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

DOLUTEGRAVIR, EMTRICITABINE and TENOFOVIR ALAFENAMIDE tablets, for oral use

WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B
See full prescribing information for complete boxed warning.

- **Tenofovir alafenamide, one component of dolutegravir, emtricitabine and tenofovir alafenamide tablets, is approved for the treatment of chronic hepatitis B virus (HBV) infection. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of dolutegravir, emtricitabine and tenofovir alafenamide tablets. Hepatic function should be monitored closely in these patients. If appropriate, initiation of anti-hepatitis B therapy may be warranted. (5.4)**

---------- INDICATIONS AND USAGE ----------
Dolutegravir, emtricitabine and tenofovir alafenamide is a three-drug combination of dolutegravir (integrase strand transfer inhibitor [INSTI]), emtricitabine (FTC) and tenofovir alafenamide (TAF), both HIV nucleoside analog reverse transcriptase inhibitors (NRTIs), and is indicated for use alone 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, emtricitabine and tenofovir alafenamide tablets alone are not recommended in patients with resistance-associated integrase substitutions or clinically suspected integrase strand transfer inhibitor resistance because the dose of dolutegravir in dolutegravir, emtricitabine and tenofovir alafenamide tablets is insufficient in these subpopulations. See the dolutegravir prescribing information. (1)
- Dolutegravir, emtricitabine, and tenofovir alafenamide tablets are not indicated for use as pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk.

---------- DOSAGE AND ADMINISTRATION ----------
- Testing: Prior to initiation of dolutegravir, emtricitabine and tenofovir alafenamide tablets, patients should be tested for hepatitis B virus infection, and estimated creatinine clearance, urine glucose, and urine protein should be obtained. (2.1)
- Adults and pediatric patients weighing at least 40 kg: One tablet daily. May be taken with or without food. (2.2)
- Renal Impairment: Dolutegravir, emtricitabine and tenofovir alafenamide tablets are not recommended in patients with estimated creatinine clearance below 30 mL per minute. (2.3)

----------DOSAGE FORMS AND STRENGTHS ----------
Tablets: 50 mg of dolutegravir, 200 mg of FTC, and 25 mg of TAF (3)

---------- CONTRAINDICATIONS ----------
- Previous hypersensitivity reaction to dolutegravir. (4)
- Coadministration with dofetilide. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Hepatotoxicity has been reported in patients receiving a dolutegravir-containing regimen. Monitoring for hepatotoxicity is recommended. (5.1)
- Hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury, have been reported. Discontinue dolutegravir, emtricitabine 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)
- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. (5.5)
- New onset or worsening renal impairment: Assess creatinine clearance, urine glucose, and urine protein in all patients before initiating dolutegravir, emtricitabine and tenofovir alafenamide tablets therapy and monitor during therapy. Monitor serum phosphorus in patients with chronic kidney disease. (5.6)
- Lactic acidosis/severe hepatomegaly with steatosis: Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.7)

---------- ADVERSE REACTIONS ----------
Dolutegravir: The most common adverse reactions of moderate to severe intensity and incidence at least 2% (in those receiving dolutegravir in any one adult trial) are insomnia, fatigue, and headache. (6.1)

Emtricitabine and Tenofovir Alafenamide: Most common adverse reaction (incidence greater than or equal to 10%, all grades) is nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Mylan Pharmaceuticals Inc. 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, emtricitabine and tenofovir alafenamide tablets with other drugs can alter the concentration of other drugs and other drugs may alter the concentrations of dolutegravir, emtricitabine and tenofovir alafenamide tablets. The potential drug-drug interactions must be considered prior to and during therapy. (4, 7, 12.3)

---------- USE IN SPECIFIC POPULATIONS ----------
- Pregnancy: Dolutegravir, emtricitabine and tenofovir alafenamide tablets should be used during pregnancy only if the potential benefit justifies the potential risk. (8.1)
- Lactation: Breastfeeding is not recommended due to the potential for HIV transmission. (8.2)
- Pediatrics: Not recommended for patients weighing less than 40 kg. (8.4)

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

Revised: 2/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

- **Tenofovir alafenamide, one component of dolutegravir, emtricitabine and tenofovir alafenamide tablets, is approved for the treatment of chronic hepatitis B virus (HBV) infection. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of dolutegravir, emtricitabine and tenofovir alafenamide tablets. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue dolutegravir, emtricitabine and tenofovir alafenamide tablets. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.4)]*.**

1 INDICATIONS AND USAGE

Dolutegravir, emtricitabine and tenofovir alafenamide tablets are 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.

Limitations of Use:

- Dolutegravir, emtricitabine and tenofovir alafenamide tablets alone are not recommended in patients with resistance-associated integrase substitutions or clinically suspected integrase strand transfer inhibitor resistance because the dose of dolutegravir in dolutegravir, emtricitabine and tenofovir alafenamide tablets is insufficient in these subpopulations. See the dolutegravir prescribing information.
- Dolutegravir, emtricitabine and tenofovir alafenamide tablets are not indicated for use as pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk.

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation of Dolutegravir, Emtricitabine and Tenofovir Alafenamide Tablets

Prior to initiation of dolutegravir, emtricitabine and tenofovir alafenamide tablets, patients should be tested for hepatitis B virus infection *[see Warnings and Precautions (5.4)]*.

Estimated creatinine clearance, urine glucose, and urine protein should be assessed before initiating dolutegravir, emtricitabine and tenofovir alafenamide tablets therapy and should be monitored during therapy in all patients *[see Warnings and Precautions (5.6)]*.

2.2 Adults and Pediatric Patients Weighing at Least 40 kg (88 lbs)

Dolutegravir, emtricitabine and tenofovir alafenamide tablets are a three-drug fixed-dose combination product containing 50 mg of dolutegravir, 200 mg of emtricitabine (FTC) and 25 mg of tenofovir alafenamide (TAF). The recommended dosage of dolutegravir, emtricitabine and tenofovir alafenamide is one tablet taken orally once daily with or without food in adults and

pediatric patients weighing at least 40 kg (88 lbs) and creatinine clearance greater than or equal to 30 mL per minute *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

2.3 Not Recommended in Patients with Severe Renal Impairment

Dolutegravir, emtricitabine and tenofovir alafenamide tablets are not recommended in patients with estimated creatinine clearance below 30 mL per minute *[see Warnings and Precautions (5.6) and Use in Specific Populations (8.7)]*.

3 DOSAGE FORMS AND STRENGTHS

Dolutegravir, emtricitabine and tenofovir alafenamide tablets are available containing 52.6 mg of dolutegravir sodium (DTG), equivalent to 50 mg of dolutegravir, 200 mg of emtricitabine (FTC) and 28.04 mg of tenofovir alafenamide fumarate (TAF), equivalent to 25 mg of tenofovir alafenamide.

- The 50 mg/200 mg/25 mg tablets are white to off-white, film-coated, oval, unscored tablets debossed with **M** on one side of the tablet and **TD1** on the other side.

4 CONTRAINDICATIONS

Dolutegravir, emtricitabine and tenofovir alafenamide tablets are contraindicated in patients:

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

5 WARNINGS AND PRECAUTIONS

5.1 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, emtricitabine 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 fixed-dose abacavir, dolutegravir, and lamivudine. Monitoring for hepatotoxicity is recommended.

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, emtricitabine 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, emtricitabine and tenofovir alafenamide tablets or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction. Dolutegravir, emtricitabine and tenofovir alafenamide tablets are contraindicated in patients who have experienced a previous hypersensitivity reaction to dolutegravir.

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

The concomitant use of dolutegravir, emtricitabine 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, emtricitabine and tenofovir alafenamide tablets and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs.

For concomitant drugs for which the interaction can be mitigated, please see Table 3 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, emtricitabine and tenofovir alafenamide tablets; review concomitant medications during therapy with dolutegravir, emtricitabine and tenofovir alafenamide tablets; and monitor for the adverse reactions associated with the concomitant drugs.

5.4 Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV

Patients with HIV-1 should be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy *[see Dosage and Administration (2.1)]*.

Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of dolutegravir, emtricitabine and tenofovir alafenamide tablets. Patients coinfected with HIV-1 and HBV who discontinue dolutegravir, emtricitabine 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, initiation of anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis, since post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

5.5 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including dolutegravir and FTC, two components of dolutegravir, emtricitabine 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, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable and can occur many months after initiation of treatment.

5.6 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 FTC + TAF with cobicistat (COBI) plus elvitegravir (EVG), there have been no cases of Fanconi syndrome or Proximal Renal Tubulopathy (PRT). In clinical trials of FTC + TAF with EVG + COBI in treatment-naïve subjects and in virally suppressed subjects switched to FTC + TAF with EVG + COBI with eGFRs greater than 50 mL per minute, renal serious adverse events or discontinuations due to renal adverse reactions were encountered in less than 1% of participants treated with FTC + TAF with EVG + COBI. In a study of virally suppressed subjects with baseline eGFRs between 30 and 69 mL per minute treated with FTC + TAF with EVG + COBI for a median duration of 43 weeks, FTC + TAF with EVG + COBI was permanently discontinued due to worsening renal function in two of 80 (3%) subjects with a baseline eGFR between 30 and 50 mL per minute *[see Adverse Reactions (6.1)]*. Dolutegravir, emtricitabine and tenofovir alafenamide tablets are not recommended in patients with estimated creatinine clearance below 30 mL per minute because data in this population are insufficient.

