	2%
Lipase		
Grade 2 (1.5 to <3.0 x ULN)	7%	8%
Grade 3 to 4 (≥3.0 x ULN)	3%	5%

ULN = Upper limit of normal.

Table 4. Mean Change from Baseline in Fasted Lipid Values (Week 144 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)	15	-2
HDL cholesterol (mg/dL)	7	4
LDL cholesterol (mg/dL)	7	-4
Triglycerides (mg/dL)	10	-9
Total cholesterol/HDL cholesterol ratio	-0.2	-0.4

HDL = High density lipoprotein; LDL = Low density lipoprotein.

[a] Subjects on lipid-lowering agents at baseline are excluded (TIVICAY plus EPIVIR, n = 30; TIVICAY plus TRUVADA, n = 23). The last available fasted, on-treatment lipid value prior to initiation of a lipid-lowering agent was carried forward in place of observed values after initiation of a lipid-lowering agent. A total of 51 and 28 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 144 weeks. A mean change from baseline of 0.144 mg/dL and 0.176 mg/dL was observed after 144 weeks of treatment with TIVICAY plus EPIVIR and TIVICAY plus TRUVADA, respectively. These changes are not considered to be clinically relevant.

Clinical Trial Experience in Adolescents

The safety of dolutegravir and lamivudine was evaluated in HIV-1-infected treatment-naïve subjects between the ages of 12 to less than 18 years and weighing at least 25 kg (N = 32) through Week 48, in an open label clinical trial, DANCE (Trial 205861). Overall, the observed safety profile in adolescent subjects was similar to those seen in adults *[see Use in Specific Populations (8.4), and Clinical Studies (14.4)]*.

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 (5.4)]*, 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, creatinine phosphokinase (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 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 (5.5), Clinical Pharmacology (12.3)]*.

7.2 Potential for Dolutegravir and Lamivudine to Affect Other Drugs

Dolutegravir, a component of dolutegravir and lamivudine, 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, dalfampridine, 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

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 *[see Drug Interactions (7.4), Clinical Pharmacology (12.3)]*. Coadministration of dolutegravir and lamivudine 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. 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 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: 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 *[see Contraindications (4)]*.
Anticonvulsant: Carbamazepine[a]	↓Dolutegravir	An additional dolutegravir 50 mg dose should be taken, separated by 12 hours from dolutegravir and lamivudine *[see Dosage and Administration (2.3)]*.
Anticonvulsants: Oxcarbazepine Phenytoin Phenobarbital	↓Dolutegravir	Avoid coadministration with dolutegravir and lamivudine because there are insufficient data to make dosing recommendations.
Antidiabetic: Metformin[a]	↑Metformin	Refer to the prescribing information for metformin for assessing the benefit and risk of concomitant use of dolutegravir and lamivudine and metformin.
Antimycobacterial: Rifampin[a]	↓Dolutegravir	An additional 50 mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir and lamivudine *[see Dosage and Administration (2.3)]*.
Herbal product: St. John's wort (*Hypericum perforatum*)	↓Dolutegravir	Avoid coadministration with dolutegravir and lamivudine 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 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 and supplements or multivitamins containing calcium or iron can be taken at the same time. Under fasting conditions, dolutegravir and lamivudine should be taken 2 hours before or 6 hours after taking supplements containing calcium or iron.
Potassium channel blocker: Dalfampridine	↑Dalfampridine	Elevated levels of dalfampridine increase the risk of seizures. The potential benefits of taking dalfampridine concurrently with dolutegravir and lamivudine should be considered against the risk of seizures in these patients.
Sorbitol[a]	↓Lamivudine	When possible, avoid use of sorbitol-containing medicines with dolutegravir and lamivudine.

↑ = 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 during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

Data from two, ongoing birth outcome surveillance studies in Botswana and Eswatini which together include over 14,000 individuals evaluated during pregnancy show similar prevalence of neural tube defects among infants born to individuals taking dolutegravir at the time of conception compared to those born to individuals taking non-dolutegravir-containing regimens at conception or infants born to HIV-negative individuals *(see Data)*.

