Table of Contents

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.

Severe acute exacerbations of hepatitis B (HBV) have been reported in HBV-infected patients who have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of dolutegravir, emtricitabine and tenofovir alafenamide tablets. Hepatic function should be monitored closely in these individuals. If appropriate, anti-hepatitis B therapy may be warranted. (5.1)

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

Dolutegravir, emtricitabine and tenofovir alafenamide tablets, 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)), is indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 25 kg. (1)

Limitations of Use:

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

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

- Pregnancy Testing: Pregnancy testing is recommended before initiation of dolutegravir in adolescents and adults of childbearing potential. (2.1, 5.3, 8.1, 8.3)
- Testing: Prior to or when initiating dolutegravir, emtricitabine and tenofovir alafenamide tablets, test for hepatitis B virus infection. Prior to or when initiating dolutegravir, emtricitabine and tenofovir alafenamide tablets, and during treatment, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. (2.1)
- Recommended dosage: One tablet taken orally once daily on an empty stomach in adults and pediatric patients weighing at least 25 kg. (2.2)
- Renal impairment: Dolutegravir, emtricitabine and tenofovir alafenamide tablets is 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 emtricitabine and 25 mg of tenofovir alafenamide (3)

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

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

---------- WARNINGS AND PRECAUTIONS ----------

- Hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury, have been reported. Discontinue dolutegravir, 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)
- Hepatotoxicity has been reported in patients receiving dolutegravir-containing regimens. Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations. Monitoring for hepatotoxicity is recommended. (5.3)
- Embryo-fetal toxicity may occur when used at the time of conception and in early pregnancy. Assess the risks and benefits of dolutegravir, emtricitabine and tenofovir alafenamide tablets and discuss with the patient to determine if alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester due to the risk of neural tube defects. Adolescents and adults of childbearing potential should be counseled on the consistent use of effective contraception. (2.1, 5.4, 8.1, 8.3)
- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. (5.6)
- New onset or worsening renal impairment: Assess creatinine clearance, estimated creatinine clearance, urine glucose, and urine protein when initiating dolutegravir, emtricitabine and tenofovir alafenamide tablets and during use on a clinically appropriate schedule in all patients. Also assess serum phosphorus in patients with chronic kidney disease. (5.7)
- Lactic acidosis/severe hepatomegaly with steatosis: Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.8)

----------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, headache and diarrhea. (6.1)
- Emtricitabine and Tenofovir Alafenamide: In HIV-1 infected patients, the most common adverse reaction (incidence greater than or equal to 10%, all grades) was nausea. (6.1)

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

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

Coadministration of dolutegravir, emtricitabine and tenofovir alafenamide tablets with other drugs can alter the concentration of other drugs and other drugs may alter the concentration 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: Assess the risks and benefits of dolutegravir, emtricitabine and tenofovir alafenamide tablets and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester or if pregnancy is confirmed in the first trimester due to the risk of neural tube defects. (2.1, 5.4, 8.1, 8.3)
- Females and males of reproductive potential: Pregnancy testing and contraception are recommended in adolescents and adults of childbearing potential. Patients should be counseled on the consistent use of effective contraception. (8.1, 8.3)
- Hepatic impairment: Dolutegravir, emtricitabine and tenofovir alafenamide tablets is not recommended in patients with severe hepatic impairment (Child-Pugh Score C). (8.7)

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

Revised: 01/2024

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

Severe acute exacerbations of hepatitis B virus (HBV) have been reported in HBV-infected patients who have discontinued products containing emtricitabine (FTC) and/or 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 infected with HBV and discontinue dolutegravir, emtricitabine and tenofovir alafenamide tablets. If appropriate, anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

Dolutegravir, emtricitabine and tenofovir alafenamide tablets is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients weighing at least 25 kg.

Limitations of Use:

- Dolutegravir, emtricitabine and tenofovir alafenamide tablets alone is not recommended in patients with resistance-associated integrase substitutions or clinically suspected integrase strand transfer inhibitor resistance because the dose of dolutegravir in dolutegravir, emtricitabine and tenofovir alafenamide tablets is insufficient in these subpopulations. See the dolutegravir prescribing information.

2 DOSAGE AND ADMINISTRATION

2.1 Pregnancy Testing before Initiation

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

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

Prior to initiation and during treatment with dolutegravir, emtricitabine and tenofovir alafenamide tablets on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus.

2.2 Recommended Dosage in Adults and Pediatric Patients Weighing at Least 25 kg (55 lbs)

Dolutegravir, emtricitabine and tenofovir alafenamide tablets is 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 tablets is one tablet taken orally once daily on an empty stomach in adults and pediatric patients weighing at least 25 kg (55 lbs) and creatinine clearance greater than or equal to 30 mL per minute.

The safety and effectiveness of dolutegravir, emtricitabine and tenofovir alafenamide tablets coadministered with an HIV-1 protease inhibitor that is administered with either ritonavir or cobicistat have not been established in pediatric subjects weighing less than 35 kg.

2.3 Not Recommended in Patients with Severe Renal Impairment

Dolutegravir, emtricitabine and tenofovir alafenamide tablets is not recommended in patients with estimated creatinine clearance below 30 mL per minute *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.6)]*.

2.4 Not Recommended in Patients with Severe Hepatic Impairment

Dolutegravir, emtricitabine and tenofovir alafenamide tablets is not recommended in patients with severe hepatic impairment (Child-Pugh Score C) *[see Use in Specific Populations (8.7)]*.

3 DOSAGE FORMS AND STRENGTHS

Dolutegravir, Emtricitabine and Tenofovir Alafenamide Tablets, 50 mg/200 mg/25 mg are white to off white, capsule shaped film coated tablets, debossed with 'T47' on one side and ‘H’ on other side. Each tablet contains 50 mg of Dolutegravir (equivalent to 52.6 mg of dolutegravir sodium), 200 mg of Emtricitabine, and 25 mg of Tenofovir alafenamide (equivalent to 28.043 mg of tenofovir alafenamide hemifumarate).

4 CONTRAINDICATIONS

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

- with previous hypersensitivity reaction to dolutegravir or any of the components of this product *[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 with comcomitant use of dolutegravir *[see Drug Interactions (7)]*.

5 WARNINGS AND PRECAUTIONS

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

All patients should be tested for the presence of chronic hepatitis B virus (HBV) before or when initiating dolutegravir, emtricitabine and tenofovir alafenamide tablets *[see Dosage and Administration (2.1)]*.

Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in HBV-infected patients who have discontinued products containing FTC and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of dolutegravir, emtricitabine and tenofovir alafenamide tablets. Patients infected with 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. HBV-uninfected patients should be offered vaccination.

5.2 Hypersensitivity Reactions

Hypersensitivity reactions have been reported with the use of dolutegravir, a component of dolutegravir, emtricitabine and tenofovir alafenamide tablets, and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. The events were reported in less than 1% of subjects receiving dolutegravir in Phase 3 clinical trials. Discontinue dolutegravir, 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 is contraindicated in patients who have experienced a previous hypersensitivity reaction to dolutegravir or any of the components of this product.