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.

Estimated creatinine clearance, urine glucose, and urine protein should be assessed before initiating dolutegravir, emtricitabine and tenofovir alafenamide tablets therapy and should be monitored during therapy in all patients. Serum phosphorus should be monitored in patients with chronic kidney disease because these patients are at greater risk of developing Fanconi syndrome on tenofovir prodrugs. Discontinue dolutegravir, emtricitabine and tenofovir alafenamide tablets in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

5.7 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 analogs, including emtricitabine, a component of dolutegravir, emtricitabine and tenofovir alafenamide tablets, and tenofovir DF, another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with dolutegravir, emtricitabine 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).

6 ADVERSE REACTIONS

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

- Hepatotoxicity *[see Warnings and Precautions (5.1)]*.
- Hypersensitivity Reactions *[see Warnings and Precautions (5.2)]*.

- Severe Acute Exacerbation of Hepatitis B *[see Boxed Warning and Warnings and Precautions (5.4)]*.
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.5)]*.
- New Onset or Worsening Renal Impairment *[see Warnings and Precautions (5.6)]*.
- Lactic Acidosis and Severe Hepatomegaly with Steatosis *[see Warnings and Precautions (5.7)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug (or a drug given in various combinations with other concomitant therapy) cannot be directly compared with rates in the clinical trials of another drug (or a drug given in the same or different combination therapy) and may not reflect the rates observed in practice.

Dolutegravir: *Clinical Trials Experience in Adult Subjects:* Treatment-Naïve Subjects: The safety assessment of dolutegravir in HIV-1-infected treatment-naïve subjects is based on the analyses of data from 2 international, multicenter, double-blind trials, SPRING-2 (ING113086) and SINGLE (ING114467).

In SPRING-2, 822 subjects were randomized and received at least 1 dose of either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily, both in combination with fixed-dose dual nucleoside reverse transcriptase inhibitor (NRTI) treatment (either fixed-dose abacavir sulfate and lamivudine [EPZICOM®] or fixed-dose emtricitabine/tenofovir DF [TRUVADA®]). There were 808 subjects included in the efficacy and safety analyses. Through 96 weeks, the rate of adverse events leading to discontinuation was 2% in both treatment arms.

In SINGLE, 833 subjects were randomized and received at least 1 dose of either dolutegravir 50 mg with fixed-dose abacavir sulfate and lamivudine (EPZICOM) once daily or fixed-dose efavirenz/emtricitabine/tenofovir DF (ATRIPLA®) once daily (study treatment was blinded through Week 96 and open-label from Week 96 through Week 144). Through 144 weeks, the rates of adverse events leading to discontinuation were 4% in subjects receiving dolutegravir 50 mg once daily + fixed-dose abacavir and lamivudine (EPZICOM) and 14% in subjects receiving fixed-dose efavirenz/emtricitabine/tenofovir DF (ATRIPLA) once daily.

Treatment-emergent adverse reactions (ARs) of moderate to severe (Grade 2 to 4) intensity observed in at least 2% of subjects in dolutegravir treatment arms in either SPRING-2 or SINGLE were insomnia (3%), headache (2%), and fatigue (2%).

In addition, Grade 1 insomnia was reported by 1% and less than 1% of subjects receiving dolutegravir and raltegravir, respectively, in SPRING-2; whereas in SINGLE the rates were 7% and 4% for dolutegravir and fixed-dose efavirenz/emtricitabine/tenofovir DF (ATRIPLA), respectively. These events were not treatment limiting.

Less Common Adverse Reactions Observed in Treatment-Naïve and Treatment-Experienced Trials: The following ARs occurred in less than 2% of treatment-naïve or treatment-experienced

subjects receiving dolutegravir in a combination regimen in any one trial. These events have been included because of their seriousness and assessment of potential causal relationship.

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

Hepatobiliary Disorders: Hepatitis.

Musculoskeletal Disorders: Myositis.

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

Renal and Urinary Disorders: Renal impairment.

Skin and Subcutaneous Tissue Disorders: Pruritus.

Laboratory Abnormalities: Treatment-Naïve Subjects: Selected laboratory abnormalities (Grades 2 to 4) with a worsening grade from baseline and representing the worst-grade toxicity in at least 2% of subjects are presented in Table 1. The mean change from baseline observed for selected lipid values is presented in Table 2.

Table 1. Selected Laboratory Abnormalities (Grades 2 to 4) in Treatment-Naïve Subjects in SPRING-2 (Week 96 Analysis)

	SPRING-2	
Laboratory Parameter Preferred Term	**Dolutegravir 50 mg Once Daily + 2 NRTIs (n = 403)**	**Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)**
ALT		
Grade 2 (> 2.5 to 5.0 x ULN)	4%	4%
Grade 3 to 4 (> 5.0 x ULN)	2%	2%
AST		
Grade 2 (> 2.5 to 5.0 x ULN)	5%	3%
Grade 3 to 4 (> 5.0 x ULN)	3%	2%
Total Bilirubin		
Grade 2 (1.6 to 2.5 x ULN)	3%	2%
Grade 3 to 4 (> 2.5 x ULN)	< 1%	< 1%
Creatine kinase		
Grade 2 (6.0 to 9.9 x ULN)	2%	5%
Grade 3 to 4 (≥ 10.0 x ULN)	7%	4%
Hyperglycemia		
Grade 2 (126 to 250 mg/dL)	6%	6%
Grade 3 (> 250 mg/dL)	< 1%	2%

Lipase		
Grade 2 (> 1.5 to 3.0 x ULN)	7%	7%
Grade 3 to 4 (> 3.0 x ULN)	2%	5%
Total neutrophils		
Grade 2 (0.75 to 0.99 x 10^9)	4%	3%
Grade 3 to 4 (< 0.75 x 10^9)	2%	2%

Table 2. Mean Change from Baseline in Fasted Lipid Values in Treatment-Naïve Subjects in SPRING-2 (Week 96 Analysis[a])

	SPRING-2	
Laboratory Parameter Preferred Term	**Dolutegravir 50 mg Once Daily + 2 NRTIs (n = 403)**	**Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)**
Cholesterol (mg/dL)	8.1	10.1
HDL cholesterol (mg/dL)	2.0	2.3
LDL cholesterol (mg/dL)	5.1	6.1
Triglycerides (mg/dL)	6.7	6.6

[a] Subjects on lipid-lowering agents at baseline were excluded from these analyses (19 subjects in each arm in SPRING-2. 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 (SPRING-2: dolutegravir n = 9, raltegravir n = 13).

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 and 13% vs. 8% with the 50 mg twice-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 (5.1)]*.

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 P1093 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) and 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.

Emtricitabine and Tenofovir Alafenamide: *Adverse Reactions in Clinical Trials of FTC + TAF with EVG + COBI in Treatment-Naïve Adults with HIV-1 Infection:* In pooled 48-week trials of antiretroviral treatment-naïve HIV-1-infected adult subjects, the most common adverse reaction in subjects treated with FTC + TAF with EVG + COBI (N = 866) (incidence greater than or equal to 10%, all grades) was nausea (10%). In this treatment group, 0.9% of subjects discontinued FTC + TAF with EVG + COBI due to adverse events during the 48-week treatment period *[see Clinical Studies (14)]*. The safety profile was similar in virologically-suppressed adults with HIV-1 infection who were switched to FTC + TAF with EVG + COBI (N = 799). Antiretroviral treatment-naïve adult subjects treated with FTC + TAF with EVG + COBI 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.

Renal Laboratory Tests: In two 48-week trials in antiretroviral treatment-naïve HIV-1-infected adults treated with FTC + TAF with EVG + COBI (N = 866) with a median baseline eGFR of 115 mL per minute, 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 FTC + TAF with EVG + COBI (N = 959) 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. In a 24-week trial in adults with renal impairment (baseline eGFR 30 to 69 mL per minute) who received FTC + TAF with EVG + COBI (N = 248), mean serum creatinine was 1.5 mg per dL at both baseline and Week 24. Median UPCR was 161 mg per gram at baseline and 93 mg per gram at Week 24.

Bone Mineral Density Effects: In the pooled analysis of two 48-week trials of antiretroviral treatment-naïve HIV-1-infected adult subjects, bone mineral density (BMD) from baseline to Week 48 was assessed by dual-energy X-ray absorptiometry (DXA). Mean BMD decreased from baseline to Week 48 -1.30% with FTC + TAF with EVG + COBI 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

FTC + TAF with EVG + COBI subjects. BMD declines of 7% or greater at the femoral neck were experienced by 7% of FTC + TAF with EVG + COBI subjects. 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 FTC + TAF with EVG + COBI group.