There are insufficient human data on the use of dolutegravir and lamivudine during pregnancy to definitively assess a drug-associated risk for birth defects and miscarriage. However, available human data from the APR with the individual components of dolutegravir and lamivudine do not indicate an increased risk of birth defects *(see Data)*. 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 (including neural tube defects) 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:

Observational studies: The first interim analysis from an ongoing birth outcome surveillance study in Botswana identified an association between dolutegravir and an increased risk of neural tube defects when dolutegravir was administered at the time of conception and in early pregnancy. A subsequent analysis was conducted based on a larger cohort from the birth outcome surveillance study in Botswana and included over 9,460 individuals exposed to dolutegravir at conception, 23,664 individuals exposed to non-dolutegravir-containing regimens, and 170,723 HIV-negative pregnant individuals. The prevalence of neural tube defects in infants delivered to individuals taking dolutegravir at conception was 0.11% (95% CI: 0.05 to 0.19%). The observed prevalence rate did not differ significantly from that of infants delivered to individuals taking non-dolutegravir-containing regimens (0.11%, 95% CI: 0.07 to 0.16%), or to HIV-negative individuals (0.06%, 95% CI: 0.05 to 0.08%).

The Eswatini birth outcome surveillance study includes 9,743 individuals exposed to dolutegravir at conception, 1,838 individuals exposed to non-dolutegravir-containing regimens, and 32,259 HIV-negative pregnant individuals. The prevalence of neural tube defects in infants delivered to individuals taking dolutegravir at conception was 0.08% (95% CI: 0.04 to 0.16%). The observed prevalence rate did not differ significantly from that of infants delivered to individuals taking non-dolutegravir-containing regimens (0.22%, 95% CI: 0.06 to 0.56%) or to HIV-negative individuals (0.08%, 95% CI: 0.06 to 0.12%). The observed prevalence of neural tube defects in infants delivered to individuals taking non-dolutegravir-containing regimens had a wide confidence interval due to low sample size.

Limitations of these birth outcome surveillance studies include insufficient data to determine if baseline characteristics were balanced between the study groups or to assess other factors such as the use of folic acid during the preconception or first trimester periods.

Antiretroviral Pregnancy Registry:

Based on prospective reports to the APR, of 1,377 exposures to dolutegravir during pregnancy resulting in live births (including 874 exposed in the first trimester), the prevalence of defects in live births was 3.3% (95% CI: 2.2% to 4.7%) following first-trimester exposure to dolutegravir-containing regimens and 5.0% (95% CI: 3.2% to 7.3%) following second-/third-trimester exposure to dolutegravir-containing regimens. In the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP), the background birth defect rate was 2.7%.

Dolutegravir has been shown to cross the placenta. In a clinical trial in Uganda and South Africa in women during the last trimester of pregnancy receiving dolutegravir 50 mg once daily, the ratio of median dolutegravir concentration in fetal umbilical cord to that in maternal peripheral plasma was 1.21 (range 0.51 to 2.11) (n = 15).

Lamivudine: Based on prospective reports to the APR of exposures to lamivudine during pregnancy resulting in live births (including over 5,600 exposed in the first trimester and over 7,500 exposed in the second/third 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 3.1% (95% CI: 2.6% to 3.6%) following first trimester exposure to lamivudine-containing regimens and 2.9% (95% CI: 2.5% to 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

Dolutegravir and lamivudine are present in human milk. There is no information on the effects of dolutegravir and lamivudine or the components of dolutegravir and lamivudine on the breastfed infant or the effects of the drugs on milk production.

Potential risks of breastfeeding include: (1) HIV-1 transmission (in HIV-1-negative infants), (2) developing viral resistance (in HIV-1-positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults.

8.4 Pediatric Use

The safety and efficacy of dolutegravir and lamivudine for the treatment of HIV-1 infection have been established in adolescents 12 years of age and older and weighing at least 25 kg. Use of dolutegravir and lamivudine for this indication is supported by DANCE trial in treatment-naïve adolescents and evidence from adequate and well-controlled trials in adults, GEMINI-1, GEMINI-2 (treatment-naïve adults) and TANGO (virologically-suppressed adults) *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14)]*. Overall, the safety and efficacy data in adolescent subjects from the DANCE trial were comparable to those observed in adults, and there was no clinically significant difference in exposure for the components of dolutegravir and lamivudine *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.4)]*.

The safety and efficacy of dolutegravir and lamivudine have not been established in pediatric patients less than 12 years of age or weighing less than 25 kg.

8.5 Geriatric Use

Clinical trials of dolutegravir and 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 dolutegravir and lamivudine 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 is not recommended for patients with creatinine clearance <30 mL/min because dolutegravir and lamivudine 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 is required for patients with creatinine clearance <30 mL/min, then the individual components should be used.