5.3 Hepatotoxicity

Hepatic adverse events have been reported in patients receiving a dolutegravir-containing regimen. Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of dolutegravir, 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.

5.4 Embryo-Fetal Toxicity

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

Pregnancy testing is recommended before initiation of dolutegravir, emtricitabine and tenofovir alafenamide tablets in adolescents and adults of childbearing potential [see Dosage and Administration (2.1)].

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

Dolutegravir, emtricitabine and tenofovir alafenamide tablets may be considered during the second and third trimesters of pregnancy if the expected benefit justifies the potential risk to the pregnant woman and the fetus.

5.5 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 4 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with dolutegravir, 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.

5.6 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.

5.7 New Onset or Worsening Renal Impairment

Postmarketing cases of renal impairment, including acute renal failure, proximal renal tubulopathy (PRT), and Fanconi syndrome have been reported with TAF-containing products; while most of these cases were characterized by potential confounders that may have contributed to the reported renal events, it is also possible these factors may have predisposed patients to tenofovir-related adverse events *[see Adverse Reactions (6.1, 6.2)]*.

Dolutegravir, emtricitabine and tenofovir alafenamide tablets is 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.

Prior to or when initiating dolutegravir, emtricitabine and tenofovir alafenamide tablets, and during treatment with dolutegravir, emtricitabine and tenofovir alafenamide tablets on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. Discontinue dolutegravir, emtricitabine and tenofovir alafenamide tablets in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

5.8 Lactic Acidosis and Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including FTC, 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:

- Severe Acute Exacerbation of Hepatitis B *[see Boxed Warning and Warnings and Precautions (5.1)]*.
- Hypersensitivity reactions *[see Warnings and Precautions (5.2)]*.
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*.
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.6)]*.
- New Onset or Worsening Renal Impairment *[see Warnings and Precautions (5.7)]*.
- Lactic Acidosis and Severe Hepatomegaly with Steatosis *[see Warnings and Precautions (5.8)]*.

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 to 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.

Clinical Trials Experience in Adult Subjects

Dolutegravir:

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 or fixed-dose emtricitabine/tenofovir DF. 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 once daily or fixed-dose efavirenz/emtricitabine/tenofovir DF 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 and 14% in subjects receiving fixed-dose efavirenz/emtricitabine/tenofovir DF once daily.

Treatment-emergent adverse reactions (ARs) of moderate to severe intensity observed in at least 2% of subjects in the dolutegravir treatment arm 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, respectively. These events were not treatment limiting.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects: In an international, multicenter, double-blind trial (ING111762, SAILING), 719 HIV-1-infected, antiretroviral treatment-experienced adults were randomized and received either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily with investigator-selected background regimen consisting of up to 2 agents, including at least one fully active agent. At 48 weeks, the rates of adverse events leading to discontinuation were 3% in subjects receiving dolutegravir 50 mg once daily + background regimen and 4% in subjects receiving raltegravir 400 mg twice daily + background regimen.

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

Less Common Adverse Reactions Observed in Treatment-Naïve and Treatment-Experienced Trials: The following 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. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 1. Selected Laboratory Abnormalities (Grades 2 to 4) in Treatment-Naïve Subjects in SPRING-2 (Week 96 Analysis) and SINGLE Trials (Week 144 Analysis)

Laboratory Parameter Preferred Term	SPRING-2		SINGLE	
	Dolutegravir 50 mg Once Daily + 2 NRTIs (n = 403)	Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)	Dolutegravir 50 mg + Abacavir Sulfate and Lamivudine Once Daily (n = 414)	Efavirenz, Emtricitabine and Tenofovir DF Once Daily (n = 419)
ALT				
Grade 2 (>2.5-5.0 x ULN)	4%	4%	3%	5%
Grade 3 to 4 (>5.0 x ULN)	2%	2%	1%	<1%
AST				
Grade 2 (>2.5-5.0 x ULN)	5%	3%	3%	4%
Grade 3 to 4 (>5.0 x ULN)	3%	2%	1%	3%
Total Bilirubin				
Grade 2 (1.6-2.5 x ULN)	3%	2%	<1%	<1%
Grade 3 to 4 (>2.5 x ULN)	<1%	<1%	<1%	<1%
Creatine kinase				
Grade 2 (6.0-9.9 x ULN)	2%	5%	5%	3%
Grade 3 to 4 (≥10.0 x ULN)	7%	4%	7%	8%
Hyperglycemia				
Grade 2 (126-250 mg/dL)	6%	6%	9%	6%
Grade 3 (>250 mg/dL)	<1%	2%	2%	<1%
Lipase				
Grade 2 (>1.5-3.0 x ULN)	7%	7%	11%	11%
Grade 3 to 4 (>3.0 x ULN)	2%	5%	5%	4%
Total neutrophils				
Grade 2 (0.75-0.99 x 10^9)	4%	3%	4%	5%
Grade 3 to 4 (<0.75 x 10^9)	2%	2%	3%	3%

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

Table 2. Mean Change from Baseline in Fasted Lipid Values in Treatment-Naïve Subjects in SPRING-2 (Week 96 Analysis[a]) and SINGLE Trials (Week 144 Analysis[a])

Laboratory Parameter Preferred Term	SPRING-2		SINGLE	
	Dolutegravir 50 mg Once Daily + 2 NRTIs (n = 403)	Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)	Dolutegravir 50 mg + Abacavir Sulfate and Lamivudine Once Daily (n = 414)	Efavirenz, Emtricitabine and Tenofovir DF Once Daily (n = 419)
Cholesterol (mg/dL)	8.1	10.1	24.0	26.7
HDL cholesterol (mg/dL)	2.0	2.3	5.4	7.2
LDL cholesterol (mg/dL)	5.1	6.1	16.0	14.6
Triglycerides (mg/dL)	6.7	6.6	13.6	31.9

HDL = high density lipoprotein; LDL = low density lipoprotein.

[a]Subjects on lipid-lowering agents at baseline were excluded from these analyses (19 subjects in each arm in SPRING-2, and in SINGLE: dolutegravir + fixed-dose abacavir sulfate and lamivudine n = 30 and fixed-dose efavirenz/emtricitabine/tenofovir df

n = 27). Ninety-four subjects initiated a lipid-lowering agent post-baseline; their last fasted on-treatment values (prior to starting the agent) were used regardless of whether they discontinued the agent (SPRING-2: dolutegravir n = 9, raltegravir n = 13; SINGLE: dolutegravir + fixed-dose abacavir sulfate and lamivudine n = 36, fixed-dose efavirenz/emtricitabine/tenofovir df n = 36).

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects: Laboratory abnormalities observed in SAILING were generally similar compared with observations seen in the treatment-naïve (SPRING-2 and SINGLE) trials.

