

DOLUTEGRAVIR, LAMIVUDINE AND TENOFOVIR ALAFENAMIDE- dolutegravir, lamivudine and tenofovir alafenamide tablet, film coated

Mylan Laboratories Limited

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

DOLUTEGRAVIR, LAMIVUDINE and TENOFOVIR ALAFENAMIDE tablets, for oral use

Initial U.S. Approval:

WARNING: POSTTREATMENT EXACERBATIONS OF HEPATITIS B

See full prescribing information for complete boxed warning.

Severe acute exacerbations of hepatitis B virus (HBV) have been reported in HBV-infected patients who have discontinued products containing lamivudine (3TC) and/or tenofovir disoproxil fumarate (TDF) and may occur with discontinuation of dolutegravir, lamivudine and tenofovir alafenamide tablets. Monitor hepatic function closely in HBV-infected patients who discontinue dolutegravir, lamivudine and tenofovir alafenamide tablets. If appropriate, initiation of anti-HBV therapy may be warranted. (5.1)

INDICATIONS AND USAGE

Dolutegravir, lamivudine and tenofovir alafenamide tablets, a combination of dolutegravir (integrase strand transfer inhibitor [INSTI]), lamivudine, and tenofovir alafenamide (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 40 kg. (1)

Limitations of Use:

- Dolutegravir, lamivudine and tenofovir alafenamide 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 alafenamide tablets is insufficient in these subpopulations. See the dolutegravir prescribing information. (1)

DOSAGE AND ADMINISTRATION

- Pregnancy Testing:** Perform pregnancy testing before initiation of dolutegravir, lamivudine and tenofovir alafenamide tablets in adolescents and adults of childbearing potential. (2.1, 5.4)
- Testing:** Prior to or when initiating dolutegravir, lamivudine and tenofovir alafenamide tablets, test for HBV infection. Prior to initiation and during use of dolutegravir, lamivudine and tenofovir alafenamide tablets, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with

- 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 alafenamide 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. Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations. Monitoring for hepatotoxicity is recommended. (5.3)
- Embryo-fetal toxicity may occur when used at the time of conception and in early pregnancy. Avoid use of dolutegravir, lamivudine and tenofovir alafenamide tablets at the time of conception through the first trimester of pregnancy due to the risk of neural tube defects. Advise adolescents and adults of childbearing potential to use effective contraception. (2.1, 5.4, 8.1, 8.3)
- New onset or worsening renal impairment: Assess creatinine clearance, urine glucose, and urine protein in all patients before initiating dolutegravir, lamivudine and tenofovir alafenamide tablets therapy and monitor during therapy. Monitor serum phosphorus in patients with chronic kidney disease. (5.6)
- Immune reconstitution syndrome: Observed in HIV-infected patients. May necessitate further evaluation and treatment (5.7)
- Lactic acidosis and severe hepatomegaly with steatosis: Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.8)
- Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue treatment as clinically appropriate. (5.9)

ADVERSE REACTIONS

- The most common adverse reactions (in those receiving the components of dolutegravir, lamivudine and tenofovir alafenamide) are nausea, insomnia, fatigue, headache, diarrhea, and depression. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Mylan at 1-877-446-3679, (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Coadministration of dolutegravir, lamivudine and tenofovir alafenamide tablets with other drugs can alter the concentration of other drugs and other drugs may alter the concentrations of dolutegravir, lamivudine and tenofovir alafenamide tablets. The potential drug-drug interactions must be considered prior to and during therapy. (4, 7, 12.3)

chronic kidney disease, also assess serum phosphorous. (2.1)

- Recommended dose in adults and pediatric patients weighing at least 40 kg: One tablet daily. May be taken with or without food. (2.2)
- Because dolutegravir, lamivudine and tenofovir alafenamide tablets is a fixed-dose product and cannot be dose adjusted, dolutegravir, lamivudine and tenofovir alafenamide tablets is not recommended in patients requiring dosage adjustment, patients with creatinine clearance less than 50 mL per minute, or patients with end-stage renal disease requiring hemodialysis. (2.3)

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

Tablet: 50 mg of dolutegravir, 300 mg of lamivudine, and 25 mg of tenofovir alafenamide (3)

----- **CONTRAINDICATIONS** -----

- Previous hypersensitivity reaction to dolutegravir, lamivudine, or tenofovir alafenamide. (4)

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

- Pregnancy: Avoid use of dolutegravir, lamivudine and tenofovir alafenamide tablets at the time of conception through the first trimester due to the risk of neural tube defects. (2.1, 5.4, 8.1)
- Lactation: Breastfeeding is not recommended due to the potential for HIV-1 transmission. (8.2)
- Females and males of reproductive potential: Pregnancy testing and contraception are recommended in adolescents and adults of childbearing potential. (8.3)
- Pediatrics: Not recommended for patients weighing less than 40 kg. (8.4)
- Dolutegravir, lamivudine and tenofovir alafenamide 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.

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WARNING: POSTTREATMENT 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 (3TC) and/or tenofovir disoproxil fumarate (TDF) and may occur with discontinuation of dolutegravir, lamivudine and tenofovir alafenamide tablets. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in HBV-infected patients who discontinue dolutegravir, lamivudine and tenofovir alafenamide 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 alafenamide tablets is indicated for use alone as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients weighing at least 40 kg.

Limitation of Use: Dolutegravir, lamivudine and tenofovir alafenamide 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 alafenamide tablets is insufficient in these subpopulations. See the full prescribing information for dolutegravir.

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation and During Treatment with Dolutegravir, Lamivudine and Tenofovir Alafenamide Tablets

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

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

Prior to initiation and during treatment with dolutegravir, lamivudine and tenofovir alafenamide 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 [see *Warnings and Precautions (5.6)*].

2.2 Recommended Dosage

Dolutegravir, lamivudine and tenofovir alafenamide tablets is a fixed-dose combination product containing 50 mg of dolutegravir, 300 mg of lamivudine (3TC), and 25 mg of tenofovir alafenamide (TAF). The recommended dosage regimen of dolutegravir, lamivudine and tenofovir alafenamide tablets in adults and pediatric patients weighing at least 40 kg (88 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 alafenamide tablets is a fixed-dose combination formulation 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)].

3 DOSAGE FORMS AND STRENGTHS

Dolutegravir, Lamivudine and Tenofovir Alafenamide Tablets contain 50 mg of dolutegravir, 300 mg of lamivudine, and 25 mg of tenofovir alafenamide.

The 50 mg/300 mg/25 mg tablets are white to off-white, film-coated, capsule shaped, unscored tablets debossed with **M** on one side of the tablet and **LD** on the other side.

4 CONTRAINDICATIONS

Dolutegravir, lamivudine and tenofovir alafenamide tablets is contraindicated in patients:

- with prior hypersensitivity reaction to dolutegravir [see *Warnings and Precautions* (5.2)], lamivudine, or tenofovir alafenamide.
- 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 alafenamide tablets.

Discontinuation of anti-HBV therapy, including 3TC and TAF, two components of dolutegravir, lamivudine and tenofovir alafenamide tablets, may be associated with severe acute exacerbations of hepatitis B. Patients infected with HBV who discontinue dolutegravir, lamivudine and tenofovir alafenamide 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 Reactions

Hypersensitivity reactions have been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. The events were reported in less than 1% of subjects receiving dolutegravir in Phase 3 clinical trials. Discontinue dolutegravir, lamivudine and tenofovir alafenamide 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 alafenamide tablets or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction.

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 alafenamide 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 Embryo-Fetal Toxicity

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

If there are plans to become pregnant or if pregnancy is confirmed within the first trimester while on dolutegravir, lamivudine and tenofovir alafenamide tablets, if possible, switch to an alternative regimen.

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

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

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

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

- Loss of therapeutic effect of dolutegravir, lamivudine and tenofovir alafenamide tablets and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs.

See Table 4 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 alafenamide tablets; review concomitant medications during therapy with dolutegravir, lamivudine and tenofovir alafenamide tablets; and monitor for the adverse reactions associated with the concomitant drugs.

5.6 New Onset or Worsening Renal Impairment

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir prodrugs in both animal toxicology studies and human trials. In clinical trials of TAF with emtricitabine (FTC), elvitegravir (EVG), and cobicistat (COBI), there have been no cases of Fanconi syndrome or Proximal Renal Tubulopathy (PRT), and renal serious adverse events or discontinuations due to renal adverse reactions were encountered in less than 1% of participants with eGFRs greater than 50 mL/minute

who received TAF. Dolutegravir, lamivudine and tenofovir alafenamide tablets is not recommended in patients with estimated creatinine clearance below 50 mL per minute.

Patients taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents including non-steroidal anti-inflammatory drugs are at increased risk of developing renal-related adverse reactions.

Prior to initiation and during treatment with dolutegravir, lamivudine and tenofovir alafenamide 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. Discontinue dolutegravir, lamivudine and tenofovir alafenamide tablets in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

5.7 Immune Reconstitution Syndrome

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

Autoimmune disorders (such as Graves' disease, polymyositis, Guillain-Barré syndrome, and autoimmune hepatitis) 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 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, a component of dolutegravir, lamivudine and tenofovir alafenamide tablets, and TDF, another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with dolutegravir, lamivudine and tenofovir alafenamide 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).

5.9 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 alafenamide tablets, should be used with caution. Treatment with dolutegravir, lamivudine and tenofovir alafenamide tablets should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur [see [Adverse Reactions \(6.1\)](#)].

6 ADVERSE REACTIONS

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

- Exacerbation 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 \(5.6\)](#)].
- Immune Reconstitution Syndrome [see [Warnings and Precautions \(5.7\)](#)].
- Lactic Acidosis and Severe Hepatomegaly with Steatosis [see [Boxed Warning, Warnings and Precautions \(5.8\)](#)].
- Pancreatitis [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.

Dolutegravir

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 sulfate 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 sulfate and lamivudine and 14% in subjects receiving fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate once daily.

