Brand Name	Dovato
Active Ingredient(s)	dolutegravir, lamivudine
Strength	50-300 mg
Dosage Form	tablet
Inactive Ingredients	hypromellose, macrogol/PEG, magnesium stearate, mannitol (E421), microcrystalline cellulose, povidone (K29/32), sodium starch glycolate, sodium stearyl fumarate, and titanium dioxide
NDC	49702-246-13
DIN	02491753
Canadian Distributor	ViiV Healthcare ULC 1400 75 Rue Queen, Montreal, Quebec, Canada H3C 2N6
NDA Number	NDA211994
US Distributor (NDA Holder)	ViiV Healthcare 5 Moore Drive, Research Triangle Park, North Carolina USA 27709
Manufacturer (Final Packager)	GlaxoSmithKline Durham, NC 27701
API Manufacturer	Not available
Relationship to Sponsor	The Sponsor may have or have had agreements with the U.S. manufacturer for rebates. The Sponsor has no relationship with the foreign manufacturer.

Current FDA-approved Package Insert

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

DOVATO (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 DOVATO. Emergence of lamivudine-resistant HBV variants associated with lamivudine-containing antiretroviral regimens has been reported. If DOVATO is used in patients co-infected with HIV-1 and HBV, additional treatment should be considered for appropriate treatment of chronic HBV; otherwise, consider an alternative regimen.

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

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

DOVATO, 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 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 per mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of DOVATO. (1)

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

- Prior to or when initiating DOVATO, test patients for hepatitis B virus (HBV) infection. (2.1)
- Pregnancy testing: Pregnancy testing is recommended before initiation of DOVATO in individuals of childbearing potential. (2.1, 5.4, 8.1, 8.3)
- One tablet taken orally once daily with or without food. (2.2)
- The dolutegravir dose (50 mg) in DOVATO is insufficient when coadministered with carbamazepine or rifampin. If DOVATO is coadministered with carbamazepine or rifampin, take one tablet of DOVATO once daily, followed by an additional dolutegravir 50-mg tablet, approximately 12 hours from the dose of DOVATO. (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 DOVATO 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 DOVATO. Monitoring for hepatotoxicity is recommended. (5.3)
- Embryo-fetal toxicity may occur when used at the time of conception and in early pregnancy. Assess the risks and benefits of DOVATO and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester due to the risk of neural tube defects. Individuals of childbearing potential should be counseled on the consistent use of effective contraception. (2.1, 5.4, 8.1, 8.3)
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. (5.5)
- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. (5.7)

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

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

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

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

- DOVATO 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 DOVATO. (4, 5.6, 7)

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

- Pregnancy: Assess the risks and benefits of DOVATO and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester or if pregnancy is confirmed in the first trimester due to the risk of neural tube defects. (2.1, 5.4, 8.1, 8.3)
- Lactation: Breastfeeding is not recommended due to the potential for HIV-1 transmission. (8.2)
- Females and males of reproductive potential: Pregnancy testing is recommended in individuals of childbearing potential. Patients should be counseled on the consistent use of effective contraception. (8.1, 8.3)
- Renal impairment: DOVATO is not recommended in patients with creatinine clearance less than 30 mL/min. (8.6)
- Hepatic impairment: DOVATO 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: 1/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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 DOVATO. Emergence of lamivudine-resistant HBV variants associated with lamivudine-containing antiretroviral regimens has been reported. If DOVATO is used in patients co-infected with HIV-1 and HBV, additional treatment should be considered for appropriate treatment of chronic HBV; otherwise, consider an alternative regimen.

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

1 INDICATIONS AND USAGE

DOVATO is indicated as a complete regimen for the treatment of HIV-1 infection in adults 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 per mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of DOVATO.

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to or When Initiating Treatment with DOVATO

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

Pregnancy testing is recommended before initiation of DOVATO in individuals of childbearing potential *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)]*.

2.2 Recommended Dosage

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

2.3 Recommended Dosage with Certain Coadministered Drugs

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

Table 1. Dosing Recommendations for DOVATO with Coadministered Drugs

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

2.4 Not Recommended in Patients with Renal Impairment

Because DOVATO is a fixed-dose tablet and cannot be dose adjusted, DOVATO is not recommended in patients with creatinine clearance less than 30 mL per minute *[see Use in Specific Populations (8.6)]*.

2.5 Not Recommended in Patients with Severe Hepatic Impairment

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

3 DOSAGE FORMS AND STRENGTHS

DOVATO tablets are oval, biconvex, white, film-coated tablets, debossed with “SV 137” on one face. Each tablet contains 50 mg of dolutegravir and 300 mg of lamivudine.

4 CONTRAINDICATIONS

DOVATO is contraindicated in patients:

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

5 WARNINGS AND PRECAUTIONS

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

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

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 DOVATO 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 DOVATO. Patients who are co-infected with HIV-1 and HBV who discontinue DOVATO should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with DOVATO. 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 DOVATO, 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 DOVATO 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 DOVATO 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 DOVATO *[see Adverse Reactions (6.1)]*. In some cases, the elevations in transaminases were consistent with immune reconstitution syndrome or HBV reactivation particularly in the setting where anti-hepatitis therapy was withdrawn. Cases of hepatic toxicity, including elevated serum liver biochemistries, hepatitis, and acute liver failure, have also been reported in patients receiving a dolutegravir-containing regimen who had no pre-existing hepatic disease or other identifiable risk factors. Drug-induced liver injury leading to liver transplant has been reported with TRIUMEQ (abacavir, dolutegravir, and lamivudine). Monitoring for hepatotoxicity is recommended.

5.4 Embryo-Fetal Toxicity

An ongoing observational study showed 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. As there is limited understanding of the association of reported types of neural tube defects with dolutegravir use, inform individuals of childbearing potential, including those actively trying to become pregnant, about the potential increased risk of neural tube defects with DOVATO. Assess the risks and benefits of DOVATO and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester *[see Use in Specific Populations (8.1, 8.3)]*.

Pregnancy testing is recommended before initiation of DOVATO in individuals of childbearing potential *[see Dosage and Administration (2.1)]*.

Individuals of childbearing potential should be counseled on the consistent use of effective contraception *[see Use in Specific Populations (8.1, 8.3)]*.

DOVATO may be considered during the second and third trimesters of pregnancy if the expected benefit justifies the potential risk to the pregnant woman and the fetus.

5.5 Lactic Acidosis and Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues, including lamivudine (a component of DOVATO). 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 DOVATO to any patient with known risk factors for liver disease. Treatment with DOVATO should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or

pronounced hepatotoxicity, which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations.

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

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

5.7 Immune Reconstitution Syndrome

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

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

Clinical Trials in Adults with No Antiretroviral Treatment History

The safety assessment of DOVATO 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 DOVATO 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 DOVATO 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 DOVATO once daily. All subjects are followed up to Week 200. Overall, the safety profile of DOVATO 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 DOVATO 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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing experience in patients receiving a dolutegravir- or lamivudine-containing regimen. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole

Redistribution/accumulation of body fat.

Endocrine and Metabolic

Hyperglycemia.

General

Weakness.

Hemic and Lymphatic

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

Hepatic and Pancreatic

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

Hepatobiliary Disorders

Acute liver failure, hepatotoxicity.

Hypersensitivity

Anaphylaxis, urticaria.

Investigations

Weight increased.

Musculoskeletal

Arthralgia, 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

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

7.2 Potential for DOVATO to Affect Other Drugs

Dolutegravir, a component of DOVATO, 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 DOVATO

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 DOVATO *[see Drug Interactions (7.4), Clinical Pharmacology (12.3)]*. Coadministration of DOVATO 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 DOVATO. 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 DOVATO 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 DOVATO: 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 DOVATO *[see Contraindications (4)]*.
Anticonvulsant: Carbamazepine[a]	↓Dolutegravir	An additional dolutegravir 50-mg dose should be taken, separated by 12 hours from DOVATO *[see Dosage and Administration (2.3)]*.

Anticonvulsants: Oxcarbazepine Phenytoin Phenobarbital	↓Dolutegravir	Avoid coadministration with DOVATO 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 DOVATO and metformin.
Antimycobacterial: Rifampin[a]	↓Dolutegravir	An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from DOVATO *[see Dosage and Administration (2.3)]*.
Herbal product: St. John's wort (*Hypericum perforatum*)	↓Dolutegravir	Avoid coadministration with DOVATO 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 DOVATO 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, DOVATO and supplements or multivitamins containing calcium or iron can be taken at the same time. Under fasting conditions, DOVATO 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 DOVATO should be considered against the risk of seizures in these patients.
Sorbitol[a]	↓Lamivudine	When possible, avoid use of sorbitol-containing medicines with DOVATO.

↑ = 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 DOVATO 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 an ongoing birth outcome surveillance study have identified an increased risk of neural tube defects when dolutegravir, a component of DOVATO, is administered at the time of conception. As defects related to closure of the neural tube occur from conception through the first 6 weeks of gestation, embryos exposed to dolutegravir from the time of conception through the first 6 weeks of gestation are at potential risk.

Advise individuals of childbearing potential, including those actively trying to become pregnant, of the potential risk of neural tube defects with use of DOVATO. Assess the risks and benefits of DOVATO and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester. A benefit-risk assessment should consider factors such as feasibility of switching to another antiretroviral regimen, tolerability, ability to maintain viral suppression, and risk of HIV-1 transmission to the infant against the risk of neural tube defects associated with in utero dolutegravir exposure during critical periods of fetal development. *[See Warnings and Precautions (5.4)]*.

There are insufficient human data on the use of DOVATO during pregnancy to definitively assess a drug-associated risk for birth defects and miscarriage. The background risk for major birth defects for the indicated population is unknown. In the U.S. general population, the

estimated background rate for major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with dolutegravir at systemic exposures (AUC) less than (rabbits) and 50 times (rats) the exposure in humans at the recommended human dose (RHD) *(see Data)*. Oral administration of lamivudine to pregnant rabbits during organogenesis resulted in embryolethality at systemic exposure (AUC) similar to the RHD; however, no adverse developmental effects were observed with oral administration of lamivudine to pregnant rats during organogenesis at plasma concentrations (C_{max}) 35 times the RHD *(see Data)*.

Data

Human Data: Dolutegravir: In a birth outcome surveillance study in Botswana, there were 7 cases of neural tube defects reported out of 3,591 deliveries (0.19%) to women who were exposed to dolutegravir-containing regimens at the time of conception. In comparison, the neural tube defect prevalence rates were 0.11% (21/19,361 deliveries) in the non-dolutegravir arm and 0.07% (87/119,630 deliveries) in the HIV-uninfected arm. Seven cases reported with dolutegravir included 3 cases of myelomeningocele, 2 cases of encephalocele, and one case each of anencephaly and iniencephaly. In the same study, no increased risk of neural tube defects was identified in women who started dolutegravir during pregnancy. Two infants out of 4,448 (0.04%) deliveries to women who started dolutegravir during pregnancy had a neural tube defect, compared with 5 infants out of 6,748 (0.07%) deliveries to women who started non-dolutegravir-containing regimens during pregnancy. The reported risks of neural tube defects by treatment groups were based on interim analyses from the ongoing surveillance study in Botswana. It is unknown if baseline characteristics were balanced between the study treatment groups. The observed trends of association could change as data accumulate.

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

Data from the birth outcome surveillance study described above and postmarketing sources with more than 1,000 pregnancy outcomes from second and third trimester exposure in pregnant women indicate no evidence of increased risk of adverse birth outcomes.

Based on prospective reports to the APR of 842 exposures to dolutegravir during pregnancy resulting in live births (including 512 exposed in the first trimester), the prevalence of defects in live births was 3.3% (95% CI: 1.9% to 5.3%) following first-trimester exposure to dolutegravir-containing regimens and 4.8% (95% CI: 2.8% to 7.8%) 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 0.51-2.11) (n = 15).

Lamivudine: Based on prospective reports to the APR of exposures to lamivudine during pregnancy resulting in live births (including over 5,300 exposed in the first trimester and over 7,400 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: 2.7% 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

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

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

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

8.3 Females and Males of Reproductive Potential

In individuals of childbearing potential currently on DOVATO who are actively trying to become pregnant or if pregnancy is confirmed in the first trimester, assess the risks and benefits of continuing DOVATO and discuss with the patient if an alternative treatment should be considered *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1)]*.

Pregnancy Testing

Pregnancy testing is recommended in individuals of childbearing potential before initiation of DOVATO *[see Dosage and Administration (2.1)]*.

Contraception

Individuals of childbearing potential who are taking DOVATO should be counseled on the consistent use of effective contraception.

8.4 Pediatric Use

The safety and efficacy of DOVATO have not been established in pediatric patients.

8.5 Geriatric Use

Clinical trials of DOVATO 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 DOVATO 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

DOVATO is not recommended for patients with creatinine clearance <30 mL/min because DOVATO is a fixed-dose combination and the dosage of the individual components cannot be adjusted. If a dose reduction of lamivudine, a component of DOVATO, 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 DOVATO 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 DOVATO 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 DOVATO 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, DOVATO should be discontinued and the individual components should be used to construct the treatment regimen.

8.7 Hepatic Impairment

No dosage adjustment of DOVATO 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, DOVATO is not recommended for patients with severe hepatic impairment.

10 OVERDOSAGE

There is no known specific treatment for overdose with DOVATO. 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.

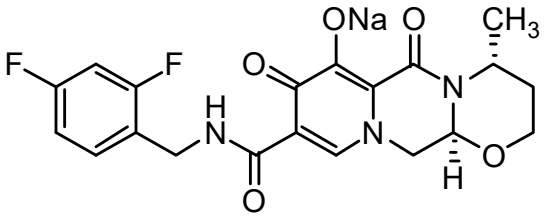
11 DESCRIPTION

DOVATO 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).

DOVATO tablets are for oral administration. Each film-coated tablet contains the active ingredients 50 mg of dolutegravir (equivalent to 52.6 mg dolutegravir sodium) and 300 mg of lamivudine and the inactive ingredients magnesium stearate, mannitol, microcrystalline cellulose, povidone K29/32, sodium starch glycolate, sodium stearyl fumarate. The tablet film-coating contains the inactive ingredients hypromellose, polyethylene glycol, titanium dioxide.

Dolutegravir

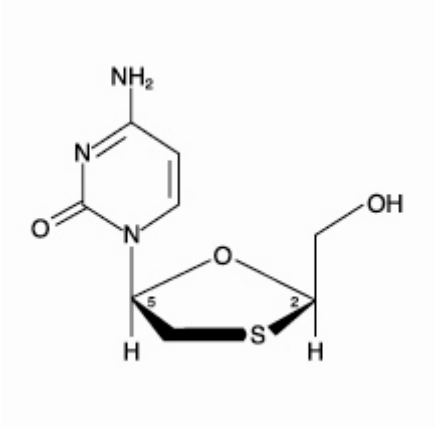
The chemical name of dolutegravir sodium is sodium (4*R*,12a*S*)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazin-7-olate. The empirical formula is $C_{20}H_{18}F_2N_3NaO_5$ and the molecular weight is 441.36 g/mol.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



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

Lamivudine

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



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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

DOVATO 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 DOVATO 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 DOVATO are provided in Table 6.

Table 6. Multiple-Dose Pharmacokinetic Parameters of the Components of DOVATO

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 DOVATO are provided in Table 7.

Table 7. Pharmacokinetic Properties of the Components of DOVATO

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 DOVATO) were observed[c]	
Distribution		
Plasma protein binding[d]	Approximately 99%	36%
Blood-to-plasma ratio	0.44 - 0.54	1.1 - 1.2
Elimination		
$t_{1/2}$ (h)	Approximately 14	13 - 19
Metabolism		
Metabolic pathways	UGT1A1 (primary) CYP3A (minor)	Not significantly metabolized
Excretion		
Major route of elimination	Metabolism	Renal, by OCT system
Urine (unchanged)	31% (<1%)[e]	Approximately 70%[f]
Feces (unchanged)	64% (53%)[e]	–

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 DOVATO (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 DOVATO 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 DOVATO 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 DOVATO 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).

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 DOVATO. The drug interaction studies described below were conducted with dolutegravir or lamivudine when used alone. Table 8 summarizes the effects of dolutegravir on the pharmacokinetics of coadministered drugs. Table 9 summarizes the effect of other drugs on the pharmacokinetics of dolutegravir when used alone and Table 10 summarizes the effect of sorbitol on the pharmacokinetics of lamivudine when used alone.

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

Coadministered Drug(s) and Dose(s)	**Dose of Dolutegravir**	**Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug with/without Dolutegravir No Effect = 1.00**		
		C_{max}	**AUC**	**C_{tau} or C_{24}**

Daclatasvir 60 mg once daily	50 mg once daily	1.03 (0.84 to 1.25)	0.98 (0.83 to 1.15)	1.06 (0.88 to 1.29)
Ethinyl estradiol 0.035 mg	50 mg twice daily	0.99 (0.91 to 1.08)	1.03 (0.96 to 1.11)	1.02 (0.93 to 1.11)
Grazoprevir 200 mg once daily	50 mg single dose	0.64 (0.44, 0.93)	0.81 (0.67, 0.97)	0.86 (0.79, 0.93)
Metformin[a] 500 mg twice daily	50 mg once daily	1.66 (1.53 to 1.81)	1.79 (1.65 to 1.93)	_
Metformin[a] 500 mg twice daily	50 mg twice daily	2.11 (1.91 to 2.33)	2.45 (2.25 to 2.66)	_
Methadone 16 to 150 mg	50 mg twice daily	1.00 (0. 94 to 1.06)	0.98 (0.91 to 1.06)	0.99 (0.91 to 1.07)
Midazolam 3 mg	25 mg once daily	_	0.95 (0.79 to 1.15)	_
Norelgestromin[b] 0.25 mg	50 mg twice daily	0.89 (0.82 to 0.97)	0.98 (0.91 to 1.04)	0.93 (0.85 to 1.03)
Sofosbuvir 400 mg once daily Metabolite (GS-331007)	50 mg once daily	0.88 (0.80, 0.98) 1.01 (0.93, 1.10)	0.92 (0.85, 0.99) 0.99 (0.97, 1.01)	NA 0.99 (0.97, 1.01)
Velpatasvir 100 mg once daily	50 mg once daily	0.94 (0.86, 1.02)	0.91 (0.84, 0.98)	0.88 (0.82, 0.94)

[a] OCT2 or 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 9. Effect of Coadministered Drugs on the Pharmacokinetics of Dolutegravir

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

Antacid (MAALOX) 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)
Daclatasvir 60 mg once daily	50 mg once daily	1.29 (1.07 to 1.57)	1.33 (1.11 to 1.59)	1.45 (1.25 to 1.68)
Ferrous fumarate 324 mg simultaneous administration (fasted)	50-mg single dose	0.43 (0.35 to 0.52)	0.46 (0.38 to 0.56)	0.44 (0.36 to 0.54)
Ferrous fumarate 324 mg simultaneous administration (fed)	50-mg single dose	1.03 (0.84 to 1.26)	0.98 (0.81 to 1.20)	1.00 (0.81 to 1.23)
Ferrous fumarate 324 mg 2 h after dolutegravir	50-mg single dose	0.99 (0.81 to 1.21)	0.95 (0.77 to 1.15)	0.92 (0.74 to 1.13)
Multivitamin (One-A-Day) simultaneous administration	50-mg single dose	0.65 (0.54 to 0.77)	0.67 (0.55 to 0.81)	0.68 (0.56 to 0.82)
Omeprazole 40 mg once daily	50-mg single dose	0.92 (0.75 to 1.11)	0.97 (0.78 to 1.20)	0.95 (0.75 to 1.21)
Prednisone 60 mg once daily with taper	50 mg once daily	1.06 (0.99 to 1.14)	1.11 (1.03 to 1.20)	1.17 (1.06 to 1.28)
Rifampin[a] 600 mg once daily	50 mg twice daily	0.57 (0.49 to 0.65)	0.46 (0.38 to 0.55)	0.28 (0.23 to 0.34)
Rifampin[b] 600 mg once daily	50 mg twice daily	1.18 (1.03 to 1.37)	1.33 (1.15 to 1.53)	1.22 (1.01 to 1.48)
Rifabutin 300 mg once daily	50 mg once daily	1.16 (0.98 to 1.37)	0.95 (0.82 to 1.10)	0.70 (0.57 to 0.87)

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

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

Table 10. Effect of Sorbitol on the Pharmacokinetics of Lamivudine

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

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 DOVATO 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 DOVATO 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 of DOVATO is supported by data from 2 randomized, double-blind, controlled trials (GEMINI-1 [NCT02831673] and GEMINI-2 [NCT02831764]) in HIV-1–infected adults with no antiretroviral treatment history, and data from a randomized, open-label, controlled trial (TANGO [NCT03446573]) in virologically suppressed HIV-1–infected adults.