In 799 virologically-suppressed TDF-treated adult subjects that switched to FTC + TAF with EVG + 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 FTC + TAF with EVG + COBI subjects. BMD declines of 7% or greater at the femoral neck were experienced by 1% of FTC + TAF with EVG + COBI subjects.

Adverse Reactions in Clinical Trials in Pediatric Subjects with HIV-1 Infection: In a 24-week, open-label trial of 23 antiretroviral treatment-naïve HIV-1-infected pediatric subjects aged 12 to less than 18 years old (weighing at least 35 kg) who received FTC + TAF with EVG + COBI, the safety of this combination was similar to that of adults. Among these pediatric subjects, mean BMD increased from baseline to Week 24, +1.7% at the lumbar spine and +0.8% for the total body less head. Mean changes from baseline BMD Z-scores were -0.10 for lumbar spine and -0.11 for total body less head at Week 24. Two subjects had significant (greater than 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. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Dolutegravir: *Hepatobiliary Disorders:* Acute liver failure, hepatotoxicity.

Musculoskeletal: Arthralgia, myalgia.

Psychiatric: Anxiety.

7 DRUG INTERACTIONS

7.1 Effect of Dolutegravir on the Pharmacokinetics of Other Agents

In vitro, dolutegravir inhibited the renal organic cation transporters, OCT2 (IC_{50} = 1.93 microM) and multidrug and toxin extrusion transporter (MATE) 1 (IC_{50} = 6.34 microM). *In vivo*, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2 and potentially MATE1. Dolutegravir may increase plasma concentrations of drugs eliminated via OCT2 or MATE1 (dofetilide and metformin, Table 3) *[see Contraindications (4) and Drug Interactions (7.3)]*.

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

In vitro, dolutegravir did not inhibit (IC_{50} greater than 50 microM) the following: cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, 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.

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.

7.2 Effect of Other Agents on the Pharmacokinetics of Dolutegravir or Emtricitabine and Tenofovir Alafenamide

Dolutegravir: Dolutegravir, one component of dolutegravir, emtricitabine and tenofovir alafenamide tablets, 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 3) *[see Drug Interactions (7.3) and Clinical Pharmacology (12.3)]*.

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

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

Emtricitabine and Tenofovir Alafenamide: TAF, one component of dolutegravir, emtricitabine and tenofovir alafenamide tablets, 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 3). 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, emtricitabine and tenofovir alafenamide tablets and development of resistance.

Coadministration of dolutegravir, emtricitabine 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*.

Based on drug interaction studies conducted with the components of emtricitabine and tenofovir alafenamide, no clinically significant drug interactions have been either observed or are expected when emtricitabine and tenofovir alafenamide 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 emtricitabine and tenofovir alafenamide is combined with the following drugs: buprenorphine, itraconazole, ketoconazole, lorazepam, methadone, midazolam, naloxone, norbuprenorphine, norgestimate/ethinyl estradiol, and sertraline.

7.3 Established and Other Potentially Significant Drug Interactions

There were no drug interaction trials conducted with dolutegravir and fixed-dose emtricitabine and tenofovir alefenamide or with the fixed-dose combination of all three components.

Information regarding potential drug interactions with dolutegravir, emtricitabine and tenofovir alafenamide (Table 3) are provided below.

These recommendations are based on either drug interaction trials or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy *[see Contraindications (4) and Clinical Pharmacology (12.3)]*.

Table 3. Established and Other Potentially Significant Drug Interactions for Dolutegravir, Emtricitabine and Tenofovir Alafenamide: Alterations in Dose May Be Recommended Based on Drug Interaction Trials or Predicted Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, TAF and/or Concomitant Drug	Clinical Comment
Antiarrhythmic: Dofetilide	↑ Dofetilide	Coadministration is contraindicated with dolutegravir, emtricitabine and tenofovir alafenamide tablets *[see Contraindications (4)]*.
Antimycobacterials: Rifabutin Rifampin Rifapentine	↓ TAF	Coadministration of dolutegravir, emtricitabine and tenofovir alafenamide tablets with rifabutin, rifampin, or rifapentine is not recommended.
Non-nucleoside reverse	↓ Dolutegravir	Use of dolutegravir, emtricitabine and

transcriptase inhibitor: Etravirine[a]		tenofovir alafenamide tablets with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir is not recommended.
Non-nucleoside reverse transcriptase inhibitor: Efavirenz[a]	↓ Dolutegravir	Adjust dose of dolutegravir to 50 mg twice daily. An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, emtricitabine and tenofovir alafenamide tablets.
Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓ Dolutegravir	Avoid coadministration with dolutegravir, emtricitabine and tenofovir alafenamide tablets because there are insufficient data to make dosing recommendations.
Protease inhibitor: Fosamprenavir/ritonavir[a]	↓ Dolutegravir	Adjust dolutegravir dose to 50 mg twice daily. An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, emtricitabine and tenofovir alafenamide tablets.
Other Agents		
Carbamazepine[a]	↓ Dolutegravir	An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, emtricitabine and tenofovir alafenamide tablets; however, use with dolutegravir, emtricitabine and tenofovir alafenamide tablets is not recommended because of the TAF component.
Carbamazepine Oxcarbazepine Phenytoin Phenobarbital	↓ Dolutegravir ↓ TAF	Consider alternative anticonvulsant.
St. John's wort (*Hypericum perforatum*)	↓ Dolutegravir ↓ TAF	Coadministration of dolutegravir, emtricitabine and tenofovir alafenamide tablets with St. John's wort is not recommended.
Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing antacids[a] or laxatives Sucralfate Buffered medications	↓ Dolutegravir	Administer dolutegravir, emtricitabine 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[a]	↓ Dolutegravir	Administer dolutegravir, emtricitabine and tenofovir alafenamide tablets 2 hours before or 6 hours after taking supplements containing calcium or iron. Alternatively, dolutegravir, emtricitabine and tenofovir alafenamide tablets and supplements containing calcium or iron can be taken together with food.
Metformin[a]	↑ Metformin	With concomitant use, limit the total daily dose of metformin to 1000 mg either when starting metformin or dolutegravir, emtricitabine and tenofovir alafenamide tablets. When stopping dolutegravir, emtricitabine and tenofovir alafenamide tablets, the metformin dose may require an adjustment. Monitoring of blood glucose when initiating concomitant use and after withdrawal of dolutegravir, emtricitabine and tenofovir alafenamide tablets is recommended.

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

7.4 Drugs Affecting Renal Function

Because FTC and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of dolutegravir, emtricitabine and tenofovir alafenamide tablets with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of FTC, 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: There are insufficient human data on the use of dolutegravir, emtricitabine and tenofovir alafenamide tablets during pregnancy to inform a drug-associated risk of birth defects and miscarriage. Tenofovir alafenamide (TAF) use in women during pregnancy has not been evaluated; however, emtricitabine (FTC) use during pregnancy has been evaluated in a limited number of women as reported to the Antiretroviral Pregnancy Registry (APR). Given the limited number of pregnancies exposed to dolutegravir-based regimens reported to the APR, no definitive conclusions can be drawn on the safety of dolutegravir, emtricitabine and tenofovir alafenamide tablets in pregnancy, and continued monitoring is ongoing through the APR. The background rate for major birth defects in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) is 2.7%. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15% to 20%.

Dolutegravir: In animal reproduction studies, no evidence of adverse developmental outcomes was observed with dolutegravir *[see Data]*. During organogenesis in the rat and rabbit, systemic exposures (AUC) to dolutegravir were less than (rabbits) and approximately 27 times (rats) the exposure in humans at the maximum recommended human dose (MRHD). In the rat pre/post-natal developmental study, maternal systemic exposure (AUC) to dolutegravir was approximately 27 times the exposure in humans at the MRHD.

Emtricitabine and Tenofovir Alafenamide: In animal studies, no adverse developmental effects were observed when the components of emtricitabine and tenofovir alafenamide were administered separately during the period of organogenesis at exposures 60 and 108 times (mice and rabbits, respectively) the FTC exposure and at exposure equal to or 53 times (rats and rabbits, respectively) the TAF exposure at the recommended daily dose of emtricitabine and tenofovir alafenamide *[see Data (8.1)]*. Likewise, no adverse developmental effects were seen when FTC was administered to mice through lactation at exposures up to approximately 60 times the exposure at the recommended daily dose of emtricitabine and tenofovir alafenamide. No adverse effects were observed in the offspring when TDF was administered through lactation at tenofovir exposures of approximately 14 times the exposure at the recommended daily dosage of emtricitabine and tenofovir alafenamide.

Data: *Human Data:* Emtricitabine: Based on prospective reports to the APR through July 2015 of 2933 exposures to FTC-containing regimens during pregnancy (including 1984 exposed in the first trimester and 949 exposed in the second/third trimester), there was no difference between FTC and overall birth defects compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of birth defects in live births was 2.4% (95% CI: 1.7% to 3.1%) with first trimester exposure to FTC-containing regimens and 2.1% (95% CI: 1.3% to 3.2%) with the second/third trimester exposure to FTC-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 also 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).