Treatment-emergent adverse reactions (ARs) of moderate to severe intensity observed in at least 2% of subjects in either treatment arm of SINGLE are provided in Table 1.

Table 1. 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	Dolutegravir 50 mg + Abacavir Sulfate 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%
General Disorders		
Fatigue	2%	2%
Skin and Subcutaneous Tissue		
Rash*	< 1%	6%
Ear and Labyrinth		
Vertigo	0	2%

* 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 only treatment-emergent AR 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 Clinical Trials

The following ARs occurred in less than 2% of 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 in SINGLE are presented in Table 2. The mean change from baseline observed for selected lipid values is presented in Table 2.

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

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

Total neutrophils	4%	5%
Grade 2 (0.75 to 0.99 x 10 ⁹)	3%	3%
Grade 3 to 4 (< 0.75 x 10 ⁹)		

ULN = Upper limit of normal

Table 3. Mean Change from Baseline in Fasted Lipid Values in Treatment-Naïve Subjects in SINGLE Trial (Week 144 Analysis*)

Laboratory Parameter Preferred Term	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

* Subjects on lipid-lowering agents at baseline were excluded from these analyses (19 subjects in each arm in SINGLE: dolutegravir + fixed-dose abacavir sulfate 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 sulfate and lamivudine n = 36 and fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate n = 36).

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 \(5.2\)](#)].

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.

Clinical Trials Experience in Pediatric Subjects

IMPAACT PI093 is an ongoing multicenter, open-label, non-comparative trial of approximately 160 HIV-1-infected pediatric subjects aged 4 weeks to less than 18 years, of which 46 treatment-experienced, INSTI-naïve subjects aged 6 to less than 18 years have been enrolled [see [Use in Specific Populations \(8.4\)](#), [Clinical Studies \(14.2\)](#)].

The adverse reaction profile was similar to that for adults. Grade 2 ARs reported by more than one subject were decreased neutrophil count (n = 3) and diarrhea (n = 2). There were no Grade 3 or 4 drug-related ARs reported. No ARs led to discontinuation.

The Grade 3 or 4 laboratory abnormalities reported in more than one subject were elevated total bilirubin (n = 3) and decreased neutrophil count (n = 2). The changes in mean serum creatinine were similar to those observed in adults.

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 \(5.9\)](#)].

TAF

Adverse Reactions in Clinical Trials of TAF Compared to TDF in Treatment-Naïve Adults with HIV-1 Infection

The safety profile of TAF (n = 866) compared to TDF (n = 867), each with FTC, EVG, and COBI, was assessed in antiretroviral treatment-naïve HIV-1 infected adults in the pooled analysis of two randomized trials (Studies 104 and 111). Adverse reactions reported in subjects treated with the TAF-containing regimen (incidence greater than or equal to 5%, all grades) occurred at a similar rate in subjects treated with the TDF-containing regimen. The most common adverse reaction was nausea. During the 48-week treatment period, 0.9% of subjects discontinued the TAF-containing regimen due to adverse events [see [Clinical Studies \(14\)](#)]. Subjects treated with the TAF-containing regimen experienced mean increases of 30 mg/dL of total cholesterol, 15 mg/dL of LDL cholesterol, 7 mg/dL of HDL cholesterol and 29 mg/dL of triglycerides after 48 weeks of use.

The safety profile was similar in virologically-suppressed adults with HIV-1 infection who were switched from a TDF-containing regimen to TAF with FTC, EVG, and COBI (N = 799).

Renal Laboratory Tests

In the pooled analysis of antiretroviral treatment-naïve trials (Studies 104 and 111), HIV-1 infected adults treated with the TAF-containing regimen (N = 866) had a median baseline eGFR of 115 mL per minute, and mean serum creatinine increased by 0.1 mg per dL from baseline to Week 48. Median urine protein-to-creatinine ratio (UPCR) was 44 mg per gram at baseline and at Week 48. In a 48-week trial in virologically-suppressed TDF-treated adults who switched to TAF with FTC, EVG, and COBI with a mean baseline eGFR of 112 mL per minute, mean serum creatinine was similar to baseline and median UPCR was 61 mg per gram at baseline and 46 mg per gram at Week 48.

Bone Mineral Density Effects

In the pooled analysis of antiretroviral treatment-naïve trials (Studies 104 and 111), bone mineral density (BMD) from baseline to Week 48 was assessed by dual-energy X-ray absorptiometry (DXA). With the TAF-containing regimen, mean BMD decreased from baseline to Week 48 by -1.30% at the lumbar spine and -0.66% at the total hip. BMD declines of 5% or greater at the lumbar spine were experienced by 10% of subjects receiving the TAF-containing regimen. BMD declines of 7% or greater at the femoral neck were experienced by 7% of subjects receiving the TAF-containing regimen. The long-term clinical significance of these BMD changes is not known. Fractures (excluding fingers and toes) were reported in 7 (0.8%) subjects in the TAF with FTC, EVG, and COBI group.

In 799 virologically-suppressed TDF-treated adult subjects who switched to TAF with FTC, EVG, and COBI, at Week 48 mean BMD increased (1.86% lumbar spine, 1.95% total hip). BMD declines of 5% or greater at the lumbar spine were experienced by 1% of subjects receiving the TAF-containing regimen. BMD declines of 7% or greater at the femoral neck were experienced by 1% of subjects receiving the TAF-containing regimen.

Adverse Reactions in Clinical Trials in Pediatric Subjects with HIV-1 Infection

In an open-label trial of antiretroviral treatment-naïve HIV-1 infected pediatric subjects between the ages of 12 to less than 18 years through 48 weeks (N = 50; cohort 1) and virologically-suppressed subjects between the ages of 6 to less than 12 years (N = 23; cohort 2) who received TAF with FTC, EVG, and COBI through 24 weeks, with the exception of a decrease in the mean CD4+ cell count observed in cohort 2 [see [Clinical Studies \(14\)](#)], the safety of this combination was similar to that of adults.

Bone Mineral Density Effects

Cohort 1: Treatment-Naïve Adolescents (12 to Less Than 18 Years)

Among the subjects in cohort 1 receiving TAF with FTC, EVG, and COBI, mean BMD increased from baseline to Week 48, +4.2% at the lumbar spine and +1.3% for the total body less head (TBLH). Mean changes from baseline BMD Z-scores were -0.07 for lumbar spine and -0.20 for TBLH at Week 48. One subject had significant (at least 4%) lumbar spine BMD loss at Week 48.

Cohort 2: Virologically-Suppressed Children (6 to Less Than 12 Years)

Among the subjects in cohort 2 receiving TAF with FTC, EVG, and COBI, mean BMD increased from baseline to Week 24, +2.9% at the lumbar spine and +1.7% for TBLH. Mean changes from baseline BMD Z-scores were -0.06 for lumbar spine and -0.18 for TBLH at Week 24. Two subjects had significant (at least 4%) lumbar spine BMD loss at Week 24.

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 alafenamide 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

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 \(5.8\)](#)], posttreatment exacerbations of hepatitis B [see [Warnings and Precautions \(5.1\)](#)]

Hypersensitivity: anaphylaxis, urticaria

Musculoskeletal: muscle weakness, CPK elevation, rhabdomyolysis

Skin: alopecia, pruritus

TAF

Skin and Subcutaneous Tissue Disorders: angioedema, urticaria, and rash

7 DRUG INTERACTIONS

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

Dolutegravir

In vitro, dolutegravir inhibited the renal organic cation transporters, OCT2 (IC₅₀ = 1.93 microM) and multidrug and toxin extrusion transporter (MATE)1 (IC₅₀ = 6.34 microM). *In vivo*, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2 and potentially MATE1. Dolutegravir may increase plasma concentrations of drugs eliminated via OCT2 or MATE1 (dofetilide and metformin, Table 4) [see [Contraindications \(4\)](#), [Drug Interactions \(7.3\)](#)].

In vitro, dolutegravir inhibited the basolateral renal transporters, organic anion transporter (OAT)1 (IC₅₀ = 2.12 microM) and OAT3 (IC₅₀ = 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 (IC₅₀ greater than 50 microM) the following: cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate (UDP)-glucuronosyl transferase 1A1 (UGT1A1), 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 TAF

Dolutegravir

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

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

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 4) [see [Drug Interactions \(7.3\)](#), [Clinical Pharmacology \(12.3\)](#)].

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

TAF

TAF is a substrate of P-gp, BCRP, OATP1B1, and OATP1B3. Drugs that strongly affect P-gp and BCRP activity may lead to changes in TAF absorption (see Table 6). Drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentration of TAF, which may lead to loss of therapeutic effect of dolutegravir, lamivudine and tenofovir alafenamide tablets and development of resistance. Coadministration of dolutegravir, lamivudine and tenofovir alafenamide tablets with other drugs that inhibit P-gp and BCRP may increase the absorption and plasma concentration of TAF. TAF is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or UGT1A1. TAF is a weak inhibitor of CYP3A *in vitro*. TAF is not an inhibitor or inducer of CYP3A *in vivo*.

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

There were no drug-drug interaction trials conducted with fixed-dose dolutegravir, lamivudine and tenofovir alafenamide tablets. Dolutegravir, lamivudine and tenofovir alafenamide tablets is intended as a complete regimen.