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

	GEMINI-1 and GEMINI-2 Pooled Data[a]			
	Week 48		**Week 144**	
Virologic Outcomes	**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)

[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 DOVATO

The efficacy of DOVATO 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 DOVATO 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 DOVATO 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 DOVATO 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 DOVATO 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, DOVATO 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 DOVATO and TBR treatment arms, respectively (Table 12).

Table 12 Virologic Outcomes of Randomized Treatment in TANGO Trial at Weeks 48 and 144 in Virologically Suppressed Subjects Who Switched to DOVATO

	Week 48[a]		Week 144	
Virologic Outcomes	**DOVATO (n = 369)**	**TBR (n = 372)**	**DOVATO (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

TBR = Tenofovir alafenamide-based regimen.

[a] Based on a 4% non-inferiority margin, DOVATO 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 DOVATO 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 DOVATO arm and 35.0 cells/mm^3 in the TBR arm.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each DOVATO tablet contains 50 mg of dolutegravir as dolutegravir sodium and 300 mg lamivudine and is an oval, biconvex, white, film-coated tablet, debossed with “SV 137” on one face.

Bottle of 30 tablets with child-resistant closure NDC 49702-246-13.

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 DOVATO. 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 DOVATO 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 DOVATO. 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 DOVATO 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 DOVATO *[see Warnings and Precautions (5.3), Adverse Reactions (6.1)]*. Inform patients that monitoring for hepatotoxicity during therapy with DOVATO is recommended.

Embryo-Fetal Toxicity

Advise individuals of childbearing potential, including those actively trying to become pregnant, to discuss the risks and benefits of DOVATO with their healthcare provider to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy. If pregnancy is confirmed in the first trimester, advise patients to contact their healthcare provider *[see Warnings and Precaution (5.4), Use in Specific Populations (8.1, 8.3)]*.

Individuals of childbearing potential taking DOVATO should be counseled on the consistent use of effective contraception *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)]*.

Lactic Acidosis/Hepatomegaly with Steatosis

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

Drug Interactions

DOVATO may interact with many drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John's wort *[see Contraindications (4), Warnings and Precautions (5.6), Drug Interactions (7)]*.

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any signs and symptoms of infection as inflammation from previous infection may occur soon after combination antiretroviral therapy, including DOVATO, 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 DOVATO during pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

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

Missed Dose

Instruct patients that if they miss a dose of DOVATO, 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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by:

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Durham, NC 27701

DVT:xPI

PATIENT INFORMATION
DOVATO (doe VAH toe)
(dolutegravir and lamivudine)
tablets

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

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

- **Resistant HBV.** Your healthcare provider will test you for HBV infection before you start treatment with DOVATO. If you have HIV-1 and hepatitis B, the HBV can change (mutate) during your treatment with DOVATO and become harder to treat (resistant). It is not known if DOVATO is safe and effective in people who have HIV-1 and HBV infection.
- **Worsening of HBV infection.** If you have HBV infection and take DOVATO, your HBV may get worse (flare-up) if you stop taking DOVATO. A "flare-up" is when your HBV infection suddenly returns in a worse way than before.
  - Do not run out of DOVATO. Refill your prescription or talk to your healthcare provider before your DOVATO is all gone.
  - **Do not stop DOVATO without first talking to your healthcare provider.**
  - If you stop taking DOVATO, 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 DOVATO**.**

For more information about side effects, see "What are the possible side effects of DOVATO?"

What is DOVATO?

DOVATO is a prescription medicine that is used without other HIV-1 medicines to treat HIV-1 infection in adults:

- 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 DOVATO is safe and effective in children.

Do not take DOVATO 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 DOVATO.
- take dofetilide. Taking DOVATO and dofetilide can cause side effects that may be serious or life-threatening.

Before you take DOVATO, 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. One of the medicines in DOVATO (dolutegravir) may harm your unborn baby.

- Your healthcare provider may prescribe a different medicine than DOVATO if you are planning to become pregnant or if pregnancy is confirmed during the first 12 weeks of pregnancy.
- If you can become pregnant, your healthcare provider may perform a pregnancy test before you start treatment with DOVATO.
- If you can become pregnant, you and your healthcare provider should talk about the use of effective birth control (contraception) during treatment with DOVATO.
- Tell your healthcare provider right away if you are planning to become pregnant, you become pregnant, or think you may be pregnant during treatment with DOVATO.

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

- are breastfeeding or plan to breastfeed. **Do not breastfeed if you take DOVATO.**
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  - DOVATO passes to your baby in your breast milk.
  - Talk with your healthcare provider about the best way to feed your baby.

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

Some medicines interact with DOVATO. 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 DOVATO.
- **Do not start taking a new medicine without telling your healthcare provider**. Your healthcare provider can tell you if it is safe to take DOVATO with other medicines.

How should I take DOVATO?

- **Take DOVATO 1 time a day exactly as your healthcare provider tells you.**
- Take DOVATO with or without food.
- Do not change your dose or stop taking DOVATO without talking with your healthcare provider.
- If you take antacids, laxatives, or other medicines that contain aluminum, magnesium, or buffered medicines, DOVATO 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 DOVATO:
  - You may take these supplements at the same time that you take DOVATO with food.
  - If you do not take these supplements with DOVATO and food, take DOVATO at least 2 hours before or 6 hours after you take these supplements.
- Do not miss a dose of DOVATO. If you miss a dose of DOVATO, 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 DOVATO.
- Do not run out of DOVATO. 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 DOVATO, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of DOVATO?

DOVATO can cause serious side effects, including:

- See **"What is the most important information I should know about DOVATO?"**
- **Allergic reactions. Call your healthcare provider right away if you develop a rash with DOVATO. Stop taking DOVATO 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 eyes
  - 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 DOVATO. 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 DOVATO.

The most common side effects of DOVATO include:

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

These are not all the possible side effects of DOVATO.

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 DOVATO?

- Store DOVATO below 86°F (30°C).

- DOVATO comes in a child-resistant package**.**

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

General information about the safe and effective use of DOVATO.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use DOVATO for a condition for which it was not prescribed. Do not give DOVATO 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 DOVATO that is written for health professionals.

What are the ingredients in DOVATO?

Active ingredients: dolutegravir and lamivudine.

Inactive ingredients: magnesium stearate, mannitol, microcrystalline cellulose, povidone K29/32, sodium starch glycolate, sodium stearyl fumarate.

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

Manufactured for:

ViiV Healthcare

ViiV Healthcare
Durham, NC 27701

by:
GlaxoSmithKline
Durham, NC 27701

DVT:xPIL

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

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 01/2023

Proposed Package Insert

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

DOVATO (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 DOVATO. Emergence of lamivudine-resistant HBV variants associated with lamivudine-containing antiretroviral regimens has been reported. If DOVATO is used in patients co-infected with HIV-1 and HBV, additional treatment should be considered for appropriate treatment of chronic HBV; otherwise, consider an alternative regimen.

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

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

DOVATO, 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 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 per mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of DOVATO. (1)

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

- Prior to or when initiating DOVATO, test patients for hepatitis B virus (HBV) infection. (2.1)
- Pregnancy testing: Pregnancy testing is recommended before initiation of DOVATO in individuals of childbearing potential. (2.1, 5.4, 8.1, 8.3)
- One tablet taken orally once daily with or without food. (2.2)
- The dolutegravir dose (50 mg) in DOVATO is insufficient when coadministered with carbamazepine or rifampin. If DOVATO is coadministered with carbamazepine or rifampin, take one tablet of DOVATO once daily, followed by an additional dolutegravir 50-mg tablet, approximately 12 hours from the dose of DOVATO. (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 DOVATO 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 DOVATO. Monitoring for hepatotoxicity is recommended. (5.3)
- Embryo-fetal toxicity may occur when used at the time of conception and in early pregnancy. Assess the risks and benefits of DOVATO and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester due to the risk of neural tube defects. Individuals of childbearing potential should be counseled on the consistent use of effective contraception. (2.1, 5.4, 8.1, 8.3)
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. (5.5)
- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. (5.7)

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

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

To report SUSPECTED ADVERSE REACTIONS, contact LifeScience Logistics at 1-855-738-6171 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- DOVATO 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 DOVATO. (4, 5.6, 7)

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

- Pregnancy: Assess the risks and benefits of DOVATO and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester or if pregnancy is confirmed in the first trimester due to the risk of neural tube defects. (2.1, 5.4, 8.1, 8.3)
- Lactation: Breastfeeding is not recommended due to the potential for HIV-1 transmission. (8.2)
- Females and males of reproductive potential: Pregnancy testing is recommended in individuals of childbearing potential. Patients should be counseled on the consistent use of effective contraception. (8.1, 8.3)
- Renal impairment: DOVATO is not recommended in patients with creatinine clearance less than 30 mL/min. (8.6)
- Hepatic impairment: DOVATO 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: 1/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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 DOVATO. Emergence of lamivudine-resistant HBV variants associated with lamivudine-containing antiretroviral regimens has been reported. If DOVATO is used in patients co-infected with HIV-1 and HBV, additional treatment should be considered for appropriate treatment of chronic HBV; otherwise, consider an alternative regimen.

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

1 INDICATIONS AND USAGE

DOVATO is indicated as a complete regimen for the treatment of HIV-1 infection in adults 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 per mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of DOVATO.

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to or When Initiating Treatment with DOVATO

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

Pregnancy testing is recommended before initiation of DOVATO in individuals of childbearing potential *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)]*.

2.2 Recommended Dosage

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

2.3 Recommended Dosage with Certain Coadministered Drugs

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

Table 1. Dosing Recommendations for DOVATO with Coadministered Drugs

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

2.4 Not Recommended in Patients with Renal Impairment

Because DOVATO is a fixed-dose tablet and cannot be dose adjusted, DOVATO is not recommended in patients with creatinine clearance less than 30 mL per minute *[see Use in Specific Populations (8.6)]*.

2.5 Not Recommended in Patients with Severe Hepatic Impairment

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

3 DOSAGE FORMS AND STRENGTHS

DOVATO tablets are oval, biconvex, white, film-coated tablets, debossed with “SV 137” on one face. Each tablet contains 50 mg of dolutegravir and 300 mg of lamivudine.

4 CONTRAINDICATIONS

DOVATO is contraindicated in patients:

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

5 WARNINGS AND PRECAUTIONS

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

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

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 DOVATO 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 DOVATO. Patients who are co-infected with HIV-1 and HBV who discontinue DOVATO should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with DOVATO. 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 DOVATO, 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 DOVATO 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 DOVATO 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 DOVATO *[see Adverse Reactions (6.1)]*. In some cases, the elevations in transaminases were consistent with immune reconstitution syndrome or HBV reactivation particularly in the setting where anti-hepatitis therapy was withdrawn. Cases of hepatic toxicity, including elevated serum liver biochemistries, hepatitis, and acute liver failure, have also been reported in patients receiving a dolutegravir-containing regimen who had no pre-existing hepatic disease or other identifiable risk factors. Drug-induced liver injury leading to liver transplant has been reported with TRIUMEQ (abacavir, dolutegravir, and lamivudine). Monitoring for hepatotoxicity is recommended.

5.4 Embryo-Fetal Toxicity

An ongoing observational study showed 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. As there is limited understanding of the association of reported types of neural tube defects with dolutegravir use, inform individuals of childbearing potential, including those actively trying to become pregnant, about the potential increased risk of neural tube defects with DOVATO. Assess the risks and benefits of DOVATO and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester *[see Use in Specific Populations (8.1, 8.3)]*.

Pregnancy testing is recommended before initiation of DOVATO in individuals of childbearing potential *[see Dosage and Administration (2.1)]*.

Individuals of childbearing potential should be counseled on the consistent use of effective contraception *[see Use in Specific Populations (8.1, 8.3)]*.

DOVATO may be considered during the second and third trimesters of pregnancy if the expected benefit justifies the potential risk to the pregnant woman and the fetus.

5.5 Lactic Acidosis and Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues, including lamivudine (a component of DOVATO). 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 DOVATO to any patient with known risk factors for liver disease. Treatment with DOVATO should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or

pronounced hepatotoxicity, which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations.

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

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

5.7 Immune Reconstitution Syndrome

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

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

Clinical Trials in Adults with No Antiretroviral Treatment History

The safety assessment of DOVATO 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 DOVATO 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 DOVATO 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 DOVATO once daily. All subjects are followed up to Week 200. Overall, the safety profile of DOVATO 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 DOVATO 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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing experience in patients receiving a dolutegravir- or lamivudine-containing regimen. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole

Redistribution/accumulation of body fat.

Endocrine and Metabolic

Hyperglycemia.

General

Weakness.

Hemic and Lymphatic

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

Hepatic and Pancreatic

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

Hepatobiliary Disorders

Acute liver failure, hepatotoxicity.

Hypersensitivity

Anaphylaxis, urticaria.

Investigations

Weight increased.

Musculoskeletal

Arthralgia, 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

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

7.2 Potential for DOVATO to Affect Other Drugs

Dolutegravir, a component of DOVATO, 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 DOVATO

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 DOVATO *[see Drug Interactions (7.4), Clinical Pharmacology (12.3)]*. Coadministration of DOVATO 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 DOVATO. 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 DOVATO 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 DOVATO: 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 DOVATO *[see Contraindications (4)]*.
Anticonvulsant: Carbamazepine[a]	↓Dolutegravir	An additional dolutegravir 50-mg dose should be taken, separated by 12 hours from DOVATO *[see Dosage and Administration (2.3)]*.

Anticonvulsants: Oxcarbazepine Phenytoin Phenobarbital	↓Dolutegravir	Avoid coadministration with DOVATO 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 DOVATO and metformin.
Antimycobacterial: Rifampin[a]	↓Dolutegravir	An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from DOVATO *[see Dosage and Administration (2.3)]*.
Herbal product: St. John's wort (*Hypericum perforatum*)	↓Dolutegravir	Avoid coadministration with DOVATO 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 DOVATO 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, DOVATO and supplements or multivitamins containing calcium or iron can be taken at the same time. Under fasting conditions, DOVATO 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 DOVATO should be considered against the risk of seizures in these patients.
Sorbitol[a]	↓Lamivudine	When possible, avoid use of sorbitol-containing medicines with DOVATO.

↑ = 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 DOVATO 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 an ongoing birth outcome surveillance study have identified an increased risk of neural tube defects when dolutegravir, a component of DOVATO, is administered at the time of conception. As defects related to closure of the neural tube occur from conception through the first 6 weeks of gestation, embryos exposed to dolutegravir from the time of conception through the first 6 weeks of gestation are at potential risk.

Advise individuals of childbearing potential, including those actively trying to become pregnant, of the potential risk of neural tube defects with use of DOVATO. Assess the risks and benefits of DOVATO and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester. A benefit-risk assessment should consider factors such as feasibility of switching to another antiretroviral regimen, tolerability, ability to maintain viral suppression, and risk of HIV-1 transmission to the infant against the risk of neural tube defects associated with in utero dolutegravir exposure during critical periods of fetal development. *[See Warnings and Precautions (5.4)]*.

There are insufficient human data on the use of DOVATO during pregnancy to definitively assess a drug-associated risk for birth defects and miscarriage. The background risk for major birth defects for the indicated population is unknown. In the U.S. general population, the

estimated background rate for major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with dolutegravir at systemic exposures (AUC) less than (rabbits) and 50 times (rats) the exposure in humans at the recommended human dose (RHD) *(see Data)*. Oral administration of lamivudine to pregnant rabbits during organogenesis resulted in embryolethality at systemic exposure (AUC) similar to the RHD; however, no adverse developmental effects were observed with oral administration of lamivudine to pregnant rats during organogenesis at plasma concentrations (C_{max}) 35 times the RHD *(see Data)*.

Data

Human Data: Dolutegravir: In a birth outcome surveillance study in Botswana, there were 7 cases of neural tube defects reported out of 3,591 deliveries (0.19%) to women who were exposed to dolutegravir-containing regimens at the time of conception. In comparison, the neural tube defect prevalence rates were 0.11% (21/19,361 deliveries) in the non-dolutegravir arm and 0.07% (87/119,630 deliveries) in the HIV-uninfected arm. Seven cases reported with dolutegravir included 3 cases of myelomeningocele, 2 cases of encephalocele, and one case each of anencephaly and iniencephaly. In the same study, no increased risk of neural tube defects was identified in women who started dolutegravir during pregnancy. Two infants out of 4,448 (0.04%) deliveries to women who started dolutegravir during pregnancy had a neural tube defect, compared with 5 infants out of 6,748 (0.07%) deliveries to women who started non-dolutegravir-containing regimens during pregnancy. The reported risks of neural tube defects by treatment groups were based on interim analyses from the ongoing surveillance study in Botswana. It is unknown if baseline characteristics were balanced between the study treatment groups. The observed trends of association could change as data accumulate.

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

Data from the birth outcome surveillance study described above and postmarketing sources with more than 1,000 pregnancy outcomes from second and third trimester exposure in pregnant women indicate no evidence of increased risk of adverse birth outcomes.

Based on prospective reports to the APR of 842 exposures to dolutegravir during pregnancy resulting in live births (including 512 exposed in the first trimester), the prevalence of defects in live births was 3.3% (95% CI: 1.9% to 5.3%) following first-trimester exposure to dolutegravir-containing regimens and 4.8% (95% CI: 2.8% to 7.8%) 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 0.51-2.11) (n = 15).