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 (5.3)]*.

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

FTC and TAF:

Adverse Reactions in Clinical Trials of FTC+TAF with Elvitegravir (EVG) plus Cobicistat (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 at Week 48; median UPCR was 61 mg per gram at baseline and 46 mg per gram at Week 48. Across these trials, 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 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. FTC+TAF with EVG+COBI was permanently discontinued due to worsening renal function in two of 80 (3%) subjects.

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.

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.

Clinical Trials Experience in Pediatric Subjects

Dolutegravir:

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

significant difference in dolutegravir exposure *[see Clinical Pharmacology (12.3)]*.

FTC and TAF:

The safety profile of FTC+TAF in pediatric subjects weighing at least 25 kg is informed by an open-label trial of antiretroviral treatment-naïve HIV-1 infected pediatric subjects between the ages of 12 to less than 18 years weighing at least 35 kg through 48 weeks (N=50; Cohort 1) and virologically-suppressed subjects between the ages of 6 to less than 12 years weighing at least 25 kg (N= 52; Cohort 2). Subjects received FTC+TAF with EVG+COBI through 48 weeks. With the exception of a decrease in the mean CD4+ cell count observed in cohort 2, the safety of this combination was similar to that in adults.

Bone Mineral Density Effects

Among the subjects in Cohort 1 *(treatment-naïve adolescents 12 to less than 18 years; at least 35 kg),* mean BMD increased from baseline to Week 48, +4.2% at the lumbar spine and +1.3% for the total body less head (TBLH). Mean changes from baseline BMD Z-scores were −0.07 for lumbar spine and −0.20 for TBLH at Week 48. One subject had significant (at least 4%) lumbar spine BMD loss at Week 48.

Among the subjects in Cohort 2 (*virologically-suppressed children (6 to less than 12 years of age and weighing at least 25 kg),* mean BMD increased from baseline to Week 48, +3.9% at the lumbar spine and +4.2% for TBLH. Mean changes from baseline BMD Z-scores were -0.24 for lumbar spine and -0.19 for TBLH at Week 48. Six subjects had significant (at least 4%) lumbar spine BMD loss at Week 48 and 2 subjects also had at least 4% TBLH BMD loss at Week 48.

Change from Baseline in CD4+ cell counts

Cohort 2: Virologically-suppressed children (6 to less than 12 years; at least 25 kg)

Cohort 2 evaluated pediatric subjects (N=52) who were virologically-suppressed and who switched from their antiretroviral regimen to FTC+TAF with EVG+COBI. Although all subjects had HIV-1 RNA < 50 copies/mL, there was a decrease from baseline in CD4+ cell count at Weeks 24 and 48. The mean baseline and mean change from baseline in CD4+ cell count and in CD4% from Week 2 to Week 48 are presented in Table 3. All subjects maintained their CD4+ cell counts above 400 cells/mm^3.

Table 3 Mean Change in CD4+ Count and CD4 Percentage from Baseline to Week 48 in Virologically-Suppressed Pediatric Patients from 6 to <12 Years Who Switched to FTC+TAF with EVG+COBI

	Baseline	Mean Change from Baseline					
		Week 2	Week 4	Week 12	Week 24	Week 32	Week 48
CD4+ Cell Count (cells/mm^3)	961(275.5)[a]	-117	-114	-112	-118	-62	-66
CD4%	38 (6.4)[a]	+0.3%	-0.1%	-0.8%	-0.8%	-1.0%	-0.6%

a. Mean (SD)

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.

Investigations

Weight increased.

Musculoskeletal

Arthralgia, myalgia.

Psychiatric

Anxiety.

TAF

Skin and Subcutaneous Tissue Disorders

Angioedema, urticaria, and rash.

Renal and Urinary Disorders

Acute renal failure, acute tubular necrosis, proximal renal tubulopathy, and Fanconi syndrome.

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, dalfampridine, and metformin, Table 4) *[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, uridyl diphosphate glucuronosyl transferase (UGT)1A1, UGT2B7, P-

glycoprotein (P-gp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, multidrug resistance protein (MRP)2, or MRP4. *In vitro,* dolutegravir did not induce CYP1A2, CYP2B6, or CYP3A4. Based on these data and the results of drug interaction trials, dolutegravir is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters.

7.2 Effect of Other Agents on the Pharmacokinetics of Dolutegravir, FTC, or TAF

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 4) *[see Drug Interactions (7.3) and Clinical Pharmacology (12.3)]*.

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

FTC and TAF: 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 4). 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*.

7.3 Established and Other Potentially Significant Drug Interactions

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

Information regarding potential drug interactions with dolutegravir, emtricitabine and tenofovir alafenamide (Table 4) 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 4. 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
HIV-1 Antiviral Agents		
Non-nucleoside reverse transcriptase inhibitor: Etravirine[a]	↓ Dolutegravir	Use of dolutegravir, emtricitabine and tenofovir alafenamide tablets with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir is not recommended.
Non-nucleoside reverse transcriptase inhibitor: Efavirenz[a]	↓ Dolutegravir	If coadministration with efavirenz is necessary, an additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, emtricitabine and tenofovir alafenamide tablets *[see Dosage and Administration (2.4)]*.
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 inhibitors: Fosamprenavir/ritonavir[a]	↓ Dolutegravir	If coadministration with fosamprenavir/ritonavir is necessary, an additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, emtricitabine and tenofovir alafenamide tablets
Tipranavir/ritonavir	↓ Dolutegravir ↓ TAF	Coadministration with dolutegravir, emtricitabine and tenofovir alafenamide tablets is not recommended because of the TAF component.
Other Agents		
Antiarrhythmics: Dofetilide	↑ Dofetilide	Coadministration is contraindicated with dolutegravir, emtricitabine and tenofovir alafenamide tablets *[see Contraindications (4)]*.
Antimycobacterials: Rifabutin Rifapentine	↓ TAF	Coadministration of dolutegravir, emtricitabine and tenofovir alafenamide tablets with rifabutin or rifapentine is not recommended.
Rifampin[a]	↓Dolutegravir ↓ TAF	Coadministration of dolutegravir, emtricitabine and tenofovir alafenamide tablets with rifampin is not recommended because of the TAF component.