Dolutegravir and TAF

Table 4 provides clinical recommendations as a result of drug interactions with dolutegravir and/or TAF. 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 4. 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*	↓ Dolutegravir	Use of dolutegravir, lamivudine and tenofovir alafenamide tablets with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir is not recommended.
Non-nucleoside reverse transcriptase inhibitor: Efavirenz*	↓ Dolutegravir	If coadministration with efavirenz is necessary, an additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, lamivudine and tenofovir alafenamide tablets.
Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓ Dolutegravir	Avoid coadministration with dolutegravir, lamivudine and tenofovir alafenamide tablets because there are insufficient data to make dosing recommendations.
Protease inhibitor: Fosamprenavir/ritonavir*	↓ Dolutegravir	If coadministration with fosamprenavir/ritonavir is necessary, an additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, lamivudine and tenofovir alafenamide tablets.
Tipranavir/ritonavir*	↓ Dolutegravir ↓ TAF	Coadministration is not recommended with dolutegravir, lamivudine and tenofovir alafenamide tablets.
Other Agents		
Dofetilide	↑ Dofetilide	Coadministration is contraindicated with dolutegravir, lamivudine and tenofovir

		alafenamide tablets [see Contraindications (4)].
Carbamazepine*	↓ Dolutegravir ↓ TAF	Consider alternative anticonvulsant. If coadministration is necessary, an additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, lamivudine and tenofovir alafenamide tablets.
Oxcarbazepine Phenytoin Phenobarbital	↓ Dolutegravir ↓ TAF	Avoid coadministration with dolutegravir, lamivudine and tenofovir alafenamide tablets because there are insufficient data to make dosing recommendations.
St. John's wort (<i>Hypericum perforatum</i>)	↓ TAF	Coadministration is not recommended with dolutegravir, lamivudine and tenofovir alafenamide tablets.
Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing antacids ^a or laxatives Sucralfate Buffered medications	↓ Dolutegravir	Administer dolutegravir, lamivudine and tenofovir alafenamide tablets 2 hours before or 6 hours after taking medications containing polyvalent cations.
Oral calcium or iron supplements, including multivitamins containing calcium or iron *	↓ Dolutegravir	Administer dolutegravir, lamivudine and tenofovir alafenamide tablets 2 hours before or 6 hours after taking supplements containing calcium or iron. Alternatively, dolutegravir and supplements containing calcium or iron can be taken together with food.
Metformin	↑ Metformin	Refer to the prescribing information of metformin for assessing the benefit and risk of concomitant use with metformin.
Rifampin*	↓ Dolutegravir ↓ TAF	Coadministration is not recommended with dolutegravir, lamivudine and tenofovir alafenamide tablets.
Rifabutin Rifapentine	↓ TAF	Coadministration is not recommended with dolutegravir, lamivudine and tenofovir alafenamide tablets.

* See [Clinical Pharmacology \(12.3\)](#) Table 10 or Table 11 for magnitude of interaction.

3TC

Drugs Inhibiting Organic Cation Transporters

3TC, a component of dolutegravir, lamivudine and tenofovir alafenamide 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 lamivudine 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 or TAF

Dolutegravir

In drug interaction trials, dolutegravir did not have a clinically relevant effect on the pharmacokinetics of the following drugs: daclatasvir, tenofovir, methadone, midazolam, rilpivirine, and oral contraceptives containing norgestimate and ethinyl estradiol. Using cross-study comparisons to historical pharmacokinetic data for each interacting drug, dolutegravir did not appear to affect the pharmacokinetics of the following drugs: atazanavir, darunavir, efavirenz, etravirine, fosamprenavir, lopinavir, ritonavir, and boceprevir.

Darunavir/ritonavir, lopinavir/ritonavir, rilpivirine, tenofovir, boceprevir, daclatasvir, prednisone, rifabutin, and omeprazole had no clinically significant effect on the pharmacokinetics of dolutegravir.

TAF

Based on drug interaction studies conducted with TAF, no clinically significant drug interactions have been either observed or are expected when TAF is combined with the following antiretroviral agents: atazanavir with ritonavir or cobicistat, darunavir with ritonavir or cobicistat, dolutegravir, efavirenz, ledipasvir, lopinavir/ritonavir, maraviroc, nevirapine, raltegravir, rilpivirine, and sofosbuvir. No clinically significant drug interactions have been either observed or are expected when TAF is combined with the following drugs: buprenorphine, itraconazole, ketoconazole, lorazepam, methadone, midazolam, naloxone, norbuprenorphine, norgestimate/ethinyl estradiol, and sertraline.

7.5 Drugs Affecting Renal Function with TAF

Because tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of TAF with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of tenofovir and other renally eliminated drugs and this may increase the risk of adverse reactions. Some examples of drugs that are eliminated by active tubular secretion 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 (5.6)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

exposed to dolutegravir from the time of conception through the first trimester of pregnancy.

There are insufficient human data on the use of dolutegravir, lamivudine and tenofovir alafenamide tablets during pregnancy to definitively assess a drug-associated risk for birth defects and miscarriage. Available data from the Antiretroviral Pregnancy Registry (APR) show no difference in rate of overall birth defects for lamivudine compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) (*see Data*). The background risk for major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background rate for major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with dolutegravir at systemic exposures (AUC) less than (rabbits) and approximately 27 times (rats) the exposure in humans at the maximum recommended human dose (MRHD) of dolutegravir (*see Data*). Oral administration of lamivudine to pregnant rabbits during organogenesis resulted in embryo lethality at systemic exposure (AUC) similar to the recommended clinical dose; however, no adverse development effects were observed with oral administration of lamivudine to pregnant rats during organogenesis at plasma concentrations (C_{max}) 35 times the recommended clinical dose (*see Data*). No adverse developmental effects were observed when TAF was administered during the period of organogenesis at exposure equal to or 53 times (rats and rabbits, respectively) the TAF exposure at the recommended daily dose of TAF (*see Data*).

Data

Human Data

Dolutegravir

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

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

3TC

Based on prospective reports from the APR of over 11,000 exposures to 3TC during pregnancy resulting in live births (including over 4,500 exposed in the first trimester), there was no difference between the overall risk of birth defects for 3TC compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of defects in live births was 3.1% (95% CI: 2.6% to 3.6%) following first trimester exposure to 3TC-containing regimens and 2.8% (95% CI: 2.5%, 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 lamivudine 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).

TAF

Based on prospective reports to the APR of 160 exposures to TAF-containing regimens during pregnancy (including 110 exposed in the first trimester and 50 exposed in the second/third trimester), there have been 3 birth defects with first trimester exposure to TAF-containing regimens.

Animal Data

Dolutegravir

Dolutegravir was administered orally at up to 1,000 mg per 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/post-partum Day 20. No adverse effects on embryo-fetal (rats and rabbits) or pre/post-natal (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/post-natal 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 lamivudine was observed in rats and rabbits at doses producing plasma concentrations (C_{max}) approximately 35 times higher than human exposure at the recommended daily dose. Evidence of early embryoletality 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.

TAF

TAF was administered orally to pregnant rats (25, 100, or 250 mg/kg/day) and rabbits (10, 30, or 100 mg/kg/day) through organogenesis (on gestation days 6 through 17, and 7 through 20, respectively). No adverse embryo-fetal effects were observed in rats and rabbits at TAF exposures approximately similar to (rats) and 53 (rabbits) times higher than the exposure in humans at the recommended daily dose of TAF. TAF is rapidly converted to tenofovir; the observed tenofovir exposures in rats and rabbits were 59 (rats) and 93 (rabbits) times higher than human tenofovir exposures at the recommended daily dose. Since TAF is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice was observed after TAF administration compared to tenofovir disoproxil fumarate (TDF, another prodrug for tenofovir) administration, a pre/postnatal development study in rats was conducted only with TDF. Doses up to 600 mg/kg/day were administered through lactation; no adverse effects were observed in the offspring on gestation day 7 (and lactation day 20) at tenofovir exposures of approximately 14 (21) times higher than the exposures in humans at the recommended daily dose of TAF.

8.2 Lactation

Risk Summary

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

It is not known whether dolutegravir or TAF is present in human breast milk, affects human milk production, or has effects on the breastfed infant. When administered to lactating rats, dolutegravir was present in milk (*see Data*). 3TC has been shown to be present in human breast milk. It is not known if 3TC affects milk production or has effects on the breastfed infant.

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

Data

Anima Data

Dolutegravir

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.

TAF

Studies in rats and monkeys have demonstrated that tenofovir is secreted in milk. Tenofovir was excreted into the milk of lactating rats following oral administration of TDF (up to 600 mg/kg/day) at up to approximately 24% of the median plasma concentration in the highest dosed animals at lactation day 11 (*see Data*). Tenofovir was excreted into the milk of lactating monkeys following a single subcutaneous (30 mg/kg) dose of tenofovir at concentrations up to approximately 4% of plasma concentration, resulting in exposure (AUC) of approximately 20% of plasma exposure.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Perform pregnancy testing in adolescents and adults of childbearing potential before initiation of dolutegravir, lamivudine and tenofovir alafenamide tablets.

Contraception

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

Advise adolescents and adults of childbearing potential who are taking dolutegravir, lamivudine and tenofovir alafenamide tablets to consistently use effective contraception.

8.4 Pediatric Use

Dolutegravir, lamivudine and tenofovir alafenamide tablets is a fixed-dose formulation which cannot be adjusted for patients weighing less than 40 kg.

8.5 Geriatric Use

Clinical trials of individual components of dolutegravir, lamivudine and tenofovir alafenamide 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 alafenamide 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 alafenamide 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 alafenamide tablets is a fixed-dose combination and the dosage of the individual components cannot be adjusted. If a dose reduction of 3TC, a component of dolutegravir, lamivudine and tenofovir alafenamide 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 (2.3)* 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 alafenamide tablets, has not been studied. Therefore, dolutegravir, lamivudine and tenofovir alafenamide 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 alafenamide 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.

TAF: Limited clinical experience is available at doses higher than the recommended dose of TAF. A single dose of 125 mg TAF (5 times the TAF dose in dolutegravir, lamivudine and tenofovir alafenamide tablets) was administered to 48 healthy subjects; no serious adverse reactions were reported. The effects of higher doses are unknown. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%.