Emtricitabine: FTC was administered orally to pregnant mice (250 mg/kg/day, 500 mg/kg/day, or 1000 mg/kg/day) and rabbits (100 mg/kg/day, 300 mg/kg/day, or 1000 mg/kg/day) through organogenesis (on gestation days 6 through 15, and 7 through 19, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with FTC in mice at exposures (area under the curve [AUC]) approximately 60 times higher and in rabbits at approximately 108 times higher than human exposures at the recommended daily dose. In a pre/post-natal development study with FTC, mice were administered doses up to 1000 mg/kg/day; no significant adverse effects directly related to drug were observed in the offspring

exposed daily from before birth (*in utero*) through sexual maturity at daily exposures (AUC) of approximately 60-fold higher than human exposures at the recommended daily dose.

Tenofovir Alafenamide: TAF was administered orally to pregnant rats (25 mg/kg/day, 100mg/kg/day, or 250 mg/kg/day) and rabbits (10 mg/kg/day, 30 mg/kg/day, 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 emtricitabine and tenofovir alafenamide. 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/post-natal 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 emtricitabine and tenofovir alafenamide.

8.2 Lactation

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

It is not known if dolutegravir, emtricitabine and tenofovir alafenamide tablets affect milk production or have effects on the breastfed child. 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, emtricitabine and tenofovir alafenamide tablets.

Dolutegravir: It is not known whether dolutegravir 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]*.

Emtricitabine and Tenofovir Alafenamide: FTC has been shown to be present in human breast milk; it is not known if TAF is present in human breast milk *[see Data (8.2)]*. Tenofovir has been shown to be present in the milk of lactating rats and rhesus monkeys after administration of TDF *[see Data (8.2)]*. It is not known if TAF can be present in animal milk. While it is not known whether TAF is present in human breast milk, FTC has been shown to be present in human breast milk *[see Data (8.2)]*.

Data: *Human Data:* Emtricitabine: Samples of breast milk obtained from five HIV-1-infected mothers show that emtricitabine is present in human milk. Breastfeeding infants whose mothers are being treated with emtricitabine may be at risk for developing viral resistance to emtricitabine. Other emtricitabine-associated risks in infants breastfed by mothers being treated with emtricitabine are unknown.

Animal 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.

Tenofovir Alafenamide: 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 (8.1)]*. 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.

8.4 Pediatric Use

Dolutegravir, emtricitabine and tenofovir alafenamide tablets should only be administered to pediatric patients with a body weight of at least 40 kg because they are a fixed-dose combination that cannot be adjusted. The safety and efficacy have been established for the individual components in this weight group.

8.5 Geriatric Use

Dolutegravir: Clinical trials of dolutegravir 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 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)]*.

Emtricitabine and Tenofovir Alafenamide: In clinical trials, 80 of the 97 subjects enrolled aged 65 years and over received FTC + TAF and EVG + COBI. No differences in safety or efficacy have been observed between elderly subjects and adults between 18 and less than 65 years of age.

8.6 Hepatic Impairment

No dosage adjustment of dolutegravir, emtricitabine and tenofovir alafenamide tablets is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of dolutegravir, emtricitabine and tenofovir alafenamide has not been studied. Therefore, dolutegravir, emtricitabine and tenofovir alefenamide tablets are not recommended for use in patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

Dolutegravir, emtricitabine and tenofovir alafenamide tablets are not recommended for patients with severe renal impairment (estimated creatinine clearance below 30 mL per min) because dolutegravir, emtricitabine and tenofovir alafenamide tablets are a fixed-dose combination and the dosage of the individual components cannot be adjusted. No dosage adjustment of dolutegravir, emtricitabine and tenofovir alafenamide tablets is recommended in patients with

mild or moderate renal impairment (estimated creatinine clearance greater than or equal to 30 mL per minute) *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There is known specific treatment for overdose with dolutegravir, emtricitabine 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.

Emtricitabine (FTC): Limited clinical experience is available at doses higher than the recommended dose of FTC. In one clinical pharmacology study, single doses of FTC 1200 mg (6 times the recommended dose of FTC) were administered to 11 subjects. No severe adverse reactions were reported. The effects of higher doses are not known.

Hemodialysis treatment removes approximately 30% of the FTC dose over a 3-hour dialysis period starting within 1.5 hours of FTC dosing (blood flow rate of 400 mL per minute and a dialysate flow rate of 600 mL per minute). It is not known whether FTC can be removed by peritoneal dialysis.

Tenofovir Alafenamide (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 200 mg/25 mg fixed-dose combination emtricitabine and tenofovir alafenamide) 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%.

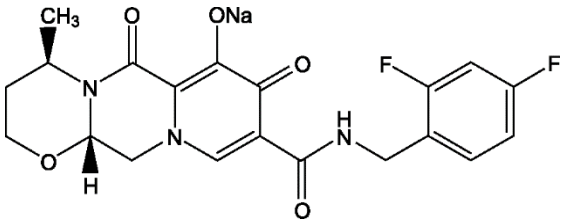
11 DESCRIPTION

Dolutegravir, emtricitabine and tenofovir alafenamide tablets are a fixed-dose combination product containing dolutegravir (DTG), emtricitabine (FTC) and tenofovir alafenamide (TAF), for oral administration.

- DTG, an HIV INST.
- FTC, a synthetic nucleoside analog of cytidine, is an HIV nucleoside analog reverse transcriptase inhibitor (HIV NRTI).
- TAF, an HIV NRTI, is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate.

Each film-coated tablet contains 52.6 mg of dolutegravir sodium, which is equivalent to 50 mg dolutegravir free acid, 200 mg of FTC and 28.04 mg of TAF, equivalent to 25 mg of tenofovir alafenamide, 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.

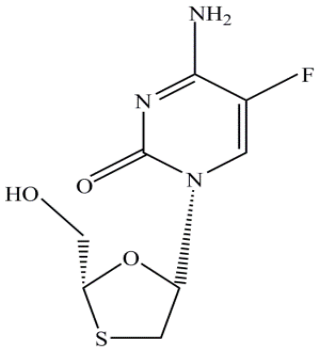
Dolutegravir: The chemical name of dolutegravir sodium is sodium (4R,12aS)-N-[(2,4-Difluoro benzyl)carbamoyl] -4-methyl-6, 8-dioxo- 3,4,6,8,12,12a-hexahydro-2H-pyrido [l',2':4,5]pyrazino[2, 1-b] [1,3] oxazin-7-olate. The molecular formula is $C_{20}H_{18}F_2N_3NaO_5$ and the molecular weight is 441.37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



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

Emtricitabine: The chemical name of FTC is 4-Amino-5-fluoro-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-2(1H)-pyrimidinone. FTC is the (-)enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5 position.

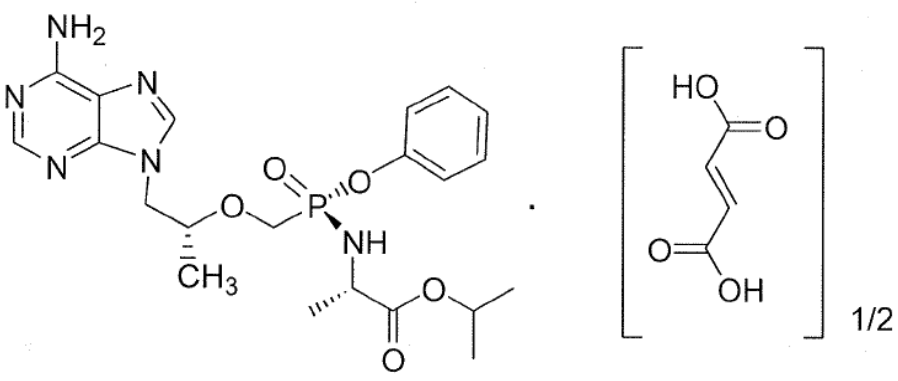
FTC has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.25 and has the following structural formula:



FTC is a white to off-white powder with a solubility of approximately 112 mg per mL in water at 25°C.

Tenofovir Alafenamide: The chemical name of tenofovir alafenamide fumarate drug substance is 9-{(R)-2-[[(S)-{[(S)-1-(isopropoxycarbonyl)ethyl]amino}phenoxy-phosphinyl] methoxy] propyl}adenine hemi fumarate.

Tenofovir alafenamide fumarate has a molecular formula of $C_{21}H_{29}O_5N_6P \bullet 1/2(C_4H_4O_4)$ and a molecular weight of 534.5 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, emtricitabine and tenofovir alafenamide tablets are a fixed-dose combination of antiretroviral drugs dolutegravir (DTG), emtricitabine (FTC) and tenofovir alafenamide (TAF) *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

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

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

Emtricitabine and Tenofovir Alafenamide: *Cardiac Electrophysiology:* 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. The effect of the other component of emtricitabine and tenofovir alafenamide, FTC, or the combination of FTC and TAF on the QT interval is not known.