Lamivudine: Based on prospective reports to the APR of exposures to lamivudine during pregnancy resulting in live births (including over 5,300 exposed in the first trimester and over 7,400 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: 2.7% 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

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

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

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

8.3 Females and Males of Reproductive Potential

In individuals of childbearing potential currently on DOVATO who are actively trying to become pregnant or if pregnancy is confirmed in the first trimester, assess the risks and benefits of continuing DOVATO and discuss with the patient if an alternative treatment should be considered *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1)]*.

Pregnancy Testing

Pregnancy testing is recommended in individuals of childbearing potential before initiation of DOVATO *[see Dosage and Administration (2.1)]*.

Contraception

Individuals of childbearing potential who are taking DOVATO should be counseled on the consistent use of effective contraception.

8.4 Pediatric Use

The safety and efficacy of DOVATO have not been established in pediatric patients.

8.5 Geriatric Use

Clinical trials of DOVATO 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 DOVATO 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

DOVATO is not recommended for patients with creatinine clearance <30 mL/min because DOVATO is a fixed-dose combination and the dosage of the individual components cannot be adjusted. If a dose reduction of lamivudine, a component of DOVATO, 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 DOVATO 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 DOVATO 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 DOVATO 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, DOVATO should be discontinued and the individual components should be used to construct the treatment regimen.

8.7 Hepatic Impairment

No dosage adjustment of DOVATO 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, DOVATO is not recommended for patients with severe hepatic impairment.

10 OVERDOSAGE

There is no known specific treatment for overdose with DOVATO. 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.

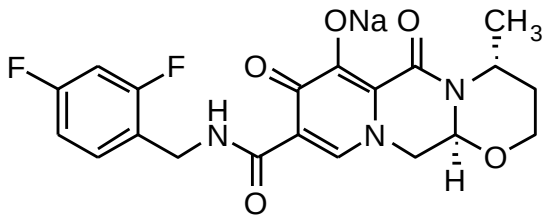
11 DESCRIPTION

DOVATO 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).

DOVATO tablets are for oral administration. Each film-coated tablet contains the active ingredients 50 mg of dolutegravir (equivalent to 52.6 mg dolutegravir sodium) and 300 mg of lamivudine and the inactive ingredients magnesium stearate, mannitol, microcrystalline cellulose, povidone K29/32, sodium starch glycolate, sodium stearyl fumarate. The tablet film-coating contains the inactive ingredients hypromellose, polyethylene glycol, titanium dioxide.

Dolutegravir

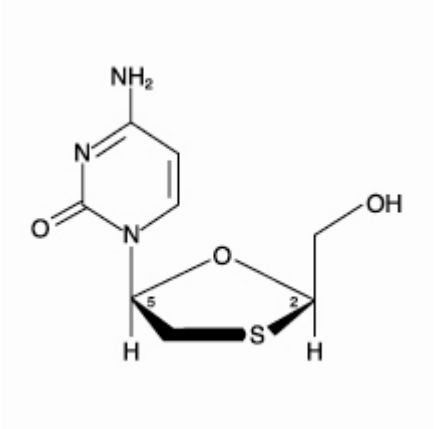
The chemical name of dolutegravir sodium is sodium (4*R*,12a*S*)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazin-7-olate. The empirical formula is $C_{20}H_{18}F_2N_3NaO_5$ and the molecular weight is 441.36 g/mol.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



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

Lamivudine

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



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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

DOVATO 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 DOVATO 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 DOVATO are provided in Table 6.

Table 6. Multiple-Dose Pharmacokinetic Parameters of the Components of DOVATO

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 DOVATO are provided in Table 7.

Table 7. Pharmacokinetic Properties of the Components of DOVATO

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 DOVATO) were observed[c]	
Distribution		
Plasma protein binding[d]	Approximately 99%	36%
Blood-to-plasma ratio	0.44 - 0.54	1.1 - 1.2
Elimination		
$t_{1/2}$ (h)	Approximately 14	13 - 19
Metabolism		
Metabolic pathways	UGT1A1 (primary) CYP3A (minor)	Not significantly metabolized
Excretion		
Major route of elimination	Metabolism	Renal, by OCT system
Urine (unchanged)	31% (<1%)[e]	Approximately 70%[f]
Feces (unchanged)	64% (53%)[e]	–

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 DOVATO (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 DOVATO 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 DOVATO 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 DOVATO 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).

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 DOVATO. The drug interaction studies described below were conducted with dolutegravir or lamivudine when used alone. Table 8 summarizes the effects of dolutegravir on the pharmacokinetics of coadministered drugs. Table 9 summarizes the effect of other drugs on the pharmacokinetics of dolutegravir when used alone and Table 10 summarizes the effect of sorbitol on the pharmacokinetics of lamivudine when used alone.

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

Coadministered Drug(s) and Dose(s)	**Dose of Dolutegravir**	**Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug with/without Dolutegravir No Effect = 1.00**		
		C_{max}	**AUC**	**C_{tau} or C_{24}**

Daclatasvir 60 mg once daily	50 mg once daily	1.03 (0.84 to 1.25)	0.98 (0.83 to 1.15)	1.06 (0.88 to 1.29)
Ethinyl estradiol 0.035 mg	50 mg twice daily	0.99 (0.91 to 1.08)	1.03 (0.96 to 1.11)	1.02 (0.93 to 1.11)
Grazoprevir 200 mg once daily	50 mg single dose	0.64 (0.44, 0.93)	0.81 (0.67, 0.97)	0.86 (0.79, 0.93)
Metformin[a] 500 mg twice daily	50 mg once daily	1.66 (1.53 to 1.81)	1.79 (1.65 to 1.93)	_
Metformin[a] 500 mg twice daily	50 mg twice daily	2.11 (1.91 to 2.33)	2.45 (2.25 to 2.66)	_
Methadone 16 to 150 mg	50 mg twice daily	1.00 (0. 94 to 1.06)	0.98 (0.91 to 1.06)	0.99 (0.91 to 1.07)
Midazolam 3 mg	25 mg once daily	_	0.95 (0.79 to 1.15)	_
Norelgestromin[b] 0.25 mg	50 mg twice daily	0.89 (0.82 to 0.97)	0.98 (0.91 to 1.04)	0.93 (0.85 to 1.03)
Sofosbuvir 400 mg once daily Metabolite (GS-331007)	50 mg once daily	0.88 (0.80, 0.98) 1.01 (0.93, 1.10)	0.92 (0.85, 0.99) 0.99 (0.97, 1.01)	NA 0.99 (0.97, 1.01)
Velpatasvir 100 mg once daily	50 mg once daily	0.94 (0.86, 1.02)	0.91 (0.84, 0.98)	0.88 (0.82, 0.94)

[a] OCT2 or 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 9. Effect of Coadministered Drugs on the Pharmacokinetics of Dolutegravir

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

Antacid (MAALOX) 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)
Daclatasvir 60 mg once daily	50 mg once daily	1.29 (1.07 to 1.57)	1.33 (1.11 to 1.59)	1.45 (1.25 to 1.68)
Ferrous fumarate 324 mg simultaneous administration (fasted)	50-mg single dose	0.43 (0.35 to 0.52)	0.46 (0.38 to 0.56)	0.44 (0.36 to 0.54)
Ferrous fumarate 324 mg simultaneous administration (fed)	50-mg single dose	1.03 (0.84 to 1.26)	0.98 (0.81 to 1.20)	1.00 (0.81 to 1.23)
Ferrous fumarate 324 mg 2 h after dolutegravir	50-mg single dose	0.99 (0.81 to 1.21)	0.95 (0.77 to 1.15)	0.92 (0.74 to 1.13)
Multivitamin (One-A-Day) simultaneous administration	50-mg single dose	0.65 (0.54 to 0.77)	0.67 (0.55 to 0.81)	0.68 (0.56 to 0.82)
Omeprazole 40 mg once daily	50-mg single dose	0.92 (0.75 to 1.11)	0.97 (0.78 to 1.20)	0.95 (0.75 to 1.21)
Prednisone 60 mg once daily with taper	50 mg once daily	1.06 (0.99 to 1.14)	1.11 (1.03 to 1.20)	1.17 (1.06 to 1.28)
Rifampin[a] 600 mg once daily	50 mg twice daily	0.57 (0.49 to 0.65)	0.46 (0.38 to 0.55)	0.28 (0.23 to 0.34)
Rifampin[b] 600 mg once daily	50 mg twice daily	1.18 (1.03 to 1.37)	1.33 (1.15 to 1.53)	1.22 (1.01 to 1.48)
Rifabutin 300 mg once daily	50 mg once daily	1.16 (0.98 to 1.37)	0.95 (0.82 to 1.10)	0.70 (0.57 to 0.87)

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

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

Table 10. Effect of Sorbitol on the Pharmacokinetics of Lamivudine

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

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 DOVATO 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 DOVATO 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 of DOVATO is supported by data from 2 randomized, double-blind, controlled trials (GEMINI-1 [NCT02831673] and GEMINI-2 [NCT02831764]) in HIV-1–infected adults with no antiretroviral treatment history, and data from a randomized, open-label, controlled trial (TANGO [NCT03446573]) in virologically suppressed HIV-1–infected adults.

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

	GEMINI-1 and GEMINI-2 Pooled Data[a]			
	Week 48		**Week 144**	
Virologic Outcomes	**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)

[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 DOVATO

The efficacy of DOVATO 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 DOVATO 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 DOVATO 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 DOVATO 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 DOVATO 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, DOVATO 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 DOVATO and TBR treatment arms, respectively (Table 12).

Table 12 Virologic Outcomes of Randomized Treatment in TANGO Trial at Weeks 48 and 144 in Virologically Suppressed Subjects Who Switched to DOVATO

	Week 48[a]		Week 144	
Virologic Outcomes	**DOVATO (n = 369)**	**TBR (n = 372)**	**DOVATO (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

TBR = Tenofovir alafenamide-based regimen.

[a] Based on a 4% non-inferiority margin, DOVATO 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 DOVATO 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 DOVATO arm and 35.0 cells/mm^3 in the TBR arm.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each DOVATO tablet contains 50 mg of dolutegravir as dolutegravir sodium and 300 mg lamivudine and is an oval, biconvex, white, film-coated tablet, debossed with “SV 137” on one face.

Bottle of 30 tablets with child-resistant closure NDC 42067-260-30.

Store below 30°C (86°F).

This drug was imported from Canada without the authorization of ViiV Healthcare or GlaxoSmithKline under the State of Florida Section 804 Importation Program.
Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

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 DOVATO. 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 DOVATO 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 DOVATO. 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 DOVATO 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 DOVATO *[see Warnings and Precautions (5.3), Adverse Reactions (6.1)]*. Inform patients that monitoring for hepatotoxicity during therapy with DOVATO is recommended.

Embryo-Fetal Toxicity

Advise individuals of childbearing potential, including those actively trying to become pregnant, to discuss the risks and benefits of DOVATO with their healthcare provider to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy. If pregnancy is confirmed in the first trimester, advise patients to contact their healthcare provider *[see Warnings and Precaution (5.4), Use in Specific Populations (8.1, 8.3)]*.

Individuals of childbearing potential taking DOVATO should be counseled on the consistent use of effective contraception *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)]*.

Lactic Acidosis/Hepatomegaly with Steatosis

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

Drug Interactions

DOVATO may interact with many drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John's wort *[see Contraindications (4), Warnings and Precautions (5.6), Drug Interactions (7)]*.

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any signs and symptoms of infection as inflammation from previous infection may occur soon after combination antiretroviral therapy, including DOVATO, 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 DOVATO during pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

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

Missed Dose

Instruct patients that if they miss a dose of DOVATO, 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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Manufactured for:

ViiV Healthcare
Durham, NC 27701

by:

GlaxoSmithKline
Durham, NC 27701

DVT:xPI

PATIENT INFORMATION
DOVATO (doe VAH toe)
(dolutegravir and lamivudine)
tablets

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

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

- **Resistant HBV.** Your healthcare provider will test you for HBV infection before you start treatment with DOVATO. If you have HIV-1 and hepatitis B, the HBV can change (mutate) during your treatment with DOVATO and become harder to treat (resistant). It is not known if DOVATO is safe and effective in people who have HIV-1 and HBV infection.
- **Worsening of HBV infection.** If you have HBV infection and take DOVATO, your HBV may get worse (flare-up) if you stop taking DOVATO. A "flare-up" is when your HBV infection suddenly returns in a worse way than before.
  - Do not run out of DOVATO. Refill your prescription or talk to your healthcare provider before your DOVATO is all gone.
  - **Do not stop DOVATO without first talking to your healthcare provider.**
  - If you stop taking DOVATO, 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 DOVATO**.**

For more information about side effects, see "What are the possible side effects of DOVATO?"

What is DOVATO?

DOVATO is a prescription medicine that is used without other HIV-1 medicines to treat HIV-1 infection in adults:

- 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 DOVATO is safe and effective in children.

Do not take DOVATO 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 DOVATO.
- take dofetilide. Taking DOVATO and dofetilide can cause side effects that may be serious or life-threatening.

Before you take DOVATO, 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. One of the medicines in DOVATO (dolutegravir) may harm your unborn baby.

- Your healthcare provider may prescribe a different medicine than DOVATO if you are planning to become pregnant or if pregnancy is confirmed during the first 12 weeks of pregnancy.
- If you can become pregnant, your healthcare provider may perform a pregnancy test before you start treatment with DOVATO.
- If you can become pregnant, you and your healthcare provider should talk about the use of effective birth control (contraception) during treatment with DOVATO.
- Tell your healthcare provider right away if you are planning to become pregnant, you become pregnant, or think you may be pregnant during treatment with DOVATO.

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

- are breastfeeding or plan to breastfeed. **Do not breastfeed if you take DOVATO.**
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  - DOVATO passes to your baby in your breast milk.
  - Talk with your healthcare provider about the best way to feed your baby.

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

Some medicines interact with DOVATO. 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 DOVATO.
- **Do not start taking a new medicine without telling your healthcare provider**. Your healthcare provider can tell you if it is safe to take DOVATO with other medicines.

How should I take DOVATO?

- **Take DOVATO 1 time a day exactly as your healthcare provider tells you.**
- Take DOVATO with or without food.
- Do not change your dose or stop taking DOVATO without talking with your healthcare provider.
- If you take antacids, laxatives, or other medicines that contain aluminum, magnesium, or buffered medicines, DOVATO 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 DOVATO:
  - You may take these supplements at the same time that you take DOVATO with food.
  - If you do not take these supplements with DOVATO and food, take DOVATO at least 2 hours before or 6 hours after you take these supplements.
- Do not miss a dose of DOVATO. If you miss a dose of DOVATO, 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 DOVATO.
- Do not run out of DOVATO. 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 DOVATO, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of DOVATO?

DOVATO can cause serious side effects, including:

- See **"What is the most important information I should know about DOVATO?"**
- **Allergic reactions. Call your healthcare provider right away if you develop a rash with DOVATO. Stop taking DOVATO 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 eyes
  - 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 DOVATO. 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 DOVATO.

The most common side effects of DOVATO include:

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

These are not all the possible side effects of DOVATO.

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 DOVATO?

- Store DOVATO below 86°F (30°C).

- DOVATO comes in a child-resistant package**.**

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

General information about the safe and effective use of DOVATO.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use DOVATO for a condition for which it was not prescribed. Do not give DOVATO 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 DOVATO that is written for health professionals.

What are the ingredients in DOVATO?

Active ingredients: dolutegravir and lamivudine.

Inactive ingredients: magnesium stearate, mannitol, microcrystalline cellulose, povidone K29/32, sodium starch glycolate, sodium stearyl fumarate.

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

Manufactured for:

ViiV Healthcare

ViiV Healthcare
Durham, NC 27701

by:
GlaxoSmithKline
Durham, NC 27701

DVT:xPIL

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

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

Revised: 01/2023

This drug was imported from Canada without the authorization of ViiV Healthcare or GlaxoSmithKline under the State of Florida Section 804 Importation Program. Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

Annotated Label Comparisons

PI Comparisons FDA VS. FLCPDIP
Differences
Updated information Adverse Reactions Contact
How Supplied/Storage and Handling added SIP804 language
Patient Information added SIP804 language
Listed new NDC #
Added Importation language & Importer name & address
Listed only drug strength purchased for program

FDA

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

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Each DOVATO tablet contains 50 mg of dolutegravir as dolutegravir sodium and 300 mg lamivudine and is an oval, biconvex, white, film-coated tablet, debossed with "SV 137" on one face.

Bottle of 30 tablets with child-resistant closure NDC 42067-260-30.

Store below 30°C (86°F).

Manufactured for:
ViiV Healthcare
ViiV Healthcare
Durham, NC 27701
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DVT:xPIL
For more information go to www.DOVATO.com or call 1-877-844-8872.

by:
GlaxoSmithKline
Durham, NC 27701

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 01/2023

FLSIP

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

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

To report SUSPECTED ADVERSE REACTIONS, contact LifeScience Logistics at 1-855-738-6171 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

16 HOW SUPPLIED/STORAGE AND HANDLING

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DVT:xPIL
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by:
GlaxoSmithKline
Durham, NC 27701

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Proposed Package Label

Label Comparisons FDA VS. FLCPDIP
Differences
NDC
GTN
Bar Codes FPO with Associated NDCs
SIP804 Importation Language
Label SIZE due to production process & adding SIP804 language
Importer Name & Address
Brand logos FPO low resolution. Native art files requested upon SIP804 approval.

Comparisons
FDA to FLSIP

Recent FDA Approved Label	US Proprietary Name	US Generic Name	US Strength	NDC	NDA or ANDA	Applicant Holder Name	Applicant Holder Address	US Active Ingredients	Date Labeling Prepared for FLSIP	LSL Proprietary Name	LSL Generic Name	FLSIP Strength	LSL NDC	LSL Relabeler Name	Applicant Holder Name	Applicant Holder Address	FLSIP Active Ingredients	FDA Comments
1/30/2023	DOVATO	dolutegravir/lamivudine	50-300 mg	49702-246-13	211994	ViiV Healthcare	Durham, NC 27701	dolutegravir/lamivudine	Aug-23	DOVATO	dolutegravir/lamivudine	50-300 mg	42067-260-30	LifeScience Logistics, LLC	ViiV Healthcare	Durham, NC 27701	dolutegravir/lamivudine	n/a

Canadian and FDA Drug Comparison

Comparisons

Canada to FDA

Active Ingredient	Canadian Submission Number	Canadian Proprietary Name	Canadian Generic Name	DIN	Date Labeling Approved	Company Name	Address	Canadian Strength	Dosage Form	# of active Ingred.	Canadian Ingredients	US Proprietary Name	US Generic Name	US Strength	NDC	NDA or ANDA	Applicant Holder Name
dolutegravir/lamivudine	259156	DOVATO	Dolutegravir-lamivudine	24491753	Revision: November 11, 2022	ViiV Healthcare ULC	75 Rue Queen, Suite 1400 Montreal, Quebec Canada H3C 2N6	50-300 mg	Oral Tablet, Once daily	2	dolutegravir/lamivudine	DOVATO	dolutegravir/lamivudine	50-300 mg	49702-246-13	NDA211994	ViiV Healthcare Durham, NC 27701

Canadian Monograph

PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**DOVATO**

dolutegravir and lamivudine tablets

50 mg dolutegravir (as dolutegravir sodium) and 300 mg lamivudine, Oral

Antiretroviral Agent

ViiV Healthcare ULC
75 Rue Queen, Suite 1400
Montreal, Quebec
Canada
H3C 2N6

Date of Initial Authorization:
Aug 22, 2019

Date of Revision:
November 15, 2022

Submission Control Number: 259156

RECENT MAJOR LABEL CHANGES

4 Dosage and Administration, 4.1 Dosing Considerations	09/2021
4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment	09/2021
7 WARNINGS AND PRECAUTIONS, Renal	09/2021
7 Warnings and Precautions, 7.1.1 Pregnant Women	09/2022
7 Warning and Precautions, 7.1.2 Breast Feeding	09/2022

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed .

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

DOVATO (dolutegravir and lamivudine) is indicated as a complete regimen for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults and adolescents 12 years of age and older and weighing at least 40 kg.

1.1 Pediatrics

Pediatrics (<18 years of age): Safety and efficacy of DOVATO in pediatric patients less than 12 years of age have not been established. There are no clinical study data with DOVATO in the adolescent population. The safety and efficacy of DOVATO in adolescents 12 years of age and older, and weighing at least 40 kg, is supported by the clinical data from studies of dolutegravir or lamivudine as single agents in combination with other antiretroviral agents in adolescents, and also by the clinical data from studies with dolutegravir in combination with lamivudine in adults (see 14 CLINICAL TRIALS, Adolescents)

1.2 Geriatrics

Geriatrics (> 65 years of age): Clinical studies of DOVATO did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from adult patients < 65 years of age.

2 CONTRAINDICATIONS

DOVATO is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

DOVATO is contraindicated in combination with drugs with narrow therapeutic windows, that are substrates of organic cation transporter 2 (OCT2), including but not limited to dofetilide, and/or fampridine (also known as dalfampridine) (see 9 DRUG INTERACTIONS).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Post-Treatment Exacerbations of Hepatitis B**
  Severe acute exacerbations of hepatitis B have been reported in patients who are infected with hepatitis B virus (HBV) and have discontinued lamivudine, a component of DOVATO. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue DOVATO. If appropriate, initiation of anti-hepatitis B therapy may be warranted (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- As with all antiretroviral drugs, therapy should be initiated by a healthcare professional experienced in the management of HIV infection.

- DOVATO can be taken with or without food.
- DOVATO is a fixed-dose tablet and should not be prescribed for patients requiring dosage adjustments, such as those with creatinine clearance less than 30 mL/min.
- DOVATO is not recommended for patients with any known or suspected viral resistance to dolutegravir or lamivudine.
- DOVATO contains lamivudine and therefore it is recommended to test for Hepatitis B virus (HBV) infection prior to or when initiating DOVATO (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).
- Perform pregnancy testing before initiation of DOVATO in individuals of childbearing potential.

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of DOVATO in adults and adolescents weighing at least 40 kg is one tablet once daily taken orally.

A separate preparation of dolutegravir (TIVICAY) is available where dose adjustment is required due to drug-drug interactions (see 9 DRUG INTERACTIONS).

Dosage Recommendation with Certain Concomitant Medications

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

Table 1 Dosing Recommendations for DOVATO with Co-administered Medications

Co-administered Drug	Dosing Recommendation
Oxcarbamazepine, carbamazepine, phenytoin, phenobarbital, St. John's wort or rifampin	Adjust dolutegravir dose to 50 mg twice daily. The additional 50 mg dose of dolutegravir should be taken, separated by 12 hours from DOVATO (see 9 DRUG INTERACTIONS).

Geriatrics (> 65 years of age)
Clinical studies of DOVATO did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from adult patients < 65 years of age.

Pediatrics (< 12 years of age)
Safety and efficacy of DOVATO in pediatric patients less than 12 years of age and weighting less than 40 kg have not been established.

Hepatic Insufficiency
No dosage adjustment of DOVATO is required in patients with mild or moderate hepatic insufficiency (Child-Pugh score A or B). DOVATO is not recommended in patients with severe hepatic insufficiency (Child-Pugh score C) as it has not been studied in these patients (see 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency).

Renal Insufficiency
DOVATO is not recommended for use in patients with a creatinine clearance less than 30 mL/min as the dose of lamivudine cannot be adjusted (see 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency and 7 WARNINGS AND PRECAUTIONS, Renal).

4.5 Missed Dose

If a dose is missed, patients should take the missed dose as soon as possible unless it is within 4 hours of their next scheduled dose. If a dose is skipped, the patient should not double the next dose.

5 OVERDOSAGE

Symptoms and signs

Experience with overdose of DOVATO or the individual components, dolutegravir and lamivudine is limited. No specific symptoms or signs have been identified.

Treatment

There is no known treatment for overdose with DOVATO. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdose, although this has not been studied. As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	tablet 50 mg dolutegravir (as dolutegravir sodium), 300 mg lamivudine	hypromellose, macrogol/PEG, magnesium stearate, mannitol (E421), microcrystalline cellulose, povidone (K29/32), sodium starch glycolate, sodium stearyl fumarate, titanium dioxide

Each film-coated tablet of DOVATO contains 50 mg dolutegravir (as 52.6 mg of dolutegravir sodium) and 300 mg lamivudine.

Dosage Forms
DOVATO tablets are oval, biconvex, white, film-coated tablets, debossed with 'SV 137' on one face.

Packaging
DOVATO tablets are supplied in opaque, white, round, HDPE (high density polyethylene) bottles closed with polypropylene child-resistant closures. Each bottle contains 30 film-coated tablets.

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General

DOVATO is a complete regimen for the treatment of HIV-1 infection; therefore, coadministration with other antiretroviral medications for treatment of HIV-1 infection is not recommended.

The safety and efficacy of DOVATO have not been studied in HIV-1-infected patients who have failed previous antiretroviral therapy and are currently not virologically suppressed.

As with other antiretroviral medicinal products, resistance testing and/or historical resistance data should guide the use of DOVATO. DOVATO should not be used in patients with known or suspected resistance to dolutegravir or lamivudine.

Patients receiving DOVATO or any other antiretroviral therapy may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Endocrine and Metabolism

- **Serum lipids and blood glucose**

  Serum lipid and blood glucose levels may increase during antiretroviral therapy. Disease control and life style changes may also be contributing factors. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders and blood glucose elevations should be managed as clinically appropriate.

Hematologic

Very rare occurrences of pure red cell aplasia have been reported with lamivudine use. Discontinuation of lamivudine has resulted in normalization of hematologic parameters in patients with suspected lamivudine-induced pure red cell aplasia.

Hepatic/Biliary/Pancreatic

- **Hepatotoxicity**

  Cases of hepatic toxicity including elevated serum liver biochemistries, hepatitis, and acute liver failure have been reported in patients receiving a dolutegravir-containing regimen who had no pre-existing hepatic disease or other identifiable risk factors. Drug-induced liver injury leading to liver transplant has been reported with TRIUMEQ. Monitoring for hepatotoxicity is recommended.

- **Post-Treatment Exacerbations of Hepatitis B in Patients Co-infected with HIV-1 and HBV**

  Prior to or when initiating DOVATO, test for HBV infection (see 4 DOSAGE AND ADMINISTRATION).

  Severe acute exacerbations of HBV have been reported in patients who are co-infected with HBV and HIV-1 and have discontinued lamivudine, a component of DOVATO. Patients who are

co-infected with HIV-1 and HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with DOVATO. If appropriate, initiation of anti-hepatitis B therapy may be warranted, especially in HBV co-infected patients with advanced liver disease or cirrhosis, since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

- **Emergence of Lamivudine-Resistant HBV**

  Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-1-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus. Consider an alternative regimen in these patients.

- **Liver chemistry changes in patients with HBV or HCV co-infection**

  Patients with underlying HBV or HCV may be at increased risk for worsening or development of transaminase elevations with use of a dolutegravir-containing regimen. Liver chemistry elevations consistent with immune reconstitution inflammatory syndrome were observed in some HBV and/or HCV co-infected patients at the start of dolutegravir therapy. Monitoring of liver chemistries is recommended in patients with HBV and/or HCV co-infection. Particular diligence should be applied in initiating or maintaining effective HBV therapy when starting therapy with DOVATO in HBV co-infected patients.

- **Lactic Acidosis/Severe Hepatomegaly with Steatosis**

  Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including lamivudine (a component of DOVATO). Treatment with DOVATO 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.

- **Hypersensitivity Reactions**

  Hypersensitivity reactions have been reported with integrase inhibitors, including dolutegravir, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury. Discontinue DOVATO and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema). Clinical status including liver aminotransferases should be monitored and appropriate therapy initiated. Delay in stopping treatment with DOVATO or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction.

Immune

- **Immune Reconstitution Inflammatory Syndrome**

  During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as MAC, CMV, PCP, and TB) which may necessitate further evaluation and treatment.

  Autoimmune disorders (such as Graves' disease, polymyositis and Guillain-Barre 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 and sometimes can be an atypical presentation.

Renal

DOVATO is not recommended for patients with creatinine clearance <30 mL/min because DOVATO is a fixed-dose combination and the dosage of the individual components cannot be adjusted. If a dose reduction of lamivudine, a component of DOVATO, is required for patients with creatinine clearance <30 mL/min, then the individual components should be used (see 4.2 Recommended Dose and Dosage Adjustment, Renal Insufficiency).

Patients with a creatinine clearance between 30 and 49 mL/min receiving DOVATO 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 DOVATO 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 DOVATO 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, DOVATO should be discontinued and the individual components should be used to construct the treatment regimen.

Reproductive Health: Female and Male Potential

- **Fertility**

  There are no data on the effects of dolutegravir or lamivudine on human male or female fertility. Animal studies indicate no effects of dolutegravir or lamivudine on male or female fertility (see 16 NON-CLINICAL TOXICOLOGY).

- **Reproduction**

  Antiretroviral Pregnancy Registry (APR): To monitor maternal-fetal outcomes of pregnant women with HIV exposed to DOVATO and other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients:

  http://www.apregistry.com

  Telephone: (800) 258-4263

  Fax: (800) 800-1052

7.1 Special Populations

7.1.1 Pregnant Women

DOVATO has not been studied in pregnant women. DOVATO should not be used in pregnant women unless the potential benefits outweigh the potential risks to the fetus. Women of childbearing potential (WOCBP) should be informed about the potential risk of neural tube defects with dolutegravir and counselled about the use of effective contraception. It is recommended that pregnancy testing is conducted prior to initiation of DOVATO If there are plans to become pregnant, or if pregnancy is confirmed within the first trimester while on DOVATO, the risks and benefits of continuing DOVATO

versus switching to another antiretroviral regimen should be discussed with the patient. Factors to consider should include feasibility of switching, tolerability, ability to maintain viral suppression, actual gestational age, risk of transmission to the infant and the available data around the potential risk of neural tube defects and other pregnancy outcomes for dolutegravir and alternative antiretroviral drugs.

In a birth outcome surveillance study in Botswana, a numerically higher rate of neural tube defects was identified with exposure to dolutegravir compared to non-dolutegravir-containing antiretroviral regimens at the time of conception, however, the difference was not statistically significant. Seven cases of neural tube defects were reported in 3,591 deliveries (0.19%) to mothers taking dolutegravir-containing regimens at the time of conception, compared with 21 cases in 19,361 deliveries (0.11%) to mothers taking non-dolutegravir-containing regimens at the time of conception (Prevalence Difference 0.09%; 95% CI -0.031, -0.30). In the same study, an increased risk of neural tube defects was not identified in women who started dolutegravir during pregnancy. Two out of 4,448 deliveries (0.04%) to mothers who started dolutegravir during pregnancy had a neural tube defect, compared with five out of 6,748 deliveries (0.07%) to mothers who started non-dolutegravir-containing regimens during pregnancy. A causal relationship of these events to the use of dolutegravir has not been established. The incidence of neural tube defects in the general population ranges from 0.5-1 case per 1,000 live births. As most neural tube defects occur within the first 4 weeks of fetal development (approximately 6 weeks after the last menstrual period) this potential risk would concern women exposed to dolutegravir at the time of conception and in early pregnancy.

Data analyzed to date from other sources including the Antiretroviral Pregnancy Registry (APR), clinical trials, and post-marketing data are insufficient to address the risk of neural tube defects with dolutegravir. From the APR, one neural tube defect has been identified in 312 (0.32%) live births with periconceptual exposures to dolutegravir. More than 1,000 outcomes from second and third trimester exposure in pregnant women indicate no evidence of increased risk of adverse birth outcomes and the APR continues to monitor for DTG safety in pregnancy.

Dolutegravir and lamivudine use during pregnancy have been evaluated in the Antiretroviral Pregnancy Registry (APR) in over 700 and 12,800 women, respectively. Available human data from the APR do not show an increased risk of major birth defects for dolutegravir or lamivudine compared to the background rate.

Dolutegravir readily crosses the placenta in humans. In HIV-infected pregnant women, the median (range) foetal umbilical cord concentrations of dolutegravir were 1.28 (1.21 to 1.28) fold greater compared with maternal peripheral plasma concentrations.

There is insufficient information on the effects of dolutegravir on neonates.

Based on prospective reports to the APR of over 700 exposures to dolutegravir during pregnancy resulting in live births (including over 450 exposed in the first trimester), there was no difference between the overall risk of birth defects for dolutegravir when compared to the background birth defect rate of 2.7% and 4.17% from two population based surveillance systems (Metropolitan Atlanta Congenital Defects Program (MACDP) with defects of 2.72 per 100 live births and the Texas Birth Defects Registry (TBDR) with 4.17 per 100 live births). The prevalence of defects in live births was 3.5% (95% CI: 2.0% to 5.6%) following first trimester exposure to dolutegravir-containing regimens and 4.2% (95% CI: 2.2% to 7.2%) following second/third trimester exposure to dolutegravir-containing regimens.

Based on prospective reports to the APR of over 12,800 exposures to lamivudine during pregnancy resulting in live births (including over 5300 exposed in the first trimester), there was no difference between the overall risk of birth defects for lamivudine when compared to the background birth defect rate of 2.7% and 4.17% from the MACPD and TBDR, respectively. The prevalence of defects in live births

was 3.1% (95% CI: 2.7% 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.

In reproductive toxicity studies in animals, no evidence of teratogenicity, reproductive function, relevant embryonic or fetal toxicity including neural tube defects was identified in rats and rabbits at ≥30 and 0.55 times human clinical exposure based on AUC, respectively (see 16 NON-CLINICAL TOXICOLOGY).

Lamivudine:

There have been reports of mild, transient elevations in serum lactate levels, which may be due to mitochondrial dysfunction, in neonates and infants exposed in utero or peri-partum to nucleoside reverse transcriptase inhibitors (NRTIs). The clinical relevance of transient elevations in serum lactate is unknown. There have also been very rare reports of developmental delay, seizures and other neurological disease. However, a causal relationship between these events and NRTI exposure in utero or peri-partum has not been established. These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Reproduction studies with lamivudine in rats and rabbits showed no evidence of teratogenicity. Evidence of early embryolethality was seen in the rabbit at lamivudine exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels ~21 times (based on Cmax) that of the recommended human dose. Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta (see 16 NON-CLINICAL TOXICOLOGY).

7.1.2 Breast-feeding

HIV-1-infected mothers should not breast-feed their infants to avoid risking postnatal transmission of HIV. Dolutegravir is excreted in human milk in small amounts. In an open-label randomised study in which HIV-infected treatment naïve pregnant women were administered a dolutegravir based regimen until two weeks post-partum, the median (range) dolutegravir breast milk to maternal plasma ratio was 0.033 (0.021 to 0.050).

Lamivudine is excreted in human milk at similar concentrations to those found in serum. Because of the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving DOVATO.

7.1.3 Pediatrics

Pediatrics (< 12 years of age): Safety and efficacy of DOVATO have not been established in pediatric patients less than 12 years of age.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): Clinical studies of DOVATO did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from adult patients < 65 years of age. In general, caution should be exercised in the administration of DOVATO in elderly patients reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following adverse drug reactions are discussed in the WARNINGS AND PRECAUTIONS section:

- Hepatotoxicity
- Severe acute exacerbation of hepatitis B in patients co-infected with HIV-1 and HBV
- Lactic acidosis and severe hepatomegaly with steatosis
- Hypersensitivity reactions
- Immune reconstitution inflammatory syndrome

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

For details on adverse reactions that have occurred in studies with dolutegravir or lamivudine, please refer to the TIVICAY and 3TC product monographs.

Treatment-Naïve Patients

The safety assessment of DOVATO in HIV-1-infected, treatment naïve adult patients with viral load ≤ 500,000 HIV-1 RNA copies per mL is based on the pooled primary Week 48, Week 96 and Week 144 analyses of data from two identical, multicenter, double-blind, controlled trials, GEMINI-1 and GEMINI-2 where dolutegravir plus lamivudine were co-administered as single agents (TIVICAY and 3TC).

A total of 1,433 adult HIV–1-infected treatment-naïve subjects were randomized to dolutegravir 50 mg plus lamivudine 300 mg, as a complete regimen once daily, or dolutegravir 50 mg plus fixed-dose combination tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC), administered once daily.

The rates of adverse events leading to discontinuation in the pooled analysis were 2% (Week 48) and 3% (Week 96) of subjects in both treatment arms. At Week 144, the rates of adverse events leading to discontinuation in the pooled analysis were 4% of subjects who received TIVICAY plus 3TC and 5% in subjects who received TIVICAY plus TRUVADA. The most common adverse events leading to discontinuation were psychiatric disorders (<1% (Week 48) and 1% (Week 96) of subjects in both treatment arms). At Week 144, the most common adverse events leading to discontinuation were psychiatric disorders: 2% of subjects who received TIVICAY plus 3TC 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 pooled analysis of GEMINI-1 and GEMINI-2 studies at Weeks 48, 96 and 144 are provided in Table 3.

The adverse reactions observed for TIVICAY plus 3TC in the pooled Week 48, Week 96 and Week 144 analyses 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. The majority of adverse reactions related to TIVICAY plus 3TC were of Grade 1 intensity.