11 DESCRIPTION

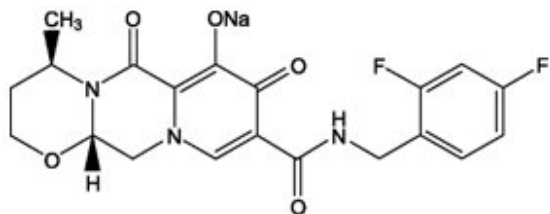
Dolutegravir, lamivudine and tenofovir alafenamide tablets are a fixed-dose combination product containing dolutegravir, lamivudine and tenofovir alafenamide fumarate, for oral administration.

- Dolutegravir, an HIV INST.
- Lamivudine, a synthetic nucleoside analogue with activity against HIV-1 and HBV.

- Tenofovir alafenamide fumarate, an HIV NRTI, is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate.

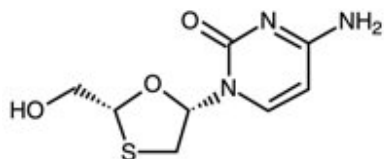
Each film-coated tablet contains 50 mg of dolutegravir, equivalent to 52.6 mg of dolutegravir sodium, 300 mg of lamivudine, 25 mg of tenofovir alafenamide, which is equivalent to 28.04 mg of tenofovir alafenamide fumarate, and the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, sodium starch glycolate (potato), talc and titanium dioxide.

Dolutegravir: The chemical name of dolutegravir sodium is Sodium (4R,12aS)-N-[(2,4-Difluorobenzyl)carbamoyl]-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazin-7-olate. The molecular formula is $C_{20}H_{18}F_2N_3NaO_5$ and the molecular weight is 441.37 g per mol. It has the following structural formula:



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

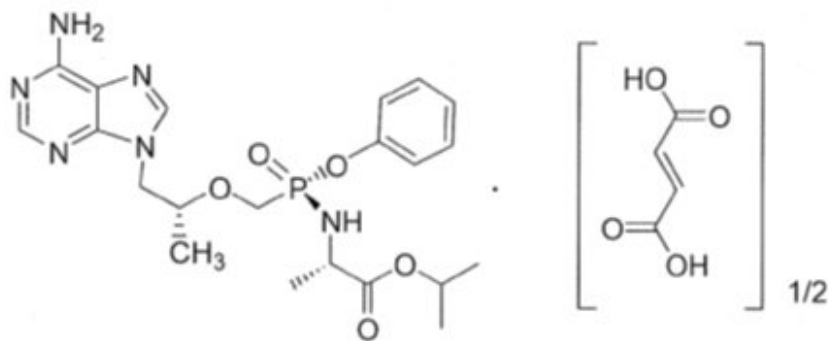
Lamivudine: The chemical name of lamivudine is (-)-1-[(2R,5S)-2-(Hydroxymethyl)-1,3-oxathiolan-5-yl] cytosine. Lamivudine is the (-)-enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)-2',3'-dideoxy, 3'-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.26 g per mol. It has the following structural formula:



Lamivudine, USP is a white to off-white solid with a solubility of approximately 70 mg per mL in water at 20°C.

Tenofovir Alafenamide: The chemical name of tenofovir alafenamide fumarate drug substance is L-alanine, N-[(S)-[[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-,1-methyl ethyl ester, (2E)-2-butenedioate (2:1).

Tenofovir alafenamide fumarate has a molecular formula of $C_{23}H_{31}N_6O_7P$ and a molecular weight of 534.5 g per mol and has the following structural formula:



Tenofovir alafenamide fumarate is a white to off-white powder or light tan powder with a solubility of 4.7 mg per mL in water at 20°C.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dolutegravir, 3TC, and TAF are HIV-1 antiviral agents [see *Microbiology (12.4)*].

12.2 Pharmacodynamics

Effects on Electrocardiogram

A thorough QT trial has been conducted for dolutegravir and TAF. The effects of 3TC as a single entity or the fixed-dose dolutegravir, lamivudine and tenofovir alafenamide tablet on the QT interval have not 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.

In a thorough QT/QTc study in 48 healthy subjects, TAF at the recommended dose or at a dose approximately 5 times the recommended dose, did not affect the QT/QTc interval and did not prolong the PR interval.

Effects on Renal Function

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

12.3 Pharmacokinetics

Pharmacokinetics in Adults

Dolutegravir, Lamivudine and Tenofovir Alafenamide Tablets

The mean systemic exposures of dolutegravir, lamivudine and tenofovir alafenamide from the combination tablets (50 mg/300 mg/25 mg) were comparable to that from TIVICAY[®] tablets of ViiV U.S.A. (containing dolutegravir 50 mg), EPIVIR[®] tablets of ViiV U.S.A. (containing lamivudine 300 mg), and DESCOPY[®] tablets of Gilead Sciences, Inc. U.S.A. (containing emtricitabine and tenofovir alafenamide 200 mg/25 mg), respectively, when single doses were administered to healthy subjects under fasted conditions. The mean systemic exposures of dolutegravir and lamivudine from the combination tablets (50 mg/300 mg/25 mg) were comparable to that from TIVICAY tablets of ViiV U.S.A. (containing dolutegravir 50 mg), and EPIVIR tablets of ViiV U.S.A. (containing lamivudine 300 mg) under fed conditions. Based on cross trial comparison, under fed conditions, the effect of food on the systemic exposure of TAF from the combination tablets is comparable to the effect of food on the systemic exposure of TAF from DESCOPY.

Dolutegravir

Following oral administration of dolutegravir, peak plasma concentrations were observed 2 to 3 hours postdose. With once-daily dosing, pharmacokinetic steady state is achieved within approximately 5 days with average accumulation ratios for AUC, C_{max}, and C_{24h} ranging from 1.2 to 1.5. Dolutegravir is a P-glycoprotein substrate *in vitro*. The absolute bioavailability of dolutegravir has not been established. Dolutegravir is highly bound (greater than or equal to 98.9%) to human plasma proteins based on *in vivo* data and binding is independent of plasma concentration of dolutegravir. The apparent volume of distribution (Vd/F) following 50-mg once-daily administration is estimated at 17.4 L based on a population pharmacokinetic analysis.

Dolutegravir is primarily metabolized via UGT1A1 with some contribution from CYP3A. After a single oral dose of [¹⁴C] dolutegravir, 53% of the total oral dose is excreted unchanged in the feces. Thirty-one percent of the total oral dose is excreted in the urine, represented by an ether glucuronide of dolutegravir (18.9% of total dose), a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose), and its hydrolytic N-dealkylation product (3.6% of total dose). Renal elimination of unchanged drug was less than 1% of the dose. Dolutegravir has a terminal half-life of approximately 14 hours and an apparent clearance (CL/F) of 1.0 L per hour based on population pharmacokinetic analyses.

The pharmacokinetic properties of dolutegravir have been evaluated in healthy adult subjects and HIV-1-infected adult subjects. Exposure to dolutegravir was generally similar between healthy subjects and HIV-1-infected subjects (Table 5).

Table 5. Dolutegravir Steady-State Pharmacokinetic Parameter Estimates in HIV-1-Infected Adults

Parameter	50 mg Once Daily Geometric Mean (% CV)
AUC ₍₀₋₂₄₎ (mcg•h/mL)	53.6 (27)
C _{max} (mcg/mL)	3.67 (20)
C _{min} (mcg/mL)	1.11 (46)

Cerebrospinal Fluid (CSF)

In 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 per mL to 18.3 ng per mL) 2 to 6 hours postdose after 16 weeks of treatment. The clinical relevance of this finding has not been established.

Polymorphisms in Drug-Metabolizing Enzymes

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).

3TC

Following oral administration, 3TC is rapidly absorbed and extensively distributed. After multiple dose oral administration of 3TC 300 mg once daily for 7 days to 60 healthy subjects, steady-state C_{\max} ($C_{\max,ss}$) was 2.04 ± 0.54 mcg per mL (mean \pm SD) and the 24 hour steady state AUC ($AUC_{24,ss}$) was 8.87 ± 1.83 mcg•hour per mL. Binding to plasma protein is low. Approximately 70% of an intravenous dose of 3TC is recovered as unchanged drug in the urine. Metabolism of 3TC is a minor route of elimination. In humans, the only known metabolite is the trans sulfoxide metabolite (approximately 5% of an oral dose after 12 hours). In most single-dose trials in HIV-1-infected subjects, HBV-infected subjects, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{1/2}$) ranged from 5 to 7 hours. In HIV-1-infected subjects, total clearance was 398.5 ± 69.1 mL per min (mean \pm SD).

TAF

The pharmacokinetic (PK) properties of the components of TAF are provided in Table 6. The multiple dose PK parameters of TAF and its metabolite tenofovir are provided in Table 7.

Table 6. Pharmacokinetic Properties of the Components of TAF

	Tenofovir Alafenamide
Absorption	
T_{\max} (h)	1
Effect of high fat meal (relative to fasting)*	AUC Ratio = 1.75 (1.64, 1.88) C_{\max} Ratio = 0.85 (0.75, 0.95)
Distribution	
% Bound to human plasma proteins	~ 80
Source of protein binding data	<i>Ex vivo</i>
Blood-to-plasma ratio	1.0
Metabolism	
Metabolism	Cathepsin A [†] (PBMCs) CES1 (hepatocytes) CYP3A (minimal)
Elimination	
Major route of elimination	Metabolism (> 80% of oral dose)
$t_{1/2}$ (h) [‡]	0.51
% Of dose excreted in urine [§]	< 1
% Of dose excreted in feces [§]	31.7

PBMCs = peripheral blood mononuclear cells; CES1 = carboxylesterase 1

* Values refer to geometric mean ratio [High-fat meal/fasting] in PK parameters and (90% confidence interval). High-calorie/high-fat meal = ~ 800 kcal, 50% fat.

[†] *In vivo*, TAF is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. *In vitro* studies have shown that TAF is metabolized to tenofovir by cathepsin A in PBMCs and macrophages; and by CES1 in hepatocytes. Upon coadministration with the moderate CYP3A inducer probe efavirenz, TAF exposure was unaffected.