12.3 Pharmacokinetics

Dolutegravir, Emtricitabine and Tenofovir Alafenamide: Dolutegravir, emtricitabine and tenofovir alafenamide from the combination tablets (50 mg/200 mg/25 mg) were comparable to that from TIVICAY® tablets of ViiV U.S.A. (containing dolutegravir 50 mg) and DESCOVY® tablets of Gilead Sciences, Inc. U.S.A. (containing emtricitabine 200 mg and tenofovir alafenamide 25 mg), respectively, when single doses were administered to healthy subjects under fasted and fed conditions.

Absorption, Distribution, Metabolism, and Excretion: *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-gp substrate *in vitro*. The absolute bioavailability of dolutegravir has not been established. Dolutegravir may be taken with or without food. Food increased the extent of absorption and slowed the rate of absorption of dolutegravir. Low-, moderate-, and high-fat meals increased dolutegravir $AUC_{(0-\infty)}$ by 33%, 41%, and 66%; increased C_{max} by 46%, 52%, and 67%; and prolonged T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively. 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 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.

Dolutegravir is primarily metabolized via UGT1A1 with some contribution from CYP3A. After a single oral dose of [^{14}C] dolutegravir, 53% of the total oral dose was excreted unchanged in feces. Thirty-one percent of the total oral dose was excreted in 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 low (less than 1% of the dose).

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).

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. The non-linear exposure of dolutegravir following 50 mg twice daily compared with 50 mg once daily in HIV-1-infected subjects (Table 4) was attributed to the use of metabolic inducers in the background antiretroviral regimens of subjects receiving dolutegravir 50 mg twice daily in clinical trials. Dolutegravir was administered without regard to food in these trials.

Table 4. Dolutegravir Steady-State Pharmacokinetic Parameter Estimates in HIV-1-Infected Adults

Parameter	50 mg Once Daily Geometric Mean[a] (%CV)	50 mg Twice Daily Geometric Mean[b] (%CV)
$AUC_{(0-24)}$ (mcg•h/mL)	53.6 (27)	75.1 (35)
C_{max} (mcg/mL)	3.67 (20)	4.15 (29)
C_{min} (mcg/mL)	1.11 (46)	2.12 (47)

[a] Based on population pharmacokinetic analyses using data from SPRING-1 and SPRING-2.
[b] Based on population pharmacokinetic analyses using data from VIKING (ING112961) and VIKING-3.

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.

Emtricitabine and Tenofovir Alafenamide: The pharmacokinetic (PK) properties of the components of emtricitabine and tenofovir alafenamide are provided in Table 5. The multiple dose PK parameters of FTC and TAF and its metabolite tenofovir are provided in Table 6.

Table 5. Pharmacokinetic Properties of the Components of Emtricitabine and Tenofovir Alafenamide

	Emtricitabine	Tenofovir Alafenamide
Absorption		
T_{max} (h)	3	1
Effect of high fat meal (relative to fasting)[a]	AUC Ratio = 0.91 (0.89, 0.93) C_{max} Ratio = 0.74 (0.69, 0.78)	AUC Ratio = 1.75 (1.64, 1.88) C_{max} Ratio= 0.85 (0.75, 0.95)
Distribution		
% Bound to human plasma proteins	< 4	~ 80
Source of protein binding data	*In vitro*	*Ex vivo*
Blood-to-plasma ratio	0.6	1.0
Metabolism		
Metabolism	Not significantly metabolized	Cathepsin A[b] (PBMCs) CES1 (hepatocytes) CYP3A (minimal)
Elimination		
Major route of elimination	Glomerular filtration and active tubular secretion	Metabolism (> 80% of oral dose)
$t_{1/2}$ (h)[c]	10	0.51
% Of dose excreted in urine[d]	70	< 1.0
% Of dose excreted in feces[d]	13.7	31.7

PBMCs = peripheral blood mononuclear cells; CES1 = carboxylesterase 1
[a] 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.
[b] *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.

[c] $t_{1/2}$ values refer to median terminal plasma half-life. Note that the pharmacologically active metabolite, tenofovir diphosphate, has a half-life of 150 to 180 hours within PBMCs.

[d] Dosing in mass balance studies: FTC (single dose administration of [^{14}C] emtricitabine after multiple dosing of emtricitabine for ten days); TAF (single dose administration of [^{14}C] tenofovir alafenamide).

Table 6. Multiple Dose PK Parameters of Emtricitabine, Tenofovir Alafenamide and its Metabolite Tenofovir Following Oral Administration with Food in HIV-Infected Adults

Parameter Mean (CV%)	Emtricitabine[a]	Tenofovir Alafenamide[b]	Tenofovir[c]
C_{max} (microgram per mL)	2.1 (20.2)	0.16 (51.1)	0.02 (26.1)
AUC_{tau} (microgram•hour per mL)	11.7 (16.6)	0.21 (71.8)	0.29 (27.4)
C_{trough} (microgram per mL)	0.10 (46.7)	NA	0.01 (28.5)

CV = Coefficient of Variation; NA = Not Applicable

[a] From Intensive PK analysis in a phase 2 trial in HIV-infected adults treated with FTC + TAF and EVG + COBI.

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

[c] 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, Emtricitabine and Tenofovir Alafenamide: The pharmacokinetics of dolutegravir, emtricitabine and tenofovir are not affected by food, hence dolutegravir, emtricitabine and tenofovir alafenamide tablets can be administered with or without food.

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

Emtricitabine: The pharmacokinetics of FTC has not been studied in subjects with hepatic impairment; however, FTC is not significantly metabolized by liver enzymes, so the impact of hepatic impairment should be limited.

Tenofovir Alafenamide: 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.

Patients with Renal Impairment: Dolutegravir, emtricitabine and tenofovir alafenamide tablets are not recommended for patients with severe renal impairment (estimated creatinine clearance below 30 mL per min) because dolutegravir, emtricitabine and tenofovir alafenamide tablets are a fixed-dose combination and the dosage of the individual components cannot be adjusted *[see Dosage and Administration (2.3)]*.

Hepatitis B (HBV) and/or Hepatitis C Virus (HCV) Co-infection: Emtricitabine and Tenofovir Alafenamide: The pharmacokinetics of FTC and TAF have not been fully evaluated in subjects coinfected with hepatitis B and/or C virus.

Dolutegravir: Population analyses using pooled pharmacokinetic data from adult trials indicated no clinically relevant effect of HCV co-infection on the pharmacokinetics of dolutegravir. There were limited data on HBV co-infection.

Gender and Race: Dolutegravir: Population analyses using pooled pharmacokinetic data from adult trials indicated gender or race had no clinically relevant effect on the exposure of dolutegravir.

Emtricitabine and Tenofovir Alafenamide: Based on population pharmacokinetic analyses, no dosage adjustment is recommended based on gender or race.

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

Emtricitabine and Tenofovir Alafenamide: Pharmacokinetics of FTC and TAF have not been fully evaluated in the elderly (65 years of age and older). Population pharmacokinetics analysis of HIV-infected subjects in Phase 2 and Phase 3 trials of FTC + TAF and EVG + 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, emtricitabine and tenofovir alafenamide tablets should not be administered to pediatric patients weighing less than 40 kg (88 lbs).

Dolutegravir: The pharmacokinetics of dolutegravir in HIV-1-infected children (n = 14) weighing at least 40 kg were similar to those observed in HIV-1-infected adults who received dolutegravir 50 mg once daily (Table 7) *[see Clinical Studies (14.2)]*.

Table 7. Dolutegravir Steady-State Pharmacokinetic Parameters in Pediatric Subjects

		Dolutegravir Pharmacokinetic Parameter Estimates Geometric Mean (%CV)		
Weight (n)	**Dose of Dolutegravir**	**C_{max} (mcg/mL)**	**$AUC_{(0-24)}$ (mcg•h/mL)**	**C_{24} (mcg/mL)**
≥ 40 kg (n = 14)	50 mg once daily	3.89 (43)	50.1 (53)	0.99 (66)

Emtricitabine and Tenofovir Alafenamide: Exposures of FTC and TAF in 24 pediatric subjects aged 12 to less than 18 years who received FTC + TAF and EVG + COBI were decreased (23% for AUC) compared to exposures achieved in treatment-naïve adults following administration of this dosage regimen *[see Use in Specific Populations (8.4)]*. These exposure differences are not thought to be clinically significant based on exposure-response relationships.

Drug Interaction Trials: The drug interaction trials described were conducted with dolutegravir, emtricitabine, and/or tenofovir alafenamide as single entities; no drug interaction trials have been conducted using the fixed-dose combination of dolutegravir, emtricitabine and tenofovir alafenamide.

Dolutegravir: Drug interaction trials were performed with dolutegravir and other drugs likely to be coadministered or commonly used as probes for pharmacokinetic interactions. The effects of dolutegravir on the exposure of coadministered drugs are summarized in Table 8 and the effects of coadministered drugs on the exposure of dolutegravir are summarized in Table 9.