Table 3 Treatment-Emergent Adverse Reactions[a] (All Grades) and at Least 2% Frequency in either treatment arm (Week 48, 96 and 144 Pooled Analyses)

System Organ Class/ Preferred Term	POOLED					
	TIVICAY + 3TC (n = 716) n (%)			TIVICAY + TRUVADA (n = 717) n (%)		
	Week 48	Week 96	Week 144	Week 48	Week 96	Week 144
Nervous system disorders						
Headache	21 (3)	21 (3)	21 (3)	30 (4)	30 (4)	30 (4)
Dizziness	8 (1)	8 (1)	8 (1)	13 (2)	13 (2)	14 (2)
Gastrointestinal disorders						
Nausea	14 (2)	14 (2)	14 (2)	39 (5)	39 (5)	40 (6)
Diarrhea	14 (2)	15 (2)	15 (2)	19 (3)	19 (3)	21 (3)
Psychiatric disorders						
Insomnia	13 (2)	15 (2)	15 (2)	18 (3)	19 (3)	20 (3)
Anxiety	N/A	11 (2)	11 (2)	N/A	5 (<1)	6 (<1)
General disorders and administration site conditions						
Fatigue	10 (1)	11 (2)	11 (2)	6 (<1)	6 (<1)	6 (<1)

[a] Frequencies of adverse reactions are based on all treatment-emergent adverse events attributed to study drug by the investigator.

The only adverse reaction of ≥ Grade 2 occurring in ≥1% of subjects treated with TIVICAY plus 3TC was headache (1%).

Virologically Suppressed Patients

The safety of DOVATO in virologically suppressed adults was based on Week 48 and Week 96 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 DOVATO once daily or continue with TBR. Overall, the safety profile of DOVATO in virologically suppressed adult subjects in the TANGO trial was similar to that of TIVICAY plus 3TC in treatment naïve subjects in the GEMINI trials.

8.2.1 Clinical Trial Adverse Reactions – Adolescents

There are no clinical study data with DOVATO in the adolescent population. However, a summary of the clinical trial adverse reactions from prior adolescent studies of dolutegravir or lamivudine are available in the respective TIVICAY, 3TC and TRIUMEQ product monographs. For the adolescent studies, there were no additional types of adverse reactions beyond those observed in the adult population.

8.3 Less Common Clinical Trial Adverse Reactions

The following adverse reactions occurred in less than 2% of patients receiving dolutegravir plus lamivudine or are from studies described in the product monographs of the individual components TIVICAY (dolutegravir) and 3TC (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 pain, abdominal discomfort, flatulence, upper abdominal pain, vomiting

General Disorders: Fever, malaise

Hepatobiliary Disorders: Hepatitis

Immune System Disorders: Hypersensitivity, immune reconstitution inflammatory syndrome

Musculoskeletal and Connective Tissue Disorders: Myositis

Nervous System Disorders: Somnolence

Psychiatric Disorders: Abnormal dreams, depression, suicidal ideation or suicide attempt (particularly in patients with a pre-existing history of depression or psychiatric illness)

Renal and Urinary Disorders: Renal impairment

Skin and Subcutaneous Tissue Disorders: Pruritus, rash

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Selected laboratory abnormalities with a worsening grade from baseline and representing the worst-grade toxicity in GEMINI-1 and GEMINI 2 are presented in Table 4. The Week 144 pooled analyses were generally consistent with Week 48 and Week 96.

Table 4 Selected Laboratory Abnormalities (Grades 2 and 3 to 4; Week 48, 96 and 144 Pooled Analyses) in GEMINI-1 and GEMINI-2 Trials

Laboratory Parameter Preferred Term	Week 48		Week 96		Week 144	
	TIVICAY + 3TC (N =716) n (%)	TIVICAY + TRUVADA (N = 717) n (%)	TIVICAY + 3TC (N = 716) n (%)	TIVICAY + TRUVADA (N = 717) n (%)	TIVICAY + 3TC (N =716) n (%)	TIVICAY + TRUVADA (N = 717) n (%)
ALT						
Grade 2 (>2.5 to 5.0 x ULN)	13 (2)	20 (3)	18 (3)	27 (4)	26 (4)	30 (4)
Grade 3 to 4 (>5.0 x ULN)	18 (3)	18 (3)	23 (3)	19 (3)	27 (4)	24 (3)
AST						
Grade 2 (>2.5 to 5.0 x ULN)	22 (3)	19 (3)	29 (4)	27 (4)	35 (5)	36 (5)
Grade 3 to 4 (>5.0 x ULN)	12 (2)	24 (3)	18 (3)	25 (3)	22 (3)	27 (4)
Total Bilirubin						
Grade 2 (1.6 to 2.5 x ULN)	9 (1)	17 (2)	16 (2)	23 (3)	19 (3)	26 (4)
Grade 3 to 4 (>2.5 x ULN)	7 (<1)	7 (<1)	8 (1)	7 (<1)	8 (1)	7 (<1)
Cholesterol						
Grade 2 (6.19 to <7.77 mmol/L)	30 (4)	14 (2)	37 (5)	18 (3)	46 (6)	24 (3)
Grade 3 to 4 (>7.77 mmol/L)	0	0	0	1 (<1)	1 (<1)	1 (<1)
Creatine kinase						
Grade 2 (6.0 to 9.9 x ULN)	26 (4)	21 (3)	29 (4)	31 (4)	37 (5)	36 (5)
Grade 3 to 4 (≥10.0 x ULN)	32 (4)	35 (5)	46 (6)	47 (7)	54 (8)	63 (9)
Hyperglycemia						
Grade 2 (6.95 to 13.89 mmol/L)	48 (7)	29 (4)	62 (9)	46 (6)	81 (11)	58 (8)
Grade 3 to 4 (>13.89 mmol/L)	5 (<1)	5 (<1)	6 (<1)	5 (<1)	6 (<1)	5 (<1)
LDL Cholesterol						
Grade 2 (4.12 to < 4.9 mmol/L)	20 (3)	12 (2)	25 (3)	15 (2)	27 (4)	21 (3)
Grade 3 to 4 (> 4.9 mmol/L)	8 (1)	3 (<1)	8 (1)	5 (<1)	11 (2)	6 (<1)
Lipase						
Grade 2 (>1.5 to 3.0 x ULN)	37 (5)	34 (5)	41 (6)	45 (6)	52 (7)	57 (8)
Grade 3 to 4 (>3.0 x ULN)	7 (<1)	19 (3)	15 (2)	29 (4)	19 (3)	35 (5)
Triglycerides						
Grade 2 (>3.42 to 5.7 mmol/L)	13 (2)	13 (2)	18 (3)	18 (3)	23 (3)	25 (3)
Grade 3 to 4 (> 5.7 mmol/L)	9 (1)	4 (<1)	10 (1)	4 (<1)	11 (2)	4 (<1)

ULN = Upper limit of normal, ALT = Alanine Aminotransferase, AST = Aspartate Aminotransferase

Changes in Clinical Laboratory Values

Dolutegravir has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function. Increases in serum creatinine occurred within the first four weeks of treatment with dolutegravir plus lamivudine and remained stable through 144 weeks. A mean change from baseline of 12.76 µmol/L (range: -31.8 µmol/L to 71.7 µmol/L) was observed after 144 weeks of treatment (see 10.2 Pharmacodynamics, Effects on Renal Function).

Small increases in total bilirubin (without clinical jaundice) were observed with dolutegravir plus lamivudine. These changes are not considered clinically relevant as they likely reflect competition between dolutegravir and unconjugated bilirubin for a common clearance pathway (UGT1A1) (see 10.3 Pharmacokinetics, Metabolism).

In the pooled analysis, few subjects in either group experienced changes in lipid profile. A small number of subjects in each treatment group experienced LDL cholesterol toxicities ≥ Grade 2, TIVICAY + 3TC 4% (Week 48) and 5% (Week 144) and TIVICAY + TRUVADA group 2% (Week 48) and 4% (Week 144). However, both treatment groups showed an overall reduction in the mean total cholesterol/HDL ratio, with a greater reduction in the TIVICAY + TRUVADA group. A small proportion of subjects in both treatment groups also had emergent triglyceride toxicities of ≥ Grade 2, TIVICAY + 3TC 3% (Week 48) and 5% (Week 144), TIVICAY + TRUVADA 2% (Week 48) and 4% (Week 144). A total of 51 and 28 subjects receiving TIVICAY + 3TC and TIVICAY + TRUVADA, respectively, initiated lipid-lowering agents post-baseline by Week 144.

Table 5 Mean Change from Baseline in Fasted Lipid Values (Week 48, 96 and 144 Pooled Analyses) in GEMINI-1 and GEMINI-2 Trials

Laboratory Parameter Preferred Term	Week 48		Week 96		Week 144	
	TIVICAY plus 3TC (n = 716)	TIVICAY plus TRUVADA (n = 717)	TIVICAY plus 3TC (n = 716)	TIVICAY plus TRUVADA (n = 717)	TIVICAY plus 3TC (n = 716)	TIVICAY plus TRUVADA (n = 717)
Cholesterol (mmol/L)	0.35	-0.18	0.39	-0.14	0.39	-0.06
HDL cholesterol (mmol/L)	0.15	0.02	0.19	0.08	0.18	0.09
LDL cholesterol (mmol/L)	0.19	-0.16	0.16	-0.17	0.18	-0.11
Triglycerides (mmol/L)	0.04	-0.08	0.13	-0.12	0.11	-0.10
Total cholesterol/HDL cholesterol ratio	-0.09	-0.26	-0.13	-0.42	-0.20	-0.41

8.5 Post-Market Adverse Reactions

These events have been chosen for inclusion due to either their seriousness, frequency of reporting, potential causal connection to dolutegravir- and/or lamivudine-containing regimens, or a combination of these factors. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Body as a whole: anaphylaxis, weakness

Blood and Lymphatic Systems Disorders: pure red cell aplasia, anemia, lymphadenopathy

Gastrointestinal Disorders: rises in serum amylase, pancreatitis, stomatitis

Hepatobiliary Disorders: acute hepatic failure, splenomegaly

Investigations: weight increased

Metabolism and Nutrition Disorders: lactic acidosis, hyperlactatemia, hepatic steatosis, hyperglycemia

Musculoskeletal and connective tissue disorders: muscle disorders including rarely rhabdomyolysis, arthralgia, myalgia

Nervous System Disorders: paresthesia, peripheral neuropathy

Skin and Subcutaneous Tissue Disorders: alopecia, urticaria, pruritus

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

DOVATO contains dolutegravir plus lamivudine and any interactions that have been identified with either component individually may occur with DOVATO. There are no significant interactions between dolutegravir and lamivudine. Because DOVATO is a complete regimen coadministration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended and information regarding potential drug-drug interactions with other antiretroviral medications is not provided. For more information on these interactions, please refer to the TIVICAY and 3TC product monographs.

9.4 Drug-Drug Interactions

Effect of Dolutegravir or Lamivudine on the Pharmacokinetics of Other Agents

Dolutegravir

In vitro, dolutegravir did not inhibit (IC_{50} >50 μM) the enzymes: cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7, or transporters: P-glycoprotein (Pgp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, or multidrug resistance protein (MRP)2 or MRP4. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6, or CYP3A4. Based on these data, dolutegravir is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters.

In vitro, dolutegravir inhibited the renal organic cation transporter 2, OCT2 (IC_{50} = 1.93 μM), multidrug and toxin extrusion transporter (MATE) 1 (IC_{50}=6.34 μM) and MATE2-K (IC_{50}=24.8 μM). *In vivo,* dolutegravir has a low potential to affect the transport of MATE2-K substrates. *In vivo*, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2. Dolutegravir may increase plasma concentrations of drugs in which excretion is dependent upon OCT2 (for example dofetilide, fampridine (also known as dalfampridine) (see 2 CONTRAINDICATIONS), metformin) or MATE1 (see Table 6).

In vitro, dolutegravir inhibited the basolateral renal transporters: organic anion transporter (OAT) 1 (IC_{50} = 2.12 μM) and OAT3 (IC_{50} = 1.97 μM). Based upon the dolutegravir unbound plasma concentration, in silico modelling, and no notable effect on the pharmacokinetics *in vivo* of the OAT substrates tenofovir and para-aminohippurate, dolutegravir has low propensity to cause drug interactions via inhibition of OAT transporters.

Lamivudine

In vitro, lamivudine does not inhibit or induce CYP enzymes (such as CYP 3A4, CYP 2C9 or CYP 2D6). Lamivudine demonstrates no or weak inhibition of the drug transporters organic anion transporter 1B1 (OATP1B1), OATP1B3, breast cancer resistance protein (BCRP) or P-glycoprotein (Pgp), multidrug and toxin extrusion protein 1 (MATE1), MATE2-K or organic cation transporter 3 (OCT3). Lamivudine is therefore not expected to affect the plasma concentrations of drugs that are substrates of these enzymes or drug transporters.

Lamivudine is an inhibitor of OCT1 and OCT2 *in vitro* with IC50 values of 17 and 33 µM, respectively, however lamivudine has low potential to affect the plasma concentrations of OCT1 and OCT2 substrates at therapeutic drug exposures (up to 300 mg).

Effect of Other Agents on the Pharmacokinetics of Dolutegravir or Lamivudine

Dolutegravir

Dolutegravir is metabolized by UGT1A1 with some contribution from CYP3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, Pgp and BCRP *in vitro*; therefore drugs that induce those enzymes and transporters, may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir.

Co-administration of dolutegravir and other drugs that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4 and/or Pgp may increase dolutegravir plasma concentration (see Table 6).

In vitro, dolutegravir is not a substrate of human organic anion transporting polypeptide (OATP)1B1, OATP1B3, or OCT1.

Coadministration of dolutegravir with polyvalent cation-containing products may lead to decreased adsorption of dolutegravir.

Lamivudine

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

Lamivudine is a substrate of the hepatic uptake transporter OCT1. As hepatic elimination plays a minor role in the clearance of lamivudine, drug interactions due to inhibition of OCT1 are unlikely to be of clinical significance.

Lamivudine is a substrate of Pgp and BCRP, however due to its high bioavailability it is unlikely that these transporters play a significant role in the absorption of lamivudine. Therefore, co-administration of drugs that are inhibitors of these efflux transporters is unlikely to affect the disposition and elimination of lamivudine.

Lamivudine is predominantly eliminated by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when the main route of administration is renal.

Established or Potential Drug Interactions

Established and theoretical interactions with selected medicinal products are listed in Table 6. The drugs listed in this table are not all-inclusive. Recommendations are based on either drug interaction studies, or potential or predicted interactions due to the expected magnitude of interaction and/or potential for serious adverse events or loss of efficacy.

Table 6 Established or Potential Drug-Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, Lamivudine, or Concomitant Drug*	Clinical Comment
DOLUTEGRAVIR		
Antiarrhythmic: Dofetilide	Dofetilide↑	Coadministration of DOVATO with dofetilide is contraindicated due to potential life-threatening toxicity caused by high dofetilide concentrations.
Potassium channel blocker: Fampridine (also known as dalfampridine)	Fampridine/dalfampridine↑	Coadministration is contraindicated with DOVATO due to the potential for seizures associated with fampridine/dalfampridine.
Anticonvulsants Oxcarbazepine Phenytoin Phenobarbital Carbamazepine[a]	Dolutegravir↓	An additional 50 mg dose of dolutegravir (TIVICAY) should be taken, separated by 12 hours from DOVATO.
Antidiabetics: Metformin[a]	Co-administered with DOVATO: Metformin ↑	Consider metformin dose adjustments when starting or stopping concomitant treatment to maintain glycemic control.
Antimycobacterials Rifampin[a]	Dolutegravir↓	An additional 50 mg dose of dolutegravir (TIVICAY) should be taken, separated by 12 hours from DOVATO.
Medications containing polyvalent cations (e.g. Mg, Al) Cation-containing antacids[a] or laxative, sucralfate, buffered medications	Dolutegravir↓	DOVATO is recommended to be administered 2 hours before or 6 hours after taking medications containing polyvalent cations.
Calcium and iron supplements[a] Includes multivitamins that contain calcium or iron.	Dolutegravir ↓	When taken with food, DOVATO and calcium and/or iron supplements or multivitamins containing calcium and/or iron can be

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, Lamivudine, or Concomitant Drug*	Clinical Comment
		taken at the same time. Under fasting conditions, DOVATO should be taken 2 hours before or 6 hours after taking supplements containing calcium and/or iron.
LAMIVUDINE		
Trimethoprim/sulfamethoxazole (Co-trimoxazole)	Lamivudine: AUC ↑ ~40% Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔	Unless the patient has renal impairment, no dosage adjustment of DOVATO is necessary. Co-administration with DOVATO is not recommended in patients with renal impairment as lamivudine dosage adjustment is not possible. The effect of coadministration of lamivudine with higher doses of co-trimoxazole used for the treatment of *Pneumocystis jiroveci* pneumonia (often referred to as PCP) and toxoplasmosis has not been studied.
Sorbitol solution (3.2 g, 10.2 g, 13.4 g)	Single dose lamivudine oral solution 300 mg Lamivudine: AUC ↓ 14%; 32%; 36% C_{max} ↓ 28%; 52%, 55%.	When possible, avoid chronic coadministration of sorbitol-containing medicines with DOVATO. Consider more frequent monitoring of HIV-1 viral load when chronic coadministration cannot be avoided.

↑ = Increase, ↓ = Decrease, ↔ = No change.

[a] For magnitude of interaction, see Table 7 and Table 8.

The effects of DTG on the exposure of co-administered drugs are shown in Table 7. The effects of co-administered drugs on the exposure of DTG are shown in Table 8.