[‡] $t_{1/2}$ values refer to median terminal plasma half-life. Note that the

pharmacologically active metabolite, tenofovir diphosphate, has a half-life of 150-180 hours within PBMCs.

§ Dosing in mass balance studies: TAF (single dose administration of [¹⁴C] tenofovir alafenamide).

Table 7. Multiple Dose PK Parameters of Tenofovir Alafenamide and its Metabolite Tenofovir Following Oral Administration with Food in HIV-Infected Adults

Parameter Mean (CV%)	Tenofovir Alafenamide*	Tenofovir†
C _{max} (microgram per mL)	0.16 (51.1)	0.02 (26.1)
AUC _{tau} (microgram•hour per mL)	0.21 (71.8)	0.29 (27.4)
C _{trough} (microgram per mL)	NA	0.01 (28.5)

CV = Coefficient of Variation; NA = Not Applicable

* From Population PK analysis in two trials of treatment-naïve adults with HIV-1 infection treated with FTC + TAF with EVG + COBI (N = 539).

† From Population PK analysis in two trials of treatment-naïve adults with HIV-1 infection treated with FTC + TAF with EVG + COBI (N = 841).

Effects of Food on Oral Absorption of Dolutegravir, Lamivudine and Tenofovir Alafenamide

The effect of food on dolutegravir, lamivudine and tenofovir alafenamide tablets has not been evaluated. Based on cross trial comparisons, the pharmacokinetics of dolutegravir, lamivudine and tenofovir alafenamide tablets is not anticipated to be significantly affected by food, hence dolutegravir, lamivudine and tenofovir alafenamide tablets can be administered with or without food.

Specific Populations

Hepatic Impairment

Dolutegravir

Dolutegravir is primarily metabolized and eliminated by the liver. 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. 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 has not been studied. Therefore, dolutegravir is not recommended for use in patients with severe hepatic impairment.

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.

TAF

Clinically relevant changes in tenofovir pharmacokinetics in subjects with hepatic impairment were not observed in subjects with mild to moderate (Child-Pugh Class A and B) hepatic impairment [see *Use in Specific Populations (8.7)*].

Renal Impairment

Because dolutegravir, lamivudine and tenofovir alafenamide tablets is a fixed-dose formulation and cannot be dose adjusted, dolutegravir, lamivudine and tenofovir alafenamide 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)*].

Table 8. Pharmacokinetics of the Components of TAF and a Metabolite (Tenofovir) in HIV Infected Adults with Renal Impairment Compared to Subjects with Normal Renal Function*

Creatinine Clearance	AUC _{tau} (microgram·hour per mL) Mean (CV%)		
	≥ 90 mL per minute (N = 18) [†]	60-89 mL per minute (N = 11) [‡]	30-59 mL per minute (N = 18)
Tenofovir Alafenamide [§]	0.23 (47.2)	0.24 (45.6)	0.26 (58.8)
Tenofovir	0.32 (14.9)	0.46 (31.5)	0.61 (28.4)

* Trial in HIV infected adults with renal impairment treated with FTC + TAF with EVG + COBI.

[†] From a phase 2 trial in HIV-infected adults with normal renal function treated with FTC + TAF with EVG + COBI.

[‡] These subjects had an eGFR ranging from 60 to 69 mL per minute.

[§] AUC_{last}

Gender

There are no significant or clinically relevant gender differences in the pharmacokinetics of the individual components (dolutegravir, lamivudine or tenofovir alafenamide) based on the available information that was analyzed for each of the individual components.

Race

There are no significant or clinically relevant racial differences in the pharmacokinetics of dolutegravir, 3TC, or TAF based on the available information that was analyzed for each of the individual components.

Geriatric Patients

Dolutegravir

Population analyses using pooled pharmacokinetic data from adult trials indicated age had no clinically relevant effect on the pharmacokinetics of dolutegravir.

3TC

The pharmacokinetics of 3TC have not been studied in subjects older than 65 years.

TAF

Population pharmacokinetics analysis of HIV-infected subjects in Phase 2 and Phase 3 trials of TAF with FTC, EVG, and COBI showed that age did not have a clinically relevant effect on exposures of TAF up to 75 years of age [see [Use in Specific Populations \(8.5\)](#)].

Pediatric Patients

Dolutegravir, lamivudine and tenofovir alafenamide tablets should not be administered to pediatric patients weighing less than 40 kg (88 lbs).

Dolutegravir and 3TC

The pharmacokinetics of the combination of dolutegravir and 3TC in pediatric subjects have not been established.

TAF

Mean exposures of TAF in 24 pediatric subjects aged 12 to less than 18 years who received TAF with FTC, EVG, and COBI were decreased (23% for AUC) compared to exposures achieved in treatment-naïve adults following administration of this dosage regimen. The TAF exposure differences are not thought to be clinically significant based on exposure-response relationships (Table 9).

Table 9. Multiple Dose PK Parameters of Emtricitabine, Tenofovir Alafenamide and its Metabolite Tenofovir Following Oral Administration of FTC + TAF with EVG + COBI in HIV-Infected Pediatric Subjects Aged 12 to less than 18 Years*

Parameter Mean (CV%)	Emtricitabine	Tenofovir Alafenamide	Tenofovir
C _{max} (microgram per mL)	2.3 (22.5)	0.17 (64.4)	0.02 (23.7)
AUC _{tau} (microgram•hour per mL)	14.4 (23.9)	0.20 [†] (50.0)	0.29 [†] (18.8)
C _{trough} (microgram per mL)	0.10 [†] (38.9)	NA	0.01 (21.4)

CV = Coefficient of Variation; NA = Not Applicable

* From Intensive PK analysis in a trial in treatment-naïve pediatric subjects with HIV-1 infection (N = 24).

† N = 23

Drug Interactions 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 alafenamide tablets. No clinically significant drug interactions are expected between dolutegravir and 3TC.

Dolutegravir

Dosing or regimens recommendations as a result of established and other potentially significant drug-drug interactions with dolutegravir are provided in Table 4 [see *Drug Interactions (7.3)*].

The effects of dolutegravir on the exposure of coadministered drugs are summarized in Table 10 and the effects of coadministered drugs on the exposure of dolutegravir are summarized in Table 11.

Table 10. Summary of Effect of Dolutegravir on the Pharmacokinetics of Coadministered Drugs

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug with/without Dolutegravir No Effect = 1.00		
			C _{max}	AUC	C _τ or C ₂₄
Daclatasvir 60 mg once daily	50 mg once daily	12	1.03 (0.84 to 1.25)	0.98 (0.83 to 1.15)	1.06 (0.88 to 1.29)
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*	1.66 (1.53 to 1.81)	1.79 (1.65 to 1.93)	–
Metformin 500 mg twice daily	50 mg twice daily	15*	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	50 mg once daily	24	0.88 (0.80, 0.98)	0.92 (0.85, 0.99)	NA

Metabolite (GS-331007)			1.01 (0.93, 1.10)	0.99 (0.97, 1.01)	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)

* The number of subjects represents the maximum number of subjects that were evaluated.

Table 11. Summary of Effect of Coadministered Drugs on the Pharmacokinetics of Dolutegravir

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00		
			C _{max}	AUC	C _τ or C ₂₄
Atazanavir 400 mg once daily	30 mg once daily	12	1.50 (1.40 to 1.59)	1.91 (1.80 to 2.03)	2.80 (2.52 to 3.11)
Atazanavir/ritonavir 300 mg/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 mg/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 mg/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 mg/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 mg/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 mg/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*	0.67 (0.61 to 0.73)	0.51 (0.48 to 0.55)	0.27 (0.24 to 0.31)
Daclatasvir 60 mg once daily	50 mg once daily	12	1.29 (1.07 to 1.57)	1.33 (1.11 to 1.59)	1.45 (1.25 to 1.68)
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† 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‡ 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)

* The number of subjects represents the maximum number of subjects that were evaluated.

† Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg twice daily.

‡ Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg once daily.

3TC

Effect of 3TC on the Pharmacokinetics of Other Agents

Based on *in vitro* study results, 3TC 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 (OCT1), 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 3TC. 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 $AUC_{(0-24)}$, 14%, 32%, and 36% in the $AUC_{(\infty)}$, and 28%, 52%, and 55% in the C_{max} of 3TC, 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 lamivudine 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 $43\% \pm 23\%$ (mean \pm SD) in lamivudine AUC_{∞} , a decrease of $29\% \pm 13\%$ in lamivudine oral clearance, and a decrease of $30\% \pm 36\%$ in 3TC renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by coadministration with lamivudine. There is no information regarding the effect on 3TC pharmacokinetics of higher doses of TMP/SMX such as those used in treat PCP.

TAF

The effects of coadministered drugs on the exposure of TAF are shown in Table 12 and the effects of TAF on the exposure of coadministered drugs are shown in Table 13 [these studies were conducted with FTC and/or TAF. For information regarding clinical recommendations, see [Drug Interactions \(7\)](#).]

Table 12. Drug Interactions: Changes in TAF Pharmacokinetic Parameters in the Presence of Coadministered Drug(s)*

Coadministered	Coadministered Drug(s) Dosage	Tenofovir Alafenamide Dosage	N	Mean Ratio of TAF PK Parameters
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Drug	(once daily) (mg)	(once daily) (mg)	N	(90% CI); No effect = 1.00		
				C _{max}	AUC	C _{min}
Atazanavir	300 (+ 100 ritonavir)	10	10	1.77 (1.28, 2.44)	1.91 (1.55, 2.35)	NC
Cobicistat	150	8	12	2.83 (2.20, 3.65)	2.65 (2.29, 3.07)	NC
Darunavir	800 (+ 150 cobicistat)	25 [†]	11	0.93 (0.72, 1.21)	0.98 (0.80, 1.19)	NC
Darunavir	800 (+ 100 ritonavir)	10	10	1.42 (0.96, 2.09)	1.06 (0.84, 1.35)	NC
Dolutegravir	50	10	10	1.24 (0.88, 1.74)	1.19 (0.96, 1.48)	NC
Efavirenz	600	40 [†]	11	0.78 (0.58, 1.05)	0.86 (0.72, 1.02)	NC
Lopinavir	800 (+ 200 ritonavir)	10	10	2.19 (1.72, 2.79)	1.47 (1.17, 1.85)	NC
Rilpivirine	25	25	17	1.01 (0.84, 1.22)	1.01 (0.94, 1.09)	NC
Sertraline	50 (dosed as a single dose)	10 [‡]	19	1.00 (0.86, 1.16)	0.96 (0.89, 1.03)	NC

NC = Not Calculated

* All interaction studies conducted in healthy volunteers.

