HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DOLUTEGRAVIR, LAMIVUDINE and TENOFOVIR DISOPROXIL FUMARATE TABLETS safely and effectively. See full prescribing information for DOLUTEGRAVIR, LAMIVUDINE and TENOFOVIR DISOPROXIL FUMARATE TABLETS.

DOLUTEGRAVIR, LAMIVUDINE and TENOFOVIR DISOPROXIL FUMARATE Tablets, for oral use

WARNING: POST TREATMENT ACUTE EXACERBATIONS OF HEPATITIS B

See full prescribing information for complete boxed warning.

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with human immunodeficiency virus type 1 (HIV-1) and hepatitis B virus (HBV) and have discontinued Lamivudine or Tenofovir Disoproxil Fumarate (TDF), two components of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.1)

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

Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, a combination of Dolutegravir (integrase strand transfer inhibitor [INSTI]), Lamivudine, and Tenofovir Disoproxil Fumarate (both nucleoside reverse transcriptase inhibitors), is indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg. (1)

Limitations of Use:

Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets alone is not recommended in patients with resistance-associated integrase substitutions or clinically suspected integrase strand transfer inhibitor resistance because the dose of dolutegravir in Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is insufficient in these subpopulations. See the dolutegravir prescribing information. (1)

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

- Testing: Prior to or when initiating Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, test for HBV infection. Prior to initiation and during use of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorous. (8.1)
- Recommended dose: in adults and pediatric patients weighing at least 35 kg: One tablet daily. May be taken with or without food. (2.2)
- If dosing with certain UGT1A or CYP3A inducers, then the recommended dolutegravir dosage regimen is 50 mg twice daily. An additional 50-mg dose of dolutegravir, separated by 12 hours from Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, should be taken. (2.4)
- Because Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is a fixed-dose product and cannot be dose adjusted, Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is not recommended in patients requiring dosage adjustment, patients with estimated creatinine clearance less than 50 mL per min, or patients with end-stage renal disease requiring hemodialysis. (2.3)

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

Tablets: 50 mg of dolutegravir, 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate. (3)

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

- Previous hypersensitivity reaction to dolutegravir, lamivudine, or tenofovir disoproxil fumarate. (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. Discontinue Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets and other suspect agents 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 dolutegravir containing regimens. Monitoring for hepatotoxicity is recommended. (5.3)
- New Onset or Worsening Renal Impairment: Can include acute renal failure and Fanconi syndrome. Avoid administering Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets with concurrent or recent use of nephrotoxic drugs. (5.4)
- Lactic Acidosis/Severe Hepatomegaly with Steatosis: Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.5)
- Immune reconstitution syndrome: May necessitate further evaluation and treatment. (5.7)
- Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue treatment as clinically appropriate. (5.8)
- Decreases in Bone Mineral Density (BMD): Consider assessment of BMD in patients with a history of pathologic fracture or other risk factors for osteoporosis or bone loss. (5.9)

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

- In adult subjects: The most common adverse reactions (in those receiving dolutegravir, lamivudine and tenofovir disoproxil fumarate) are insomnia, fatigue, headache, diarrhea, rash, pain, and depression. (6.1)
- In pediatric subjects: The most common adverse reactions (in those receiving Lamivudine) are fever and cough. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aspen SA Operations at 08002337736 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Co-administration of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets with other drugs can alter the concentration of other drugs and other drugs may alter the concentrations of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets. The potential drug-drug interactions must be considered prior to and during therapy. (4, 7, 12.3)

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

- Pediatrics: Not recommended for patients weighing less than 35 kg. (8.4)
- Dolutegravir, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets is not recommended in patients with creatinine clearance less than 50 mL per min or patients with end-stage renal disease requiring hemodialysis. (8.6)

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

Revised: 5/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: POST TREATMENT ACUTE EXACERBATIONS OF HEPATITIS B

Severe acute exacerbations of hepatitis B virus (HBV) have been reported in HBV-infected patients who have discontinued products containing lamivudine or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are infected with HBV and discontinue Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is indicated as a complete regimen for the treatment of human immunodeficiency virus type-1 (HIV-1) infection in adults and pediatric patients weighing at least 35 kg.

Limitation of Use:

- Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets alone are not recommended in patients with resistance-associated integrase substitutions or clinically suspected integrase strand transfer inhibitor resistance because the dose of dolutegravir in Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is insufficient in these subpopulations. See the full prescribing information for dolutegravir.

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets

Prior to or when initiating Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, test for HBV infection.

Prior to initiation and during use of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorous.

2.2 Recommended Dosage

Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is a fixed-dose combination product containing 50 mg of dolutegravir, 300 mg of lamivudine (3TC), and 300 mg of tenofovir disoproxil fumarate (TDF). The recommended dosage regimen of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets in adults and pediatric patients weighing at least 35 kg (77 lbs) is one tablet once daily orally with or without food.

2.3 Not Recommended Due to Lack of Dosage Adjustment

Because Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is a fixed-dose combination product and cannot be dose adjusted, it is not recommended in patients requiring dosage adjustment, patients with creatinine clearance less than 50 mL per min, or patients with end-stage renal disease (ESRD) requiring hemodialysis *[see Use in Specific Populations (8.6)]*.

2.4 Dosage Recommendation with Certain Concomitant Medications

The dolutegravir dose (50 mg) in Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 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 Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets with Co-administered Medications

Co-administered Drug	Dosing Recommendation
Efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, carbamazepine, or rifampin	The recommended dolutegravir dosage regimen is 50 mg twice daily. An additional dolutegravir 50 mg tablet, separated by 12 hours from Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, should be taken.

3 DOSAGE FORMS AND STRENGTHS

Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets contain 50 mg of dolutegravir, 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate. The tablets are oval, white, biconvex, film-coated tablets marked with 'I10' on one side and plain on the other side.

4 CONTRAINDICATIONS

Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is contraindicated in patients:

- with previous hypersensitivity reaction to dolutegravir *[see Warnings and Precautions (5.2)]*,or any of the components of this product.
- receiving dofetilide, due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events with concomitant use of dolutegravir *[see Drug Interactions (7)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Severe Acute Exacerbation of Hepatitis B in Patients with HBV Infection

All patients should be tested for the presence of chronic hepatitis B virus (HBV) before or when initiating Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets. Discontinuation of anti-HBV therapy, including 3TC and TDF, two components of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, may be associated with severe acute exacerbations of hepatitis B. Patients infected with HBV who discontinue Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

5.2 Hypersensitivity Reaction

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

5.3 Hepatotoxicity

Hepatic adverse events have 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 use of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets *[see Adverse Reactions (6.1)]*. In some cases, the elevations in transaminases were consistent with immune reconstitution syndrome or hepatitis B reactivation particularly in the setting where anti-hepatitis therapy was withdrawn. Cases of hepatic toxicity, including elevated serum liver biochemistries, hepatitis, and acute liver failure have been reported in patients receiving a dolutegravir-containing regimen without pre-existing hepatic disease or other identifiable risk factors. Drug-induced liver injury leading to liver transplant has been reported with combination abacavir, dolutegravir, and lamivudine. Monitoring for hepatotoxicity is recommended.

5.4 New Onset or Worsening Renal Impairment

TDF, a component of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of TDF *[see Adverse Reactions (6.1)]*.

Prior to initiation and during use of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus.

Avoid Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions (7.3)]*. Cases of acute renal failure after initiation of high dose or multiple NSAIDs have been reported in patients with HIV-1 infection and risk factors for renal dysfunction who appeared stable on TDF. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.

Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in patients at risk of renal dysfunction.

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 3TC or TDF, two components of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, alone or in combination with other antiretrovirals. Treatment with Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

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

The concomitant use of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets and other drugs may result in known or potentially significant drug interactions, some of which may lead to *[see Contraindications (4) and Drug Interactions (7)]:*

- Loss of therapeutic effect of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs.

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

5.7 Immune Reconstitution Syndrome

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

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

5.8 Pancreatitis

In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, 3TC, a component of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, should be used with caution. Treatment with Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur *[see Adverse Reactions (6.1)]*.

5.9 Bone Loss and Mineralization Defects

Bone Mineral Density (BMD)

In clinical trials in adults with HIV-1 infection, TDF, a component of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, was associated with slightly greater decreases in BMD and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators *[see*

Adverse Reactions (6.1)]. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving TDF.

Clinical trials evaluating TDF in pediatric subjects were conducted. Under normal circumstances, BMD increases rapidly in pediatric patients. In HIV-1 infected subjects aged 2 years to less than 18 years, bone effects were similar to those observed in adult subjects and suggest increased bone turnover. Total body BMD gain was less in the TDF-treated HIV-1 infected subjects as compared to the control groups. Similar trends were observed in HBV-infected pediatric subjects 12 years to less than 18 years of age. In all pediatric trials, normal skeletal growth (height) was not affected for the duration of the clinical trials.

The effects of TDF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk in adults and pediatric subjects 2 years and older are unknown. The long-term effect of lower spine and total body BMD on skeletal growth in pediatric patients, and in particular, the effects of long-duration exposure in younger children is unknown.

Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. Assessment of BMD should be considered for adult and pediatric patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. If bone abnormalities are suspected then appropriate consultation should be obtained.

Mineralization Defects

Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of TDF use *[see Adverse Reactions (6.2)]*. Arthralgias and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving TDF-containing products *[see Warnings and Precautions (5.4)].*

6 ADVERSE REACTIONS

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

- Exacerbations of Hepatitis B *[see Boxed Warning, Warnings and Precautions (5.1)]*.
- Hypersensitivity Reactions *[see Warnings and Precautions (5.2)]*.
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*.
- New Onset or Worsening Renal Impairment *[see Warnings and Precautions (5.4)]*.
- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[see Warnings and Precautions (5.5)].*
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.7)]*.
- Pancreatitis *[see Warnings and Precautions (5.8)]*.
- Bone Loss and Mineralization Defects *[see Warnings and Precautions (5.9)]*.

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 Experience in Adult Subjects

Dolutegravir, 3TC, TDF

Treatment-Naïve Subjects: In SINGLE, 833 adult subjects were randomized and received at least one dose of either dolutegravir 50 mg with fixed-dose abacavir and lamivudine once daily or fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate once daily (study treatment was blinded through Week 96 and open-label from Week 96 through Week 144). Through 144 weeks, the rate of adverse events leading to discontinuation was 4% in subjects receiving dolutegravir 50 mg once daily + fixed-dose abacavir and lamivudine and 14% in subjects receiving fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate once daily.

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

Table 2: Treatment-Emergent Adverse Reactions of at Least Moderate Intensity (Grades 2 to 4) and at Least 2% Frequency in Treatment-Naïve Subjects in SINGLE Trial (Week 144 Analysis)

System Organ Class/ Preferred Term	SINGLE	
	Dolutegravir 50 mg + Abacavir and Lamivudine Once Daily (n = 414)	**Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate Once Daily (n = 419)**
Psychiatric		
Insomnia	3%	3%
Depression	1%	2%
Abnormal dreams	<1%	2%
Nervous System		
Dizziness	<1%	5%
Headache	2%	2%
Gastrointestinal		
Nausea	<1%	3%
Diarrhea	<1%	2%
Skin and Subcutaneous Tissue		
Rash[a]	<1%	6%
General Disorders		
Fatigue	2%	2%
Ear and Labyrinth		
Vertigo	0	2%

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

In addition, Grade 1 insomnia was reported by 7% and 4% of subjects receiving dolutegravir and fixed-dose efavirenz, emtricitabine, and tenofovir disoproxil fumarate, respectively. These events were not treatment limiting.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects: In an international, multicenter, double-blind trial (ING111762, SAILING), 719 HIV-1-infected, antiretroviral treatment-experienced adults

were randomized and received either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily with investigator-selected background regimen consisting of up to 2 agents, including at least one fully active agent. At 48 weeks, the rates of adverse events leading to discontinuation were 3% in subjects receiving dolutegravir 50 mg once daily + background regimen and 4% in subjects receiving raltegravir 400 mg twice daily + background regimen.