Patients with a creatinine clearance between 30 and 49 mL/min receiving dolutegravir and lamivudine may experience a 1.6- to 3.3-fold higher lamivudine exposure (AUC) than patients with a creatinine clearance ≥50 mL/min. There are no safety data from randomized, controlled trials comparing dolutegravir and lamivudine to the individual components in patients with a creatinine clearance between 30 and 49 mL/min who received dose-adjusted lamivudine. In the original lamivudine registrational trials in combination with zidovudine, higher lamivudine exposures were associated with higher rates of hematologic toxicities (neutropenia and anemia), although discontinuations due to neutropenia or anemia each occurred in <1% of subjects. Patients with a sustained creatinine clearance between 30 and 49 mL/min who receive dolutegravir and lamivudine should be monitored for hematologic toxicities. If new or worsening neutropenia or anemia develop, dose adjustment of lamivudine, per lamivudine prescribing information, is recommended. If lamivudine dose adjustment is indicated, dolutegravir and lamivudine should be discontinued and the individual components should be used to construct the treatment regimen.

8.7 Hepatic Impairment

No dosage adjustment of dolutegravir and lamivudine 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 is not recommended for patients with severe hepatic impairment.

10 OVERDOSAGE

There is no known specific treatment for overdose with dolutegravir and lamivudine. 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 integrase strand transfer inhibitor (INSTI), and lamivudine (also known as 3TC), a nucleoside analogue reverse transcriptase inhibitor (NRTI).

Dolutegravir and lamivudine tablets are for oral administration. Each film-coated tablet contains the active ingredients 50 mg of dolutegravir (equivalent to 52.622 mg dolutegravir sodium) and 300 mg of lamivudine USP and the inactive ingredients magnesium stearate, mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, sodium stearyl fumarate. The tablet film-coating contains the inactive ingredients hypromellose, polyethylene glycol and titanium dioxide.

Dolutegravir

The chemical name of dolutegravir sodium is sodium (4*R*,12a*S*)-9-((2,4-difluorobenzyl)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 441.37 g/mol. It has the following structural formula:

PATIENT INFORMATION
Dolutegravir and Lamivudine
(DOE loo TEG ra vir and la MIV ue deen)
tablets

What is the most important information I should know about dolutegravir and lamivudine tablets?

If you have both human immunodeficiency virus-1 (HIV-1) infection and Hepatitis B virus (HBV) infection, dolutegravir and lamivudine tablets can cause serious side effects, including:

- **Resistant HBV. Your healthcare provider will test you for HBV infection before you start treatment with dolutegravir and lamivudine tablets. If you have HIV-1 and hepatitis B, the HBV can change (mutate) during your treatment with dolutegravir and lamivudine tablets and become harder to treat (resistant). It is not known if dolutegravir and lamivudine tablets are safe and effective in people who have HIV-1 and HBV infection.**
- **Worsening of HBV infection.** If you have HBV infection and take dolutegravir and lamivudine tablets, your HBV may get worse (flare-up) if you stop taking dolutegravir and lamivudine tablets. A "flare-up" is when your HBV infection suddenly returns in a worse way than before.
  - Do not run out of dolutegravir and lamivudine tablets. Refill your prescription or talk to your healthcare provider before your dolutegravir and lamivudine tablets are all gone.
  - **Do not stop dolutegravir and lamivudine tablets without first talking to your healthcare provider.**
  - If you stop taking dolutegravir and lamivudine tablets, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your liver function and monitor your HBV infection. It may be necessary to give you a medicine to treat hepatitis B. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking dolutegravir and lamivudine tablets.

For more information about side effects, see "What are the possible side effects of dolutegravir and lamivudine tablets?"

What is dolutegravir and lamivudine tablet?

Dolutegravir and lamivudine tablet is a prescription medicine that is used without other HIV-1 medicines to treat HIV-1 infection in adults and adolescents 12 years of age and older who weigh at least 55 pounds (25 kg):

- who have not received HIV-1 medicines in the past, or
- to replace their current HIV-1 medicines when their healthcare provider determines that they meet certain requirements.

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

It is not known if dolutegravir and lamivudine tablets are safe and effective in children less than 12 years of age or weighing less than 55 pounds (25 kg).

Do not take dolutegravir and lamivudine tablets if you:

- have ever had an allergic reaction to a medicine that contains dolutegravir or lamivudine. See the end of this Patient Information for a complete list of ingredients in dolutegravir and lamivudine tablets.
- take dofetilide. Taking dolutegravir and lamivudine tablets and dofetilide can cause side effects that may be serious or life-threatening.

Before you take dolutegravir and lamivudine tablets, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had liver problems, including hepatitis B or C infection.
- have kidney problems.
- are pregnant or plan to become pregnant. Talk to your healthcare provider about the benefits and risks of treatment with dolutegravir and lamivudine tablets during pregnancy.
- **Pregnancy Registry.** There is a pregnancy registry for those who take dolutegravir and lamivudine tablets 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. Dolutegravir and lamivudine passes to your baby in your breast milk. Talk with your healthcare provider about the following risks to your baby from breastfeeding during treatment with dolutegravir and lamivudine tablets:
  - the HIV-1 virus may pass to your baby if your baby does not have HIV-1 infection.
  - the HIV-1 virus may become harder to treat if your baby has HIV-1 infection.
  - your baby may get side effects from dolutegravir and lamivudine tablets.