[†] Study conducted with DESCOVY (FTC/TAF).

[‡] Study conducted with FTC + TAF with EVG + COBI.

Table 13. Drug Interactions: Changes in PK Parameters for Coadministered Drug in the Presence of FTC and/or TAF*

Coadministered Drug	Coadministered Drug Dosage (once daily) (mg)	Tenofovir Alafenamide Dosage (once daily) (mg)	N	Mean Ratio of Coadministered Drug PK Parameters(90% CI); No effect = 1.00		
				C _{max}	AUC	C _{min}
Atazanavir	300 + 100 ritonavir	10	10	0.98 (0.89, 1.07)	0.99 (0.96, 1.01)	1.00 (0.96, 1.04)
Darunavir	800 + 150 cobicistat	25 [†]	11	1.02 (0.96, 1.07)	0.99 (0.92, 1.06)	0.97 (0.82, 1.12)

				1.09)	1.07)	1.15)
Darunavir	800 + 100 ritonavir	10	10	0.99 (0.91, 1.08)	1.01 (0.96, 1.06)	1.13 (0.95, 1.34)
Dolutegravir	50 mg	10	10	1.15 (1.04, 1.27)	1.02 (0.97, 1.08)	1.05 (0.97, 1.13)
Lopinavir	800 + 200 ritonavir	10	10	1.00 (0.95, 1.06)	1.00 (0.92, 1.09)	0.98 (0.85, 1.12)
Midazolam [†]	2.5 (single dose, orally)	25	18	1.02 (0.92, 1.13)	1.13 (1.04, 1.23)	NC
	1 (single dose, intravenous)			0.99 (0.89, 1.11)	1.08 (1.04, 1.14)	NC
Rilpivirine	25	25	16	0.93 (0.87, 0.99)	1.01 (0.96, 1.06)	1.13 (1.04, 1.23)
Sertraline	50 (single dose)	10 [§]	19	1.14 (0.94, 1.38)	0.93 (0.77, 1.13)	NC

NC = Not Calculated

* All interaction studies conducted in healthy volunteers.

† Study conducted with DESCOPY (FTC/TAF).

‡ A sensitive CYP3A4 substrate.

§ Study conducted with FTC + TAF with EVG + COBI.

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 IC₅₀ values of 2.7 nM and 12.6 nM.

3TC

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

Tenofovir Alafenamide

TAF is a phosphonoamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analog). Plasma exposure to TAF allows for permeation into cells and then TAF is intracellularly converted to tenofovir through hydrolysis by

cathepsin A. Tenofovir is subsequently phosphorylated by cellular kinases to the active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV-1 replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination.

Tenofovir has activity against HIV-1. Cell culture studies have shown that both tenofovir and FTC can be fully phosphorylated when combined in cells. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of toxicity to mitochondria in cell culture.

Antiviral Activity in Cell Culture

Dolutegravir

Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean EC₅₀ 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 EC₅₀ 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 EC₅₀ values ranging from 0.02 nM to 2.14 nM for HIV-1. Dolutegravir EC₅₀ 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 PBMCs using standard susceptibility assays. EC₅₀ values were in the range of 0.003 to 15 microM (1 microM = 0.23 mcg per mL). The median EC₅₀ values of lamivudine were 60 nM (range: 20 to 70 nM), 35 nM (range: 30 to 40 nM), 30 nM (range: 20 to 90 nM), 20 nM (range: 3 to 40 nM), 30 nM (range: 1 to 60 nM), 30 nM (range: 20 to 70 nM), 30 nM (range: 3 to 70 nM), and 30 nM (range: 20 to 90 nM) against HIV-1 clades A-G and group O viruses (n = 3 except n = 2 for clade B) respectively. The EC₅₀ 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 lamivudine by 3.5-fold in MT-4 cells.

Tenofovir Alafenamide

The antiviral activity of TAF against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells and CD4-T lymphocytes. The EC₅₀ values for TAF ranged from 2.0 to 14.7 nM.

TAF displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including sub-types A, B, C, D, E, F, and G (EC₅₀ values ranged from 0.10 to 12.0 nM) and strain specific activity against HIV-2 (EC₅₀ values ranged from 0.91 to 2.63 nM).

In a study of TAF with a broad panel of representatives from the major classes of approved anti-HIV agents (NRTIs, NNRTIs, INSTIs, and PIs) no antagonism was observed for these combinations.

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.

3TC

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

Tenofovir Alafenamide

HIV-1 isolates with reduced susceptibility to TAF were selected in cell culture. HIV-1 isolates selected by TAF expressed a K65R substitution in HIV-1 RT, sometimes in the presence of S68N or L429I substitutions; in addition, a K70E substitution in HIV-1 RT was observed.

Resistance in Clinical Subjects

Dolutegravir

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

TAF

The resistance profile of TAF in combination with other antiretroviral agents for the treatment of HIV-1 infection is based on studies of FTC + TAF with EVG + COBI in the treatment of HIV-1 infection. In a pooled analysis of antiretroviral-naïve subjects, genotyping was performed on plasma HIV-1 isolates from all subjects with HIV-1 RNA greater than 400 copies per mL at confirmed virologic failure, at Week 48, or at time of early study drug discontinuation. Genotypic resistance developed in 7 of 14 evaluable subjects. The resistance-associated substitutions that emerged were M184V/I (N = 7) and K65R (N = 1). Three subjects had virus with emergent R, H, or E at the polymorphic Q207 residue in reverse transcriptase.

Cross-Resistance

Dolutegravir

The single INSTI-resistance substitutions T66K, I151L, and S153Y conferred a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.3-fold to 3.6-fold from reference). Combinations of multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148, and substitutions at E138/G140/Q148 showed a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.5-fold to 21-fold from reference). In HIV-2 mutants, combinations of substitutions A153G/N155H/S163G and E92Q/T97A/N155H/S163D conferred 4-fold decreases in dolutegravir susceptibility, and E92Q/N155H and G140S/Q148R showed 8.5-fold and 17-fold decreases in dolutegravir susceptibility, respectively.

3TC

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

these select M184V substitutions.

TAF

Tenofovir resistance substitutions K65R and K70E result in reduced susceptibility to abacavir, didanosine, emtricitabine, lamivudine, and tenofovir.

HIV-1 with multiple thymidine analog substitutions (M41L, D67N, K70R, L210W, T215F/Y, K219Q/E/N/R), or multinucleoside resistant HIV-1 with a T69S double insertion mutation or with a Q151M substitution complex including K65R, showed reduced susceptibility to TAF in cell culture.

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 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 the recommended 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.

TAF

Since TAF is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice was observed after TAF administration compared to TDF administration, carcinogenicity studies were conducted only with TDF. Long-term oral carcinogenicity studies of TDF in mice and rats were carried out at exposures up to approximately 10 times (mice) and 4 times (rats) those observed in humans at the recommended dose of TDF (300 mg) for HIV-1 infection. The tenofovir exposure in these studies was approximately 167 times (mice) and 55 times (rat) those observed in humans after administration of the daily recommended dose of TAF. At the high dose in female mice, liver adenomas were increased at tenofovir exposures approximately 10 times (300 mg TDF) and 167 times (TAF) the exposure observed in humans. In rats, the study was negative for carcinogenic findings.

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 2000 mg per kg, producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV-1 infection.

TAF

TAF was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays.

Impairment of Fertility

Dolutegravir and 3TC

Dolutegravir or 3TC did not affect male or female fertility in rats at doses associated with exposures approximately 44 or 112 times (respectively) higher than the exposures in humans at the doses of 50 mg and 300 mg (respectively).

TAF

There were no effects on fertility, mating performance or early embryonic development when TAF was administered to male rats at a dose equivalent to 62 times (25 mg TAF) the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 14 days prior to mating through Day 7 of gestation.

13.2 Animal Toxicology and/or Pharmacology

TAF

Minimal to slight infiltration of mononuclear cells in the posterior uvea was observed in dogs with similar severity after three and nine month administration of TAF; reversibility was seen after a three month recovery period. No eye toxicity was observed in the dog at systemic exposures of 5 (TAF) and 15 (tenofovir) times the exposure seen in humans with the recommended daily TAF dose.

14 CLINICAL STUDIES

14.1 Adult Subjects

Dolutegravir, Lamivudine

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 sulfate 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, and 53% had CD4+ cell count less than 350 cells per mm³; 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 14.

Table 14. 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*	8.3% (95% CI: 2.0% 14.6%) [†]	
Virologic nonresponse		
Data in window not < 50 copies/mL		
Discontinued for lack of efficacy	10%	7%
Discontinued for other reasons	4%	< 1%
while not suppressed	3%	3%
Changes in ART regimen	3%	4%
	0	0
No virologic data		
Reasons		
Discontinued study/study drug due to adverse event or death [‡]		
Discontinued study/study drug for other reasons [§]	18%	30%
Missing data during window but on study	4%	14%
	12%	13%
	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		
African-American/African Heritage/Other	72%	71%
	71%	47%

* Adjusted for pre-specified stratification factors.

[†] 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 alafenamide group, with a treatment difference of 7.4% and 95% CI of (2.5%, 12.3%).

[‡] 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.