The only treatment-emergent adverse reaction of moderate to severe intensity with at least 2% frequency in either treatment group was diarrhea, 2% (6 of 354) in subjects receiving dolutegravir 50 mg once daily + background regimen and 1% (5 of 361) in subjects receiving raltegravir 400 mg twice daily + background regimen.

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

Gastrointestinal Disorders: Abdominal pain, abdominal discomfort, flatulence, upper abdominal pain, vomiting.
Hepatobiliary Disorders: Hepatitis.
Musculoskeletal Disorders: Myositis.
Psychiatric Disorders: Suicidal ideation, attempt, behavior, or completion. These events were observed primarily in subjects with a pre-existing history of depression or other psychiatric illness.
Renal and Urinary Disorders: Renal impairment.
Skin and Subcutaneous Tissue Disorders: Pruritus.

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

Table 3: Selected Laboratory Abnormalities (Grades 2 to 4) in Treatment-Naïve Subjects in SINGLE Trial (Week 144 Analysis)

	SINGLE	
Laboratory Parameter Preferred Term	**Dolutegravir 50 mg + Abacavir and Lamivudine Once Daily (n = 414)**	**Efavirenz/Emtricitabine/ Tenofovir Disoproxil Fumarate Once Daily (n = 419)**
ALT		
Grade 2 (>2.5 to 5.0 x ULN)	3%	5%
Grade 3 to 4 (>5.0 x ULN)	1%	<1%
AST		
Grade 2 (>2.5 to 5.0 x ULN)	3%	4%

Laboratory Parameter Preferred Term	SINGLE	
	Dolutegravir 50 mg + Abacavir and Lamivudine Once Daily (n = 414)	**Efavirenz/Emtricitabine/ Tenofovir Disoproxil Fumarate Once Daily (n = 419)**
Grade 3 to 4 (>5.0 x ULN)	1%	3%
Total Bilirubin		
Grade 2 (1.6 to 2.5 x ULN)	<1%	<1%
Grade 3 to 4 (>2.5 x ULN)	<1%	<1%
Creatine kinase		
Grade 2 (6.0 to 9.9 x ULN)	5%	3%
Grade 3 to 4 (≥10.0 x ULN)	7%	8%
Hyperglycemia		
Grade 2 (126 to 250 mg/dL)	9%	6%
Grade 3 (>250 mg/dL)	2%	<1%
Lipase		
Grade 2 (>1.5 to 3.0 x ULN)	11%	11%
Grade 3 to 4 (>3.0 x ULN)	5%	4%
Total neutrophils		
Grade 2 (0.75 to 0.99 x 10^9)	4%	5%
Grade 3 to 4 (<0.75 x 10^9)	3%	3%

ALT = Alanine aminotransferase; AST =Aspartate aminotransferase; ULN = Upper limit of normal.

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

Laboratory Parameter Preferred Term	SINGLE	
	Dolutegravir 50 mg + Abacavir and Lamivudine Once Daily (n = 414)	**Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate Once Daily (n = 419)**
Cholesterol (mg/dL)	24.0	26.7
HDL cholesterol (mg/dL)	5.4	7.2
LDL cholesterol (mg/dL)	16.0	14.6
Triglycerides (mg/dL)	13.6	31.9

HDL = high density lipoprotein; LDL = low density lipoprotein

[a] Subjects on lipid-lowering agents at baseline were excluded from these analyses (19 subjects in each arm in SINGLE: dolutegravir + fixed-dose abacavir and lamivudine n = 30 and fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate n = 27). Ninety-four subjects initiated a lipid-lowering agent post-baseline; their last fasted on-treatment values (prior to starting the agent) were used regardless if they discontinued the agent dolutegravir + fixed-dose abacavir and lamivudine n = 36 and fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate n = 36).

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects: Laboratory abnormalities observed in SAILING were generally similar compared with observations seen in the treatment-naïve trial.

Hepatitis B and/or Hepatitis C Virus Co-infection: In Phase 3 trials, subjects with hepatitis B and/or C virus co-infection were permitted to enroll provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal. Overall, the safety profile in subjects with hepatitis B and/or C virus co-infection was similar to that observed in subjects without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or C virus co-infection for all treatment groups. Grades 2 to 4 ALT abnormalities in hepatitis B and/or C co-infected compared with HIV mono-infected subjects receiving dolutegravir were observed in 18% vs. 3% with the 50-mg once-daily dose. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C at the start of therapy with dolutegravir, particularly in the setting where anti-hepatitis therapy was withdrawn *[see Warnings and Precautions (5.3)]*.

Changes in Serum Creatinine: Dolutegravir has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function *[see Clinical Pharmacology (12.2)]*. Increases in serum creatinine occurred within the first 4 weeks of treatment and remained stable through 96 weeks. In treatment-naïve subjects, a mean change from baseline of 0.15 mg per dL (range: -0.32 mg per dL to 0.65 mg per dL) was observed after 96 weeks of treatment. Creatinine increases were comparable by background NRTIs and were similar in treatment-experienced subjects.

TDF

Adverse Reactions from Clinical Trials Experience in HIV-1 Infected Adults: More than 12,000 subjects have been treated with TDF alone or in combination with other antiretroviral medicinal products for periods of 28 days to 215 weeks in clinical trials and expanded access programs. More than 1,500 subjects have received TDF 300 mg once daily in clinical trials; over 11,000 subjects have received TDF in expanded access programs.

The most common adverse reactions (incidence greater than or equal to 10%, Grades 2 to 4) identified from any of the 3 large controlled clinical trials include rash, diarrhea, headache, pain, depression, asthenia, and nausea.

Changes in Bone Mineral Density: In HIV-1-infected adult subjects in Study 903, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in subjects receiving TDF + 3TC + efavirenz (EFV) (-2.2% ± 3.9) compared with subjects receiving stavudine (d4T) + 3TC + EFV (-1.0% ± 4.6) through 144 weeks. Changes in BMD at the hip were similar between the two treatment groups (-2.8% ± 3.5 in the TDF group vs. -2.4% ± 4.5 in the d4T group). In both groups, the majority of the reduction in BMD occurred in the first 24 weeks to 48 weeks of the trial and this reduction was sustained through Week 144. Twenty-eight percent of TDF-treated subjects vs. 21% of the d4T-treated subjects lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 subjects in the TDF group and 6 subjects in the d4T group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C telopeptide, and urinary N telopeptide) and higher serum parathyroid hormone levels and 1,25 Vitamin D levels in the TDF group relative to the d4T group; however, except for bone-specific alkaline phosphatase, these changes resulted in values that remained within the normal range *[see Warnings and Precautions (5.9)]*.

Clinical Trials Experience in Pediatric Subjects:

The safety and pharmacokinetics of dolutegravir in HIV-1–infected pediatric subjects was evaluated in the IMPAACT P1093 trial and weight-band-based pharmacokinetic substudies of the ODYSSEY trial. IMPAACT

P1093 is an ongoing multicenter, open-label, non-comparative trial of HIV-1-infected pediatric subjects aged 4 weeks to less than 18 years *[see Clinical Studies (14.2)]*. ODYSSEY is an ongoing open-label, randomized, non-inferiority trial to evaluate the safety, efficacy, and pharmacokinetic parameters of dolutegravir plus two NRTIs compared with standard of care in HIV-1-infected pediatric subjects younger than 18 years. Overall, the safety data in these pediatric studies were similar to those seen in adults, and there was no clinically significant difference in dolutegravir exposure *[see Clinical Pharmacology (12.3)]*.

3TC

Pancreatitis: Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced pediatric subjects receiving 3TC alone or in combination with other antiretroviral agents. In an open-label dose-escalation trial (NUCA2002), 14 subjects (14%) developed pancreatitis while receiving monotherapy with 3TC. Three of these subjects died of complications of pancreatitis. In a second open-label trial (NUCA2005), 12 subjects (18%) developed pancreatitis. In Trial ACTG300, pancreatitis was not observed in 236 subjects randomized to 3TC plus zidovudine. Pancreatitis was observed in 1 subject in this trial who received open-label 3TC in combination with zidovudine and ritonavir following discontinuation of didanosine monotherapy *[see Warnings and Precautions (5.8)]*.

6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postmarketing use for each of the individual components of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Dolutegravir:

Blood and Lymphatic Systems
Sideroblastic anemia

Hepatobiliary Disorders
Acute liver failure, hepatotoxicity.

Investigations
Weight increased.

Musculoskeletal
Arthralgia, myalgia.

Psychiatric
Anxiety

3TC:

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)]*, post-treatment exacerbations of hepatitis B *[see Warning and Precautions (5.1)]*.

Hypersensitivity Anaphylaxis, urticaria.

Musculoskeletal
Muscle weakness, CPK elevation, rhabdomyolysis.

Skin
Alopecia, pruritus.

TDF:
Immune System Disorders
allergic reaction, including angioedema.

Metabolism and Nutrition Disorders
lactic acidosis, hypokalemia, hypophosphatemia.

Respiratory, Thoracic, and Mediastinal Disorders
Dyspnea.

Gastrointestinal Disorders
pancreatitis, increased amylase, abdominal pain.

Hepatobiliary Disorders
hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT).

Skin and Subcutaneous Tissue Disorders
Rash.

Musculoskeletal and Connective Tissue Disorders
rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy.

Renal and Urinary Disorders
acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria.

General Disorders and Administration Site Conditions
Asthenia.

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

7 DRUG INTERACTIONS

7.1 Effect of Dolutegravir, 3TC, or TDF on the Pharmacokinetics of Other Agents

Dolutegravir:

In vitro, dolutegravir inhibited the renal organic cation transporters, OCT2 (IC_{50} = 1.93 microM) and multidrug and toxin extrusion transporter (MATE) 1 (IC_{50} = 6.34 microM). *In vivo*, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2 and potentially MATE1. Dolutegravir may increase plasma concentrations of drugs eliminated via OCT2 or MATE1 (dofetilide, dalfampridine, metformin, Table 5) *[see Contraindications (4), Drug Interactions (7.3)]*.

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

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

7.2 Effect of Other Agents on the Pharmacokinetics of Dolutegravir, 3TC, or TDF

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

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

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

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

7.3 Significant Drug Interactions for Dolutegravir, 3TC, or TDF

There were no drug-drug interaction trials conducted with fixed-dose Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets.

Dolutegravir:

Table 5 provides clinical recommendations as a result of drug interactions with dolutegravir. These recommendations are based on either drug interaction trials or predicted interactions due to the expected

magnitude of interaction and potential for serious adverse events or loss of efficacy *[see Clinical Pharmacology (12.3)]*.