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, TAF and/or Concomitant Drug	Clinical Comment
Anticonvulsants: Carbamazepine[a] Oxcarbazepine Phenytoin Phenobarbital	↓ Dolutegravir ↓ TAF	Consider alternative anticonvulsant. If coadministration is necessary, an additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, emtricitabine and tenofovir alafenamide tablets.
	↓ Dolutegravir ↓ TAF	Avoid coadministration with dolutegravir, emtricitabine and tenofovir alafenamide tablets because there are insufficient data to make dosing recommendations.
Herbal Products: St. John's wort *(Hypericum perforatum)*	↓ Dolutegravir ↓ TAF	Avoid coadministration with dolutegravir, emtricitabine and tenofovir alafenamide tablets because there are insufficient data to make dosing recommendations.
Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing antacids[a] or laxatives Sucralfate Buffered medications	↓ Dolutegravir	Administer dolutegravir, 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	When taken with food, dolutegravir, emtricitabine and tenofovir alafenamide tablets and supplements or multivitamins containing calcium or iron can be taken at the same time. Under fasting conditions, dolutegravir, emtricitabine and tenofovir alafenamide tablets should be taken 2 hours before or 6 hours after taking supplements containing calcium or iron.
Potassium channel blockers: Dalfampridine	↑Dalfampridine	Elevated levels of dalfampridine increase the risk of seizures. The potential benefits of taking dalfampridine concurrently with dolutegravir, emtricitabine and tenofovir alafenamide tablets should be considered against the risk of seizures in these patients.
Anti-diabetic medications: Metformin[a]	↑ Metformin	Refer to the prescribing information of metformin for assessing the benefit and risk of concomitant use with metformin.

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

7.4 Drugs without Clinically Significant Interactions with Dolutegravir, FTC, and TAF

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

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.

7.5 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 emtricitabine and tenofovir alafenamide 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 (5.7)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Data from an ongoing birth outcome surveillance study has identified an increased risk of neural tube defects when dolutegravir, one component of dolutegravir, emtricitabine and tenofovir alafenamide tablets, is administered at the time of conception. As defects related to closure of the neural tube occur from conception through the first 6 weeks of gestation, embryos exposed to dolutegravir from the time of conception through the first 6 weeks of gestation are at potential risk.

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

Available data from the APR show no statistically significant difference in the overall

risk of overall major birth defects for emtricitabine (FTC) or tenofovir alafenamide (TAF) compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) *(see Data)*. The rate of miscarriage for individual drugs is not reported in the APR.

There are insufficient human data on the use of dolutegravir, emtricitabine and tenofovir alafenamide tablets during pregnancy to definitively assess a drug-associated risk of birth defects and miscarriage. The background risk for major birth defects for the indicated population is unknown. In the U.S. general population, the estimated background rate for major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with dolutegravir at systemic exposures (AUC) less than (rabbits) and approximately 27 times (rats) the exposure in humans at the maximum recommended human dose (MRHD) of dolutegravir *[see Data]*. No adverse developmental effects were observed when FTC and TAF 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 FTC and TAF *[see Data]*. 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 FTC. 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 TAF.

Data

Human Data

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

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

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

Based on prospective reports to the APR of 842 exposures to dolutegravir during pregnancy resulting in live births (including 512 exposed in the first trimester), the prevalence of defects in live births was 3.3% (95% CI: 1.9% to 5.3%) following first-trimester exposure to dolutegravir-containing regimens and 4.8% (95% CI: 2.8% to 7.8%) following second-/third-trimester exposure to dolutegravir-containing regimens. In the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP), the background birth defect rate was 2.7%.

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

FTC and TAF: Prospective reports from the APR of overall major birth defects in pregnancies exposed to FTC and TAF are compared with a U.S. background major birth defect rate. Methodological limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates women and infants from a limited geographic area, and does not include outcomes for births that occurred at less than 20 weeks gestation.

FTC: Based on prospective reports to the APR of over 5,400 exposures to FTC-containing regimens during pregnancy resulting in live births (including over 3,900 exposed in the first trimester and over 1,500 exposed in the second/third trimester), the prevalence of birth defects in live births was 2.6% (95% CI: 2.2% to 3.2%) and 2.7% (95% CI: 1.9% to 3.7%) following first and second/third trimester exposure, respectively, to FTC-containing regimens.

TAF: Based on prospective reports to the APR of over 660 exposures to TAF-containing regimens during pregnancy resulting in live births (including over 520 exposed in the first trimester and over 130 exposed in the second/third trimester), the prevalence of birth defects in live births was 4.2% (95% CI: 2.6% to 6.3%) and 3.0% (95% CI: 0.8% to 7.5%) following first and second/third trimester exposure, respectively, to TAF-containing regimens.

Animal Data

Dolutegravir*:* Dolutegravir was administered orally at up to 1,000 mg per kg daily to pregnant rats and rabbits on Gestation Days 6 to 17 and 6 to 18, respectively, and to rats on Gestation Day 6 to lactation/postpartum Day 20. No adverse effects on embryo-fetal

(rats and rabbits) or pre/postnatal (rats) development were observed at up to the highest dose tested. During organogenesis, systemic exposures (AUC) to dolutegravir in rabbits were less than the exposure in humans at the MRHD and in rats were approximately 27 times the exposure in humans at the MRHD. In the rat pre/postnatal development study, decreased body weight of the developing offspring was observed during lactation at a maternally toxic dose (approximately 27 times human exposure at the MRHD).

FTC: FTC was administered orally to pregnant mice (250 mg/kg/day, 500 mg/kg/day, or 1,000 mg/kg/day) and rabbits (100 mg/kg/day, 300 mg/kg/day, or 1,000 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 (AUC) approximately 60 times higher and in rabbits at approximately 108 times higher than human exposures at the recommended daily dose. In a pre/postnatal development study with FTC, mice were administered doses up to 1,000 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.

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

8.2 Lactation

Risk Summary

Dolutegravir is present in human milk. It is not known whether dolutegravir affects human milk production or has effects on the breastfed infant. Based on limited data, FTC has been shown to be present in human breast milk; it is not known if TAF is present in human breast milk. Tenofovir has been shown to be present in the milk of lactating rats and rhesus monkeys after administration of TDF *(see Data)*. It is not known if TAF is present in animal milk.

It is not known if FTC and TAF affect milk production or have effects on the breastfed child.

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

Data

Animal Data

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

8.3 Females and Males of Reproductive Potential

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

Pregnancy Testing

Pregnancy testing is recommended in adolescents and adults of childbearing potential before initiation of dolutegravir, emtricitabine and tenofovir alafenamide tablets *[see Dosage and Administration (2.1)]*.

Contraception

Adolescents and adults of childbearing potential who are taking dolutegravir, emtricitabine and tenofovir alafenamide tablets should be counseled on the consistent use of effective contraception.

8.4 Pediatric Use

The safety and effectiveness of dolutegravir, emtricitabine and tenofovir alafenamide tablets for the treatment of HIV-1 infection in pediatric patients weighing at least 25 kg was established through studies with the individual components *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.2)]*. Dolutegravir, emtricitabine and tenofovir alafenamide tablets is a fixed-dose combination product which cannot be adjusted for pediatric patients weighing less than 25 kg.

The safety and effectiveness of dolutegravir, emtricitabine and tenofovir alafenamide tablets coadministered with an HIV-1 protease inhibitor that is administered with either

ritonavir or cobicistat have not been established in pediatric subjects weighing less than 35 kg *[see Dosage and Administration (2.2)]*.

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 of *[See Clinical Pharmacology (12.3)]*.