Dosing or regimen recommendations as a result of established and other potentially significant drug-drug interactions with dolutegravir are provided in Table 3 *[see Drug Interactions (7.3)]*.

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

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug with/without Dolutegravir No Effect = 1.00		
			C_{max}	AUC	C_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)
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)
Metformin 500 mg twice daily	50 mg once daily	15[a]	1.66 (1.53 to 1.81)	1.79 (1.65 to 1.93)	_
Metformin 500 mg twice daily	50 mg twice daily	15[a]	2.11 (1.91 to 2.33)	2.45 (2.25 to 2.66)	_
Methadone 16 to 150 mg	50 mg twice daily	11	1.00 (0.94 to 1.06)	0.98 (0.91 to 1.06)	0.99 (0.91 to 1.07)
Midazolam 3 mg	25 mg once daily	10	_	0.95 (0.79 to 1.15)	_
Norelgestromin 0.25 mg	50 mg twice daily	15	0.89 (0.82 to 0.97)	0.98 (0.91 to 1.04)	0.93 (0.85 to 1.03)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.10 (0.99 to 1.22)	1.06 (0.98 to 1.16)	1.21 (1.07 to 1.38)
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)

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

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

Coadministered Drug(s) and Dose(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)
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)

Boceprevir 800 mg every 8 hours	50 mg once daily	13	1.05 (0.96 to 1.15)	1.07 (0.95 to 1.20)	1.08 (0.91 to 1.28)
Calcium carbonate 1200 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 1200 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 1200 mg 2 h after dolutegravir	50 mg single dose	11	1.00 (0.78 to 1.29)	0.94 (0.72 to 1.23)	0.90 (0.68 to 1.19)
Carbamazepine 300 mg twice daily	50 mg once daily	16[c]	0.67 (0.61 to 0.73)	0.51 (0.48 to 0.55)	0.27 (0.24 to 0.31)
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[a] 600 mg once daily	50 mg twice daily	11	0.57 (0.49 to 0.65)	0.46 (0.38 to 0.55)	0.28 (0.23 to 0.34)
Rifampin[b] 600 mg once daily	50 mg twice daily	11	1.18 (1.03 to 1.37)	1.33 (1.15 to 1.53)	1.22 (1.01 to 1.48)
Rifabutin 300 mg once daily	50 mg once daily	9	1.16 (0.98 to 1.37)	0.95 (0.82 to 1.10)	0.70 (0.57 to 0.87)

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

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

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

Emtricitabine and Tenofovir Alafenamide: The effects of coadministered drugs on the exposure of TAF are shown in Table 10 and the effects of emtricitabine and tenofovir alafenamide or its components on the exposure of coadministered drugs are shown in Table 11 [these studies were conducted with fixed-dose emtricitabine and tenofovir alafenamide or the components of fixed-

dose emtricitabine and tenofovir alafenamide (FTC or TAF) administered alone]. For information regarding clinical recommendations, *see Drug Interactions (7).*

Table 10. Drug Interactions: Changes in TAF Pharmacokinetic Parameters in the Presence of Coadministered Drug(s)[a]

Coadministered Drug	Coadministered Drug(s) Dosage (once daily) (mg)	Tenofovir Alafenamide Dosage (once daily) (mg)	N	Mean Ratio of TAF PK Parameters (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[b]	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
Efavirenz	600	40[b]	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[c]	19	1.00 (0.86, 1.16)	0.96 (0.89, 1.03)	NC

NC = Not Calculated

[a] All interaction studies conducted in healthy volunteers.

[b] Study conducted with emtricitabine and tenofovir alafenamide (FTC/TAF).

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

Table 11. Drug Interactions: Changes in PK Parameters for Coadministered Drug in the Presence of Emtricitabine and Tenofovir Alafenamide or the Individual Components[a]

Coadministered Drug	Coadministered Drug(s) 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[b]	11	1.02 (0.96, 1.09)	0.99 (0.92, 1.07)	0.97 (0.82, 1.15)
Darunavir	800 + 100	10	10	0.99	1.01	1.13

	ritonavir			(0.91, 1.08)	(0.96, 1.06)	(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[c]	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 (dosed as a single dose)	10[d]	19	1.14 (0.94, 1.38)	0.93 (0.77, 1.13)	NC

NC = Not Calculated

[a] All interaction studies conducted in healthy volunteers.

[b] Study conducted with emtricitabine and tenofovir alafenamide (FTC/TAF).

[c] A sensitive CYP3A4 substrate.

[d] 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 IC_{50} values of 2.7 nM and 12.6 nM.

Emtricitabine: FTC, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5′-triphosphate is a weak inhibitor of mammalian DNA polymerases α, β, Ɛ, and mitochondrial DNA polymerase γ.

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 EC_{50} values of 0.5 nM (0.21 ng per mL) to 2.1 nM (0.85 ng per mL) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells. Dolutegravir exhibited antiviral activity against 13 clinically diverse clade B isolates with a mean EC_{50} value of 0.52 nM in a viral integrase susceptibility assay using the integrase coding region from clinical isolates. Dolutegravir demonstrated antiviral activity in cell culture against a panel of HIV-1 clinical isolates (3 in each group of M clades A, B, C, D, E, F, and G, and 3 in group O) with EC_{50} values ranging from 0.02 nM to 2.14 nM for HIV-1. Dolutegravir EC_{50} values against 3 HIV-2 clinical isolates in PBMC assays ranged from 0.09 nM to 0.61 nM.

Emtricitabine: The antiviral activity of FTC against laboratory and clinical isolates of HIV-1 was assessed in T lymphoblastoid cell lines, the MAGI-CCR5 cell line, and primary peripheral blood mononuclear cells. The EC_{50} values for FTC were in the range of 0.0013 to 0.64 micromolar. FTC displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007 to 0.075 micromolar) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.007 to 1.5 micromolar).

In a study of FTC with a broad panel of representatives from the major classes of approved anti-HIV agents (NRTIs, non-nucleoside reverse transcriptase inhibitors [NNRTIs], integrase strand transfer inhibitors [INSTIs], and PIs) no antagonism was observed for these combinations.

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 EC_{50} 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 (EC_{50} values ranged from 0.10 to 12.0 nM) and strain specific activity against HIV-2 (EC_{50} 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: *Dolutegravir:* The antiviral activity of dolutegravir was not antagonistic when combined with the INSTI, raltegravir; non-nucleoside reverse transcriptase inhibitors (NNRTIs), efavirenz or nevirapine; the nucleoside reverse transcriptase inhibitors (NRTIs), abacavir or stavudine; the protease inhibitors (PIs), amprenavir or lopinavir; the CCR5 co-receptor antagonist, maraviroc; or the fusion inhibitor, enfuvirtide. Dolutegravir antiviral activity was not antagonistic when combined with the HBV reverse transcriptase inhibitor, adefovir, or inhibited by the antiviral, ribavirin.

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

Q148R or Q148H substitutions selected for additional substitutions in integrase that conferred decreased susceptibility to dolutegravir (fold-change increase of 13 to 46). The additional integrase substitutions included T97A, E138K, G140S, and M154I. Passage of mutant viruses containing both G140S and Q148H selected for L74M, E92Q, and N155H.
Emtricitabine: HIV-1 isolates with reduced susceptibility to FTC were selected in cell culture and in subjects treated with FTC. Reduced susceptibility to FTC was associated with M184V or I substitutions in HIV-1 RT.

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.

In Clinical Trials: Emtricitabine and Tenofovir Alafenamide: The resistance profile of emtricitabine and tenofovir alafenamide 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.

One subject was identified with emergent resistance to FTC or TAF (M184M/I) out of 4 virologic failure subjects in a clinical study of virologically-suppressed subjects who switched from a regimen containing FTC + TDF to FTC + TAF with EVG + COBI (N = 799).

Cross-Resistance: *Dolutegravir:* The single integrase strand transfer inhibitor-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.

Emtricitabine: FTC-resistant viruses with the M184V or I substitution were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir, and zidovudine.

Viruses harboring substitutions conferring reduced susceptibility to stavudine and zidovudine-thymidine analog substitutions (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to FTC. HIV-1 containing the K103N substitution or other substitutions associated with resistance to NNRTIs was susceptible to FTC.

Tenofovir Alafenamide: 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

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.

Emtricitabine: In long-term carcinogenicity studies of FTC, no drug-related increases in tumor incidence were found in mice at doses up to 750 mg per kg per day (23 times the human systemic exposure at the recommended dose of 200 mg per day in emtricitabine and tenofovir alafenamide) or in rats at doses up to 600 mg per kg per day (28 times the human systemic exposure at the recommended dose in emtricitabine and tenofovir alafenamide).

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

FTC did not affect fertility in male rats at approximately 140 times or in male and female mice at approximately 60 times higher exposures (AUC) than in humans given the recommended 200 mg daily dosage in emtricitabine and tenofovir alafenamide. Fertility was normal in the offspring of mice exposed daily from before birth (*in utero*) through sexual maturity at daily exposures (AUC) of approximately 60 times higher than human exposures at the recommended 200 mg daily dosage in emtricitabine and tenofovir alafenamide.