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

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir and/or Concomitant Drug	Clinical Comment
HIV-1 Antiviral Agents		
Non-nucleoside reverse transcriptase inhibitor: Etravirine[a]	↓Dolutegravir	Use of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir is not recommended.
Non-nucleoside reverse transcriptase inhibitor: Efavirenz[a]	↓Dolutegravir	An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets *[see Dosage and Administration (2.4)]*.
Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓Dolutegravir	Avoid coadministration with Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets because there are insufficient data to make dosing recommendations.
Protease inhibitor: Fosamprenavir/ritonavir[a] Tipranavir/ritonavir[a]	↓Dolutegravir	An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets *[see Dosage and Administration (2.4)]*.
Other Agents		
Dofetilide	↑Dofetilide	Coadministration is contraindicated with Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets *[see Contraindications (4)]*.
Carbamazepine[a]	↓Dolutegravir	An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets *[see Dosage and Administration (2.4)]*.
Oxcarbazepine Phenytoin Phenobarbital St. John's wort (*Hypericum perforatum*)	↓Dolutegravir	Avoid coadministration with Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets because there are insufficient data to make dosing recommendations.

Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing antacids[a] or laxatives Sucralfate Buffered medications	↓Dolutegravir	Administer Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 2 hours before or 6 hours after taking medications containing polyvalent cations.
Oral calcium or iron supplements, including multivitamins containing calcium or iron[a]	↓Dolutegravir	When taken with food, Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets and supplements or multivitamins containing calcium or iron can be taken at the same time. Under fasting conditions, Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets should be taken 2 hours before or 6 hours after taking supplements containing calcium or iron.
Potassium channel blocker: Dalfampridine	↑Dalfampridine	Elevated levels of dalfampridine increase the risk of seizures. The potential benefits of taking dalfampridine concurrently with Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets should be considered against the risk of seizures in these patients.
Metformin	↑Metformin	Refer to the prescribing information for metformin for assessing the benefit and risk of concomitant use with metformin.
Rifampin[a]	↓Dolutegravir	An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets *[see Dosage and Administration (2.4)]*.

[a] *See Clinical Pharmacology (12.3) Table 8 or Table 9 for magnitude of interaction.*

TDF:

Table 6 provides a listing of established or clinically significant drug interactions. The drug interactions described are based on studies conducted with TDF *[see Clinical Pharmacology (12.3)]*.

Table 6: Established and Significant[a] Drug Interactions for TDF: Alteration in Dose orRegimen May Be Recommended Based on Drug Interaction Trials

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
NRTI: didanosine	↑ didanosine	Patients receiving TDF, a component of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, and didanosine should be monitored closely for didanosine-associated adverse reactions. Discontinue didanosine in patients who develop didanosine-associated adverse reactions. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis, and neuropathy. Suppression of CD4+ cell counts has been observed in patients receiving tenofovir disoproxil fumarate with didanosine 400 mg daily. In patients weighing greater than 60 kg, reduce the didanosine dose to 250 mg when it is coadministered with TDF. In patients weighing less than 60 kg, reduce the didanosine dose to 200 mg when it is co-administered with TDF. When co-administered, TDF and Videx EC (didanosine enteric-coated) may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat).
HIV-1 Protease Inhibitors: atazanavir	↓ atazanavir	When co-administered with Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, atazanavir 300 mg should be given with ritonavir 100 mg.
lopinavir/ritonavir atazanavir/ritonavir darunavir/ritonavir	↑ tenofovir	Monitor patients receiving Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets concomitantly with lopinavir/ritonavir, ritonavir-boosted atazanavir, or ritonavir-boosted darunavir for TDF-associated adverse reactions. Discontinue Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets in patients who develop TDF-associated adverse reactions.
Hepatitis C Antiviral Agents: sofosbuvir/velpatasvir sofosbuvir/velpatasvir /voxilaprevir	↑ tenofovir	Monitor patients receiving Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets concomitantly with EPCLUSA® (sofosbuvir/velpatasvir) for adverse reactions associated with TDF.

ledipasvir/sofosbuvir		Monitor patients receiving Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets concomitantly with HARVONI® (ledipasvir/sofosbuvir) without an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination, for adverse reactions associated with TDF. In patients receiving Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets concomitantly with HARVONI and an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination, consider an alternative HCV or antiretroviral therapy, as the safety of increased tenofovir concentrations in this setting has not been established. If coadministration is necessary, monitor for adverse reactions associated with TDF.

[a.] This table is not all inclusive.
[b.] ↑=Increase, ↓=Decrease

Drugs Affecting Renal Function:
Tenofovir is primarily eliminated by the kidneys *[see Clinical Pharmacology (12.3)]*. Coadministration of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets with drugs that are eliminated by active tubular secretion may increase serum concentrations of tenofovir and/or coadministered drug. Some examples include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs *[see Warnings and Precautions (5.4)]*. Drugs that decrease renal function may increase concentration of tenofovir.

Do not administer Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets with HEPSERA (adefovir dipivoxil).

Drugs Inhibiting Organic Cation Transporters:
3TC, a component of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, is predominantly eliminated in the urine by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system (e.g., trimethoprim) *[see Clinical Pharmacology (12.3)]*. No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of 3TC.

Sorbitol:
Coadministration of single doses of 3TC and sorbitol resulted in a sorbitol dose-dependent reduction in 3TC. When possible, avoid use of sorbitol-containing medicines with 3TC *[see Clinical Pharmacology (12.3)]*.

7.4 Drugs Without Clinically Significant Interactions with Dolutegravir

Based on drug interaction trial results, the following drugs can be coadministered with dolutegravir without a dose adjustment: atazanavir/ritonavir, darunavir/ritonavir, elbasvir/grazoprevir, methadone, midazolam, omeprazole, oral contraceptives containing norgestimate and ethinyl estradiol, prednisone, rifabutin, rilpivirine, sofosbuvir/velpatasvir, and tenofovir *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

There are insufficient human data on the use of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets during pregnancy to definitively assess a drug-associated risk for birth defects and miscarriage. However, available human data from the Antiretroviral Pregnancy Registry (APR) do not indicate an increased risk of birth defects *(see Data)*. The background risk for major birth defects for the indicated population is unknown. In the U.S. general population, the estimated background rate for major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

In animal reproduction studies, no evidence of adverse developmental outcomes (including neural tube defects) was observed with dolutegravir at systemic exposures (AUC) less than (rabbits) and approximately 27 times (rats) the exposure in humans at the maximum recommended human dose (MRHD) of dolutegravir *(see Data)*. Oral administration of 3TC to pregnant rabbits during organogenesis resulted in embryo lethality at a systemic exposure (AUC) similar to the recommended clinical dose; however, no adverse development effects were observed with oral administration of 3TC to pregnant rats during organogenesis at plasma concentrations (C_{max}) 35 times the recommended clinical dose *(see Data).* No adverse developmental effects were observed when TDF was administered at doses/exposures ≥14 (TDF) and 2.7 (tenofovir) times those of the recommended daily dose of TDF *(see Data).*

Data

Human Data

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

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

Limitations of these birth outcome surveillance studies include insufficient data to determine if baseline

characteristics were balanced between the study groups or to assess other factors such as the use of folic acid during the preconception or first trimester periods.

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

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

3TC: Based on prospective reports to the APR of over 11,000 exposures to 3TC 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), the prevalence of defects in live births was 3.1% (95% CI: 2.7% to 3.6%) following first trimester exposure to 3TC-containing regimens and 2.9% (95% CI: 2.5% to 3.3%) following second/third trimester exposure to 3TC-containing regimens.

3TC pharmacokinetics were studied in pregnant women during 2 clinical trials conducted in South Africa. The trials assessed pharmacokinetics in 16 women at 36 weeks' gestation using 150 mg 3TC twice daily with zidovudine, 10 women at 38 weeks' gestation using 150 mg 3TC twice daily with zidovudine, and 10 women at 38 weeks' gestation using 3TC 300 mg twice daily without other antiretrovirals. These trials were not designed or powered to provide efficacy information. 3TC 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 3TC crosses the placenta in humans. Based on limited data at delivery, median (range) amniotic fluid concentrations of 3TC were 3.9 (1.2 to 12.8)–fold greater compared with paired maternal serum concentration (n = 8).

TDF: Based on prospective reports from the APR exposures to TDF-containing regimens during pregnancy resulting in live births (including over 4,000 exposed in the first trimester and over 1,700 exposed in the second/third trimester), the prevalence of major birth defects in live births was 2.4% (95% CI: 2.0% to 2.9%) and 2.4% (95% CI: 1.7% to 3.2%) following first and second/third trimester exposure, respectively, to TDF-containing regimens..

Methodological limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates women and infants from a limited geographic area, and does not include outcomes for births that occurred at <20 weeks gestation.

Animal Data:
Dolutegravir: Dolutegravir was administered orally at up to 1,000 mg/kg daily to pregnant rats and rabbits on Gestation Days 6 to 17 and 6 to 18, respectively, and 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 at up to the highest dose tested. During organogenesis, systemic exposures (AUC) to dolutegravir in rabbits were less than the exposure in humans at the MRHD and in rats were approximately 27 times the exposure in humans at the

MRHD. In the rat pre/postnatal development study, decreased body weight of the developing offspring was observed during lactation at a maternally toxic dose (approximately 27 times human exposure at the MRHD).

3TC: 3TC was administered orally to pregnant rats (at 90, 600, and 4,000 mg per kg per day) and rabbits (at 90, 300, and 1,000 mg per kg per day and at 15, 40, and 90 mg per kg per day) during organogenesis (on gestation Days 7 through 16 [rat] and 8 through 20 [rabbit]). No evidence of fetal malformations due to 3TC was observed in rats and rabbits at doses producing plasma concentrations (C_{max}) approximately 35 times higher than human exposure at the recommended daily dose. Evidence of early embryo lethality was seen in the rabbit at system 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 recommended daily dose. Studies in pregnant rats showed that 3TC is transferred to the fetus through the placenta. In the fertility/pre-and postnatal development study in rats, 3TC was administered orally at doses of 180, 900, and 4,000 mg per kg per day (from prior to mating through postnatal Day 20). In the study, development of the offspring, including fertility and reproductive performance, was not affected by maternal administration of 3TC.

TDF: TDF was administered orally to pregnant rats (at 0, 50, 150, or 450 mg/kg/day) and rabbits (at 0, 30, 100, or 300 mg/kg/day) through organogenesis (on gestation days 7 through 17, and 6 through 18, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with TDF in rats at doses up to 14 times the human dose based on body surface area comparisons and in rabbits at doses up to 19 times the human dose based on body surface area comparisons. In a pre/postnatal development study in rats, TDF was administered orally through lactation at doses up to 600 mg/kg/day; no adverse effects were observed in the offspring at tenofovir exposures of approximately 2.7 times higher than human exposures at the recommended daily dose of TDF.

8.2 Lactation

Risk Summary

Dolutegravir and 3TC are present in human milk. Based on published data, tenofovir has been shown to be present in human milk. It is not known whether dolutegravir, 3TC, or tenofovir affects human milk production or has effects on the breastfed infant.

Potential risks of breastfeeding include: (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.

Data

Human Data

TDF: In a study of 50 breastfeeding women on a tenofovir-containing regimen between 1 and 24 weeks postpartum (median 13 weeks), after 7 days of treatment, tenofovir was undetectable in the plasma of most infants. There were no serious adverse events.