Table 7 Summary of Effect of Dolutegravir on the Pharmacokinetics of Co-administered Drugs

Co-administered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Co-administered Drug With/Without Dolutegravir No Effect = 1.00		
			C_τ or C_{24}	AUC	C_{max}
Daclatasvir 60 mg once daily	50 mg once daily	12	1.06 (0.88 to 1.29)	0.98 (0.83 to 1.15)	1.03 (0.84 to 1.25)
Ethinyl estradiol 0.035 mg	50 mg twice daily	15	1.02 (0.93, 1.11)	1.03 (0.96, 1.11)	0.99 (0.91, 1.08)
Methadone 16 to 150 mg	50 mg twice daily	12	0.99 (0.91, 1.07)	0.98 (0.91, 1.06)	1.00 (0.94, 1.06)
Midazolam 3 mg	25 mg once daily	10	_	0.95 (0.79, 1.15)	_
Norgestimate 0.25 mg	50 mg twice daily	15	0.93 (0.85, 1.03)	0.98 (0.91, 1.04)	0.89 (0.82, 0.97)
Metformin 500 mg twice daily	50 mg once daily	14	_	1.79 (1.65, 1.93)	1.66 (1.53, 1.81)
Metformin 500 mg twice daily	50 mg twice daily	14	_	2.45 (2.25, 2.66)	2.11 (1.91, 2.33)

Table 8 Summary of Effect of Co-administered Drugs on the Pharmacokinetics of Dolutegravir

Co-administered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters With/Without Co-administered Drugs No Effect = 1.00		
			C_τ or C_{24}	AUC	C_{max}
Maalox®	50 mg single dose	16	0.26 (0.21, 0.31)	0.26 (0.22, 0.32)	0.28 (0.23, 0.33)
Maalox® 2 hrs after dolutegravir	50 mg single dose	16	0.70 (0.58, 0.85)	0.74 (0.62, 0.90)	0.82 (0.69, 0.98)
Calcium Carbonate 1200 mg simultaneous administration (fasted)	50 mg single dose	12	0.61 (0.47, 0.80)	0.61 (0.47, 0.80)	0.63 (0.50, 0.81)
Calcium Carbonate 1200 mg simultaneous administration (fed)	50 mg single dose	11	1.08 (0.81, 1.42)	1.09 (0.84, 1.43)	1.07 (0.83, 1.38)
Calcium Carbonate 1200 mg 2 hrs after dolutegravir	50 mg single dose	11	0.90 (0.68, 1.19)	0.94 (0.72, 1.23)	1.00 (0.78, 1.29)
Ferrous Fumarate 324 mg simultaneous administration (fasted)	50 mg single dose	11	0.44 (0.36, 0.54)	0.46 (0.38, 0.56)	0.43 (0.35, 0.52)

Co-administered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters With/Without Co-administered Drugs No Effect = 1.00		
			C_τ or C_{24}	AUC	C_{max}
Ferrous Fumarate 324 mg simultaneous administration (fed)	50 mg single dose	11	1.00 (0.81, 1.23)	0.98 (0.81, 1.20)	1.03 (0.84, 1.26)
Ferrous Fumarate 324 mg 2 hrs after dolutegravir	50 mg single dose	10	0.92 (0.74, 1.13)	0.95 (0.77, 1.15)	0.99 (0.81, 1.21)
Multivitamin One tablet once daily	50 mg single dose	16	0.68 (0.56, 0.82)	0.67 (0.55, 0.81)	0.65 (0.54, 0.77)
Omeprazole 40 mg once daily	50 mg single dose	12	0.95 (0.75, 1.21)	0.97 (0.78, 1.20)	0.92 (0.75, 1.11)
Prednisone 60 mg once daily with taper	50 mg once daily	12	1.17 (1.06, 1.28)	1.11 (1.03, 1.20)	1.06 (0.99, 1.14)
Rifampin[a] 600 mg once daily	50 mg twice daily[a]	11	0.28 (0.23, 0.34)	0.46 (0.38, 0.55)	0.57 (0.49, 0.65)
Rifampin[b] 600 mg once daily	50 mg twice daily[b]	11	1.22 (1.01, 1.48)	1.33 (1.15, 1.53)	1.18 (1.03, 1.37)
Rifabutin 300 mg once daily	50 mg once daily	9	0.70 (0.57, 0.87)	0.95 (0.82, 1.10)	1.16 (0.98, 1.37)
Carbamazepine 300 mg twice daily	50 mg once daily	14	0.27 (0.24, 0.31)	0.51 (0.48, 0.55)	0.67 (0.61, 0.73)
Daclatasvir 60 mg once daily	50 mg once daily	12	1.45 (1.25 to 1.68)	1.33 (1.11 to 1.59)	1.29 (1.07 to 1.57)

[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.

Drugs with No Observed or Predicted Interactions with DOVATO

Based on drug interaction studies conducted with DOVATO or the components of DOVATO, no clinically significant drug interactions have been either observed or are expected when DOVATO is administered with the following drugs: hormonal contraceptives containing norgestimate and ethinyl estradiol, methadone, midazolam, omeprazole, prednisone, rifabutin, daclatasvir, sofosbuvir/velpatasvir, trimethoprim-sulfamethoxazole (except in renal impairment, see Table 6), and calcium carbonate, ferrous fumarate, or cation-containing multivitamin supplements (when taken with food, see Table 6).

9.5 Drug-Food Interactions

DOVATO can be taken with or without food (see 10 CLINICAL PHARMACOLOGY).

9.6 Drug-Herb Interactions

No interaction study has been conducted, however, St. John's Wort is a potent CYP3A inducer and may potentially decrease dolutegravir plasma concentration. In adults and adolescent patients, an additional dose of TIVICAY 50 mg separated by 12 hours from DOVATO may be considered when taken together with St. John's Wort.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral Deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. *In vitro*, dolutegravir dissociates slowly from the active site of the wild type integrase-DNA complex (t ½ 71 hours). Strand transfer biochemical assays using purified HIV-1 integrase and pre-processed substrate DNA resulted in IC_{50} values of 2.7 nM and 12.6 nM.

Lamivudine is a synthetic nucleoside analogue, an (-) enantiomer of a dideoxy analogue of cytidine. Lamivudine is metabolized by intracellular kinases to its triphosphate (TP), which is the active moiety (lamivudine triphosphate or L-TP) Lamivudine is a nucleoside reverse transcriptase inhibitor (NRTI), and is a potent, selective inhibitor of HIV-1 and HIV-2 replication *in vitro. In vitro* L-TP has an intracellular half-life of approximately 10.5 to 15.5 hours. L-TP is a substrate for and a competitive inhibitor of HIV reverse transcriptase (RT). Inhibition of RT is via viral DNA chain termination after nucleoside analogue incorporation. L-TP shows significantly less affinity for host cell DNA polymerases and is a weak inhibitor of mammalian α, β, and γ DNA polymerases.

10.2 Pharmacodynamics

In a randomized, dose-ranging trial, HIV 1 infected patients treated with dolutegravir monotherapy demonstrated rapid and dose-dependent antiviral activity with mean declines from baseline to Day 11 in HIV-1 RNA of 1.5, 2.0, and 2.5 $\log_{10}$ for dolutegravir 2 mg, 10 mg, and 50 mg once daily, respectively. This antiviral response was maintained for 3 to 4 days after the last dose in the 50 mg group.

Effects on Electrocardiogram

Dolutegravir

In a randomized, placebo-controlled, cross-over trial, 42 healthy subjects received single dose oral administrations of placebo, dolutegravir 250 mg suspension (exposures approximately 3-fold of the 50 mg once-daily dose at steady state), and moxifloxacin (400 mg, active control) in random sequence. Dolutegravir did not prolong the QTc interval for 24 hours post dose. After baseline and placebo adjustment, the maximum mean QTc change based on Fridericia correction method (QTcF) was 1.99 msec (1-sided 95% upper CI: 4.53 msec).

Effects on Renal Function

The effect of dolutegravir on serum creatinine clearance (CrCl), glomerular filtration rate (GFR) using iohexol as the probe and effective renal plasma flow (ERPF) using para-aminohippurate (PAH) as the probe was evaluated in an open-label, randomized, 3-arm, parallel, placebo-controlled study in 37

healthy subjects, who were administered dolutegravir 50 mg once daily (n=12), 50 mg twice daily (n=13) or placebo once daily (n=12) for 14 days. A modest decrease in CrCl was observed with dolutegravir within the first week of treatment, consistent with that seen in clinical studies. Dolutegravir at both doses had no significant effect on GFR or ERPF. These data support *in vitro* studies which suggest that the small increases in creatinine observed in clinical studies are due to the nonpathologic inhibition of the organic cation transporter 2 (OCT2) in the proximal renal tubules, which mediates the tubular secretion of creatinine.

In the pooled analysis of GEMINI-1 and GEMINI-2 studies in treatment-naïve adult patients at the Week 48 and 96 analyses, TIVICAY + 3TC had an increase in the estimated GFR using cystatin C adjusted CKD-EPI equation (adjusted mean change from baseline of 6.3 (Week 48) and 10.7 (Week 96) mL/min/1.73 m2). Change from baseline analysis showed that urine albumin/creatinine and protein/creatinine ratios decreased at Week 48 and 96 compared to baseline in the TIVICAY + 3TC group (urine albumin/creatinine Week 48/baseline ratio of 0.914 and urine albumin/creatinine Week 96/baseline ratio of 0.934; protein/creatinine Week 48/baseline ratio of 0.869 and protein/creatinine Week 96/baseline ratio of 0.878).

At Week 144, the TIVICAY + 3TC group had a greater increase in the estimated GFR using cystatin C adjusted CKD-EPI equation, compared with the TIVICAY + TRUVADA group (adjusted mean change from baseline of 12.2 and 10.6 mL/min/1.73 m^2, respectively; p = 0.008). Change from baseline analysis showed that urine albumin/creatinine increased and protein/creatinine ratios decreased at Week 144 compared to baseline in the TIVICAY + 3TC group (urine albumin/creatinine of 1.046 and protein/creatinine of 0.994).

10.3 Pharmacokinetics

In a fasted comparative bioavailability study, the dolutegravir C_{max} was equivalent and the dolutegravir AUC_T was 16% higher when comparing the DOVATO tablet to dolutegravir 50 mg co-administered with lamivudine 300 mg. The higher DTG AUC_T does not significantly affect patient safety or antiviral efficacy based on historical clinical efficacy and safety data for DTG 50 mg BID. The lamivudine AUC_T was equivalent when comparing the DOVATO tablet to lamivudine 300 mg co-administered with dolutegravir 50 mg. Lamivudine C_{max} for the DOVATO tablet was 32% higher than lamivudine 300 mg co-administered with dolutegravir 50 mg. The higher lamivudine C_{max}, which reflects differences in the rate of absorption but not extent of absorption, does not significantly affect patient safety or antiviral efficacy based on historical clinical efficacy and safety data at higher lamivudine doses/exposures. Following multiple oral doses of DOVATO in HIV-infected, treatment experienced subjects in the Phase III TANGO study, the steady state dolutegravir and lamivudine AUC and C_{max} were similar to historical exposures.

The pharmacokinetic (PK) properties of the components of DOVATO are provided in Table 9.

Table 9 Pharmacokinetic Properties of the Components of DOVATO

	Dolutegravir	Lamivudine
Absorption		
AUC_T [a] (μg.h/mL)	52.3 (31.5)	13.4 (18.1)
C_{max} [a] (μg/mL)	2.91 (30.6)	3.22 (29.3)
T_{max} [a] (h)	2.5 (0.5, 6.0)	1 (0.5, 3.5)
Effect of high-fat meal (relative to fasting)[b]	AUC_I % Ratio 132.6 (118.4, 148.5)	AUC_I % Ratio 91.1 (86.6, 95.9)

	Dolutegravir	Lamivudine
Distribution		
% Bound to human plasma proteins	~99	<36
Source of protein binding data	*in vitro*	*in vitro*
Blood-to-plasma ratio	0.44-0.54	1.1 - 1.2[c]
Metabolism		
Metabolic pathways	UGT1A1 CYP3A (minor)	Not significantly metabolized
Elimination		
Major route of elimination	Metabolism	Renal, by the organic cationic transport system
$t_{1/2}$ (h)	~14	18-19
% of dose excreted as total [^{14}C] (unchanged drug) in urine	31 (<1)[d]	ND (~70)[e]
% of dose excreted as total [^{14}C] (unchanged drug) in feces	64 (53)[d]	ND (ND)

ND: not determined

a. Single dose PK parameters presented as geometric mean (CVb) except for T_{max} which is presented as median (range)
b. Geometric mean ratio (fed/fasted) in PK parameters and (90% confidence interval). High- calorie/high-fat meal = ~900 kcal, 56% fat
c. Lamivudine blood-to-plasma ratio (B/P) was calculated based on the percent (p) of blood lamivudine associated with erythrocytes (53% to 57%) and the hematocrit value (H) using the equation B/P = (1 -H)(1-p)
d. Based on single-dose, mass-balance study of [^{14}C] dolutegravir
e. Based on 24-hour urine collection obtained after oral or IV administration (NUCB1001)

Absorption

Dolutegravir and lamivudine are rapidly absorbed following oral administration. The absolute bioavailability of dolutegravir has not been established. The absolute bioavailability of oral lamivudine in adults is 80 to 85%. For DOVATO, the median time to maximal plasma concentrations (t_{max}) is 2.5 hours for dolutegravir and 1.0 hour for lamivudine, when dosed under fasted conditions.

Following multiple oral doses of dolutegravir 50 mg once daily, the geometric mean steady state pharmacokinetic parameter estimates are 53.6 µg.h/mL for AUC_{24}, 3.67 µg/mL for C_{max}, and 1.11 µg/mL for C_{24}. Following multiple-dose oral administration of lamivudine 300 mg once daily for seven days the mean steady-state C_{max} is 2.04 µg/mL and the mean AUC_{24} is 8.87 µg.h/mL.

- **Effect of Food on Oral Absorption**
  DOVATO may be administered with or without food. Administration of DOVATO with a high-fat, high-calorie meal increased dolutegravir AUC_T and C_{max} by 32% and 21%, respectively, and decreased the lamivudine C_{max} by 32% compared to fasted conditions. The lamivudine AUC_T was not affected by a high-fat, high-calorie meal. These changes are not clinically significant.

Distribution

Dolutegravir is highly bound (≥ 98.9%) to human plasma proteins based on *in vivo* data and binding is independent of plasma dolutegravir concentration. The apparent volume of distribution (Vd/F) following 50 mg once daily oral administration was estimated at 17.4 L based on population pharmacokinetic analysis. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays low plasma protein binding (less than 36%).

- ***Cerebrospinal Fluid (CSF)***

  In 12 treatment-naïve patients on dolutegravir plus abacavir/lamivudine, the median dolutegravir concentration in CSF was 18 ng/mL (ranging from 4 to 23 ng/mL) 2 to 6 hours post-dose after 2 weeks of treatment. The clinical relevance of this finding has not been established. The mean ratio of CSF/serum lamivudine concentrations 2 to 4 h after oral administration was approximately 12%. The true extent of CNS penetration of lamivudine and its relationship with any clinical efficacy is unknown.

Metabolism

Dolutegravir is primarily metabolized via UGT1A1 with a minor CYP3A component (9.7% of total dose administered in a human mass balance study). Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged drug is low (<1% of the dose). Metabolism of lamivudine is a minor route of elimination. Lamivudine is predominately cleared unchanged by renal excretion. The likelihood of metabolic interactions with lamivudine is low due to the small extent of hepatic metabolism (less than 10%).

Elimination

Dolutegravir has a terminal half-life of approximately 14 hours and an apparent clearance (CL/F) of 0.9-1.05 L/hr based on population pharmacokinetic analyses.

Fifty-three percent of total oral dose is excreted unchanged in the faeces. It is unknown if all or part of this is due to unabsorbed drug or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen.

The observed lamivudine half life of elimination is 18 to 19 hours. For patients receiving lamivudine 300 mg once daily, the terminal intracellular half-life of lamivudine-TP was 16 to 19 hours. The mean systemic clearance of lamivudine is approximately 0.32 L/h/kg, predominantly by renal clearance (> 70%) via the organic cationic transport system.

Special Populations and Conditions

- **Pediatrics:** DOVATO has not been studied in the pediatric population.
  - **Dolutegravir:** In a pediatric study including 23 antiretroviral treatment-experienced HIV-1 infected adolescents aged 12 to 18 years of age, the pharmacokinetics of dolutegravir was evaluated in 10 adolescents and showed that dolutegravir 50 mg once daily dosage resulted in dolutegravir exposure in pediatric subjects comparable to that observed in adults who received dolutegravir 50 mg once daily (Table 10).

Table 10 Pediatric pharmacokinetic parameters (n=10)

Age/weight	Dolutegravir Dose	Dolutegravir Pharmacokinetic Parameter Estimates Geometric Mean (CV%)		
		$AUC_{(0-24)}$ μg.hr/mL	C_{max} μg/mL	C_{24} μg/mL
12 to <18 years ≥ 40 kg [a]	50 mg once daily [a]	46 (43)	3.49 (38)	0.90 (59)

[a] One subject weighing 37 kg received 35 mg once daily.

- **Lamivudine:** Limited data are available in adolescents receiving a daily dose of 300 mg of lamivudine. Pharmacokinetic parameters are comparable to those reported in adults.

- **Geriatrics:** Population pharmacokinetic analysis of dolutegravir using data in HIV-1 infected adults showed that there was no clinically relevant effect of age on dolutegravir exposure. Pharmacokinetic data for dolutegravir and lamivudine in subjects of >65 years old are limited.
- **Gender:** Population pharmacokinetic analyses revealed no clinically relevant effect of gender on the exposure of dolutegravir. No clinically relevant differences in the pharmacokinetics of lamivudine have been observed between men and women.
- **Pregnancy and Breast-feeding:** The pharmacokinetics of lamivudine during late pregnancy were similar to that of non-pregnant adults. In humans, consistent with passive transmission of lamivudine across the placenta, lamivudine concentrations in infant serum at birth were similar to those in maternal and cord serum at delivery.

  There are limited pharmacokinetic data on the use of dolutegravir in pregnancy.
- **Genetic Polymorphism:** In a meta-analysis using pharmacogenomics samples collected in clinical studies in healthy subjects, subjects with UGT1A1 (n=7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n=41).
- **Ethnic origin**: Population PK analyses using pooled pharmacokinetic data from adult studies revealed no clinically relevant effect of race on the exposure of dolutegravir.
- **Hepatic Insufficiency:** Pharmacokinetic data has been obtained for dolutegravir and lamivudine alone.

  Data obtained for lamivudine in patients with moderate to severe hepatic impairment and for dolutegravir in patients with moderate hepatic impairment show that the pharmacokinetics are not significantly affected by hepatic dysfunction. Dolutegravir is primarily metabolized and eliminated by the liver. In a study comparing 8 subjects with moderate hepatic impairment (Child-Pugh score B) to 8 matched healthy adult controls, exposure of dolutegravir from a single 50 mg dose was similar between the two groups. The effect of severe hepatic impairment (Child-Pugh score C) on the pharmacokinetics of dolutegravir has not been studied.
- **Hepatitis B or Hepatitis C Co-infection:** Population pharmacokinetic analysis indicated that hepatitis C virus co-infection had no clinically relevant effect on the exposure to dolutegravir. There are limited pharmacokinetic data on hepatitis B co-infection.

- **Renal Insufficiency:** Pharmacokinetic data have been obtained for dolutegravir and lamivudine alone. DOVATO should not be used in patients with creatinine clearance of less than 30 mL/min because, whilst no dosage adjustment of dolutegravir is necessary in patients with renal impairment, dose reduction is required for the lamivudine component.

  Studies with lamivudine show that plasma concentrations (AUC) are increased in patients with renal dysfunction due to decreased clearance.

  Renal clearance of unchanged drug is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of dolutegravir was performed in subjects (n = 8) with severe renal impairment (CLcr <30 mL/min). No clinically important pharmacokinetic differences between subjects with severe renal impairment (CLcr <30 mL/min) and matching healthy subjects were observed. Dolutegravir AUC, C_{max}, and C_{24} were lower by 40%, 23%, and 43%, respectively, in subjects with severe renal impairment as compared with matched healthy controls.

11 STORAGE, STABILITY AND DISPOSAL

Store DOVATO up to 30°C.