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 dolutegravir and lamivudine tablets. Keep a list of your medicines and show it to 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 dolutegravir and lamivudine tablets.
- **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take dolutegravir and lamivudine tablets with other medicines.

How should I take dolutegravir and lamivudine tablets?

- **Take dolutegravir and lamivudine tablets 1 time a day exactly as your healthcare provider tells you.**
- Take dolutegravir and lamivudine tablets with or without food.
- Do not change your dose or stop taking dolutegravir and lamivudine tablets without talking with your healthcare provider.
- If you take antacids, laxatives, or other medicines that contain aluminum, magnesium, or buffered medicines, dolutegravir and lamivudine tablets should be taken at least 2 hours before or 6 hours after you take these medicines.
- If you need to take iron or calcium supplements, including multivitamins that contain iron or calcium, by mouth during treatment with dolutegravir and lamivudine tablets:
  - You may take these supplements at the same time that you take dolutegravir and lamivudine tablets with food.
  - If you do not take these supplements with dolutegravir and lamivudine tablets and food, take dolutegravir and lamivudine tablets at least 2 hours before or 6 hours after you take these supplements.
- Do not miss a dose of dolutegravir and lamivudine tablets. If you miss a dose of dolutegravir and lamivudine tablets, take it as soon as you remember. Do not take 2 doses at the same time or take more than your prescribed dose.
- Stay under the care of a healthcare provider during treatment with dolutegravir and lamivudine tablets.
- Do not run out of dolutegravir and lamivudine tablets. 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 dolutegravir and lamivudine, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of dolutegravir and lamivudine tablets?

Dolutegravir and lamivudine tablets can cause serious side effects, including:

- **See "What is the most important information I should know about dolutegravir and lamivudine tablets?"**
- **Allergic reactions. Call your healthcare provider right away**

Dimensions	400 x 600 mm (Book Fold: 40x60 mm)
Customer/Country	Hetero Labs Limited / Access
Spec	Printed on 40 gsm bible paper
Pantone Colours	Black
Pharmacodes	Front Side: XXXXX and Back Side: XXXXX

Note: Pharma Code Position will be change based on Machine folding feasibility. Version:00

if you develop a rash with dolutegravir and lamivudine tablets. Stop taking dolutegravir and lamivudine tablets and get medical help right away if you develop a rash with any of the following signs or symptoms:

- fever
- generally ill feeling
- tiredness
- muscle or joint aches
- blisters or sores in mouth
- blisters or peeling of the skin
- redness or swelling of the eye
- swelling of the mouth, face, lips, or tongue
- problems breathing

- **Liver problems. People with a history of hepatitis B or C virus may have an increased risk of developing new or worsening changes in certain liver tests during treatment with dolutegravir and lamivudine tablets. Liver problems, including liver failure, have also happened in people without a history of liver disease or other risk factors. Your healthcare provider may do blood tests to check your liver. Tell your healthcare provider right away if you get any of the following signs or symptoms of liver problems:**
  - your skin or the white part of your eyes turns yellow (jaundice)
  - dark or "tea-colored" urine
  - light-colored stools (bowel movements)
  - nausea or vomiting
  - loss of appetite
  - pain, aching, or tenderness on the right side of your stomach area
- **Too much lactic acid in your blood (lactic acidosis). Too much lactic acid is a serious medical emergency that can lead to death.**
  Tell 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 light-headed
  - have a fast or irregular heartbeat
- **Lactic acidosis can also lead to severe liver problems, which can lead to death. Your liver may become large (hepatomegaly) and you may develop fat in your liver (steatosis). Tell your healthcare provider right away if you get any of the signs or symptoms of liver problems which are listed above under "Liver problems". You may be more likely to get lactic acidosis or severe 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 dolutegravir and lamivudine tablets.**

The most common side effects of dolutegravir and lamivudine tablets include:

- headache
- nausea
- diarrhea
- trouble sleeping
- tiredness
- anxiety

These are not all the possible side effects of dolutegravir and lamivudine tablets.

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 dolutegravir and lamivudine tablets?

- Store dolutegravir and lamivudine tablets below 86°F (30°C).
- Dolutegravir and lamivudine tablets come in a child-resistant package.

Keep dolutegravir and lamivudine tablets and all medicines out of the reach of children.