FTC and TAF

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 Renal Impairment

Dolutegravir, emtricitabine and tenofovir alafenamide tablets is not recommended for patients with severe renal impairment (estimated creatinine clearance below 30 mL per min) because dolutegravir, emtricitabine and tenofovir alafenamide tablets is 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)]*. There is inadequate information to recommend appropriate dosing of dolutegravir, emtricitabine and tenofovir alafenamide in patients requiring dialysis.

8.7 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 alafenamide tablets are not recommended for use in patients with severe hepatic impairment *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There is no 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.

FTC: Limited clinical experience is available at doses higher than the recommended dose of FTC. In one clinical pharmacology study, single doses of FTC 1,200 mg (6 times the recommended 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.

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 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%.

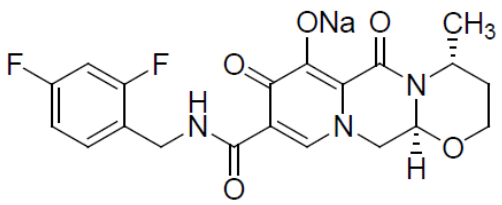
11 DESCRIPTION

Dolutegravir, emtricitabine and tenofovir alafenamide tablets contains dolutegravir sodium (DTG), emtricitabine (FTC) and tenofovir alafenamide fumarate (TAF).

Each film coated tablet is for oral administration and contains 50 mg of dolutegravir (equivalent to 52.6 mg of dolutegravir sodium), 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide (equivalent to 28.043 mg of tenofovir alafenamide hemifumarate) and the following inactive ingredients: croscarmellose sodium, magnesium stearate, mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, and sodium stearyl fumarate. The film coating contains polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Dolutegravir, present as dolutegravir sodium, is an HIV INSTI. The chemical name of dolutegravir sodium is Sodium (4R, 12as)-9-((2,4-difluorobenzyl)carbamoyl)-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1', 2': 4, 5] pyrazino [2,1-b] [1,3]oxazin-7-olate.

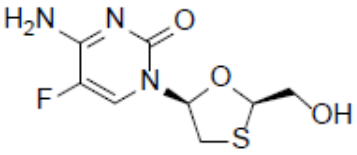
The empirical formula is $C_{20}H_{18}F_2N_3NaO_5$ and the molecular weight is 441.37 g per mol. It has the following structural formula:



Dolutegravir sodium is an off-white or white to light yellow color powder and is very slightly soluble in methanol and practically insoluble in acetonitrile.

The chemical name of emtricitabine (FTC) is (2R-cis)-4-Amino-5-fluoro-1-[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.

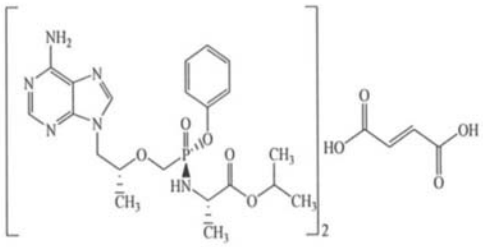
FTC has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.25 and has the following structural formula:



FTC is a white to off-white powder, freely soluble in water and in methanol, practically insoluble in methylene chloride.

Tenofovir alafenamide is present as tenofovir alafenamide hemifumarate with the chemical name of isopropyl N-{(S)-({[(2R)1-(6amino-9H-purin-9-yl}-2-propanyl]oxy} methyl)(phenoxy)phosphoryl]-L-alaninate(2E)-2-butenedioate (2:1).

Tenofovir alafenamide hemifumarate has an empirical formula of $C_{46}H_{62}N_{12}O_{14}P_2$ and a formula weight of 1068.39 and has the following structural formula:



Tenofovir alafenamide hemifumarate is a white to off-white powder, soluble in dimethyl formamide and slightly soluble in methanol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dolutegravir, emtricitabine and tenofovir alafenamide tablets is a fixed-dose combination of HIV-1 antiretroviral drugs dolutegravir, FTC, and TAF *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Effects of Dolutegravir 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 of FTC or TAF on Electrocardiogram

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.

Effects of Dolugravir 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.

12.3 Pharmacokinetics in Adults

Dolutegravir, *Emtricitabine and Tenofovir Alafenamide*: The mean systemic exposures of dolutegravir, emtricitabine and tenofovir alafenamide from the combination tablets (50 mg/200 mg/25 mg) were comparable to that from Tivicay tablets of ViiV Healthcare (containing dolutegravir 50 mg) and Descovy tablets of Gilead Sciences, Inc. (containing emtricitabine 200 mg and tenofovir alafenamide 25 mg), respectively, when single doses were administered to healthy subjects under fasted conditions.

The effect of food on the pharmacokinetics of this fixed-dose combination of dolutegravir, emtricitabine, and tenofovir alafenamide has not been determined.

Absorption, Distribution, Metabolism, and Excretion

Dolutegravir: The pharmacokinetic properties of dolutegravir have been evaluated in healthy adult subjects and HIV-1–infected adult subjects. Exposure to dolutegravir was generally similar between healthy subjects and HIV-1–infected subjects. Dolutegravir steady-state pharmacokinetic parameter estimates in HIV-1- infected adults are reported in Table 5.

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

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

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

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

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

Cerebrospinal Fluid (CSF): In 12 treatment-naïve subjects on dolutegravir 50 mg daily plus abacavir/lamivudine, the median dolutegravir concentration in CSF was 13.2 ng per mL (range: 3.74 ng 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.

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.

In a meta-analysis of healthy subject trials, subjects with UGT1A1 (n = 7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n = 41).

After a single oral dose of [^{14}C] dolutegravir, 53% of the total oral dose 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).

FTC and TAF: The pharmacokinetic properties of FTC and TAF are provided in Table 6. The multiple dose pharmacokinetic parameters of FTC and TAF and its metabolite tenofovir are provided in Table 7.

Table 6. Pharmacokinetic Properties of the Components of Fixed-Dose 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 10 days); TAF (single dose administration of [^{14}C] tenofovir alafenamide).

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

Parameter Mean	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).

Specific Populations

Pediatric Patients: Dolutegravir, emtricitabine and tenofovir alafenamide tablets is a fixed-dose combination product which cannot be adjusted for patients weighing less than 25 kg (55 lbs).

Dolutegravir: The pharmacokinetics of dolutegravir were evaluated in the IMPAACT P1093 trial and in 2 weight-band-based pharmacokinetic substudies from the ODYSSEY trial. Mean dolutegravir $AUC_{0\text{-}24h}$ and C_{24h} in HIV-1-infected pediatric subjects were comparable to those in adults after 50 mg once daily or 50 mg twice daily.

FTC and TAF: Exposures of FTC and TAF achieved in 23 pediatric subjects between the ages of 6 to less than 12 years and weighing at least 25 kg (55 lbs) who received FTC+TAF with EVG+COBI were higher (20% to 80% for AUC) than exposures achieved in adults following the administration of this dosage regimen; however, the increase was not considered clinically significant (Table 8).