Tenofovir Alafenamide: 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 emtricitabine and tenofovir alafenamide. At the high dose in female mice, liver adenomas were increased at tenofovir exposures approximately 10 times (300

mg TDF) and 167 times (emtricitabine and tenofovir alafenamide) the exposure observed in humans. In rats, the study was negative for carcinogenic findings.

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

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

***Tenofovir Alafenamide*:** Minimal to slight infiltration of mononuclear cells in the posterior uvea was observed in dogs with similar severity after 3 and 9 month administration of TAF; reversibility was seen after a 3 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 in emtricitabine and tenofovir alafenamide.

14 CLINICAL STUDIES

14.1 Adult Subjects

Dolutegravir: *Treatment-Naïve Subjects:* In SPRING-2, 822 subjects were randomized and received at least 1 dose of either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily, both in combination with fixed-dose dual NRTI treatment (either abacavir sulfate and lamivudine [EPZICOM] or emtricitabine/tenofovir DF [TRUVADA]). There were 808 subjects included in the efficacy and safety analyses. At baseline, the median age of subjects was 36 years, 13% female, 15% non-white, 11% had hepatitis B and/or C virus co-infection, 2% were CDC Class C (AIDS), 28% had HIV-1 RNA greater than 100,000 copies per mL, 48% had CD4+ cell count less than 350 cells per mm^3, and 39% received fixed-dose abacavir sulfate and lamivudine (EPZICOM); these characteristics were similar between treatment groups.

Outcomes for SPRING-2 (Week 96 analysis) are found in Table 12.

Table 12. Virologic Outcomes of Randomized Treatment in SPRING-2 at Week 96

	SPRING-2 Week 96	
	Dolutegravir 50 mg Once Daily + 2 NRTIs (n = 403)	**Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)**
HIV-1 RNA < 50 copies/mL	82%	78%
Treatment difference[a]	4.9% (95% CI: -0.6%, 10.3%)[d]	
Virologic nonresponse	5%	10%
Data in window not < 50 copies/mL	1%	3%
Discontinued for lack of efficacy	2%	3%

Discontinued for other reasons while not suppressed	< 1%	3%
Change in ART regimen	< 1%	< 1%
No virologic data Reasons	12%	12%
Discontinued study/study drug due to adverse event or death[b]	2%	2%
Discontinued study/study drug for other reasons[c]	8%	9%
Missing data during window but on study	2%	< 1%
Proportion (%) of Subjects with HIV-1 RNA < 50 copies/mL by Baseline Category		
Plasma viral load (copies/mL)		
≤ 100,000	84%	83%
> 100,000	79%	63%
Gender		
Male	84%	79%
Female	70%	68%
Race		
White	83%	78%
African-American/African Heritage/Other	77%	75%

[a] Adjusted for pre-specified stratification factors.

[b] Includes subjects who discontinued due to an adverse event or death at any time point if this resulted in no virologic data on treatment during the analysis window.

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

[d] The primary endpoint was assessed at Week 48 and the virologic success rate was 88% in the group receiving dolutegravir and 86% in the raltegravir group, with a treatment difference of 2.6% and 95% CI of (-1.9%, 7.2%).

SPRING-2: Virologic outcomes were also comparable across baseline characteristics including CD4+ cell count, age, and use of EPZICOM or TRUVADA as NRTI background regimen. The median change in CD4+ cell counts from baseline was 276 cells per mm^3 in the group receiving dolutegravir and 264 cells per mm^3 for the raltegravir group at 96 weeks.

There was no treatment-emergent resistance to dolutegravir or to the NRTI background.

Emtricitabine and Tenofovir Alafenamide: In trials of FTC + TAF with EVG + COBI in HIV-1-infected adults as initial therapy in those with no antiretroviral treatment history (N = 866) 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), 92% and 96% of patients in the two populations, respectively, had HIV-1 RNA less than 50 copies per mL at Week 48.

In a trial in 248 HIV-1-infected adult patients with estimated creatinine clearance greater than 30 mL per minute but less than 70 mL per minute, 95% (235/248) of the combined population of treatment-naïve subjects (N = 6) began on FTC + TAF with EVG + COBI and those previously virologically-suppressed on other regimens (N = 242) and switched to FTC + TAF with EVG + COBI had HIV-1 RNA less than 50 copies per mL at Week 24.

14.2 Pediatric Subjects

Dolutegravir: Dolutegravir, in combination with other antiretroviral drugs was evaluated in treatment-experienced, INSTI-naïve, HIV-1-infected subjects aged 6 to less than 18years 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

The 50 mg/200 mg/25 mg tablets are white to off-white, film-coated, oval, unscored tablets debossed with **M** on one side of the tablet and **TD1** on the other side. They are available as follows:

NDC 65015-293-14
bottles of 30 tablets with desiccant, induction seal and non-child-resistant cap

NDC 65015-293-18
bottles of 90 tablets with desiccant, induction seal and non-child-resistant cap

Store below 30°C (86°F).

Protect from moisture.

Dispense only in original container.

17 PATIENT COUNSELING INFORMATION

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

Post-Treatment Acute Exacerbation of Hepatitis B in Patients with HBV Coinfection: Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued products containing TDF, and may likewise occur with discontinuation of dolutegravir, emtricitabine and tenofovir alafenamide tablets *[see Warnings and Precautions (5.4)]*. Advise the patient to not discontinue dolutegravir, emtricitabine and tenofovir alafenamide tablets without first informing their healthcare provider.

Drug Interactions: Dolutegravir, emtricitabine and tenofovir alafenamide tablets may interact with other 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, emtricitabine 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, one component of dolutegravir, emtricitabine and tenofovir alafenamide tablets *[see Warnings and Precautions (5.1)]*. Advise patients that laboratory monitoring for hepatoxicity during therapy with dolutegravir, emtricitabine and tenofovir alafenamide tablets is recommended, especially for patients with liver disease, such as hepatitis B or C.

Immune Reconstitution Syndrome: Advise patients to inform their healthcare provider immediately of any signs or symptoms of infection, as in some patients with advanced HIV infection (AIDS), as inflammation from previous infections may occur soon after combination antiretroviral therapy, including when dolutegravir, emtricitabine and tenofovir alafenamide tablets are started *[see Warnings and Precautions (5.5)]*.

New Onset or Worsening Renal Impairment: Advise patients to avoid taking dolutegravir, emtricitabine and tenofovir alafenamide tablets with concurrent or recent use of nephrotoxic agents. Renal impairment, including cases of acute renal failure, has been reported in association with the use of tenofovir prodrugs *[see Warnings and Precautions (5.6)]*.

Lactic Acidosis and Severe Hepatomegaly: Inform patients that some HIV medicines, including dolutegravir, emtricitabine and tenofovir alafenamide tablets, can cause a rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly) *[see Warnings and Precautions (5.7)]*.

Lactation: Instruct women 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 Dosage: Instruct patients that if they miss a dose of dolutegravir, emtricitabine 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.

Inform patients that it is important to take dolutegravir, emtricitabine and tenofovir alafenamide tablets on a regular dosing schedule with or without food and to avoid missing doses as it can result in development of resistance *[see Dosage and Administration (2.2)]*.

Storage: Instruct patients to store dolutegravir, emtricitabine and tenofovir alafenamide tablets in the original package, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant.

Patient Information

Dolutegravir, Emtricitabine and Tenofovir Alafenamide Tablets

(doe″ loo teg′ ra vir em′′ trye sye′ ta been ten of′ oh vir al′′ a fen′ a mide)

Important: Ask your healthcare provider or pharmacist about medicines that should not be taken with dolutegravir, emtricitabine and tenofovir alafenamide tablets. For more information, see the section **"What should I tell my healthcare provider before taking dolutegravir, emtricitabine and tenofovir alafenamide tablets?"**

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

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

- **Worsening of Hepatitis B virus infection. Dolutegravir, emtricitabine and tenofovir alafenamide tablets are not for use to treat chronic hepatitis B virus (HBV) infection. If you have hepatitis B virus (HBV) infection and take dolutegravir, emtricitabine and tenofovir alafenamide tablets, your HBV may get worse (flare-up) if you stop taking dolutegravir, emtricitabine and tenofovir alafenamide tablets. A "flare-up" is when your HBV infection suddenly returns in a worse way than before.**
  - It is not known if dolutegravir, emtricitabine and tenofovir alafenamide tablets are safe and effective in people who have both HIV-1 and HBV infection.
  - Do not run out of dolutegravir, emtricitabine and tenofovir alafenamide tablets. Refill your prescription or talk to your healthcare provider before your dolutegravir, emtricitabine and tenofovir alafenamide tablets are all gone.
  - Do not stop taking dolutegravir, emtricitabine and tenofovir alafenamide tablets without first talking to your healthcare provider.
  - If you stop taking dolutegravir, emtricitabine and tenofovir alafenamide tablets, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your HBV infection. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking dolutegravir, emtricitabine and tenofovir alafenamide tablets.
- **Allergic reactions**. Call your healthcare provider right away if you develop a rash with dolutegravir, emtricitabine and tenofovir alafenamide tablets. **Stop taking dolutegravir, emtricitabine 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

- **Liver problems.** People with a history of hepatitis B or C virus may have an increased risk of developing new or worsening changes in certain liver tests during treatment with dolutegravir, emtricitabine and tenofovir alafenamide tablets. Liver problems, including liver failure, have also happened in people without a history of liver disease or other risk factors. Your healthcare provider may do blood tests to check your liver. Also, serious liver problems can happen in people who take dolutegravir, emtricitabine and tenofovir alafenamide tablets. In some cases, these serious liver problems can lead to death. Your liver may become large (hepatomegaly) and you may develop fat in your liver (steatosis). **Call your healthcare provider right away if you develop any of the following signs or symptoms of liver problems**:
  - your skin or the white part of your eyes turns yellow (jaundice)
  - dark or "tea-colored" urine
  - light-colored stools (bowel movements)
  - nausea or vomiting
  - loss of appetite
  - pain, aching, or tenderness on the right side of your stomach area

For more information about side effects, see the section "What are the possible side effects of dolutegravir, emtricitabine and tenofovir alefenamide tablets?