General information about the safe and effective use of dolutegravir and lamivudine tablets.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use dolutegravir and lamivudine tablets for a condition for which it was not prescribed. Do not give dolutegravir and lamivudine tablets to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about dolutegravir and lamivudine tablets that is written for health professionals.

What are the ingredients in dolutegravir and lamivudine tablets?

Active ingredients: dolutegravir and lamivudine.

Inactive ingredients: magnesium stearate, mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, sodium stearyl fumarate.

The tablet film-coating contains: hypromellose, polyethylene glycol, titanium dioxide.

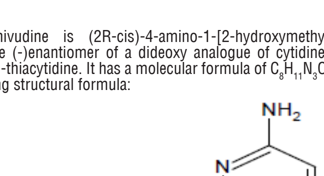
Manufactured by:

HETERO
HETERO LABS LIMITED
Unit-III,22-110, I.D.A., Jeedimetla,
Hyderabad – 500055, Telangana
INDIA

For more information, call Hetero Labs Limited at 1-866-495-1995.

This Patient Information has been approved by the U.S. Food and Drug Administration.

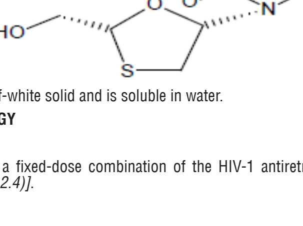
Revised: 04/2024



Dolutegravir sodium is an off-white or white to light yellow color powder.

Lamivudine

The chemical name of lamivudine is (2R-cis)-4-amino-1-[2-hydroxymethyl-1,3-oxathiolan-5-yl]-2(1H)-pyrimidinone. 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 229.26 g/mol. It has the following structural formula:



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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dolutegravir and lamivudine 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 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 is provided in Table 6.

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

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%)

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.

[a] Based on dolutegravir 50 mg once-daily dosage administered to antiretroviral treatment-naive adults.

[b] Based on lamivudine 300 mg once-daily dosage administered to healthy subjects.

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

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

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) were observed[c]	
Distribution		
Plasma protein binding[d]	Approximately 99%	36%
Blood-to-plasma ratio	0.44 to 0.54	1.1 to 1.2
Elimination		
$t_{1/2}$ (h)	Approximately 14	13 to 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]	–

T_{max} = Time to maximum concentration (C_{max}); $t_{1/2}$ = Elimination half-life; UGT = Uridine diphosphate glucuronosyl transferase; CYP = Cytochrome P450; OCT = Organic cation transporter.
[a] After administration of dolutegravir and lamivudine (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.

Specific Populations

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

Patients with Renal Impairment: The pharmacokinetics for the individual components of dolutegravir and lamivudine have been evaluated in patients with renal impairment. See the U.S. prescribing information for the individual components, TIVICAY (dolutegravir) and EPIVIR (lamivudine).

Patients with Hepatic Impairment: The pharmacokinetics for the individual components of dolutegravir and lamivudine have been evaluated in patients with varying degrees of hepatic impairment. See the U.S. prescribing information for the individual components, TIVICAY (dolutegravir) and EPIVIR (lamivudine).

Pediatric Subjects: In adolescents receiving dolutegravir and lamivudine, dolutegravir and lamivudine exposures were higher as compared to adults; however the differences in exposure were not considered clinically significant. Lamivudine and dolutegravir exposures were within the observed ranges at the recommended doses in adults and pediatrics receiving the individual components of dolutegravir and lamivudine (Table 8).

Table 8. Pharmacokinetic Parameters Following Dolutegravir and Lamivudine in Adolescent Subjects Aged 12 to Less than 18 Years Weighing at Least 25 kg (n = 32)

Age/weight	Dose	Pharmacokinetic Parameter Estimates Geometric Mean (CV%)		
		$AUC_{(0-24)}$ mcg·h/mL	C_{max} mcg/mL	C_{24} mcg/mL
12 to <18 years and ≥25 kg	Dolutegravir 50 mg once daily	78.2 (91.6)	6.71 (69.5)	1.46 (154)
12 to <18 years and ≥25 kg	Lamivudine 300 mg once daily	14.7 (112)	2.95 (82.8)	0.106 (312)

Pregnant women: Lamivudine: Lamivudine pharmacokinetics were studied in 36 pregnant women during 2 clinical trials conducted in South Africa. Lamivudine pharmacokinetics in pregnant women were similar to those seen in non-pregnant adults and in postpartum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples.

Drug Interaction Studies

Clinical Studies: No drug interaction studies were conducted with dolutegravir and lamivudine. The drug interaction studies described below were conducted with dolutegravir or lamivudine when used alone. Table 9 summarizes the effects of dolutegravir on the pharmacokinetics of coadministered drugs. Table 10 summarizes the effect of other drugs on the pharmacokinetics of dolutegravir when used alone and Table 11 summarizes the effect of sorbitol on the pharmacokinetics of lamivudine when used alone.