Table 8: Multiple Dose PK Parameters of Emtricitabine, Tenofovir Alafenamide and its Metabolite Tenofovir Following Oral Administration of FTC+TAF with EVG+COBI in HIV-Infected Pediatric Subjects Aged 6 to less than 12 Years[a]

Parameter Mean (CV%)	Emtricitabine	Tenofovir Alafenamide	Tenofovir
C_{max} (microgram per mL)	3.4 (27.0)	0.31 (61.2)	0.03 (20.8)
AUC_{tau} (microgram•hour per mL)	20.6[b] (18.9)	0.33 (44.8)	0.44 (20.9)
C_{trough} (microgram per mL)	0.11 (24.1)	NA	0.02 (24.9)

CV = Coefficient of Variation; NA = Not Applicable

a. From Intensive PK analysis in a trial in virologically-suppressed pediatric subjects with HIV-1 infection (N=23).

b. N=22

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

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

Parameter Mean (CV%)	Emtricitabine	Tenofovir Alafenamide	Tenofovir
C_{max} (microgram per mL)	2.3 (22.5)	0.17 (64.4)	0.02 (23.7)

AUC_{tau} (microgram•hour per mL)	14.4 (23.9)	0.20[b] (50.0)	0.29[b] (18.8)
C_{trough} (microgram per mL)	0.10[b] (38.9)	NA	0.01 (21.4)

CV = Coefficient of Variation; NA = Not Applicable
a. From Intensive PK analysis in a trial in treatment-naïve pediatric subjects with HIV-1 infection (N=24).
b. N=23

Geriatric Patients: Dolutegravir*:* Population pharmacokinetic analysis indicated age had no clinically relevant effect on the pharmacokinetics of dolutegravir.

FTC and TAF: 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)]*.

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 is a fixed-dose combination product and the dosage of the individual components cannot be adjusted *[see Dosage and Administration (2.3)]*.
Patients with Hepatic Impairment: Dolutegravir*:* In a trial comparing 8 subjects with moderate hepatic impairment (Child-Pugh Score B) with 8 matched healthy controls, exposure of dolutegravir from a single 50-mg dose was similar between the 2 groups. The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir has not been studied.

FTC: 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.

TAF: Clinically relevant changes in tenofovir pharmacokinetics in subjects with hepatic impairment were not observed in subjects with mild to moderate (Child-Pugh Class A and B) hepatic impairment.

Hepatitis B Virus (HBV) and/or Hepatitis C Virus (HCV) Co-infection: 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.

FTC and TAF: The pharmacokinetics of FTC and TAF have not been fully evaluated in subjects infected with hepatitis B and/or C virus.

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

FTC and TAF: Based on population pharmacokinetic analyses, there are no clinically meaningful differences based on race or gender.

Drug Interaction Studies

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

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

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

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug with/without Dolutegravir No Effect = 1.00		
			C_{max}	AUC	C_τ or C_{24}
Elbasvir 50 mg once daily	50 mg single dose	12	0.97 (0.89, 1.05)	0.98 (0.93, 1.04)	0.98 (0.93, 1.03)
Ethinyl estradiol 0.035 mg	50 mg twice daily	15	0.99 (0.91 to 1.08)	1.03 (0.96 to 1.11)	1.02 (0.93 to 1.11)
Grazoprevir 200 mg once daily	50 mg single dose	12	0.64 (0.44, 0.93)	0.81 (0.67, 0.97)	0.86 (0.79, 0.93)
Metformin 500 mg twice daily	50 mg once daily	15[a]	1.66 (1.53 to 1.81)	1.79 (1.65 to 1.93)	–
Metformin 500 mg twice daily	50 mg twice daily	15[a]	2.11 (1.91 to 2.33)	2.45 (2.25 to 2.66)	–
Methadone 16 to 150 mg	50 mg twice daily	11	1.00 (0.94 to 1.06)	0.98 (0.91 to 1.06)	0.99 (0.91 to 1.07)
Midazolam 3 mg	25 mg once daily	10	–	0.95 (0.79 to 1.15)	–
Norelgestromin 0.25 mg	50 mg twice daily	15	0.89 (0.82 to 0.97)	0.98 (0.91 to 1.04)	0.93 (0.85 to 1.03)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.10 (0.99 to 1.22)	1.06 (0.98 to 1.16)	1.21 (1.07 to 1.38)
Sofosbuvir 400 mg once daily Metabolite (GS-331007)	50 mg once daily	24	0.88 (0.80, 0.98) 1.01 (0.93, 1.10)	0.92 (0.85, 0.99) 0.99 (0.97, 1.01)	NA 0.99 (0.97, 1.01)
Tenofovir disoproxil fumarate 300 mg once daily	50 mg once daily	15	1.09 (0.97 to 1.23)	1.12 (1.01 to 1.24)	1.19 (1.04 to 1.35)
Velpatasvir 100 mg once daily	50 mg once daily	24	0.94 (0.86, 1.02)	0.91 (0.84, 0.98)	0.88 (0.82, 0.94)