Healthcare professionals should recommend that their patients return all unused medications to a pharmacy for proper disposal.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special requirements for use or handling of this product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Dolutegravir

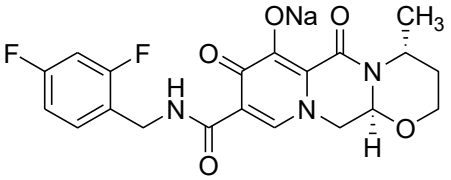
Proper name: dolutegravir sodium

Chemical name: sodium (4*R*,12a*S*)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazin-7-olate

Molecular formula and molecular mass: $C_{20}H_{18}F_2N_3NaO_5$

441.36 g/mol

Structural formula:



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

Drug Substance

Lamivudine

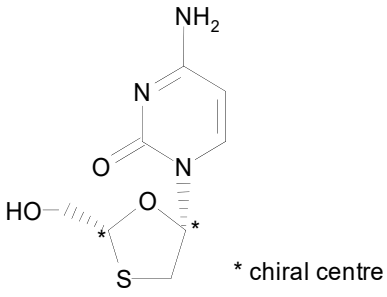
Proper name: lamivudine

Chemical name: 2(1H)-Pyrimidinone, 4-amino-1-[2- (hydroxymethyl)-1,3-oxathiolan-5-yl]-(2R-cis)-

Molecular formula and molecular mass: $C_8H_{11}N_3O_3S$

229.3

Structural formula:



Physicochemical properties: Lamivudine is a white to off-white crystalline solid with a melting point of 176°C and is soluble in water.

14 CLINICAL TRIALS

The efficacy of DOVATO is supported by data from two randomized, double-blind, controlled trials (GEMINI-1 [204861] and GEMINI-2 [205543]) in HIV-1-infected treatment naïve adults, and data from a randomized, open-label, controlled trial (TANGO [204862]) in virologically suppressed HIV-1-infected adults.

14.1 Clinical Trials by indication

Treatment Naïve

GEMINI-1 and GEMINI-2 are identical 148-week, Phase III, randomized, double-blind, multicenter, parallel-group, non-inferiority controlled trials. A total of 1433 HIV-1 infected antiretroviral treatment-naïve adult subjects received treatment in the trials. Subjects were enrolled with a screening plasma HIV-1 RNA of 1000 c/mL to ≤ 500,000 c/mL. Subjects were randomized to a two-drug regimen of TIVICAY (dolutegravir 50 mg) plus 3TC (lamivudine 300mg) administered once daily or to a three-drug regimen TIVICAY (dolutegravir 50 mg) plus TRUVADA (tenofovir/emtricitabine 200mg/300mg) 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 for the ITT-E population).

The demographic baseline characteristics were similarly distributed between treatment arms (see Table 11).

Table 11 Summary of Baseline Characteristics for Studies GEMINI-1, GEMINI-2, and Pooled Data (ITT-E Population)

	GEMINI-1		GEMINI-2		POOLED	
	TIVICAY + 3TC	TIVICAY + TRUVADA	TIVICAY + 3TC	TIVICAY + TRUVADA	TIVICAY + 3TC	TIVICAY + TRUVADA
	N=356 (%)	N=358 (%)	N=360 (%)	N=359 (%)	N=716 (%)	N=717 (%)
Baseline HIV-1 RNA (c/mL)						
<100,000	282 (79)	282 (78)	294 (82)	282 (79)	576 (80)	564 (79)
≥100,000 to <500,000	70 (20)	69 (19)	57(16)	69 (19)	127 (18)	138 (19)
≥500,000	4 (1)	7 (2)	9 (3)	8 (2)	13 (2)	15 (2)
Baseline CD4+ (log_{10} cells/mm^3)						
Median	427.0	435.5	427.5	442.0	427.0	438.0
Min., Max.	19, 1399	19, 1305	19, 1364	19, 1497	19, 1399	19, 1497
Baseline CD4+ (cells/mm^3), n (%)						
<50	5 (1)	4 (1)	3 (<1)	5 (1)	8 (1)	9 (1)
50 to <200	26 (7)	25 (7)	29 (8)	20 (6)	55 (8)	45 (6)
200 to <350	92 (26)	79 (22)	87 (24)	87 (24)	179 (25)	166 (23)

	GEMINI-1		GEMINI-2		POOLED	
	TIVICAY + 3TC	TIVICAY + TRUVADA	TIVICAY + 3TC	TIVICAY + TRUVADA	TIVICAY + 3TC	TIVICAY + TRUVADA
	N=356 (%)	N=358 (%)	N=360 (%)	N=359 (%)	N=716 (%)	N=717 (%)
350 to <500	99 (28)	120 (34)	105 (29)	108 (30)	204 (28)	228 (32)
≥500	134 (38)	130 (36)	136 (38)	139 (39)	270 (38)	269 (38)
Age (y) median (range)	32.0 (18-69)	33.0 (18-66)	32.0 (18-72)	33.0 (18-70)	32.0 (18-72)	33.0 (18-70)
Sex						
Female	59 (17)	52 (15)	54 (15)	46 (13)	113 (16)	98 (14)
Male	297 (83)	306 (85)	306 (85)	313 (87)	603 (84)	619 (86)
Race, n (%)						
American Indian or Alaska Native	31 (9)	28 (8)	21 (6)	29 (8)	52 (7)	57 (8)
Asian	37 (10)	42 (12)	34 (9)	30 (8)	71 (10)	72 (10)
Black/African American	39 (11)	36 (10)	51 (14)	35 (10)	90 (13)	71 (10)
Native Hawaiian or other Pacific Islander	2 (<1)	0	0	1 (<1)	2 (<1)	1 (<1)
White	244 (69)	247 (69)	240 (67)	252 (70)	484 (68)	499 (70)
Multiple Heritage	3 (<1)	5 (1)	14 (4)	12 (3)	17 (2)	17 (2)
Hepatitis B & C Test Results						
B only	0	0	0	0	0	0
C only	26 (7)	28 (8)	13 (4)	21 (6)	39 (5)	49 (7)
B and C	0	0	0	0	0	0
Neither	329 (92)	330 (92)	347 (96)	338 (94)	676 (94)	668 (93)
Missing	1 (<1)	0	0	0	1 (<1)	0
CDC Category						
Stage 0	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)
Stage 1	128 (36)	126 (35)	129 (36)	137 (38)	257 (36)	263 (37)
Stage 2	194 (54)	204 (57)	198 (55)	189 (53)	392 (55)	393 (55)
Stage 3	33 (9)	28 (8)	33 (9)	32 (9)	66 (9)	60 (8)

TIVICAY = dolutegravir, 3TC = lamivudine, TRUVADA = tenofovir disoproxil fumarate/emtricitabine

Study Results:

TIVICAY plus 3TC remained non-inferior to TIVICAY plus TRUVADA through 144 weeks in GEMINI-1 and GEMINI-2 studies. This was supported by the pooled analysis, see **Table 12**.

Table 12 Virologic Outcomes of Randomized Treatment at Week 48, 96 and 144 in GEMINI studies (Snapshot Algorithm, ITT-E Population)

	TIVICAY + 3TC (N=716), n (%)			TIVICAY + TRUVADA (N=717), n (%)		
	Week 48	Week 96	Week 144	Week 48	Week 96	Week 144
HIV-1 RNA <50 copies/mL	(655/716) 91%	(616/716) 86%	(584/716) 82%	(669/717) 93%	(642/717) 90%	(599 /717) 84%
Treatment Difference[†] (95% confidence intervals)	Week 48: -1.7% (95% CI: -4.4%, 1.1%) Week 96: -3.4% (95% CI: -6.7%, 0.0%) Week 144: -1.8% (95% CI: -5.8%, 2.1%)					
Virologic non response	20 (3%)	22 (3%)	23 (3%)	13 (2%)	14 (2%)	21 (3%)
Reasons						
Data in window and ≥50 copies/mL	8 (1%)	4 (<1%)	4 (<1%)	5 (<1%)	4 (<1%)	5 (<1%)
Discontinued for lack of efficacy	5 (<1%)	9 (1%)	10 (1%)	2 (<1%)	3 (<1%)	4 (<1%)
Discontinued for other reasons and ≥50 copies/mL	5 (<1%)	7 (1%)	7 (<1%)	5 (<1%)	6 (<1%)	11 (2%)
Change in ART	2 (<1%)	2 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
No virologic data at Week 48, 96 or 144 window	41 (6%)	78 (11%)	109 (15%)	35 (5%)	61 (9%)	97 (14%)
Reasons						
Discontinued study due to adverse event or death	10 (1%)	22 (3%)	29 (4%)	13 (2%)	21 (3%)	32 (4%)
Discontinued study for other reasons	29 (4%)	56 (8%)	78 (11%)	22 (3%)	38 (5%)	64 (9%)
Missing data during window but on study	2 (<1%)	0	2 (<1%)	0	2 (<1%)	1 (<1%)
	n/N (%)			n/N (%)		
Baseline Plasma Viral Load (copies/mL)						
≤100,000	526 / 576 (91%)	499 / 576 (87%)	(469/576) 81%	531 / 564 (94%)	510 / 564 (90%)	471/564 (84%)
>100,000	129 / 140 (92%)	117 / 140 (84%)	(115/140) 82%	138 / 153 (90%)	132 / 153 (86%)	(128/153) 84%
Baseline CD4+ (cells/ mm^3)						
≤200	50 / 63 (79%)[a]	43 / 63 (68%)[b]	(42/63) 67%	51 / 55 (93%)	48 / 55 (87%)	(42/55) 76%
>200	605 / 653 (93%)	573/ 653 (88%)	(542/653) 83%	618 / 662 (93%)	594 /662 (90%)	(557/662) 84%
Gender						
Male	555 / 603 (92%)	523 / 603 (87%)	(500/603) 83%	580 / 619 (94%)	557 / 619 (90%)	(517/619) 84%
Female	100 / 113 (88%)	93 / 113 (82%)	(84/113) 74%	89 / 98 (91%)	85 / 98 (87%)	(82/98) 84%

	TIVICAY + 3TC (N=716), n (%)			TIVICAY + TRUVADA (N=717), n (%)		
	Week 48	Week 96	Week 144	Week 48	Week 96	Week 144
Race						
White	451 / 484 (93%)	429 / 484 (89%)	409/484 (85%)	473 / 499 (95%)	453 / 499 (91%)	429/499 (86%)
African-American/African Heritage/Asian/Other	204 / 232 (88%)	187 / 232 (81%)	175/232 (75%)	196 / 218 (90%)	189/218 (87%)	170/218 (78%)
Age (years)						
<50	597 / 651 (92%)	561/651 (86%)	(530/651) 81%	597 / 637 (94%)	572 / 637 (90%)	(533/637) 84%
≥50	58 / 65 (89%)	55 / 65 (85%)	(54/65) 83%	72 / 80 (90%)	70 / 80 (88%)	(66/80) 83%

The adjusted mean change from baseline in CD4+ cell count based on the pooled analysis at Week 48 was 224 cells/mm^3 for the group receiving TIVICAY + 3TC, and 217 cells/mm^3 for the TIVICAY + TRUVADA group. The adjusted mean change from baseline in CD4+ cell count based on the pooled analysis at Week 96 was 269 cells/mm^3 for the group receiving TIVICAY + 3TC, and 259 cells/mm^3 for the TIVICAY + TRUVADA group.

Virologic outcomes by baseline CD4+ (cells/mm^3) in GEMINI-1 and GEMINI-2 pooled analysis are shown in **Table 12**. In both studies, lower response rates (HIV-1 RNA<50 copies/mL) were observed in patients with baseline CD4+ ≤ 200 cells/mm^3. These findings were seen irrespective of baseline plasma HIV-1 RNA.

At 144 weeks in the GEMINI 1 and GEMINI 2 studies, the TIVICAY + 3TC group (82% with plasma HIV 1 RNA < 50 copies/mL [pooled data]) remained non-inferior to TIVICAY + TRUVADA group (84% with plasma HIV 1 RNA < 50 copies/mL [pooled data]). The results of the pooled analysis were in line with those of the individual studies, for which the secondary endpoint (difference in proportion of participants with <50 copies/mL plasma HIV 1 RNA at Week 144 based on the Snapshot algorithm for TIVICAY + 3TC versus TIVICAY + TRUVADA) was met. The adjusted difference in proportions and 95% CI for the pooled data was -1.8% (-5.8, 2.1). The adjusted differences of -3.6% (95% CI: -9.4, 2.1) for GEMINI-1 and 0.0% (95% CI: -5.3, 5.3) for GEMINI 2 were within the prespecified non-inferiority margin of 10%.

The mean adjusted increase from baseline in CD4+ T-cell counts based on the pooled analysis was 302 cells/mm^3 in the TIVICAY+3TC arm and 300 cells/mm^3 in the TIVICAY + TRUVADA arm, at Week 144.

Virologically Suppressed

The efficacy of DOVATO in HIV-infected, antiretroviral therapy experienced, virologically suppressed subjects is supported by data from a Phase III, 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 tenofovir alafenamide based regimen (TBR) received treatment. Subjects were randomized in a 1:1 ratio to receive DOVATO once daily or continue with TBR. Randomization was stratified by baseline third agent class (protease inhibitor [PI], integrase inhibitor [INSTI], or non-nucleoside reverse transcriptase inhibitor [NNRTI]). The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 c/mL (virologic non-response) as per the FDA Snapshot category at Week 48 (Snapshot algorithm adjusting for randomization stratification factor: Baseline Third Agent Class [INSTI, PI, NNRTI]).

At baseline the median age of subjects was 39 years, 8% were female and 21% non-white, 5% were CDC Stage 3 (AIDS) and 98% subjects had Baseline CD4+ cell count ≥200 cells/mm3; these characteristics were similar between treatment arms. Subjects had been on ART for a median of 2.8 years and 2.9 years prior to Day 1 for the DOVATO and TBR arms, respectively. Most subjects were on INSTI-based TBR, 78% and 80% in the DOVATO and TBR arms, respectively.

Study Results

In the primary 48 week analysis in TANGO, DOVATO was non-inferior to TBR, with <1% of subjects in both arms experiencing virologic failure (HIV-1 RNA ≥50 c/mL) based on the Snapshot algorithm (Table 13).

Table 13 Virologic Outcomes of Randomized Treatment of TANGO at Week 48 and Week 96 (Snapshot algorithm)

	Week 48		Week 96	
	DTG/3TC FDC (N=369) n (%)	**TBR (N=372) n (%)**	**DTG/3TC FDC (N=369) n (%)**	**TBR (N=372) n (%)**
Virologic non response (≥50 copies/mL)**	1 (<1%)	2 (<1%)	1 (<1%)	4 (1%)
Treatment Difference[†] (95% confidence intervals)	-0.3% (95% CI: -1.2%, 0.7%)		-0.8% (95% CI: -2.0%, 0.4%)	
Reasons				
Data in window and ≥50 copies/mL	0	0	0	1 (<1%)
Discontinued for lack of efficacy	0	2 (<1%)	0	3 (<1%)
Discontinued for other reasons and ≥50 copies/mL	1 (<1%)	0	1 (<1%)	0
Change in ART	0	0	0	0
HIV-1 RNA <50 copies/mL	(344/369) 93%	(346/372) 93%	(317/369) 86%	(294/372) 79%
No virologic data at Week 48 and 96 window	24 (6%)	24 (6%)	51 (14%)	74 (20%)
Reasons				
Discontinued study due to adverse event or death	12 (3%)	1 (<1%)	17 (5%)	4 (1%)
Discontinued study for other reasons	12 (3%)	22 (6%)	18 (5%)	40 (11%)
Missing data during window but on study (Non-COVID-19 related)	0	1 (<1%)	0	2 (<1%)
Missing data during window but on study (COVID-19 related)	-	-	16 (4%)	28 (8%)

HIV-1 RNA <50 copies/mL by baseline covariates	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Baseline CD4+ (cells/ mm^3)				
<500	92 / 98 (94%)	68/74(92%)	80/98 (82%)	62/74 (84%)
≥500	252/271(93%)	278/298(93%)	237/271(87%)	232/298(78%)
Baseline Third Agent Class				
NNRTI	49 / 51 (96%)	42 / 48 (88%)	47/51 (92%)	36/48 (75%)
INSTI	268/289(93%)	276/296(93%)	245/289(85%)	232/296(78%)
PI	27 / 29 (93%)	28/28 (100%)	25/29 (86%)	26/28 (93%)
Gender				
Male	323/344(94%)	319/339(94%)	297/344(86%)	272/339(80%)
Female	21 / 25 (84%)	27 / 33 (82%)	20/25 (80%)	22/33 (67%)
Race				
White	279/297(94%)	272/289(94%)	257/297(87%)	232/289(80%)
African-American/African Heritage/Other	65 / 72 (90%)	74 / 83 (89%)	60/72 (83%)	62/83 (75%)
Age (years)				
<50	271/290(93%)	260/280(93%)	250/290(86%)	218/280(78%)
≥50	73 / 79 (92%)	86 / 92 (93%)	67/79 (85%)	76/92 (83%)

TBR = tenofovir alafenamide based regimen; INSTI = Integrase inhibitor; NNRTI = Non-nucleoside reverse transcriptase inhibitor; PI = Protease Inhibitor, N = Number of subjects in each treatment group

†Based on CMH-stratified analysis adjusting for Baseline third agent class (PI, NNRTI, INSTI).

**Based on a 4% non-inferiority margin, DOVATO is non-inferior to TBR at Week 48 in the primary analysis (proportion of subjects with plasma HIV-1 RNA ≥50 c/mL) because the upper bound of the 95% CI for the adjusted treatment difference is less than 4%

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+ count at Week 48 was 22.5 cells/mm^3 in subjects who received DOVATO and 11.0 cells/mm^3 in subjects who received the TBR.

At 96 weeks in the TANGO study, the proportion of subjects with HIV-1 RNA ≥50 c/mL (Snapshot) was 0.3% and 1.1% in the DOVATO and TBR groups, respectively. Based on a non-inferiority margin of 4%, DOVATO remained non-inferior to TBR, as the upper bound of the 95% CI for the adjusted treatment difference (-2.0%, 0.4%) was less than 4% for the ITT E Population.

The median change from baseline in CD4+ T-cell counts at Week 96 was 61 cells/mm^3 in the DOVATO FDC arm and 45 cells/mm^3 in the TBR arm.

Adolescents

There are no clinical study data with DOVATO in the adolescent population. However, the safety and efficacy of DOVATO in adolescents 12 years of age and older, and weighting at least 40 kg, is supported by the clinical trial data from prior adolescent studies of dolutegravir or lamivudine available in the respective TIVICAY, 3TC and TRIUMEQ product monographs, and also by clinical data from the GEMINI trials with dolutegravir plus lamivudine in adults.

14.2 Comparative Bioavailability Studies

A single-dose, randomized, open-label, 2-period, 2-sequence crossover study was conducted in healthy, adult male and female volunteers (n=76; 50 males and 26 females) to evaluate the comparative bioavailability of an oral 1 x DOVATO (50 mg dolutegravir/300 mg lamivudine) fixed dose combination tablet versus concurrent oral administration of 1 x Dolutegravir 50 mg tablet and EPIVIR (lamivudine 300 mg) tablet under fasting conditions. The effect of a high-fat, high-calorie meal on the bioavailability of the fixed dose combination tablet was also evaluated in a sub-set of the volunteers (n=16; 10 males and 6 females). The comparative bioavailability results from 74 completed subjects (49 males and 25 females) are summarized in tabular format below.