Table 9. 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}
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] Organic cation transporter (OCT)2 or multidrug and toxin extrusion (MATE)1 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 10. 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} 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) 2 h after dolutegravir	50 mg single dose	0.82 (0.69 to 0.98)	0.74 (0.62 to 0.90)	0.70 (0.58 to 0.85)
Calcium carbonate 1,200 mg simultaneous administration (fasted)	50 mg single dose	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)
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 11. 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%

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.
[a] Coadministered with a single dose of lamivudine 300 mg.

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 affect 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 = 0.23 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 144, none of the 12 subjects in the dolutegravir plus lamivudine group or the 9 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.

No subject who received dolutegravir and lamivudine in the TANGO trial met the protocol-defined confirmed virologic withdrawal criteria through Week 144. No emergent INSTI- or NRTI-resistance was detected by genotypic or phenotypic analyses of the last on-treatment isolate from one subject who received dolutegravir and lamivudine with HIV-1 RNA ≥400 copies/mL at withdrawal. No emergent resistance was detected by genotypic or phenotypic analyses of HIV-1 integrase, protease, or reverse transcriptase at the time of virologic failure in 3 subjects in the TBR arm who met the confirmed virologic withdrawal criteria.

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 Description of Clinical Trials

The efficacy and safety of dolutegravir and lamivudine were evaluated in the studies summarized in Table 12.

Table 12. Trials Conducted with Dolutegravir and Lamivudine in HIV-1–Infected Subjects

Population	Trial	Trial Arms	Timepoint (Week)
Adults: Treatment-naïve	GEMINI-1 [NCT02831673] GEMINI-2 [NCT02831764]	Pooled presentation TIVICAY plus EPIVIR (n = 716) TIVICAY plus TRUVADA (n = 717)	144
Virologically suppressed	TANGO [NCT03446573]	Dolutegravir and lamivudine (n = 369) TBR (n = 372)	144
Adolescents: Treatment-naïve (12 to less than 18 years and weighing at least 25 kg)	DANCE [NCT03682848]	Dolutegravir and lamivudine (n = 32)	48

TBR = Tenofovir alafenamide-based regimen.

14.2 Clinical Trial Results in HIV-1–Infected Adult Subjects 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, 69% 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.

Week 144 outcomes (including outcomes by key baseline covariates) for the pooled GEMINI-1 and GEMINI-2 trials are shown in Table 13. The results of the pooled analysis are consistent with the results from the individual trials, for which the secondary endpoint is the difference in proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Week 144 based on the Snapshot algorithm for TIVICAY plus EPIVIR versus TIVICAY plus TRUVADA. The proportions of subjects with plasma HIV-1 RNA <50 copies/mL in the group receiving TIVICAY plus EPIVIR versus TIVICAY plus TRUVADA were 79% and 83%, respectively, in GEMINI-1 and 84% in both treatment arms of GEMINI-2. The adjusted difference was -3.6 % (95% CI: -9.4%, 2.1) for GEMINI-1 and 0.0% (95% CI: -5.3%, 5.3%) for GEMINI-2. At Week 144, no subjects who met the protocol-defined confirmed virologic withdrawal criteria had any treatment-emergent substitutions associated with resistance to dolutegravir or NRTIs.

Table 13. Pooled Virologic Outcomes of Randomized Treatment of HIV-1–Infected Adults with No Antiretroviral Treatment History in GEMINI-1 and GEMINI-2 Trials at Weeks 48 and 144 (Snapshot Algorithm)