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

8.4 Pediatric Use

The safety and effectiveness of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets for

treatment of HIV-1 infection in pediatric patients weighing at least 35 kg was established through studies with the individual components *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.2)]*.

Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is a fixed-dose combination product which cannot be adjusted for patients weighing less than 35 kg.

8.5 Geriatric Use

Clinical trials of individual components of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is not recommended for patients with creatinine clearance less than 50 mL per min or patients with end-stage renal disease (ESRD) requiring hemodialysis because Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is a fixed-dose combination product and the dosage of the individual components cannot be adjusted. If a dose reduction of 3TC or TDF, two components of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, is required for patients with creatinine clearance less than 50 mL per min, then the individual components should be used *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child- Pugh Score A or B). The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir, a component of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, has not been studied. Therefore, Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is not recommended for use in patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There is no known specific treatment for overdose with Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required.

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

3TC: Because a negligible amount of 3TC 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 3TC overdose event.

TDF: Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of TDF, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

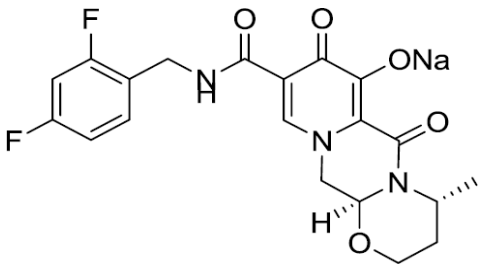
11 DESCRIPTION

Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets contain an integrase enzyme inhibitor (dolutegravir), a synthetic nucleoside analogue (lamivudine) and an acyclic nucleoside phosphonate (nucleotide) analog (tenofovir).

Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is for oral administration and contain 50 mg of dolutegravir (equivalent to 52.6 mg of dolutegravir sodium), 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil).

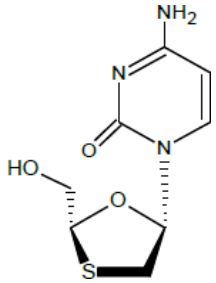
Each tablet contains the following inactive ingredients: croscarmellose sodium, lactose monohydrate, mannitol, microcrystalline cellulose, povidone k-30, pregelatinized starch, sodium starch glycolate type A and sodium stearyl fumarate with the following film coating system: polyethylene glycol 3350, polyvinyl alcohol, talc and titanium dioxide.

Dolutegravir: Dolutegravir as dolutegravir sodium, an HIV INSTI. The chemical name of dolutegravir sodium is sodium 2H-Pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide,N-[(2,4-difluorophenyl)methyl]-3,4,6,8,12,12a-hexahydro-7-hydroxy-4-methyl-6,8-dioxo-, sodium salt (1:1), (4R,12aS)- The empirical formula is $C_{20}H_{18}F_2N_3NaO_5$ and the molecular weight is 441.36 g per mol. It has the following structural formula:



Dolutegravir sodium is a white to pale yellow powder and slightly soluble in DMSO, very slightly soluble in water and methanol, practically insoluble in acetone, acetonitrile, ethyl acetate, dichloromethane, tetrahydrofuran, triethylamine and methyl tert-butyl ether.

Lamivudine: It is a synthetic nucleoside analogue with activity against HIV-1 and HBV. The chemical name of lamivudine is 4-Amino-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-2(1H)-pyrimidinone. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.26 g per mol. It has the following structural formula:

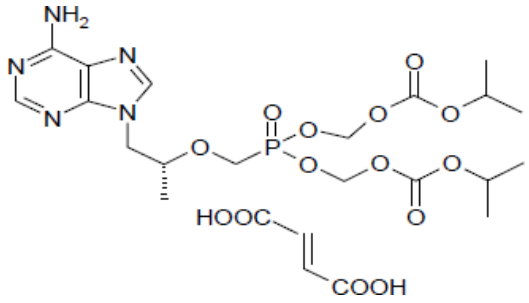


Lamivudine is a white to off-white solid, soluble in water.

Tenofovir disoproxil fumarate (TDF): (a prodrug of tenofovir) which is a fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir.

The chemical name of TDF is 9-[(R)-2- [[Bis[[(isopropoxycarbonyl)oxy] methoxy] phosphinyl] methoxy]

propyl] adenine fumarate (1:1). It has a molecular formula of $C_{19}H_{30}N_5O_{10}P.C_4H_4O_4$ and a molecular weight of 635.52. It has the following structural formula:



Tenofovir disoproxil fumarate is a white to off white powder, freely soluble in dimethylformamide and soluble in methanol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is a fixed-dose combination product of the HIV-1 antiretroviral agents dolutegravir, 3TC, and TDF *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Effects on Electrocardiogram

A thorough QT trial has been conducted for dolutegravir. Neither the effects 3TC nor TDF as single entities or the combination of dolutegravir, lamivudine and tenofovir disoproxil fumarate on the QT interval have been evaluated.

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

Effects of Dolutegravir on Renal Function

The effect of dolutegravir on renal function was evaluated in an open-label, randomized, 3-arm, parallel, placebo-controlled trial in healthy subjects (n = 37) who received dolutegravir 50 mg once daily (n = 12), dolutegravir 50 mg twice daily (n = 13), or placebo once daily (n = 12) for 14 days. A decrease in creatinine clearance, as determined by 24-hour urine collection, was observed with both doses of dolutegravir after 14 days of treatment in subjects who received 50 mg once daily (9% decrease) and 50 mg twice daily (13% decrease). Neither dose of dolutegravir had a significant effect on the actual glomerular filtration rate (determined by the clearance of probe drug, iohexol) or effective renal plasma flow (determined by the clearance of probe drug, para-amino hippurate) compare with the placebo.

12.3 Pharmacokinetics

Pharmacokinetics in Adults

Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets: The mean systemic exposures of dolutegravir, lamivudine and tenofovir from the combination tablets (50 mg/300 mg/300 mg) were comparable

to that from TIVICAY® tablets of ViiV Healthcare USA (containing dolutegravir 50 mg), EPIVIR® tablets of ViiV Healthcare USA (containing lamivudine 300 mg) and VIREAD tablets of Gilead Sciences, Inc. USA (containing tenofovir disoproxil fumarate 300 mg), respectively, when single doses were administered to healthy subjects under fasted and fed conditions.

Absorption, Distribution, Metabolism and Excretion

Dolutegravir: The pharmacokinetic properties of dolutegravir have been evaluated in healthy adult subjects and HIV-1-infected adult subjects. Exposure to dolutegravir was generally similar between healthy subjects and HIV-1-infected subjects. Dolutegravir steady-state pharmacokinetic parameter estimates in HIV-1-infected adults are reported in Table 7.

Table 7: Dolutegravir Steady-State Pharmacokinetic Parameter Estimates inHIV-1-Infected Adults

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

Following oral administration of dolutegravir, peak plasma concentrations were observed 1 to 3 hours postdose. With once-daily dosing, pharmacokinetic steady-state is achieved within approximately 5 days with average accumulation ratios for AUC, C_{max}, and C_{24h} ranging from 1.2 to 1.5.

Dolutegravir is a P-gp substrate *in vitro*. The absolute bioavailability of dolutegravir has not been established.

Dolutegravir is highly bound (greater than or equal to 98.9%) to human plasma proteins based on in vivo data and binding is independent of plasma concentration of dolutegravir. The apparent volume of distribution (Vd/F) following 50 mg once-daily administration is estimated at 17.4 L based on a population pharmacokinetic analysis.

Cerebrospinal Fluid (CSF): In 12 treatment-naïve subjects on dolutegravir 50 mg daily plus abacavir/lamivudine, the median dolutegravir concentration in CSF was 13.2 ng per mL (range: 3.74 ng/mL to 18.3 ng/mL) 2 to 6 hours post-dose after 16 weeks of treatment. The clinical relevance of this finding has not been established.

Dolutegravir has a terminal half-life of approximately 14 hours and an apparent clearance (CL/F) of 1.0 L/ h based on population pharmacokinetic analyses.

Dolutegravir is primarily metabolized via UGT1A1 with some contribution from CYP3A.

In a meta-analysis of healthy subject trials, 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).

After a single oral dose of [^{14}C] dolutegravir, 53% of the total oral dose is excreted unchanged in the feces. Thirty-one percent of the total oral dose is excreted in the urine, represented by an ether glucuronide of

dolutegravir (18.9% of total dose), a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose), and its hydrolytic N-dealkylation product (3.6% of total dose). Renal elimination of unchanged drug was less than 1% of the dose.

***3TC**:* The steady-state pharmacokinetic properties of the 3TC 300 mg tablet once daily for 7 days compared with the 3TC 150-mg tablet twice daily for 7 days were assessed in a crossover trial in 60 healthy subjects. 3TC 300 mg once daily resulted in lamivudine exposures that were similar to 3TC 150 mg twice daily with respect to plasma $AUC_{24,ss}$; however, $C_{max,ss}$ was 66% higher and the trough value was 53% lower compared with the 150-mg twice-daily regimen. Intracellular lamivudine triphosphate exposures in peripheral blood mononuclear cells were also similar with respect to $AUC_{24,ss}$ and $C_{max24,ss}$; however, trough values were lower compared with the 150-mg twice-daily regimen. Inter-subject variability was greater for intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough concentrations.

The apparent volume of distribution after IV administration of 3TC to 20 subjects was 1.3 ± 0.4 L per kg, suggesting that 3TC distributes into extravascular spaces. Volume of distribution was independent of dose and did not correlate with body weight.

Binding of 3TC to human plasma proteins is less than 36%. In vitro studies showed that over the concentration range of 0.1 to 100 mcg per mL, the amount of 3TC associated with erythrocytes ranged from 53% to 57% and was independent of concentration.

Metabolism of 3TC is a minor route of elimination. In humans, the only known metabolite of lamivudine is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours). Serum concentrations of this metabolite have not been determined. 3TC is not significantly metabolized by cytochrome P450 enzymes.

The majority of 3TC is eliminated unchanged in urine by active organic cationic secretion. In 9 healthy subjects given a single 300-mg oral dose of 3TC, renal clearance was 199.7 ± 56.9 mL per min (mean ± SD).

In most single-dose trials in HIV-1-infected subjects, HBV-infected subjects, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{½}$) ranged from 5 to 7 hours. In HIV-1-infected subjects, total clearance was 398.5 ± 69.1 mL per min (mean ± SD).

***TDF**:* TDF is a water soluble diester prodrug of the active ingredient tenofovir. Following oral administration of TDF, maximum tenofovir serum concentrations (C_{max}) are achieved in 1.0 ± 0.4 hour. C_{max} and AUC values are 0.30 ± 0.09 µg/mL and 2.29 ± 0.69 µg•hr/mL, respectively. Less than 0.7% of tenofovir binds to human plasma proteins in vitro and the binding is independent of concentration over the range of 0.01 to 25 µg/mL. In vitro studies indicate that neither tenofovir disoproxil nor tenofovir are substrates of CYP enzymes. Following single dose, oral administration of TDF, the terminal elimination half-life of tenofovir is approximately 17 hours. After multiple oral doses of TDF 300 mg once daily (under fed conditions), 32 ± 10% of the administered dose is recovered in urine over 24 hours. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion.

Effect of Food on Oral Absorption of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets

Food is unlikely to have a clinically meaningful effect on systemic exposure of dolutegravir, lamivudine, and tenofovir following the administration of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets.