Table 14 Summary of the Comparative Bioavailability Data for Dolutegravir

Dolutegravir (1 x 50 mg) FASTED CONDITIONS From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (μg.h/mL)	52.3 54.8 (30.5)	45.2 48.4 (36.9)	115.8	(107.2, 125.1)
AUC_I (μg.h/mL)	54.6 57.2 (31.2)	47.2 50.8 (37.8)	115.5	(107.0, 124.7)
C_{max} (μg/mL)	2.91 3.04 (28.7)	2.55 2.70 (32.1)	114.1	(105.3, 123.6)
T_{max}[3] (h)	2.50 (0.500, 6.00)	2.50 (0.500, 5.01)		
$T_{½}$ (h)[4]	15.2 (18.1)	15.4 (17.8)		

1 DOVATO (50 mg dolutegravir/300 mg lamivudine) fixed-dose combination tablets.
2 Dolutegravir 50 mg tablet and lamivudine 300 mg tablet, administered concurrently.
3 Expressed as median (range) only.
4 Expressed as the arithmetic mean (CV%) only.

Table 15 Summary of the Comparative Bioavailability Data for Lamivudine

Lamivudine (1 x 300 mg) FASTED CONDITIONS From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (μg.h/mL)	13.4 13.6 (17.9)	12.5 12.7 (18.9)	107.0	(104.6, 109.5)
AUC_I (μg.h/mL)	13.6[3] 13.8 (17.6)	12.8[3] 13.0 (18.2)	106.4	(104.2, 108.7)[3]
C_{max} (μg/mL)	3.22 3.44 (28.4)	2.44 2.53 (26.7)	131.8	(126.2, 137.6)
T_{max}[4] (h)	1.00 (0.500, 3.50)	1.00 (0.500, 4.00)		
$T_{½}$ (h)[5]	19.5 (31.1)	20.1 (33.5)		

1 DOVATO (50 mg dolutegravir/300 mg lamivudine) fixed-dose combination tablets.
2 Dolutegravir 50 mg tablet and lamivudine 300 mg tablet, administered concurrently.
3 n=73. One subject was excluded from the statistical analysis of AUC_I because >20% of AUC_I was extrapolated and λz time duration <2x calculated $t_{1/2}$.
4 Expressed as median (range).
5 Expressed as the arithmetic mean (CV%) only.

15 MICROBIOLOGY

Antiviral Activity in cell culture

Dolutegravir

Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean EC_{50} values of 0.51 nM to 2.1 nM in peripheral blood mononuclear cells (PBMCs) and MT-4 cells.

In a viral integrase susceptibility assay using the integrase coding region from 13 clinically diverse clade B isolates, dolutegravir demonstrated antiviral potency similar to reference laboratory strains, with a mean EC_{50} of 0.52 nM. When tested in PBMC assays against a panel consisting of 24 HIV-1 clinical isolates [group M (clade A, B, C, D, E, F and G) and group O] and 3 HIV-2 clinical isolates, the geometric

mean EC_{50} was 0.20 nM and EC_{50} values ranged from 0.02 to 2.14 nM for HIV-1, while the geometric mean EC_{50} was 0.18 nM and EC_{50} values ranged from 0.09 to 0.61 nM for HIV-2 isolates.

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. EC50 values were in the range of 0.003 μM to 2 μM (1 μM = 0.23 μg/mL). The EC50 values of lamivudine against different HIV-1 clades (A to G) ranged from 0.001 to 0.120 μM, and against HIV-2 isolates from 0.002 to 0.041 μM in PBMCs. Ribavirin (50μM) decreased the anti-HIV-1 activity of lamivudine by 3.5-fold in MT-4 cells.

Antiviral Activity in combination with other antiviral agents

Dolutegravir
The following drugs were not antagonistic with dolutegravir in *in-vitro* assessments conducted in checkerboard format: stavudine, abacavir, efavirenz, nevirapine, lopinavir, amprenavir, enfuvirtide, maraviroc, adefovir and raltegravir. In addition, the anti-HCV drug ribavirin had no apparent effect on dolutegravir activity.

Lamivudine
No antagonistic effects *in vitro* were seen with lamivudine and other antiretrovirals (tested agents: abacavir, didanosine, nevirapine, zalcitabine, and zidovudine).

Effect of Human Serum and Serum Proteins
In vitro studies suggested a 75-fold shift in EC_{50} of dolutegravir in the presence of 100% human serum (by method of extrapolation), and the protein adjusted EC_{90} (PA-EC_{90}) in PBMCs for dolutegravir was estimated to be 0.064 μg/mL. Dolutegravir trough concentration for a single 50 mg dose in integrase inhibitor naïve patients was 1.20 μg/mL, 19 times higher than the estimated PA-EC_{90}. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays low plasma protein binding (less than 36%).

Resistance in vitro and in vivo (dolutegravir)

Isolation from wild type HIV-1 and activity against resistant strains
Viruses highly resistant to dolutegravir were not observed during the 112 day passage of strain IIIB, with a 4.1-fold maximum fold change (FC) observed for the passaged resistant virus populations with substitutions at the conserved IN positions S153Y and S153F.
Passage of the wild type HIV-1 strain NL432 in the presence of dolutegravir selected for E92Q (passage population virus FC=3.1) and G193E (passage population virus FC=3.2) substitutions on Day 56.
Additional passage of wildtype subtype B, C, and A/G viruses in the presence of dolutegravir selected for R263K (site-directed mutant FC = 1.5), G118R (site-directed mutant FC = 10), and S153T.

Treatment-naïve HIV-1 infected subjects receiving dolutegravir
No INI-resistant mutations or treatment emergent resistance to the NRTI backbone therapy were isolated with dolutegravir 50 mg once daily in treatment–naive studies.

Resistance in vitro and in vivo (lamivudine)

HIV-1 resistance to lamivudine involves the development of a M184I or M184V amino acid change close to the active site of the viral RT. This variant arises both during *in vitro* selection and in HIV-1

infected patients treated with lamivudine-containing antiretroviral therapy. M184V mutants display greatly reduced susceptibility to lamivudine and show diminished viral replicative capacity *in vitro*.

Resistance in vivo (dolutegravir plus lamivudine)

No subjects that met the protocol-defined confirmed virologic withdrawal (CVW) criteria across the pooled GEMINI-1 and GEMINI-2 studies through Week 144 or in the TANGO study through Week 96 had emergent INSTI or NRTI resistance substitutions.

Cross-resistance

Cross resistance between lamivudine and antiretrovirals from other classes (e.g. protease inhibitors (PI) or non-nucleoside reverse transcriptase inhibitors (NNRTIs)), is unlikely.

Site-directed INSTI mutant virus
Dolutegravir activity was determined against a panel of 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 greater than 2-fold decrease in dolutegravir susceptibility (range: 2.3-fold to 3.6-fold from reference). Combinations of multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148, and substitutions at E138/G140/Q148 showed a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.5-fold to 21-fold from reference).

Recombinant resistant clinical isolates
Dolutegravir activity was measured for 705 raltegravir resistant recombinant isolates from clinical practice; 93.9% (662/705) of the isolates had a dolutegravir FC ≤10 and 1.8% had a DTG FC >25. Mutants with Y143 and N155 pathway had mean FCs of 1.2 and 1.5, respectively, while Q148 + 1 mutant and Q148 + ≥2 mutants mean FCs were 4.8 and 6.0, respectively.

Cross-resistance conferred by the M184V reverse transcriptase
Cross-resistance is limited within the nucleoside inhibitor class of antiretroviral agents. Zidovudine and stavudine maintain their antiretroviral activities against lamivudine-resistant HIV-1. Abacavir and tenofovir maintain antiretroviral activity against lamivudine-resistant HIV-1 harbouring only the M184V mutation.

16 NON-CLINICAL TOXICOLOGY

Carcinogenicity/mutagenicity: Dolutegravir was not mutagenic or clastogenic using *in vitro* tests in bacteria and cultured mammalian cells, and an *in vivo* rodent micronucleus assay. Dolutegravir was not carcinogenic in long term studies in the mouse and rat.

Lamivudine was not mutagenic in bacterial tests, but like many nucleoside analogues it shows activity in the *in vitro* mammalian tests such as the mouse lymphoma assay. This is consistent with the known activity of other nucleoside analogues. The results from two *in vivo* rat micronucleus tests with lamivudine were negative.

Lamivudine did not show any genotoxic activity in additional *in vivo* studies in rats (metaphase analysis of bone marrow and unscheduled DNA synthesis). The results of long-term carcinogenicity studies in mice and rats did not show any carcinogenic potential at exposures approximately 11 to 65 times higher than human clinical exposure based on AUC.

Fertility: Fertility studies in the rat have shown that dolutegravir and lamivudine had no effect on male or female fertility. Dolutegravir did not affect male or female fertility in rats at doses up to 1000 mg/kg/day, the highest dose tested (33 times the 50 mg human clinical exposure, based on AUC). Lamivudine did not affect male or female fertility in rats at doses up to 2000 mg/kg BID, the highest dose tested (>90 times the 300 mg human clinical exposure, based on AUC).

Reproductive and Developmental Toxicology: In a peri-/post-natal/juvenile toxicity study with lamivudine in rats, some histological inflammatory changes at the ano-rectal junction and slight diffuse epithelial hyperplasia of the cecum were observed in dams and pups at the high-dose level. An increased incidence of urination upon handling was also seen in some offspring at exposures >50 times the human clinical exposure based on C_{max}. In addition, a reduction in testes weight was observed in juvenile males (at exposures >125 times the human clinical exposure based on C_{max}) which was associated with slight to moderate dilatation of the seminiferous tubules.

17 SUPPORTING PRODUCT MONOGRAPHS

1. 3TC (tablets, 300 mg 150 mg; oral solution, 10 mg/mL; lamivudine), submission control #202946, Product Monograph, ViiV Healthcare ULC. (May 12, 2017)
2. TIVICAY (tablets, 10, 25, and 50 mg dolutegravir), submission control #217790, Product Monograph, ViiV Healthcare ULC. (Aug 27, 2018).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrDOVATO

dolutegravir and lamivudine tablets

Read this carefully before you start taking **DOVATO** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **DOVATO**.

Serious Warnings and Precautions

Worsening of hepatitis B virus in people who have HIV-1 infection

- If you have a hepatitis B infection, you should not stop taking DOVATO without talking to your healthcare professional.
- If you have to stop taking DOVATO your hepatitis may worsen.
- Your healthcare professional will monitor your liver function for several months and may give you a new medication to treat your hepatitis B infection.

What is DOVATO used for?

- DOVATO is used to treat HIV (human immunodeficiency virus) infection in adults and adolescents over the age of 12 years and weighing at least 40 kg.

How does DOVATO work?

DOVATO contains two medicines that are used to treat HIV infection: Dolutegravir and Lamivudine.

These medicines work together to reduce the amount of virus in your body and keep it at a low level.

This helps maintain the number of CD4+ cell count in your blood. CD4+ cells are a type of white blood cells that are important in helping your body to fight infection.

DOVATO does not cure HIV infection.

What are the ingredients in DOVATO?

Medicinal ingredients: 50 mg dolutegravir (as dolutegravir sodium), 300 mg lamivudine.

Non-medicinal ingredients: hypromellose, macrogol / PEG, magnesium stearate, mannitol (E421), microcrystalline cellulose, povidone (K29/32), sodium starch glycolate, sodium stearyl fumarate, titanium dioxide

DOVATO comes in the following dosage forms:

50 mg dolutegravir / 300 mg lamivudine fixed dose combination tablets.

Do not use DOVATO if:

- You are allergic *(hypersensitive)* to:
  - dolutegravir (TIVICAY, TRIUMEQ or JULUCA)
  - lamivudine (3TC, KIVEXA, COMBIVIR, TRIZIVIR or TRIUMEQ)
  - any of the other ingredients or components of the container of DOVATO. See "What are the ingredients in DOVATO?".
- You are taking dofetilide (to treat heart conditions).
- You are taking fampridine (also known as dalfampridine) used to treat multiple sclerosis.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take DOVATO. Talk about any health conditions or problems you may have, including if you:

- have had kidney or liver problems, including hepatitis B or C infection.
- have ever had a severe skin rash when taking dolutegravir (TIVICAY, TRIUMEQ or JULUCA) or lamivudine (3TC, KIVEXA, COMBIVIR, or TRIUMEQ).
- have ever had high levels of acid in the blood (lactic acidosis).
- have ever had an increase in your blood sugar (glucose) or levels of fats (lipids) in your blood.
- you have symptoms of an infection or inflammation, as these may flare up while on HIV treatment or you may have even stronger reactions to new infections than you would normally have.

Other warnings you should know about:

Pregnancy

Talk to your healthcare professional if you are pregnant or plan to become pregnant. Your healthcare professional will consider the benefit to you and the risk to your baby when taking DOVATO while you are pregnant.

- Taking DOVATO at the time of becoming pregnant or during the first 12 weeks of pregnancy may increase the risk of a type of birth defect called neural tube defect such as spina bifida (malformed spinal cord).
- In babies and infants exposed to one of the ingredients in DOVATO during pregnancy or labour, small temporary increases in blood levels of a substance called lactate have been observed. There have also been very rare reports of diseases that affect the nervous system such as delayed development and seizures.
- There is a registry for women who take antiretroviral medicines during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare professional about how you can take part in this registry.
- If you could get pregnant while taking DOVATO, you need to use a reliable method of birth control to prevent pregnancy.

Breastfeeding

Do not breastfeed while taking DOVATO. There is a risk of passing HIV-1 to your baby if you breastfeed. DOVATO can also be passed through breast milk and harm your baby. If you are breastfeeding or planning to breastfeed, talk with your healthcare professional about the best way to feed your baby.

Infecting others with HIV

DOVATO will not stop you from passing HIV to others, although this risk is lower if you take your HIV medicine as instructed by your healthcare professional. You should take steps to avoid this by:

- Using condoms when you have oral or penetrative sex.
- Not reusing or sharing needles, syringes, or other injection equipment.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with DOVATO:

- antacids to treat indigestion and heartburn and laxatives to treat constipation.
  - Some antacids and laxatives can stop DOVATO from being absorbed into your body and not make it work as well.
  - DOVATO should be taken at least 2 hours before or 6 hours after you take an antacid or laxative.
  - Other acid-lowering medicines like ranitidine and omeprazole can be taken at the same time as DOVATO.
- calcium and iron supplements (non-antacids).
  - Taking these supplements at the same time as DOVATO can stop DOVATO from being absorbed into your body and not make it work as well.
  - DOVATO should be taken at least 2 hours before or 6 hours after you take these supplements.
  - You can take supplements containing calcium or iron at the same time as DOVATO if you take both with food.
- metformin (medicine to treat diabetes)
- rifampin (medicine to treat some bacterial infections, such as tuberculosis (TB))
- phenytoin and phenobarbital (medicine to treat epilepsy)
- oxcarbazepine and carbamazepine (medicine to treat epilepsy and bipolar disorder)
- St. John's wort (Hypericum perforatum), a herbal remedy to treat depression
- sorbitol-containing medicines (usually liquids) used regularly
- trimethoprim/sulfamethoxazole (combination of medicines used to treat infections)

Talk to your healthcare professional for further advice if you are taking any of these medicines. For some of these medicines, your healthcare professional may need to adjust the dose of one of your medicines in order for it to work properly.

How to take DOVATO:

Always take DOVATO every day exactly as your healthcare professional has told you to.

DOVATO can be taken with or without food.

Check with your healthcare professional if you're not sure.

Usual dose:

The usual dose of DOVATO in adults and adolescents 12 years of age and older and weighing at least 40 kg is one tablet taken once a day.

Take DOVATO for as long as your healthcare professional recommends. Don't stop unless your healthcare professional advises you to.

Overdose:

If you think you, or a person you are caring for, have taken too much DOVATO, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, take DOVATO as soon as you remember.

If your next dose is due within 4 hours, skip the dose you missed and take the next one at the usual time. Then continue your treatment as before.

Don't take a double dose to make up for a missed dose.

What are possible side effects from using DOVATO?

These are not all the possible side effects you may have when taking DOVATO. If you experience any side effects not listed here, tell your healthcare professional.

- headache
- diarrhea
- drowsiness
- feeling sick (nausea)
- trouble sleeping (insomnia)
- anxiety
- itching (pruritus)
- any new infections
- kidney problems
- vomiting
- stomach pain
- stomach discomfort
- intestinal gas (flatulence)
- fever
- feeling tired (fatigue)
- muscle pain
- dizziness
- abnormal dream
- feeling sleepy
- feelings of deep sadness and unworthiness (depression)

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON			
Hypersensitivity (allergic reactions): skin rash, fever, lack of energy, swelling of the mouth or face causing difficulty in breathing, muscle or joint aches			✓
Anemia (low red blood cell count): paleness of the skin, fatigue, rapid heart rate, shortness of breath		✓	
Neutropenia (low white blood cell count): fever and symptoms of infection such as cough		✓	
Thrombocytopenia (low platelet count): bruising easily, heavy bleeding		✓	
Liver problems and blood test results: • inflammation (Hepatitis), • bilirubin increase (substance produced by liver), • increase of muscle enzymes (CPK), • increase in a kidney function blood test result (creatinine)		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE			
Lactic Acidosis (high level of acid in the blood): Weight loss, fatigue, malaise, abdominal pain, unusual muscle pain, feeling dizzy or lightheaded, fast or irregular heartbeat, shortness of breath, feeling unusually cold, especially in arms and legs, severe hepatomegaly (swollen and enlarged liver) with symptoms of liver problems such as nausea, vomiting, abdominal pain, weakness and diarrhea		✓	
Liver failure: • extremely high liver blood test results, • yellowing of the skin and the whites of the eyes, • dark/tea coloured urine, • pale coloured stools/ bowel movements, • nausea/vomiting, • loss of appetite, • pain, aching/tenderness on right side below ribs		✓	
Suicidal thoughts or actions (mainly in patients who have had depression or mental health problems before)		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store DOVATO up to 30°C.

Keep out of reach and sight of children.

Do not throw any medicines away in the garbage, down the sink drain or in the toilet. Give all unused medicines to your local pharmacy for proper disposal. This will help to protect the environment.

If you want more information about DOVATO:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.viivhealthcare.ca, or by calling 1-877-393-8448.

This leaflet was prepared by ViiV Healthcare ULC

Last Revised November 15, 2022

Marketing Status in United States

Drug Databases (https://www.fda.gov/Drugs/InformationOnDrugs/)

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

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Product Details for NDA 211994

DOVATO (DOLUTEGRAVIR SODIUM; LAMIVUDINE)
EQ 50MG BASE;300MG
Marketing Status: Prescription

Active Ingredient: DOLUTEGRAVIR SODIUM; LAMIVUDINE
Proprietary Name: DOVATO
Dosage Form; Route of Administration: TABLET; ORAL
Strength: EQ 50MG BASE;300MG
Reference Listed Drug: Yes
Reference Standard: Yes
TE Code:
Application Number: N211994
Product Number: 001
Approval Date: Apr 8, 2019
Applicant Holder Full Name: VIIV HEALTHCARE CO
Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=001&Appl_No=211994&Appl_type=N)