Virologic Outcomes	GEMINI-1 and GEMINI-2 Pooled Data[a]			
	Week 48		Week 144	
	TIVICAY plus EPIVIR (n = 716)	TIVICAY plus TRUVADA (n = 717)	TIVICAY plus EPIVIR (n = 716)	TIVICAY plus TRUVADA (n = 717)
HIV-1 RNA <50 copies/mL	91%	93%	82%	84%
Treatment Difference (95% CI)[b]	-1.7% (-4.4%, 1.1%)		-1.8% (-5.8%, 2.1%)	
Virologic nonresponse	3%	2%	3%	3%
Reasons				
Data in window ≥50 copies/mL	1%	<1%	<1%	<1%
Discontinued for lack of efficacy	<1%	<1%	1%	<1%
Discontinued for other reasons and ≥50 copies/mL	<1%	<1%	<1%	2%
Change in ART	<1%	<1%	<1%	<1%
No virologic data at Week 48 or Week 144 window	6%	5%	15%	14%
Reasons				
Discontinued trial due to adverse event or death	1%	2%	4%	4%
Discontinued trial for other reasons	4%	3%	11%	9%
Missing data during window but on trial	<1%	0	<1%	<1%
Proportion (%) of Subjects with HIV-1 RNA <50 copies/mL by Baseline Category				
	% (n/N)	% (n/N)	% (n/N)	% (n/N)
Plasma Viral Load (copies/mL) ≤100,000	91% (526/576)	94% (531/564)	81% (469/576)	84% (471/564)
>100,000	92% (129/140)	90% (138/153)	82% (115/140)	84% (128/153)
$CD4^+$ (cells/mm^3) ≤200	79% (50/63)	93% (51/55)	67% (42/63)	76% (42/55)
>200	93% (605/653)	93% (618/662)	83% (542/653)	84% (557/662)
Gender Male	92% (555/603)	94% (580/619)	83% (500/603)	84% (517/619)
Female	88% (100/113)	91% (89/98)	74% (84/113)	84% (82/98)
Race White	93% (447/480)	95% (471/497)	85% (409/484)	86% (429/499)
African-American/African Heritage	84% (83/99)	84% (64/76)	67% (60/90)	73% (52/71)
Asian	94% (67/71)	94% (68/72)	79% (56/71)	82% (59/72)
Other	88% (58/66)	92% (66/72)	83% (59/71)	79% (59/75)
Ethnicity Hispanic or Latino	90% (193/215)	93% (216/232)	83% (178/215)	85% (197/232)
Not Hispanic or Latino	92% (462/501)	93% (453/485)	81% (406/501)	83% (402/485)
Age (years) <50	92% (597/651)	94% (597/637)	81% (530/651)	84% (533/637)
≥50	89% (58/65)	90% (72/80)	83% (54/65)	83% (66/80)

ART = antiretroviral treatment.

[a] The results of the pooled analysis are similar to the individual trials, for which the primary endpoint (proportion of subjects with plasma HIV-1 RNA <50 copies/mL 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.

[b] 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. The other Snapshot outcomes (HIV-1 RNA ≥50 copies/mL and no virologic data in the visit window) were combined into a single category for the analysis.

The primary endpoint was assessed at Week 48 and the virologic success rate was 91% in the group receiving TIVICAY plus EPIVIR and 93% in the group receiving TIVICAY plus TRUVADA, with a treatment difference of -1.7% (95% CI: -4.4%, 1.1%) in the pooled data. The results of the pooled analysis are similar to the individual trials, for which the primary endpoint (proportion of subjects with plasma HIV-1 RNA <50 copies/mL 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.

The adjusted mean change from baseline in $CD4^+$ cell count based on the pooled analysis at Week 144 was 302 cells/mm^3 for the group receiving TIVICAY plus EPIVIR and 300 cells/mm^3 for the group receiving TIVICAY plus TRUVADA.

14.3 Clinical Trial Results in HIV-1–Infected Virologically Suppressed Adult Subjects Who Switched to Dolutegravir and Lamivudine

The efficacy of dolutegravir and lamivudine in HIV-1–infected, antiretroviral treatment-experienced, virologically suppressed subjects is supported by data from a 200-week, Phase 3, randomized, open-label, multicenter, parallel-group, non-inferiority controlled trial (TANGO). A total of 741 adult HIV-1–infected subjects who were on a stable suppressive TBR received treatment in the trial. Subjects were randomized in a 1:1 ratio to receive dolutegravir and lamivudine once daily or continue with their TBR for up to 148 weeks; at Week 148, the subjects randomized to continue with their TBR were switched to dolutegravir and lamivudine once daily. All subjects are followed up to Week 200. Randomization was stratified by baseline third-agent class (protease inhibitor [PI], INSTI, or non-nucleoside reverse transcriptase inhibitor [NNRTI]). The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL (virologic non-response) at Week 48 (Snapshot algorithm adjusting for randomization stratification factor).

At baseline, the median age of subjects was 39 years, 8% were female, 21% non-white, 5% were CDC Class C (AIDS), and 98% of subjects had baseline $CD4^+$ cell count ≥200 cells/mm^3; these characteristics were similar between treatment arms. Subjects receiving dolutegravir and lamivudine and a TBR had been on an antiretroviral regimen for a median of 2.8 and 2.9 years, respectively, prior to Day 1. Most subjects were on an integrase inhibitor-based TBR (78% and 80% of subjects who received dolutegravir and lamivudine and a TBR, respectively).