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

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 mm³ in the group receiving dolutegravir + fixed-dose abacavir sulfate and lamivudine and 332 cells per mm³ 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 mm³ (15.6 cells per mm³, 78.2 cells per mm³) (adjusted for pre-specified stratification factors: baseline HIV-1 RNA, and baseline CD4+ cell count).

Dolutegravir

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%]).

TAF

In trials of TAF with FTC, EVG, and COBI in HIV-1 infected adults as initial therapy in those with no antiretroviral treatment history (N = 866) (Study 104, NCT01780506 and Study 111, NCT01797445) and to replace a stable antiretroviral regimen in those who were virologically-suppressed for at least 6 months with no known resistance substitutions (N = 799) (Study 109, NCT01815736), 92% and 96% of patients in the two populations, respectively, had HIV-1 RNA less than 50 copies per mL at Week 48.

14.2 Pediatric Subjects

The efficacy of the individual components of dolutegravir, lamivudine and tenofovir alafenamide tablets for the treatment of HIV-1 infection was evaluated in pediatric patients enrolled in the IMPAACT P1093 trial (NCT01302847), the ARROW trial (NCT02028676), or Study 106 (NCT01854775) 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. Subjects aged 12 to less than 18 years were enrolled in Cohort I and subjects aged 6 to less than 12 years were enrolled in Cohort IIA. At 48 weeks, 61% (14/23) of subjects aged 12 to less than 18 years treated with 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) received lamivudine 300 mg and abacavir 600 mg, as either the single entities or as fixed-dose abacavir sulfate 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.
- TAF with FTC, EVG, and COBI was evaluated in an open-label, single arm trial (Study 106) in 50 treatment-naïve HIV-1 infected adolescents aged 12 to less than 18 years (cohort 1) and 23 virologically suppressed children aged 6 to less than 12 years (cohort 2). In cohort 1 at Week 48, the virologic response rate (i.e., HIV-1 RNA less than 50 copies per mL) was 92% (46/50), and the mean increase from baseline in CD4+ cell count was 224 cells per mm³. In cohort 2 at Week 24, 100% of subjects remained virologically suppressed. From a mean (SD) baseline CD4+ cell count of 966 (201.7), the mean change from baseline in CD4+ cell count was -150 cells/mm³ and the mean (SD) change in CD4% was -1.5% (3.7%) at Week 24. All subjects maintained CD4+ cell counts above 400 cells/mm³ [see [Adverse Reactions \(6.1\)](#) and [Use in Specific Populations \(8.4\)](#)].

16 HOW SUPPLIED/STORAGE AND HANDLING

Dolutegravir, Lamivudine and Tenofovir Alafenamide Tablets are available containing 50 mg of dolutegravir, 300 mg of lamivudine, and 25 mg of tenofovir alafenamide.

The 50 mg/300 mg/25 mg tablets are white to off-white, film-coated, capsule shaped, unscored tablets debossed with **M** on one side of the tablet and **LD** on the other side. They are available as follows:

NDC 65015-308-14

bottles of 30 tablets with desiccant, induction seal and non-child-resistant cap

NDC 65015-308-18

bottles of 90 tablets with desiccant, induction seal and non-child-resistant cap

NDC 65015-308-33

bottles of 180 tablets with desiccant, induction seal and non-child-resistant cap

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](#)).

Drug Interactions: Dolutegravir, lamivudine and tenofovir alafenamide 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 \(4\)](#), [Drug Interactions \(7\)](#)].

Hypersensitivity Reactions: Advise patients to immediately contact their healthcare provider if they develop rash. Instruct patients to immediately stop taking dolutegravir, lamivudine and tenofovir alafenamide 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, lamivudine and tenofovir alafenamide tablets [see [Warnings and Precautions \(5.3\)](#)]. Advise patients that laboratory monitoring for hepatotoxicity during therapy with dolutegravir, lamivudine and tenofovir alafenamide tablets is recommended, especially for patients with liver disease, such as hepatitis B or C.

Lactic Acidosis/Hepatomegaly: Inform patients that lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Dolutegravir, lamivudine and tenofovir alafenamide 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 \(5.8\)](#)].

Patients with Hepatitis B or C Co-infection: Inform patients that severe acute exacerbations of hepatitis B have been reported in patients infected with hepatitis B virus (HBV) who have discontinued TDF and 3TC, two components of dolutegravir, lamivudine and tenofovir alafenamide tablets. Advise patients not to discontinue dolutegravir, lamivudine and tenofovir alafenamide tablets without first informing their healthcare provider. All patients should be tested for HBV infection before or when starting dolutegravir, lamivudine and tenofovir alafenamide tablets and those who are infected with HBV need close medical follow-up for several months after stopping dolutegravir, lamivudine and tenofovir alafenamide tablets to monitor for exacerbations of hepatitis [see [Warnings and Precautions \(5.1\)](#)].

Risk of Pancreatitis: Advise parents or guardians to monitor pediatric patients for signs and symptoms of pancreatitis [see [Warnings and Precautions \(5.9\)](#)].

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 creatinine clearance less than 50 mL/min or patients with end-stage renal disease (ESRD) requiring hemodialysis to avoid dolutegravir, lamivudine and tenofovir alafenamide tablets with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple NSAIDs) for patients [see *Dosage and Administration (2.3)*, *Warnings and Precautions (5.6)*].

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

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

Immune Reconstitution Syndrome: Advise patients to inform their healthcare provider immediately of any signs and symptoms of infection as inflammation from previous infection may occur soon after combination antiretroviral therapy, including when dolutegravir, lamivudine and tenofovir alafenamide tablets is started [see *Warnings and Precautions (5.7)*].

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

Missed Dose: Instruct patients that if they miss a dose of dolutegravir, lamivudine and tenofovir alafenamide 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 dolutegravir, lamivudine and tenofovir alafenamide tablets in the original package, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant.

Other brands listed are the registered trademarks of their respective owners and are not trademarks of Mylan Laboratories Limited.

Rx only

Patient Information

Dolutegravir, Lamivudine and Tenofovir Alafenamide Tablets

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

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

- Worsening of Hepatitis B virus (HBV) infection. Your healthcare provider will test you for HBV before starting treatment with dolutegravir, lamivudine and tenofovir alafenamide tablets. If you have HBV infection and take dolutegravir, lamivudine and tenofovir alafenamide tablets, your HBV may get worse (flare-up) if you stop taking dolutegravir, lamivudine and tenofovir alafenamide 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 alafenamide tablets. Refill your prescription or talk to your healthcare provider before your dolutegravir, lamivudine and tenofovir alafenamide tablets is all gone.
 - **Do not** stop taking dolutegravir, lamivudine and tenofovir alafenamide tablets without first talking to your healthcare provider.
 - If you stop taking dolutegravir, lamivudine and tenofovir alafenamide tablets, your healthcare provider will need to check your health often and do blood tests regularly 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 alafenamide tablets.

- **Allergic reactions.** Call your healthcare provider right away if you develop a rash with dolutegravir, lamivudine and tenofovir alafenamide tablets. **Stop taking dolutegravir, lamivudine and tenofovir alafenamide 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 function tests during treatment with dolutegravir, lamivudine and tenofovir alafenamide 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 get any of the following signs or symptoms of liver problems:

- your skin or the white part of your eyes turns yellow (jaundice)
- dark or “tea-colored” urine
- light-colored stools (bowel movements)
- loss of appetite for several days or longer
- nausea or vomiting
- pain, aching, or tenderness on the right side of your stomach area

For more information about side effects, see “What are the possible side effects of dolutegravir, lamivudine and tenofovir alafenamide tablets?”

What is dolutegravir, lamivudine and tenofovir alafenamide tablets?

Dolutegravir, lamivudine and tenofovir alafenamide tablets is a prescription medicine that is used to treat Human Immunodeficiency Virus type 1 (HIV-1) infection in adults and children who weigh at least 88 pounds (40 kg).

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

Dolutegravir, lamivudine and tenofovir alafenamide tablets contains 3 prescription medicines, dolutegravir, lamivudine and tenofovir alafenamide.

Do not take dolutegravir, lamivudine and tenofovir alafenamide tablets if you:

- take dofetilide (TIKOSYN®). Taking dolutegravir, lamivudine and tenofovir alafenamide tablets and dofetilide (TIKOSYN) can cause side effects that may be serious or life-threatening.
- are allergic to dolutegravir or any of the ingredients in dolutegravir, lamivudine and tenofovir alafenamide tablets. See the end of this Patient Information leaflet for a complete list of ingredients in dolutegravir, lamivudine and tenofovir alafenamide tablets.

Before you take dolutegravir, lamivudine and tenofovir alafenamide tablets, tell your healthcare provider if you:

- have had liver problems, including hepatitis B or C infection.
- have kidney problems, including end-stage renal disease (ESRD) that requires dialysis.
- are pregnant or plan to become pregnant. One of the medicines in dolutegravir, lamivudine and tenofovir alafenamide tablets called dolutegravir may harm your unborn baby.

- **You should not take dolutegravir, lamivudine and tenofovir alafenamide tablets at the time of becoming pregnant or during the first 12 weeks of pregnancy.** Your healthcare provider may change your medicine during this time in your pregnancy.
 - If you can become pregnant, your healthcare provider will perform a pregnancy test before you start treatment with dolutegravir, lamivudine and tenofovir alafenamide tablets.
 - If you can become pregnant, you should consistently use effective birth control (contraception) during treatment with dolutegravir, lamivudine and tenofovir alafenamide tablets.
 - Tell your healthcare provider right away if you are planning to become pregnant, you become pregnant, or think you may be pregnant during treatment with dolutegravir, lamivudine and tenofovir alafenamide tablets.
- are breastfeeding or plan to breastfeed. **Do not breastfeed if you take dolutegravir, lamivudine and tenofovir alafenamide tablets.**
 - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby. Talk with your healthcare provider about the best way to feed your baby.