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

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

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00		
			C_{max}	AUC	C_τ or C_{24}
Atazanavir 400 mg once daily	30 mg once daily	12	1.50 (1.40 to 1.59)	1.91 (1.80 to 2.03)	2.80 (2.52 to 3.11)
Atazanavir/ritonavir 300/100 mg once daily	30 mg once daily	12	1.34 (1.25 to 1.42)	1.62 (1.50 to 1.74)	2.21 (1.97 to 2.47)
Darunavir/ritonavir 600/100 mg twice daily	30 mg once daily	15	0.89 (0.83 to 0.97)	0.78 (0.72 to 0.85)	0.62 (0.56 to 0.69)
Efavirenz 600 mg once daily	50 mg once daily	12	0.61 (0.51 to 0.73)	0.43 (0.35 to 0.54)	0.25 (0.18 to 0.34)
Elbasvir/grazoprevir 50/200 mg once daily	50 mg single dose	12	1.22 (1.05, 1.40)	1.16 (1.00, 1.34)	1.14 (0.95, 1.36)
Etravirine 200 mg twice daily	50 mg once daily	16	0.48 (0.43 to 0.54)	0.29 (0.26 to 0.34)	0.12 (0.09 to 0.16)
Etravirine + darunavir/ritonavir 200 mg + 600/100 mg twice daily	50 mg once daily	9	0.88 (0.78 to 1.00)	0.75 (0.69 to 0.81)	0.63 (0.52 to 0.76)
Etravirine + lopinavir/ritonavir 200 mg + 400/100 mg twice daily	50 mg once daily	8	1.07 (1.02 to 1.13)	1.11 (1.02 to 1.20)	1.28 (1.13 to 1.45)
Fosamprenavir/ritonavir 700 mg/100 mg twice daily	50 mg once daily	12	0.76 (0.63 to 0.92)	0.65 (0.54 to 0.78)	0.51 (0.41 to 0.63)
Lopinavir/ritonavir 400/100 mg twice daily	30 mg once daily	15	1.00 (0.94 to 1.07)	0.97 (0.91 to 1.04)	0.94 (0.85 to 1.05)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.13 (1.06 to 1.21)	1.12 (1.05 to 1.19)	1.22 (1.15 to 1.30)
Tenofovir 300 mg once daily	50 mg once daily	15	0.97 (0.87 to 1.08)	1.01 (0.91 to 1.11)	0.92 (0.82 to 1.04)
Tipranavir/ritonavir 500/200 mg twice daily	50 mg once daily	14	0.54 (0.50 to 0.57)	0.41 (0.38 to 0.44)	0.24 (0.21 to 0.27)
Antacid (MAALOX) simultaneous administration	50 mg single dose	16	0.28 (0.23 to 0.33)	0.26 (0.22 to 0.32)	0.26 (0.21 to 0.31)
Antacid (MAALOX) 2 h after dolutegravir	50 mg single dose	16	0.82 (0.69 to 0.98)	0.74 (0.62 to 0.90)	0.70 (0.58 to 0.85)
Calcium carbonate 1,200 mg simultaneous administration (fasted)	50 mg single dose	12	0.63 (0.50 to 0.81)	0.61 (0.47 to 0.80)	0.61 (0.47 to 0.80)
Calcium carbonate 1,200 mg simultaneous administration (fed)	50 mg single dose	11	1.07 (0.83 to 1.38)	1.09 (0.84 to 1.43)	1.08 (0.81 to 1.42)
Calcium carbonate 1,200 mg 2 h after dolutegravir	50 mg single dose	11	1.00 (0.78 to 1.29)	0.94 (0.72 to 1.23)	0.90 (0.68 to 1.19)
Carbamazepine 300 mg twice daily	50 mg once daily	16[a]	0.67 (0.61 to 0.73)	0.51 (0.48 to 0.55)	0.27 (0.24 to 0.31)
Ferrous fumarate 324 mg simultaneous administration (fasted)	50 mg single dose	11	0.43 (0.35 to 0.52)	0.46 (0.38 to 0.56)	0.44 (0.36 to 0.54)

Ferrous fumarate 324 mg simultaneous administration (fed)	50 mg single dose	11	1.03 (0.84 to 1.26)	0.98 (0.81 to 1.20)	1.00 (0.81 to 1.23)
Ferrous fumarate 324 mg 2 h after dolutegravir	50 mg single dose	10	0.99 (0.81 to 1.21)	0.95 (0.77 to 1.15)	0.92 (0.74 to 1.13)
Multivitamin (One-A-Day) simultaneous administration	50 mg single dose	16	0.65 (0.54 to 0.77)	0.67 (0.55 to 0.81)	0.68 (0.56 to 0.82)
Omeprazole 40 mg once daily	50 mg single dose	12	0.92 (0.75 to 1.11)	0.97 (0.78 to 1.20)	0.95 (0.75 to 1.21)
Prednisone 60 mg once daily with taper	50 mg once daily	12	1.06 (0.99 to 1.14)	1.11 (1.03 to 1.20)	1.17 (1.06 to 1.28)
Rifampin[b] 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[c] 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] The number of subjects represents the maximum number of subjects that were evaluated.
[b] Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg twice daily.
[c] Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg once daily.

FTC and TAF: The effects of coadministered drugs on the exposure of TAF are shown in Table 12 and the effects of emtricitabine and tenofovir alafenamide or its components on the exposure of coadministered drugs are shown in Table 13 [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 12 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
Dolutegravir	50	10	10	1.24 (0.88, 1.74)	1.19 (0.96, 1.48)	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	1.01	NC

				(0.84, 1.22)	(0.94, 1.09)	
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 13 Drug Interactions: Changes in PK Parameters for Coadministered Drug in the Presence of Fixed-Dose Emtricitabine and Tenofovir Alafenamide or the Individual Components[a]

Coadministered Drug	Coadministered Drug Dosage (once daily) (mg)	Tenofovir Alafenamide Dosage (once daily) (mg)	N	Mean Ratio of Coadministered Drug PK Parameters (90% CI); No effect = 1.00		
				C_{max}	AUC	C_{min}
Atazanavir	300 +100 ritonavir	10	10	0.98 (0.89, 1.07)	0.99 (0.96, 1.01)	1.00 (0.96, 1.04)
Darunavir	800 +150 cobicistat	25[b]	11	1.02 (0.96, 1.09)	0.99 (0.92, 1.07)	0.97 (0.82, 1.15)
Darunavir	800 +100 ritonavir	10	10	0.99 (0.91, 1.08)	1.01 (0.96, 1.06)	1.13 (0.95, 1.34)
Dolutegravir	50 mg	10	10	1.15 (1.04, 1.27)	1.02 (0.97, 1.08)	1.05 (0.97, 1.13)
Lopinavir	800 +200 ritonavir	10	10	1.00 (0.95, 1.06)	1.00 (0.92, 1.09)	0.98 (0.85, 1.12)
Midazolam[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 (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.

FTC: 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.

TAF: 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.

FTC: 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 1.3-640 nM. FTC displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 7-75 nM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 7-1,500 nM).

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.

TAF: 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).

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 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.

TAF: 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.

Resistance

Cell Culture: **Dolutegravir:** Dolutegravir-resistant viruses were selected in cell culture starting from different wild-type HIV-1 strains and clades. Amino acid substitutions 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.

FTC: 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.

TAF: 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

Dolutegravir*:* No subject who received dolutegravir 50-mg once-daily in the treatment arms of treatment-naïve trials SPRING-2 (96 weeks) and SINGLE (144 weeks) had a detectable decrease in susceptibility to dolutegravir or background NRTIs in the resistance analysis subset (n = 12 with HIV-1 RNA greater than 400 copies per mL at

failure or last visit and having resistance data). Two virologic failure subjects in SINGLE had treatment-emergent G/D/E193D and G193G/E integrase substitutions at Week 84 and Week 108, respectively, and 1 subject with 275 copies per mL HIV-1 RNA had a treatment-emergent Q157Q/P integrase substitution detected at Week 24. None of these subjects had a corresponding decrease in dolutegravir susceptibility. No treatment-emergent genotypic resistance to the background regimen was observed in the dolutegravir arm in either the SPRING-2 or SINGLE trials.