Specific Populations

***Pediatric Patients**:* Dolutegravir, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets is a fixed-dose

combination product which cannot be adjusted for patients weighing less than 35 kg (77 lbs).

Dolutegravir: The pharmacokinetics of dolutegravir were evaluated in the IMPAACT P1093 trial and in weight-band-based pharmacokinetic substudies from the ODYSSEY trial. Mean dolutegravir $AUC_{0\text{-}24h}$ and C_{24h} in HIV-1-infected pediatric subjects were comparable to those in adults after 50 mg once daily or 50 mg twice daily.

TDF: Steady-state pharmacokinetics of tenofovir were evaluated in 8 HIV-1 infected pediatric subjects (12 to less than 18 years). Mean ± SD C_{max} and AUC_{tau} are 0.38 ± 0.13 mcg/mL and 3.39 ± 1.22 mcg•hr/mL, respectively. Tenofovir exposure achieved in these pediatric subjects receiving oral daily doses of TDF 300 mg was similar to exposures achieved in adults receiving once-daily doses of TDF 300 mg.

Geriatric Patients: Population pharmacokinetic analysis indicated age had no clinically relevant effect on the pharmacokinetics of dolutegravir. The pharmacokinetics of tenofovir or 3TC have not been studied in subjects older than 65 years.

Male and Female Patients: There are no significant or clinically relevant gender differences in the pharmacokinetics of the individual components (dolutegravir or 3TC) based on the available information that was analyzed for each of the individual components. Tenofovir pharmacokinetics are similar in male and female populations.

Racial Groups: There are no significant or clinically relevant racial differences in the pharmacokinetics of the individual components (dolutegravir or 3TC) based on the available information that was analyzed for each of the individual components. There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences of tenofovir among these populations.

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

3TC: The pharmacokinetic properties of 3TC have been determined in adults with impaired hepatic function. Pharmacokinetic parameters were not altered by diminishing hepatic function. Safety and efficacy of 3TC have not been established in the presence of decompensated liver disease.

TDF*:* The pharmacokinetics of tenofovir following a 300 mg single dose of tenofovir disoproxil fumarate have been studied in non-HIV infected subjects with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects. No change in TDF dosing is required in patients with hepatic impairment.

Patients with Renal Impairment*:*
Because Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is a fixed-dose product and cannot be dose adjusted, Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is not recommended in patients with creatinine clearance less than 50 mL per min or patients with end-stage renal disease (ESRD) requiring hemodialysis *[see Dosage and Administration (2.3)]*.

Drug Interaction Studies

The drug interaction trials described were conducted with dolutegravir, 3TC, and/or TDF as single entities; no drug interaction trials have been conducted using the fixed-dose Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets.

Dolutegravir: Dosing or regimen recommendations as a result of established and other potentially significant drug-drug interactions with dolutegravir are provided in Table 5 *[see Drug Interactions (7.3)]*.

The effects of dolutegravir on the exposure of coadministered drugs are summarized in Table 8 and the effects of coadministered drugs on the exposure of dolutegravir are summarized in Table 9.

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

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug with/without Dolutegravir No Effect = 1.00		
			C_{max}	AUC	$C\tau$ or C_{24}
Elbasvir 50 mg once daily	50 mg single dose	12	0.97 (0.89, 1.05)	0.98 (0.93, 1.04)	0.98 (0.93, 1.03)
Ethinyl estradiol 0.035 mg	50 mg twice daily	15	0.99 (0.91 to 1.08)	1.03 (0.96 to 1.11)	1.02 (0.93 to 1.11)
Grazoprevir 200 mg once daily	50 mg single dose	12	0.64 (0.44, 0.93)	0.81 (0.67, 0.97)	0.86 (0.79, 0.93)
Metformin 500 mg twice daily	50 mg once daily	15[a]	1.66 (1.53 to 1.81)	1.79 (1.65 to 1.93)	–
Metformin 500 mg twice daily	50 mg twice daily	15[a]	2.11 (1.91 to 2.33)	2.45 (2.25 to 2.66)	–
Methadone 16 to 150 mg	50 mg twice daily	11	1.00 (0. 94 to 1.06)	0.98 (0.91 to 1.06)	0.99 (0.91 to 1.07)
Midazolam 3 mg	25 mg once daily	10	–	0.95 (0.79 to 1.15)	–
Norelgestromin 0.25 mg	50 mg twice daily	15	0.89 (0.82 to 0.97)	0.98 (0.91 to 1.04)	0.93 (0.85 to 1.03)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.10 (0.99 to 1.22)	1.06 (0.98 to 1.16)	1.21 (1.07 to 1.38)
Sofosbuvir 400 mg once daily Metabolite (GS-331007)	50 mg once daily	24	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)
Tenofovir disoproxil fumarate 300 mg once daily	50 mg once daily	15	1.09 (0.97 to 1.23)	1.12 (1.01 to 1.24)	1.19 (1.04 to 1.35)
Velpatasvir 100 mg once daily	50 mg once daily	24	0.94 (0.86, 1.02)	0.91 (0.84, 0.98)	0.88 (0.82, 0.94)

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

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

Coadministered Drug(s) and	Dose of	n	Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00

Dose(s)	Dolutegravir		C_{max}	AUC	$C\tau$ or C_{24}
Atazanavir 400 mg once daily	30 mg once daily	12	1.50 (1.40 to 1.59)	1.91 (1.80 to 2.03)	2.80 (2.52 to 3.11)
Atazanavir/ritonavir 300/100 mg once daily	30 mg once daily	12	1.34 (1.25 to 1.42)	1.62 (1.50 to 1.74)	2.21 (1.97 to 2.47)
Darunavir/ritonavir 600/100 mg twice daily	30 mg once daily	15	0.89 (0.83 to 0.97)	0.78 (0.72 to 0.85)	0.62 (0.56 to 0.69)
Efavirenz 600 mg once daily	50 mg once daily	12	0.61 (0.51 to 0.73)	0.43 (0.35 to 0.54)	0.25 (0.18 to 0.34)
Elbasvir/grazoprevir 50/200 mg once daily	50 mg single dose	12	1.22 (1.05, 1.40)	1.16 (1.00, 1.34)	1.14 (0.95, 1.36)
Etravirine 200 mg twice daily	50 mg once daily	16	0.48 (0.43 to 0.54)	0.29 (0.26 to 0.34)	0.12 (0.09 to 0.16)
Etravirine + darunavir/ritonavir 200 mg + 600/100 mg twice daily	50 mg once daily	9	0.88 (0.78 to 1.00)	0.75 (0.69 to 0.81)	0.63 (0.52 to 0.76)
Etravirine + lopinavir/ritonavir 200 mg + 400/100 mg twice daily	50 mg once daily	8	1.07 (1.02 to 1.13)	1.11 (1.02 to 1.20)	1.28 (1.13 to 1.45)
Fosamprenavir/ritonavir 700 mg/100 mg twice daily	50 mg once daily	12	0.76 (0.63 to 0.92)	0.65 (0.54 to 0.78)	0.51 (0.41 to 0.63)
Lopinavir/ritonavir 400/100 mg twice daily	30 mg once daily	15	1.00 (0.94 to 1.07)	0.97 (0.91 to 1.04)	0.94 (0.85 to 1.05)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.13 (1.06 to 1.21)	1.12 (1.05 to 1.19)	1.22 (1.15 to 1.30)
Tenofovir 300 mg once daily	50 mg once daily	15	0.97 (0.87 to 1.08)	1.01 (0.91 to 1.11)	0.92 (0.82 to 1.04)
Tipranavir/ritonavir 500/200 mg twice daily	50 mg once daily	14	0.54 (0.50 to 0.57)	0.41 (0.38 to 0.44)	0.24 (0.21 to 0.27)
Antacid (MAALOX) Simultaneous administration	50 mg single dose	16	0.28 (0.23 to 0.33)	0.26 (0.22 to 0.32)	0.26 (0.21 to 0.31)
Antacid (MAALOX) 2 h after dolutegravir	50 mg single dose	16	0.82 (0.69 to 0.98)	0.74 (0.62 to 0.90)	0.70 (0.58 to 0.85)
Calcium carbonate 1,200 mg simultaneous administration (fasted)	50 mg single dose	12	0.63 (0.50 to 0.81)	0.61 (0.47 to 0.80)	0.61 (0.47 to 0.80)
Calcium carbonate 1,200 mg simultaneous administration (fed)	50 mg single dose	11	1.07 (0.83 to 1.38)	1.09 (0.84 to 1.43)	1.08 (0.81 to 1.42)
Calcium carbonate 1,200 mg 2 h after dolutegravir	50 mg single dose	11	1.00 (0.78 to 1.29)	0.94 (0.72 to 1.23)	0.90 (0.68 to 1.19)
Carbamazepine 300 mg twice daily	50 mg once daily	16[c]	0.67 (0.61 to 0.73)	0.51 (0.48 to 0.55)	0.27 (0.24 to 0.31)
Ferrous fumarate 324 mg simultaneous administration (fasted)	50 mg single dose	11	0.43 (0.35 to 0.52)	0.46 (0.38 to 0.56)	0.44 (0.36 to 0.54)
Ferrous fumarate 324 mg simultaneous administration (fed)	50 mg single dose	11	1.03 (0.84 to 1.26)	0.98 (0.81 to 1.20)	1.00 (0.81 to 1.23)
Ferrous fumarate 324 mg 2 h after dolutegravir	50 mg single dose	10	0.99 (0.81 to 1.21)	0.95 (0.77 to 1.15)	0.92 (0.74 to 1.13)
Multivitamin (One-A-Day) Simultaneous administration	50 mg single dose	16	0.65 (0.54 to 0.77)	0.67 (0.55 to 0.81)	0.68 (0.56 to 0.82)
Omeprazole 40 mg once daily	50 mg single dose	12	0.92 (0.75 to 1.11)	0.97 (0.78 to 1.20)	0.95 (0.75 to 1.21)
Prednisone 60 mg once daily with taper	50 mg once daily	12	1.06 (0.99 to 1.14)	1.11 (1.03 to 1.20)	1.17 (1.06 to 1.28)

Rifampin[a] 600 mg once daily	50 mg twice daily	11	0.57 (0.49 to 0.65)	0.46 (0.38 to 0.55)	0.28 (0.23 to 0.34)
Rifampin[b] 600 mg once daily	50 mg twice daily	11	1.18 (1.03 to 1.37)	1.33 (1.15 to 1.53)	1.22 (1.01 to 1.48)
Rifabutin 300 mg once daily	50 mg once daily	9	1.16 (0.98 to 1.37)	0.95 (0.82 to 1.10)	0.70 (0.57 to 0.87)

[a] Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg twice daily.
[b] Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg once daily.
[c] The number of subjects represents the maximum number of subjects that were evaluated.

3TC: Effect of 3TC on the Pharmacokinetics of Other Agents: Based on in vitro study results, lamivudine at therapeutic drug exposures is not expected to affect the pharmacokinetics of drugs that are substrates of the following transporters: organic anion transporter polypeptide 1B1/3 (OATP1B1/3), breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), multidrug and toxin extrusion protein 1 (MATE1, MATE2-K, organic cation transporter 1 (OCT)1, OCT2, or OCT3.