What are dolutegravir, emtricitabine and tenofovir alafenamide tablets?
Dolutegravir, emtricitabine and tenofovir alafenamide tablets are a prescription medicine that is used alone as a complete regimen to treat Human Immunodeficiency Virus (HIV-1) infection in adults and children who weigh at least 40 kg (88 pounds).

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

Dolutegravir, emtricitabine and tenofovir alafenamide tablets are **not** for use to help reduce the risk of getting HIV-1 infection by sexual contact in adults at high risk.

Dolutegravir, emtricitabine and tenofovir alafenamide tablets contain 3 prescription medicines, dolutegravir, emtricitabine and tenofovir alafenamide.

It is not known if dolutegravir, emtricitabine and tenofovir alafenamide tablets are safe and effective in children who weigh less than 40 kg (88 pounds) or in children who have received certain types of medicine for HIV-1 infection.

Who should not take dolutegravir, emtricitabine and tenofovir alafenamide tablets?
Do not take dolutegravir, emtricitabine and tenofovir alafenamide tablets if you:

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

threatening.

What should I tell my healthcare provider before taking dolutegravir, emtricitabine and tenofovir alafenamide tablets?

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

- have ever had an allergic reaction to dolutegravir, emtricitabine and tenofovir alafenamide tablets.
- have or have had liver problems, including hepatitis B or C virus infection.
- have kidney problems
- are pregnant or plan to become pregnant. It is not known if dolutegravir, emtricitabine and tenofovir alafenamide tablets will harm your unborn baby. Tell your healthcare provider if you become pregnant during treatment with dolutegravir, emtricitabine and tenofovir alafenamide tablets.
- are breastfeeding or plan to breastfeed. **Do not breastfeed if you take dolutegravir, emtricitabine and tenofovir alafenamide tablets.**
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  - At least one of the medicines in dolutegravir, emtricitabine and tenofovir alafenamide tablets can pass to your baby in your breast milk. It is not known if the other medicines in dolutegravir, emtricitabine and tenofovir alafenamide tablets can pass into your breast milk.

  Talk with your healthcare provider about the best way to feed your baby during treatment with dolutegravir, emtricitabine and tenofovir alafenamide tablets.

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

Some medicines interact with dolutegravir, emtricitabine and tenofovir alafenamide tablets. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with dolutegravir, emtricitabine 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, emtricitabine and tenofovir alafenamide tablets with other medicines.

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

- **Take dolutegravir, emtricitabine and tenofovir alafenamide tablets exactly as your healthcare provider tells you to take them.**
- Do not miss a dose of dolutegravir, emtricitabine and tenofovir alafenamide tablets.
- If you miss a dose of dolutegravir, emtricitabine and tenofovir alafenamide tablets, take it as soon as you remember. Do not take 2 doses at the same time or take more than your prescribed dose.
- Do not change your dose or stop taking dolutegravir, emtricitabine and tenofovir alafenamide tablets without first talking with your healthcare provider. Stay under a healthcare provider's care during treatment with dolutegravir, emtricitabine and tenofovir alafenamide tablets.

- Take dolutegravir, emtricitabine and tenofovir alafenamide tablets 1 time each day with or without food.
- If you take antacids, laxatives, or other medicines that contain aluminum, magnesium, or buffered medicines, dolutegravir, emtricitabine 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, emtricitabine and tenofovir alafenamide tablets:
  - If you take dolutegravir, emtricitabine and tenofovir alafenamide tablets with food, you may take these supplements at the same time that you take dolutegravir, emtricitabine and tenofovir alafenamide tablets.
  - If you do not take dolutegravir, emtricitabine and tenofovir alafenamide tablets with food, take dolutegravir, emtricitabine and tenofovir alafenamide tablets at least 2 hours before or 6 hours after you take these supplements.
- Do not run out of dolutegravir, emtricitabine 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, emtricitabine and tenofovir alafenamide tablets, call your healthcare provider or go to the nearest hospital emergency room right away.

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

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

- **See "What is the most important information I should know about dolutegravir, emtricitabine and tenofovir alafenamide tablets?"**
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having any new symptoms after you start taking dolutegravir, emtricitabine and tenofovir alafenamide tablets.
- **New or worse kidney problems, including kidney failure.** Your healthcare provider should do blood and urine tests to check your kidneys before you start and during treatment with dolutegravir, emtricitabine and tenofovir alafenamide tablets. Your healthcare provider may tell you to stop taking dolutegravir, emtricitabine and tenofovir alafenamide tablets if you develop new or worse kidney problems.
- **Too much lactic acid in your blood (lactic acidosis).** Too much lactic acid is a serious but rare medical emergency that can lead to death. Tell your healthcare provider right away if you get these symptoms: weakness or being more tired than usual, unusual muscle pain, being short of breath or fast breathing, stomach pain with nausea and vomiting, cold or blue hands and feet, feel dizzy or lightheaded, or a fast or abnormal heartbeat.
- **The most common side effects of dolutegravir, emtricitabine and tenofovir alafenamide tablets include:**
  - trouble sleeping
  - nausea
  - tiredness
  - headache

These are not all the possible side effects of dolutegravir, emtricitabine and tenofovir alafenamide tablets. For more information, ask your healthcare provider or pharmacist.

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

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

- Store dolutegravir, emtricitabine and tenofovir alafenamide tablets below 30°C (86°F).
- Keep dolutegravir, emtricitabine and tenofovir alafenamide tablets in their original container.
- Keep the container tightly closed.
- The bottle of dolutegravir, emtricitabine and tenofovir alafenamide tablets contains a desiccant packet to help keep your medicine dry (protect it from moisture). Do not remove the desiccant packet from the bottle.

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

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

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use dolutegravir, emtricitabine and tenofovir alafenamide tablets for a condition for which they were not prescribed. Do not give dolutegravir, emtricitabine 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 healthcare provider or pharmacist for information about dolutegravir, emtricitabine and tenofovir alafenamide tablets that is written for health professionals. For more information, call Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX).

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

Active ingredient: dolutegravir, emtricitabine 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.

Mylan®

Manufactured by:
Mylan Laboratories Limited
Hyderabad—500 096, India

Each film-coated tablet contains:

Dolutegravir Sodium 52.6 mg (equivalent to Dolutegravir)	50 mg
Emtricitabine	200 mg
Tenofovir Alafenamide Fumarate 28.04 mg (equivalent to Tenofovir Alafenamide)	25 mg

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 65015-293-14

Dolutegravir, Emtricitabine and Tenofovir Alafenamide Tablets

50 mg/200 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, Emtricitabine and Tenofovir Alafenamide Tablets

30 Tablets **Rx only**

Mylan.com

Mylan

N 3 65015 29314 5

75060468

Dispense only in original container.
Keep container tightly closed.
Code No.: MP/DRUGS/25/1/2014

VARNISH FREE AREA

Prompt "LOT" & "EXP"
will be printed together
with Variable Data Coading.

Each film-coated tablet contains:

Dolutegravir Sodium 52.6 mg (equivalent to Dolutegravir)	50 mg
Emtricitabine	200 mg
Tenofovir Alafenamide Fumarate 28.04 mg (equivalent to Tenofovir Alafenamide)	25 mg

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 65015-293-18

Dolutegravir, Emtricitabine and Tenofovir Alafenamide Tablets

50 mg/200 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, Emtricitabine and Tenofovir Alafenamide Tablets

90 Tablets **Rx only**

Mylan.com

Mylan

N 3 65015 29318 3

75060469

Dispense only in original container.
Keep container tightly closed.
Code No.: MP/DRUGS/25/1/2014

VARNISH FREE AREA

Prompt “LOT” & “EXP”
will be printed together
with Variable Data Coading.