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

FTC and TAF: The resistance profile of FTC and TAF in combination with other antiretroviral agents for the treatment of HIV-1 infection is based on studies of FTC + TAF with EVG + COBI in the treatment of HIV-1 infection. In a pooled analysis of antiretroviral-naïve subjects, genotyping was performed on plasma HIV-1 isolates from all subjects with HIV-l 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: **Site-Directed Integrase Strand Transfer Inhibitor-Resistant Mutant HIV-1 and HIV-2 Strains:**

The susceptibility of dolutegravir was tested against 60 INSTI-resistant site-directed mutant HIV-1 viruses (28 with single substitutions and 32 with 2 or more substitutions) and 6 INSTI-resistant site-directed mutant HIV-2 viruses. The single INSTI-resistance substitutions T66K, I151L, and S153Y conferred a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.3-fold to 3.6-fold from reference). Combinations of multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148, and substitutions at E138/G140/Q148 showed a

greater than 2-fold decrease in dolutegravir susceptibility (range: 2.5-fold to 21-fold from reference). In HIV-2 mutants, combinations of substitutions A153G/N155H/S163G and E92Q/T97A/N155H/S163D conferred 4-fold decreases in dolutegravir susceptibility, and E92Q/N155H and G140S/Q148R showed 8.5-fold and 17-fold decreases in dolutegravir susceptibility, respectively.

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

FTC: 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.

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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 dose of 50 mg twice daily.

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

In a study conducted in rats, there were no effects on mating or fertility with dolutegravir up to 1,000 mg per kg per day. This dose is associated with an exposure that is approximately 24 times higher than the exposure in humans a dose of 50 mg twice daily.

Emtribicine (FTC)

In long-term oral carcinogenicity studies of FTC, no drug-related increases in tumor incidence were found in mice at doses up to 750 mg/kg/day (26 times the human systemic exposure at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (31 times the human systemic exposure at the therapeutic dose). 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-fold or in male and female mice at approximately 60-fold higher exposures (AUC) than in humans given the recommended 200 mg daily dose. 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-fold higher than human exposures at the recommended 200 mg daily dose.

Tenofovir Alafenamide (TAF)

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

TAF: 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.

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 fixed-dose abacavir sulfate and lamivudine or fixed-dose emtricitabine/tenofovir DF). 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 sultate and lamivudine; these characteristics were similar between treatment groups.

Outcomes for SPRING-2 (Week 96 analysis) are found in Table 14. There was no treatment-emergent resistance to dolutegravir or to the NRTI background.

Table 14. 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	12%	12%
Reasons		
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	84%	79%

Male Female	70%	68%
Race White African-American/African Heritage/Other	 83% 77%	 78% 75%

NRTI = nucleoside reverse transcriptase inhibitor

[a] Adjusted for pre-specified stratification factors.

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

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

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

In SPRING-2, virologic outcomes were also comparable across baseline characteristics including CD4+ cell count, age, and use of fixed-dose abacavir sulfate and lamivudine or fixed-dose emtricitabine/tenofovir DF 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.

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

FTC and TAF: 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 adults 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 18 years in a 48-week open-label, multicenter, dose-finding clinical trial, IMPAACT P1093 (NCT01302847). Subjects aged 12 to less than 18 years were enrolled in Cohort 1 and subjects aged 6 to less than 12 years were enrolled in Cohort 2A. At 48 weeks, 61%

(14/23) of subjects aged 12 to less than 18 years treated with dolutegravir once daily plus optimized background therapy achieved virologic response defined as HIV-1 RNA less than 50 copies per mL. Across both cohorts, virologic suppression at Week 48 was achieved in 67% (16/24) of subjects weighing at least 40 kg.

FTC and TAF: An open-label, single arm trial of FTC+TAF with EVG+COBI enrolled 50 treatment-naïve HIV-1 infected adolescents aged 12 to less than 18 years weighing at least 35 kg (cohort 1) and 52 virologically suppressed children aged 6 to less than 12 years weighing at least 25 kg (cohort 2). In cohort 1, the virologic response rate (i.e., HIV-1 RNA less than 50 copies per mL) was 92% (46/50) and the mean increase from baseline in CD4+ cell count was 224 cells per mm^3 at Week 48. In cohort 2, 98% (51/52) of subjects remained virologically suppressed at Week 48. From a mean (SD) baseline CD4+ cell count of 961 (275.5) cells per mm^3, the mean change from baseline in CD4+ cell count was -66 cells per mm^3 and the mean (SD) change in CD4% was -0.6% (4.4%) at Week 48. All subjects maintained CD4+ cell counts above 400 cells/mm^3 *[see Adverse Reactions (6.1)]*.

In a separate open-label single arm trial of FTC+TAF with bictegravir that enrolled 24 virologically-suppressed children at least 2 years of age and weighing at least 14 to less than 25 kg (cohort 3), 91% (20/22) of subjects remained virologically suppressed at Week 24. From a mean (SD) baseline CD4+ count of 1104 (440), the mean (SD) change from baseline in CD4+ cell count was −126 (264) cells per mm^3, and the mean (SD) change in CD4% was 0.2% (4.4%) at Week 24.

16 HOW SUPPLIED/STORAGE AND HANDLING

Dolutegravir, emtricitabine and tenofovir alafenamide tablets, 50 mg/200 mg/25 mg are white to off white, capsule shaped film coated tablets, debossed with ‘T47’ on one side and ‘H’ on other side.

They are supplied as follows:

Bottles of 30 tablets with desiccant and child-resistant cap	NDC 68554-3172-0
Bottles of 100 tablets with desiccant and child-resistant cap	NDC 68554-3172-1

Store below 30°C (86°F).

Store and dispense in the original bottle and keep the bottle tightly closed to protect from moisture. Do not remove desiccant. Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

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

Post-Treatment Acute Exacerbation of Hepatitis B in Patients with HBV Infection

Inform patients that severe acute exacerbations of hepatitis B have been reported in patients who are infected with HBV and have discontinued products containing FTC and/or TDF, and may likewise occur with discontinuation of dolutegravir, emtricitabine and tenofovir alafenamide tablets *[see Warnings and Precautions (5.1)]*. Advise HBV-

infected patients 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 many drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John's wort *[see Contraindications (4), Warnings and Precautions (5.5), Drug Interactions (7)]*.

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 (5.3)]*. 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.

Embryo-Fetal Toxicity

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

Adolescents and adults of childbearing potential taking dolutegravir, emtricitabine and tenofovir alafenamide tablets should be counseled on the consistent use of effective contraception *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)]*.

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any signs or symptoms of infection as inflammation from previous infection may occur soon after combination antiretroviral therapy, including when dolutegravir, emtricitabine and tenofovir alafenamide tablets is started *[see Warnings and Precautions (5.6)]*.

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. Postmarketing cases of renal impairment, including acute renal failure, have been reported *[see Warnings and Precautions (5.7)]*.

Lactic Acidosis and Severe Hepatomegaly

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with use of drugs similar to dolutegravir, emtricitabine and tenofovir alafenamide tablets. Treatment with dolutegravir, emtricitabine and tenofovir alafenamide tablets should be suspended in patients who develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity *[see Warnings and Precautions (5.8)]*.

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.

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.

Manufactured by:

HETERO™
HETERO LABS LIMITED 2xxxxxx
22-110, I.D.A., Jeedimetla,
Hyderabad - 500055, India.

Revised: 01/2024