Effect of Other Agents on the Pharmacokinetics of 3TC: 3TC is a substrate of MATE1, MATE2-K, and OCT2 *in vitro*. Trimethoprim (an inhibitor of these drug transporters) has been shown to increase 3TC plasma concentrations. This interaction is not considered clinically significant as no dose adjustment of 3TC is needed.

3TC is a substrate of P-gp and BCRP; however, considering its absolute bioavailability (87%), it is unlikely that these transporters play a significant role in the absorption of lamivudine. Therefore, coadministration of drugs that are inhibitors of these efflux transporters is unlikely to affect the disposition and elimination of 3TC.

Interferon Alfa: There was no significant pharmacokinetic interaction between 3TC and interferon alfa in a trial of 19 healthy male subjects.

Ribavirin: In vitro data indicate ribavirin reduces phosphorylation of 3TC, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and 3TC (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected subjects.

Sorbitol (Excipient): 3TC and sorbitol solutions were coadministered to 16 healthy adult subjects in an open-label, randomized-sequence, 4-period, crossover trial. Each subject received a single 300-mg dose of 3TC oral solution alone or coadministered with a single dose of 3.2 grams, 10.2 grams, or 13.4 grams of sorbitol in solution. Coadministration of 3TC with sorbitol resulted in dose-dependent decreases of 20%, 39%, and 44% in the $AUC_{(0\ to\ 24)}$, 14%, 32%, and 36% in the $AUC_{(\infty)}$, and 28%, 52%, and 55% in the C_{max}; of lamivudine, respectively.

Trimethoprim/Sulfamethoxazole: 3TC and TMP/SMX were coadministered to 14 HIV-1-positive subjects in a single-center, open-label, randomized, crossover trial. Each subject received treatment with a single 300-mg dose of 3TC and TMP 160 mg/SMX 800 mg once a day for 5 days with concomitant administration of 3TC 300 mg with the fifth dose in a crossover design. Coadministration of TMP/SMX with 3TC resulted in an increase of 43% ± 23% (mean ± SD) in 3TC AUC_{∞}, a decrease of 29% ±13% in 3TC oral clearance, and a decrease of 30% ± 36% in 3TC renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by coadministration with 3TC. There is no information regarding the effect on 3TC pharmacokinetics of higher doses of TMP/SMX such as those used in treat PCP.

Zidovudine: No clinically significant alterations in 3TC or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-1-infected adult subjects given a single dose of zidovudine (200 mg) in combination with multiple doses of 3TC (300 mg every 12 hours).

TDF: At concentrations substantially higher (~300-fold) than those observed *in vivo*, tenofovir did not inhibit *in vitro* drug metabolism mediated by any of the following human CYP isoforms: CYP3A4, CYP2D6, CYP2C9, or CYP2E1. However, a small (6%) but statistically significant reduction in metabolism of CYP1A substrate was observed.

Based on the results of *in vitro* experiments and the known elimination pathway of tenofovir, the potential for CYP-mediated interactions involving tenofovir with other medicinal products is low.

TDF has been evaluated in healthy volunteers in combination with other antiretroviral and potential concomitant drugs. Tables 10 and 11 summarize pharmacokinetic effects of co-administered drug on tenofovir pharmacokinetics and effects of TDF on the pharmacokinetics of co-administered drug.

TDF is a substrate of P-gp and breast cancer resistance protein (BCRP) transporters. When TDF is co-administered with an inhibitor of these transporters, an increase in absorption may be observed.

No clinically significant drug interactions have been observed between TDF and efavirenz, methadone, nelfinavir, oral contraceptives, ribavirin, or sofosbuvir.

Table 10: Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir[a] in the Presence of the Coadministered Drug

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters[b] (90% CI)		
			Cmax	AUC	Cmin
Atazanavir[c]	400 once daily × 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Atazanavir/ Ritonavir[c]	300/100 once daily	12	↑ 34 (↑ 20 to ↑ 51)	↑ 37 (↑ 30 to ↑ 45)	↑ 29 (↑ 21 to ↑ 36)
Darunavir/ Ritonavir[d]	300/100 twice daily	12	↑ 24 (↑ 8 to ↑ 42)	↑ 22 (↑ 10 to ↑ 35)	↑ 37 (↑ 19 to ↑ 57)
Indinavir	800 three times daily × 7 days	13	↑ 14 (↓ 3 to ↑ 33)	↔	↔
Ledipasvir/ Sofosbuvir[e,f]	90/400 once daily × 10 days	24	↑ 47 (↑ 37 to ↑ 58)	↑ 35 (↑ 29 to ↑ 42)	↑ 47 (↑ 38 to ↑ 57)
Ledipasvir/ Sofosbuvir[e,g]		23	↑ 64 (↑ 54 to ↑ 74)	↑ 50 (↑ 42 to ↑ 59)	↑ 59 (↑ 49 to ↑ 70)
Ledipasvir/ Sofosbuvir[h]	90/400 once daily × 14 days	15	↑ 79 (↑ 56 to ↑ 104)	↑ 98 (↑ 77 to ↑ 123)	↑ 163 (↑ 132 to↑ 197)
Lopinavir/ Ritonavir	400/100 twice daily × 14 days	24	↔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)
Saquinavir/ Ritonavir	1000/100 twice daily × 14 days	35	↔	↔	↑ 23 (↑ 16 to ↑ 30)
Sofosbuvir[i]	400 single dose	16	↑ 25 (↑ 8 to ↑ 45)	↔	↔
Sofosbuvir/ Velpatasvir[j]	400/100 once daily	24	↑ 44 (↑ 33 to ↑ 55)	↑ 40 (↑ 34 to ↑ 46)	↑ 84 (↑ 76 to ↑ 92)
Sofosbuvir/ Velpatasvir[k]	400/100 once daily	30	↑ 46 (↑ 39 to ↑ 54)	↑ 40 (↑ 34 to ↑ 45)	↑ 70 (↑ 61 to ↑ 79)

Sofosbuvir/ Velpatasvir/ Voxilaprevir[l]	400/100/100 + Voxilaprevir[m] 100 once daily	29	↑ 48 (↑ 36 to ↑ 61)	↑ 39 (↑ 32 to ↑ 46)	↑ 47 (↑ 38 to ↑ 56)
Tacrolimus	0.05 mg/kg twice daily × 7 days	21	↑ 13 (↑ 1 to ↑ 27)	↔	↔
Tipranavir/ Ritonavir[n]	500/100 twice daily	22	↓ 23 (↓ 32 to ↓ 13)	↓ 2 (↓ 9 to ↑ 5)	↑ 7 (↓ 2 to ↑ 17)
	750/200 twice daily (23 doses)	20	↓ 38 (↓ 46 to ↓ 29)	↑ 2 (↓ 6 to ↑ 10)	↑ 14 (↑ 1 to ↑ 27)

a. Subjects received TDF tablets 300 mg once daily.
b. Increase = ↑; Decrease = ↓; No Effect = ↔
c. Atazanavir Prescribing Information.
d. Darunavir Prescribing Information.
e. Data generated from simultaneous dosing with (ledipasvir/sofosbuvir). Staggered administration (12 hours apart) provided similar results.
f. Comparison based on exposures when administered as atazanavir/ritonavir + FTC/TDF.
g. Comparison based on exposures when administered as darunavir/ritonavir + FTC/TDF.
h. Study conducted with EFV/FTC/TDF coadministered with ledipasvir/sofosbuvir; coadministration with ledipasvir/sofosbuvir also results in comparable increases in tenofovir exposure when TDF is administered as FTC/rilpivirine/TDF, or FTC/TDF + dolutegravir.
i. Study conducted with EFV/FTC/TDF coadministered with sofosbuvir.
j. Study conducted with FTC/rilpivirine/TDF coadministered with sofosbuvir/velpatasvir; coadministration with sofosbuvir/velpatasvir also results in comparable increases in tenofovir exposures when TDF is administered as EFV/FTC/TDF, elvitegravir/cobicistat/FTC/TDF, FTC/TDF + atazanavir/ritonavir, or FTC/TDF + darunavir/ritonavir.
k. Administered as raltegravir + FTC/TDF.
l. Comparison based on exposures when administered as darunavir + ritonavir + FTC/TDF.
m. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.
n. Tipranavir Prescribing Information.

No effect on the pharmacokinetic parameters of the following co-administered drugs was observed with TDF: abacavir, didanosine (buffered tablets), emtricitabine, entecavir, and 3TC.

Table 11: Drug Interactions: Changes in Pharmacokinetic Parameters for Co-administered Drug in the Presence of TDF

Co-administered Drug	**Dose of Co-administered Drug (mg)**	**N**	**% Change of Tenofovir Pharmacokinetic Parameters[b,a] (90% CI)**		
			C_{max}	**AUC**	**C_{min}**
Abacavir	300 once	8	↑12 (↓1 to ↑26)	↔	NA
Atazanavir[b]	400 once daily × 14 days	34	↓21 (↓27 to ↓14)	↓25 (↓30 to ↓19)	↓40 (↓48 to ↓32)
Atazanavir[b]	Atazanavir/ Ritonavir 300/100 once daily × 42 days	10	↓28 (↓50 to ↑5)	↓25[c] (↓42 to ↓3)	↓23[c] (↓46 to ↑10)
Darunavir[d]	Darunavir/Ritonavir 300/100 once daily	12	↑ 16 (↓6 to ↑42)	↑21 (↓ 5 to ↑54)	↑24 (↓10 to ↑69)
Didanosine[e]	250 once, simultaneously with tenofovir and a light meal[f]	33	↓20[g] (↓32 to ↓7)	↔[g]	NA

Emtricitabine	200 once daily × 7 days	17	↔	↔	↑20 (↑12 to ↑29)
Entecavir	1 mg once daily × 10 days	28	↔	↑13 (↑11 to ↑15)	↔
Indinavir	800 three times daily × 7 days	12	↓11 (↓30 to ↑12)	↔	↔
Lamivudine	150 twice daily × 7 days	15	↓24 (↓34 to ↓12)	↔	↔
Lopinavir	Lopinavir/Ritonavir 400/100 twice daily × 14 days	24	↔	↔	↔
Ritonavir			↔	↔	↔
Saquinavir	Saquinavir/Ritonavir 1,000/100 twice daily × 14 days	32	↑22 (↑6 to ↑41)	↑29[h] (↑12 to ↑48)	↑47[h] (↑23 to ↑76)
Ritonavir			↔	↔	↑ 23 (↑3 to ↑46)
Tacrolimus	0.05 mg/kg twice daily 7 days	21	↔	↔	↔
Tipranavir[i]	Tipranavir/Ritonavir 500/100 twice daily	22	↓17 (↓26 to ↓6)	↓ 18 (↓25 to ↓9)	↓21 (↓30 to ↓10)
	Tipranavir/Ritonavir 750/200 twice daily (23 doses)	20	↓11 (↓16 to ↓4)	↓9 (↓15 to ↓3)	↓ 12 (↓22 to 0)

a Increase = ↑; Decrease = ↓; No Effect = ↔; NA = Not Applicable
b Atazanavir Prescribing Information.
c In subjects with HIV-1 infection, addition of TDF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2.3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.
d Darunavir Prescribing Information.
e Didanosine Prescribing Information. Subjects received didanosine enteric-coated capsules.
f 373 kcal, 8.2 g fat
g Compared with didanosine (enteric-coated) 400 mg administered alone under fasting conditions.
h Increases in AUC and C_{min} are not expected to be clinically relevant; hence no dose adjustments are required when TDF and ritonavir boosted saquinavir are co-administered.
i Tipranavir Prescribing Information.