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

Some medicines interact with dolutegravir, lamivudine and tenofovir alafenamide tablets. Dolutegravir, lamivudine and tenofovir alafenamide tablets may affect the way other medicines work, and other medicines may affect how dolutegravir, lamivudine and tenofovir alafenamide tablets work. 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 alafenamide 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 alafenamide tablets with other medicines.

How should I take dolutegravir, lamivudine and tenofovir alafenamide tablets?

- Take dolutegravir, lamivudine and tenofovir alafenamide tablets exactly as your healthcare provider tells you to take them.
- Take dolutegravir, lamivudine and tenofovir alafenamide tablets at the same time every day.
- Take dolutegravir, lamivudine and tenofovir alafenamide each day with or without food.
- If you take antacids, laxatives, or other medicines that contain aluminum, magnesium, or buffered medicines, dolutegravir, lamivudine and tenofovir alafenamide 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, lamivudine and tenofovir alafenamide tablets:
 - If you take dolutegravir, lamivudine and tenofovir alafenamide tablets with food, you may take these supplements at the same time that you take dolutegravir, lamivudine and tenofovir alafenamide tablets.
 - If you do not take dolutegravir, lamivudine and tenofovir alafenamide tablets with food, take dolutegravir, lamivudine and tenofovir alafenamide tablets at least 2 hours before or 6 hours after you take these supplements.
- For adults and children weighing at least 40 kg (88 lbs), the usual dose of dolutegravir, lamivudine and tenofovir alafenamide 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 miss a dose of dolutegravir, lamivudine and tenofovir alafenamide tablets. If you miss a dose of dolutegravir, lamivudine and tenofovir alafenamide tablets, take them as soon as you remember. If it is almost time for your next dose of dolutegravir, lamivudine and tenofovir alafenamide tablets, do not take the missed

dose. Take the next dose of dolutegravir, lamivudine and tenofovir alafenamide tablets at your regular time.

- Do not take 2 doses at the same time or take more dolutegravir, lamivudine and tenofovir alafenamide tablets than prescribed.
- Stay under the care of a healthcare provider during treatment with dolutegravir, lamivudine and tenofovir alafenamide tablets.
- Do not run out of dolutegravir, lamivudine and tenofovir alafenamide 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 alafenamide tablets, go to the nearest hospital emergency room right away.

What should I avoid while taking dolutegravir, lamivudine and tenofovir alafenamide tablets?

You should avoid taking medicines that contain sorbitol during treatment with dolutegravir, lamivudine and tenofovir alafenamide tablets.

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

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

- See “**What is the most important information I should know about dolutegravir, lamivudine and tenofovir alafenamide tablets?**”
- **Risk of inflammation of the pancreas (pancreatitis).** Children may be at risk for developing pancreatitis during treatment with dolutegravir, lamivudine and tenofovir alafenamide tablets if they:
 - have taken nucleoside analogue medicines in the past
 - have a history of pancreatitis
 - have other risk factors for pancreatitis

Call your healthcare provider right away if your child develops signs and symptoms of pancreatitis including severe upper stomach-area pain, with or without nausea and vomiting. Your healthcare provider may tell you to stop giving dolutegravir, lamivudine and tenofovir alafenamide tablets to your child if their symptoms and blood test results show that your child may have pancreatitis.

- **New or worse kidney problems, including kidney failure.** Your healthcare provider may do blood and urine tests to check your kidneys before and during treatment with dolutegravir, lamivudine and tenofovir alafenamide tablets. Tell your healthcare provider if you get signs and symptoms of kidney problems, including bone pain that does not go away or worsening bone pain, pain in your arms, hands, legs or feet, broken (fractured) bones, muscle pain or weakness.
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having new symptoms after you start taking dolutegravir, lamivudine and tenofovir alafenamide tablets.
- **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
- feel dizzy or light-headed
- have a fast or irregular heartbeat

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

- trouble sleeping
- nausea
- diarrhea
- tiredness
- headache
- depression

Tell your healthcare provider about 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 alafenamide tablets.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 [S](#).

How should I store dolutegravir, lamivudine and tenofovir alafenamide tablets?

- Store dolutegravir, lamivudine and tenofovir alafenamide tablets below 30°C (86°F).
- Keep dolutegravir, lamivudine and tenofovir alafenamide tablets in the original container.
- Keep the bottle tightly closed. The bottle contains a desiccant that helps to keep the tablets dry. Do not remove desiccant.
- Do not use dolutegravir, lamivudine and tenofovir alafenamide tablets if the seal over the bottle opening is broken or missing.

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

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

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

For more information, call Mylan at 1-877-446-3679 [S](#) (1-877-INFO-RX [S](#)).

What are the ingredients in dolutegravir, lamivudine and tenofovir alafenamide tablets?

Active ingredients: dolutegravir, lamivudine and tenofovir alafenamide.

Inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, sodium starch glycolate (potato), talc and titanium dioxide.

Manufactured by:

Mylan Laboratories Limited, Hyderabad – 500 096, India

The brands listed are trademarks of their respective owners.

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 9/2019

Manufactured by:

Mylan Laboratories Limited

Hyderabad — 500 096, India

750XXXXX

Revised: 9/2019

MXI:PDLTAT:RX1

PRINCIPAL DISPLAY PANEL – 50 mg/300 mg/25 mg

NDC 65015-308-14

**Dolutegravir, Lamivudine
and Tenofovir Alafenamide
Tablets
50 mg/300 mg/25 mg**

**Note to pharmacist: Do not cover ALERT box with
pharmacy label.**

**ALERT: Find out about medicines that should NOT be taken with
Dolutegravir, Lamivudine and Tenofovir Alafenamide Tablets**

30 Tablets Rx only

Mylan.com

Each film-coated tablet contains:

Dolutegravir 50 mg
(equivalent to 52.6 mg of Dolutegravir
Sodium)

Lamivudine, USP 300 mg

Tenofovir Alafenamide 25 mg
(equivalent to 28.04 mg of Tenofovir
Alafenamide Fumarate)

Usual Dosage: See accompanying
prescribing information.

**Keep this and all medication out of the
reach of children.**

Store below 30°C (86°F).




Manufactured by:

Mylan Laboratories Limited
Hyderabad – 500 096, India

Store and dispense in original bottle, protect
from moisture, and keep bottle tightly closed.

Do not remove desiccant.

Code No.: MP/DRUGS/25/1/2014

Each film-coated tablet contains: Dolutegravir 50 mg (equivalent to 52.6 mg of Dolutegravir Sodium) Lamivudine, USP 300 mg Tenofovir Alafenamide 25 mg (equivalent to 28.04 mg of Tenofovir Alafenamide Fumarate) Usual Dosage: See accompanying prescribing information. Keep this and all medication out of the reach of children. Store below 30°C (86°F). Manufactured by: Mylan Laboratories Limited Hyderabad – 500 096, India	NDC 65015-308-14	 N 3 65015-308-14 6 Store and dispense in original bottle, protect from moisture, and keep bottle tightly closed. Do not remove desiccant. Code No.: MP/DRUGS/25/1/2014	 75065870
	Dolutegravir, Lamivudine and Tenofovir Alafenamide Tablets	50 mg/300 mg/25 mg	(43 x 18 mm) Varnish Free area for Variable Data Coding
	Note to pharmacist: Do not cover ALERT box with pharmacy label. <div style="border: 1px solid red; padding: 2px; display: inline-block; color: red;"> ALERT: Find out about medicines that should NOT be taken with Dolutegravir, Lamivudine and Tenofovir Alafenamide Tablets </div>	30 Tablets Rx only	
	Mylan.com		

Prompt "LOT" & "EXP" will be printed along with Variable Data online Coding (see e.g. below)

LOT 1234567
 EXP MMM.YYYY
 *SNO 0000000000
 *GTIN 00000000000000
 *(wherever is applicable)

DOLUTEGRAVIR, LAMIVUDINE AND TENOFOVIR ALAFENAMIDE

dolutegravir, lamivudine and tenofovir alafenamide tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:65015-308
Route of Administration	ORAL		

Active Ingredient/Active Moiety			
Ingredient Name	Basis of Strength	Strength	
DOLUTEGRAVIR (UNII: DKO1W9H7M1) (DOLUTEGRAVIR - UNII:DKO1W9H7M1)	DOLUTEGRAVIR	50 mg	
LAMIVUDINE (UNII: 2T8Q726O95) (LAMIVUDINE - UNII:2T8Q726O95)	LAMIVUDINE	300 mg	
TENOFOVIR ALAFENAMIDE (UNII: EL9943AG5J) (TENOFVIR ALAFENAMIDE MONOFUMARATE - UNII:H2S5S51WW6)	TENOFOVIR ALAFENAMIDE	25 mg	

Inactive Ingredients		
Ingredient Name	Strength	
CROSCARMELOSE SODIUM (UNII: M28OL1HH48)		
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)		
MAGNESIUM STEARATE (UNII: 70097M6I30)		
MANNITOL (UNII: 3OWL53L36A)		

MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	
POLYVINYL ALCOHOL, UNSPECIFIED (UNII: 532B59J990)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	WHITE (white to off-white)	Score	no score
Shape	OVAL (capsule shaped)	Size	18mm
Flavor		Imprint Code	M;LD
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:65015-308-14	30 in 1 BOTTLE; Type 0: Not a Combination Product	12/31/2020	
2	NDC:65015-308-18	90 in 1 BOTTLE; Type 0: Not a Combination Product	12/31/2020	
3	NDC:65015-308-33	180 in 1 BOTTLE; Type 0: Not a Combination Product	12/31/2020	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA210865	12/31/2020	

Labeler - Mylan Laboratories Limited (650547156)

Registrant - Mylan Pharmaceuticals Inc. (059295980)

Establishment

Name	Address	ID/FEI	Business Operations
Mylan Laboratories Limited		859649433	ANALYSIS(65015-308) , MANUFACTURE(65015-308) , PACK(65015-308) , LABEL(65015-308)

Revised: 9/2019

Mylan Laboratories Limited