In the primary 48 week analysis, <1% of subjects in both arms experienced virologic failure (HIV-1 RNA ≥50 copies/mL) at Week 48 based on the Snapshot algorithm. Based on a 4% non-inferiority margin, dolutegravir and lamivudine was non-inferior to TBR in the primary analysis (proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL), as the upper bound of the 95% CI for the adjusted treatment difference (-1.2%, 0.7%) was less than 4%.

At Week 144, the proportion of subjects with HIV-1 RNA ≥50 copies/mL (Snapshot) was 0.3% and 1.3% in the dolutegravir and lamivudine and TBR treatment arms, respectively (Table 14).

Table 14. Virologic Outcomes of Randomized Treatment in TANGO Trial at Weeks 48 and 144 in Virologically Suppressed Subjects Who Switched to Dolutegravir and Lamivudine

Virologic Outcomes	Week 48[a]		Week 144	
	Dolutegravir and lamivudine (n = 369)	TBR (n = 372)	Dolutegravir and lamivudine (n = 369)	TBR (n = 372)
Virologic nonresponse (≥50 copies/mL)	<1%	1%	<1%	1%
Treatment Difference (95% CI)[b]	-0.3% (-1.2%, 0.7%)		-1.1% (-2.4%, 0.2%)	
HIV-1 RNA <50 copies/mL[c]	93%	93%	86%	82%
Reasons for virologic nonresponse				
Data in window ≥50 copies/mL	0	0	0	0
Discontinued for lack of efficacy	0	1%	0	1%
Discontinued for other reasons and ≥50 copies/mL	<1%	0	<1%	0
Change in ART	0	0	0	<1%
Reasons for no virologic data at Week 48 or Week 144 window	7%	6%	14%	17%
Discontinued trial due to adverse event or death	3%	<1%	6%	2%
Discontinued trial for other reasons	3%	6%	7%	15%
Missing data during window but on trial[d]	0	<1%	1%	0

ART = antiretroviral treatment; TBR = Tenofovir alafenamide-based regimen.
[a] Based on a 4% non-inferiority margin, dolutegravir and lamivudine is non-inferior to TBR at Week 48 in the primary analysis (proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL) because the upper bound of the 95% CI for the adjusted treatment difference is less than 4%.
[b] Based on Cochran–Mantel–Haenszel-stratified analysis adjusting for baseline third-agent class (PI, INSTI, or NNRTI). The other Snapshot outcomes (HIV-1 RNA <50 copies/mL and no virologic data in the visit window) were combined into a single category for the analysis, and subjects who had no virologic data at Week 144 were assumed to have virologic response (<50 copies/mL).
[c] At Week 144 in the secondary analysis (proportion of subjects achieving plasma HIV-1 RNA <50 copies/mL), the adjusted treatment difference was 4.2% (95% CI: -1.1%, 9.5%).
[d] Five (5) and 2 subjects in the dolutegravir and lamivudine and TBR arms, respectively, had no Week 144 Snapshot data due to Coronavirus Disease 2019 (COVID-19).

In TANGO, treatment outcomes between treatment arms were similar across the stratification factor, baseline third-agent class (PI, INSTI, or NNRTI), and across subgroups by age, sex, race, baseline $CD4^+$ cell count, CDC HIV disease stage, and countries. The median change from baseline in $CD4^+$ T-cell count at Week 144 was 36.0 cells/mm^3 in the dolutegravir and lamivudine arm and 35.0 cells/mm^3 in the TBR arm.

14.4 Clinical Trial Results in Adolescent Subjects

The 48 week efficacy of dolutegravir and lamivudine was evaluated in an open-label multicenter trial (DANCE) in 30 evaluable treatment-naïve HIV-1–infected adolescents aged 12 to less than 18 years and weighing at least 25 kg. Eighty-seven percent (26/30) of subjects achieved HIV-1 RNA <50 copies/mL at Week 48, and the mean increase from baseline in CD4+ cell count was 234 cells/mm^3 at Week 48 *[see Adverse Reactions (6.1), Use in Specific Populations (8.4) and Clinical Pharmacology (12.3)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each dolutegravir and lamivudine tablet contains 50 mg of dolutegravir as dolutegravir sodium and 300 mg lamivudine USP and is a white to off white colored, film coated, oval shaped bevel edged biconvex tablet debossed with 'D54' on one side and 'H' on another side.

Bottle of 30 tablets with child-resistant closure	NDC 68554-3185-0
Bottle of 90 tablets with child-resistant closure	NDC 68554-3185-1

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 tablets is recommended.

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 (5.4)]*.

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 (5.5), 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

Inform individuals with HIV-1 infection that the potential risks of breastfeeding include: (1) HIV-1 transmission (in HIV-1–negative infants), (2) developing viral resistance (in HIV-1–positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults *[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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