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 deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. 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.

3TC: 3TC is a synthetic nucleoside analogue. Intracellularly, 3TC is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of lamivudine-TP is inhibition of HIV-1 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue.

TDF: TDF is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. TDF requires

initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate, an obligate chain terminator. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase (RT) by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Antiviral Activity in Cell Culture

Dolutegravir: Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean EC_{50} values of 0.5 nM (0.21 ng per mL) to 2.1 nM (0.85 ng per mL) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells. Dolutegravir exhibited antiviral activity against 13 clinically diverse clade B isolates with a 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, B, C, D, E, F, and 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 3 HIV-2 clinical isolates in PBMC assays ranged from 0.09 nM to 0.61 nM.

3TC: The antiviral activity of 3TC against HIV-1 was assessed in a number of cell lines including monocytes and fresh human PBMCs using standard susceptibility assays. EC_{50} values were in the range of 0.003 to 15 microM (1 microM = 0.23 mcg per mL). The median EC_{50} values of 3TC were 60 nM (range: 20 to 70 nM), 35 nM (range: 30 to 40 nM), 30 nM (range: 20 to 90 nM), 20 nM (range: 3 to 40 nM), 30 nM (range: 1 to 60 nM), 30 nM (range: 20 to 70 nM), 30 nM (range: 3 to 70 nM), and 30 nM (range: 20 to 90 nM) against HIV-1 clades A-G and group O viruses (n = 3 except n = 2 for clade B) respectively. The EC_{50} values against HIV-2 isolates (n = 4) ranged from 0.003 to 0.120 microM in PBMCs. 3TC was not antagonistic to all tested anti-HIV agents. Ribavirin (50 microM) used in the treatment of chronic HCV infection decreased the anti-HIV-1 activity of 3TC by 3.5-fold in MT-4 cells.

TDF: The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC_{50} values for tenofovir were in the range of 0.04 microM to 8.5 microM. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values ranged from 0.5 microM to 2.2 microM) and strain-specific activity against HIV-2 (EC_{50} values ranged from 1.6 microM to 5.5 microM).

Antiviral Activity in Combination with Other Antiviral Agents

Neither dolutegravir nor 3TC were antagonistic to all tested anti-HIV agents. See full prescribing information for dolutegravir and 3TC.

Resistance in Cell Culture

Dolutegravir: Dolutegravir-resistant viruses were selected in cell culture starting from different wild-type HIV-1 strains and clades. Amino acid substitutions E92Q, G118R, S153F or Y, G193E or R263K emerged in different passages and conferred decreased susceptibility to dolutegravir of up to 4-fold. Passage of mutant viruses containing the Q148R or Q148H substitutions selected for additional substitutions in integrase that conferred decreased susceptibility to dolutegravir (fold-change increase of 13 to 46). The additional integrase substitutions included T97A, E138K, G140S, and M154I. Passage of mutant viruses containing both G140S and Q148H selected for L74M, E92Q, and N155H.

3TC: 3TC-resistant variants of HIV-1 have been selected in cell culture. Genotypic analysis showed that resistance was predominantly due to a methionine to valine or isoleucine (M184V/I) substitution in reverse

transcriptase.

TDF: HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R substitution in RT and showed a 2- to 4-fold reduction in susceptibility to tenofovir. In addition, a K70E substitution in HIV-1 RT has been selected by tenofovir and results in low-level reduced susceptibility to tenofovir. K65R substitutions developed in some subjects failing a TDF regimen.

Resistance in Clinical Subjects

Dolutegravir:

Treatment-Naïve Subjects: No subject who received 50-mg once-daily in SINGLE had a detectable decrease in susceptibility to dolutegravir or background NRTIs in the resistance analysis subset (n = 12 with HIV-1 RNA greater than 400 copies per mL at failure or last visit and having resistance data). Two virologic failure subjects in SINGLE had treatment-emergent G/D/E193D and G193G/E integrase substitutions at Week 84 and Week 108, respectively, and 1 subject with 275 copies per mL HIV-1 RNA had a treatment-emergent Q157Q/P integrase substitution detected at Week 24. None of these subjects had a corresponding decrease in dolutegravir susceptibility. No treatment-emergent genotypic resistance to the background regimen was observed in the SINGLE trial.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects: In the dolutegravir arm of the SAILING trial for treatment-experienced and INSTI-naïve subjects (n = 354), treatment-emergent integrase substitutions were observed in 6 of 28 (21%) subjects who had virologic failure and resistance data. In 5 of the 6 subjects' isolates emergent INSTI substitutions included L74L/M/I, Q95Q/L, V151V/I (n = 1 each), and R263K (n = 2). The change in dolutegravir phenotypic susceptibility for these 5 subject isolates was less than 2-fold. One subject isolate had pre-existing raltegravir resistance substitutions E138A, G140S, and Q148H at baseline and had additional emergent INSTI-resistance substitutions T97A and E138A/T with a corresponding 148-fold reduction in dolutegravir susceptibility at failure. In the comparator raltegravir arm, 21 of 49 (43%) subjects with post-baseline resistance data had evidence of emergent INSTI-resistance substitutions (L74M, E92Q, T97A, E138Q, G140S/A, Y143R/C, Q148H/R, V151I, N155H, E157Q, and G163K/R) and raltegravir phenotypic resistance.

Cross-Resistance

Dolutegravir: *Dolutegravir: Site-Directed Integrase Strand Transfer Inhibitor-Resistant Mutant HIV-1 and HIV-2 Strains:* 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) and 6 INSTI-resistant site-directed mutant HIV-2 viruses. The single INSTI-resistance substitutions T66K, I151L, and S153Y conferred a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.3-fold to 3.6-fold from reference). Combinations of multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148, and substitutions at E138/G140/Q148 showed a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.5-fold to 21-fold from reference). In HIV-2 mutants, combinations of substitutions A153G/N155H/S163G and E92Q/T97A/N155H/S163D conferred 4-fold decreases in dolutegravir susceptibility, and E92Q/N155H and G140S/Q148R showed 8.5-fold and 17-fold decreases in dolutegravir susceptibility, respectively.

Reverse Transcriptase Inhibitor- and Protease Inhibitor-Resistant Strains: Dolutegravir demonstrated equivalent antiviral activity against 2 NNRTI-resistant, 3 NRTI-resistant, and 2 PI resistant HIV-1 mutant clones compared with the wild-type strain.

3TC: Cross-resistance has been observed among reverse transcriptase inhibitors. 3TC-resistant HIV-1 mutants were cross-resistant in cell culture to didanosine (ddI). Cross-resistance is also expected with abacavir and

emtricitabine as these select M184V substitutions.

TDF: Cross resistance among certain HIV-1 NRTIs has been recognized. The K65R and K70E substitutions selected by tenofovir are also selected in some HIV-1 infected subjects treated with abacavir or ddI. HIV-1 isolates with this substitution also showed reduced susceptibility to emtricitabine and 3TC. Therefore, cross resistance among these drugs may occur in patients whose virus harbors the K65R or K70E substitution. HIV-1 isolates from subjects (N=20) whose HIV-1 expressed a mean of three zidovudine-associated reverse transcriptase substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N), showed a 3.1-fold decrease in the susceptibility to tenofovir. Subjects whose virus expressed an L74V substitution without zidovudine resistance associated substitutions (N=8) had reduced response to TDF. Limited data are available for subjects whose virus expressed a Y115F substitution (N=3), Q151M substitution (N=2), or T69 insertion (N=4), all of whom had a reduced response.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Dolutegravir: Two-year carcinogenicity studies in mice and rats were conducted with dolutegravir. Mice were administered doses of up to 500 mg per kg, and rats were administered doses of up to 50 mg per kg. In mice, no significant increases in the incidence of drug-related neoplasms were observed at the highest doses tested, resulting in dolutegravir AUC exposures approximately 14 times higher than those in humans at the maximum recommended dose of 50 mg twice daily. In rats, no increases in the incidence of drug-related neoplasms were observed at the highest dose tested, resulting in dolutegravir AUC exposures 10 times and 15 times higher in males and females, respectively, than those in humans at a dose of 50 mg twice daily.

3TC: Long-term carcinogenicity studies with 3TC in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) the human exposures at the recommended dose of 300 mg.

TDF: Long-term oral carcinogenicity studies of TDF in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.

Mutagenesis

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

3TC: 3TC was mutagenic in an L5178Y mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. 3TC 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. 3TC showed no evidence of in vivo genotoxic activity in the rat at oral doses of up to 2,000 mg per kg, producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV-1 infection.

TDF: TDF was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus assay, TDF was negative when administered to male mice.

Impairment of Fertility

Dolutegravir and 3TC: Dolutegravir or 3TC did not affect male or female fertility in rats at doses associated with exposures approximately 24 or 47 to 70 times (respectively) higher than the exposures in humans at the maximum recommended doses.

TDF: There were no effects on fertility, mating performance or early embryonic development when TDF was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats.

13.2 Animal Toxicology and/or Pharmacology

TDF: Tenofovir and TDF administered in toxicology studies to rats, dogs, and monkeys at exposures (based on AUCs) greater than or equal to 6 fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

Evidence of renal toxicity was noted in 4 animal species. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2 to 20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

14 CLINICAL STUDIES

14.1 Adult Subjects Dolutegravir:

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

Week 144 (open-label-phase analysis which followed the Week 96 double-blind phase) outcomes for SINGLE are provided in Table 12.

Table 12: Virologic Outcomes of Randomized Treatment in SINGLE at 144 Weeks (Snapshot Algorithm)

	Dolutegravir 50 mg + Abacavir Sulfate and Lamivudine Once Daily (n = 414)	**Efavirenz, Emtricitabine, and Tenofovir DF Once Daily (n = 419)**
HIV-1 RNA <50 copies/mL	71%	63%
Treatment difference[a]	8.3% (95% CI: 2.0% 14.6%)[d]	
Virologic nonresponse	10%	7%
Data in window not <50 copies/mL	4%	<1%

Discontinued for lack of efficacy	3%	3%
Discontinued for other reasons while not suppressed	3%	4%
Changes in ART regimen	0	0
No virologic data	18%	30%
Reasons		
Discontinued study/study drug due to adverse event or death[b]	4%	14%
Discontinued study/study drug for other reasons[c]	12%	13%
Missing data during window but on study	2%	3%
Proportion (%) of Subjects with HIV-1 RNA <50 copies/mL by Baseline Category		
Plasma viral load (copies/mL)		
≤100,000	73%	64%
>100,000	69%	61%
Gender		
Male	72%	66%
Female	69%	48%
Race		
White	72%	71%
African-American/African Heritage/Other	71%	47%

NRTI = nucleoside reverse transcriptase inhibitor

[a] Adjusted for pre-specified stratification factors.
[b] Includes subjects who discontinued due to an adverse event or death at any time point if this resulted in no virologic data on treatment during the analysis window.
[c] Other includes reasons such as withdrew consent, loss to follow-up, moved, and protocol deviation.
[d] The primary endpoint was assessed at Week 48 and the virologic success rate was 88% in the group receiving dolutegravir and 81% in the fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate group, with a treatment difference of 7.4% and 95% CI of (2.5%, 12.3%).

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

There was no treatment-emergent resistance to dolutegravir, abacavir, or 3TC.

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

14.2 Pediatric Subjects
The efficacy of the individual components of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets for the treatment of HIV-1 infection was evaluated in pediatric patients enrolled in the IMPAACT P1093 trial (NCT01302847) or the ARROW trial (NCT02028676), as summarized below.

- Dolutegravir, in combination with other antiretroviral drugs was evaluated in treatment-experienced, INSTI-naïve, HIV-1–infected subjects aged 6 to less than 18 years in a 48-week open-label, multicenter, dose-finding clinical trial, IMPAACT P1093 (NCT01302847). Subjects aged 12 to less than 18 years were enrolled in Cohort 1 and subjects aged 6 to less than 12 years were enrolled in Cohort 2A. At 48 weeks, 61% (14/23) of subjects aged 12 to less than 18 years treated with dolutegravir once daily plus optimized background therapy achieved virologic response defined as HIV-1 RNA less than 50 copies per mL. Across both cohorts, virologic suppression at Week 48 was achieved in 67% (16/24) of subjects weighing at least 40 kg.
- Lamivudine once daily, with abacavir and a third antiretroviral drug, was evaluated in a randomized, multicenter trial (ARROW) in HIV-1–infected, treatment-naïve subjects. Subjects randomized to once-daily dosing (n = 336) and who weighed at least 25 kg received lamivudine 300 mg and abacavir 600 mg, as either the single entities or as fixed-dose abacavir and lamivudine. At Week 96, 67% of subjects receiving abacavir and lamivudine once-daily in combination with a third antiretroviral drug, had HIV-1 RNA less than 80 copies per mL.

16 HOW SUPPLIED/STORAGE AND HANDLING

Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, 50 mg/300 mg/300 mg are oval, white, biconvex, film-coated tablets marked with 'I10' on one side and plain on the other side and supplied as follows:

Bottle of 30 tablets with desiccant and child-resistant closure (52719-130-30)
Bottle of 90 tablets with desiccant and child-resistant closure (52719-130-90)

Store below 30°C (86°F).
Store and dispense in original bottle, protect from moisture, and keep bottle tightly closed. Do not remove desiccant. Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

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

Severe Acute Exacerbation of Hepatitis B in Patients with HBV Infection

Inform patients that severe acute exacerbations of hepatitis B have been reported in patients infected with hepatitis B virus (HBV) who have discontinued 3TC and TDF, two components of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets. Advise patients not to discontinue Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets without first informing their healthcare provider. All patients should be tested for HBV infection before or when starting Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets and those who are infected with HBV need close medical follow-up for several months after stopping Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets to monitor for exacerbations of hepatitis *[see Warnings and Precautions (5.1)]*.

Drug Interactions

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

Do not administer Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets with HEPSERA (adefovir dipivoxil) *[see Drug Interactions (7.3)]*.

Hypersensitivity Reactions

Advise patients to immediately contact their healthcare provider if they develop rash. Instruct patients to immediately stop taking Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets and other suspect agents, 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) *[see Warnings and Precautions (5.2)]*.

Hepatotoxicity

Inform patients that hepatotoxicity has been reported with dolutegravir, a component of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets *[see Warnings and Precautions (5.3), Adverse Reactions (6.1)]*. Inform patients that monitoring for hepatoxicity during therapy with Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is recommended.

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any signs or symptoms of infection as inflammation from previous infection may occur soon after combination antiretroviral therapy, including when Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is started *[see Warnings and Precautions (5.7)]*.

Lactation

Inform individuals with HIV-1 infection that the potential risks of breastfeeding include: (1) HIV-1 transmission (in HIV-1–negative infants), (2) developing viral resistance (in HIV-1– positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults [see *Use in Specific Populations (8.2)*].

Missed Dose

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

Storage

Instruct patients to store the Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets in the original bottle, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant.

Lactic Acidosis/Hepatomegaly

Inform patients that lactic acidosis and severe hepatomegaly with steatosis including fatal cases, have been reported. Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets should be suspended in any patients who develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity (including nausea, vomiting, unusual or unexpected stomach discomfort, and weakness) *[see Warnings and Precautions (5.5)]*.

Risk of Pancreatitis

Advise parents or guardians to monitor pediatric patients for signs and symptoms of pancreatitis *[see Warnings and Precautions (5.8)]*.

New Onset or Worsening Renal Impairment

Inform patients that renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported. Advise patients with impaired renal function (i.e., creatinine clearance less than 50 mL per min) or patients with end-stage renal disease (ESRD) requiring hemodialysis to avoid Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple NSAIDs) for patients *[see Dosage and Administration (2.4), Warnings and Precautions (5.4)]*.

Bone Loss and Mineralization Defects

Inform patients that decreases in bone mineral density have been observed with the use of TDF, a component of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets. Consider bone monitoring in patients who have a history of pathologic bone fracture or at risk for osteopenia *[see Warnings and Precautions (5.9)]*.

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Gqeberha
6020
Republic of South Africa

PATIENT INFORMATION
Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate
(DOE loo TEG ra vir, la MIV ue deen and ten OF oh vir dye soe PROX il FUE ma rate)
Tablets

What is the most important information I should know about Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets?

Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets can cause serious side effects, including:

- **Worsening of hepatitis B infection (HBV).** Your healthcare provider will test you for HBV before starting treatment with Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets. **If you have HBV infection and take Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, your HBV may get worse (flare-up) if you stop taking Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets.** A "flare-up" is when your HBV infection suddenly returns in a worse way than before.
  - **Do not** run out of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets. Refill your prescription or talk to your healthcare provider before your Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is all gone.
  - **Do not stop** taking Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets without first talking to your healthcare provider.

If you stop taking Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your HBV infection. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets.

What is Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets?

- Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is a prescription medicine to treat Human Immunodeficiency Virus (HIV-1) infection in adults and children who weigh at least 77 pounds (35 kg).
  - HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).
  - Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets contain 3 prescription medicines, dolutegravir, lamivudine and tenofovir disoproxil fumarate.

Do not take Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets if you:

- are allergic to dolutegravir or lamivudine, or any of the ingredients in Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets. See the end of this Patient Information for a complete list of ingredients in Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets.
- take dofetilide. Taking Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets and dofetilide can cause side effects that may be serious or life-threatening.

Before taking Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had liver problems, including hepatitis B or C virus infection.
- have kidney problems or receive kidney dialysis treatment.
- have bone problems
- are pregnant or plan to become pregnant. Talk to your healthcare provider about the benefits and risks of treatment with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets during pregnancy.

- are breastfeeding or plan to breastfeed. Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets pass to your baby in your breast milk. Talk with your healthcare provider about the following risks to your baby from breastfeeding during treatment with Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets:
  the HIV-1 virus may pass to your baby if your baby does not have HIV-1 infection.
  the HIV-1 virus may become harder to treat if your baby has HIV-1 infection.
  your baby may get side effects from Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets.

Tell your healthcare provider about the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Some medicines interact with Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

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

How should I take Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets?

- Take Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets exactly as your healthcare provider tells you to take it. Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets is taken by itself (not with other HIV-1 medicines) to treat HIV-1 infection.
- Take Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets with or without food.
- For adults and children weighing at least 77 pounds (35 kg), the usual dose of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is one tablet each day. An extra dose of dolutegravir only may be necessary for certain populations. Your healthcare provider will inform you if you need to take the extra dolutegravir dose.
- Do not change your dose, switch medicines or stop taking Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets without first talking with your healthcare provider.
- If you take antacids, laxatives, or other medicines that contain aluminum, magnesium, or buffered medicines, Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets should be taken at least 2 hours before or 6 hours after you take these medicines.

- If you need to take iron or calcium supplements by mouth during treatment with dolutegravir, emtricitabine and tenofovir disoproxil fumarate tablets:
  - If you take Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets with food, you may take these supplements at the same time that you take Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets.
  - If you do not take Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets with food, take Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets at least 2 hours before or 6 hours after you take these supplements.
- Do not miss a dose of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets.
- If you miss a dose of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, take it as soon as you remember. Do not take 2 doses at the same time or take more than your prescribed dose.
- Stay under the care of a healthcare provider during treatment with Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets.
- Do not run out of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets. The virus in your blood may increase and the virus may become harder to treat. When your supply starts to run low, get more from your healthcare provider or pharmacy.
- If you take too many Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets?

Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets can cause serious side effects including:

- **See "What is the most important information I should know about Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets?"**
- **Allergic reactions.** Call your healthcare provider right away if you develop a rash with Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets. **Stop taking Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets and get medical help right away if you develop a rash with any of the following signs or symptoms:**
  - fever
  - generally ill feeling
  - tiredness
  - muscle or joint aches
  - blisters or sores in mouth
  - blisters or peeling of the skin
  - redness or swelling of the eyes
  - swelling of the mouth, face, lips, or tongue
  - problems breathing
- **Serious liver problems.** People with a history of hepatitis B or C virus may have an increased risk of developing new or worsening changes in certain liver tests during treatment with Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets. In some cases, severe liver problems can lead to death. Your liver may become large (hepatomegaly) and you may develop fat in your liver (steatosis). **Call your healthcare provider right away if you develop 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 for several days or longer
  - pain, aching, or tenderness on the right side of your stomach area

- **New or worse kidney problems, including kidney failure.** Your healthcare provider should do blood and urine tests to check your kidneys before you start and during treatment with Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets. Your healthcare provider may tell you to stop taking Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets if you develop new or worse kidney problems.
- **Too much lactic acid in your blood (lactic acidosis).** Lactic acidosis 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
- have a fast or irregular heartbeat
- feel dizzy or light-headed
- **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 any new symptoms after you start taking Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets.
- **Risk of inflammation of the pancreas (pancreatitis).** Children may be at risk for developing pancreatitis during treatment with Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets if they have taken nucleoside analogue medicines, have a history of pancreatitis in the past, have other risk factors for pancreatitis.
- **Bone problems** can happen in some people who take Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets. Bone problems include bone pain, softening or thinning (which may lead to fractures). Your healthcare provider may need to do additional tests to check your bones.

The most common side effects of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets include:

- Rash
- Headache
- Pain
- Diarrhea
- Depression
- Trouble sleeping
- Tiredness

The most common side effects of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets in children include fever and cough.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets?

- Store Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets below 30°C (86°F).
- Keep Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets in their original container.
- Keep the bottle tightly closed. The bottle of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets contains a desiccant that helps to keep the tablets dry (protect it from moisture). Do not remove desiccant.

Keep Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets and all medicines out of the reach of children.

General information about the safe and effective use of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets.

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

What are the ingredients in Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets?

Active ingredient: dolutegravir sodium, lamivudine, and tenofovir disoproxil fumarate.

Inactive ingredients: croscarmellose sodium, lactose monohydrate, mannitol, microcrystalline cellulose, povidone k-30, pregelatinized starch, sodium starch glycolate type A and sodium stearyl fumarate with the following film coating system: polyethylene glycol 3350, polyvinyl alcohol, talc and titanium dioxide.

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Manufactured By
Aspen SA (OSD) Operations (Pty) Ltd
Corner of Fairclough and Gibaud Road
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This Patient Information has been approved by the U.S. Food and Drug Administration Revised: 5/2026