Royality Country

Rx EMTRICITABINE+DOLUTEGRAVIR+ TENOFOVIR ALAFENAMIDE
DIFACTA
200 mg/50 mg/25 mg film-coated tablet
Antiretroviral (Direct Acting Antivirals)

Rx EMTRICITABINE+DOLUTEGRAVIR+TENOFOVIR ALAFENAMIDE

DIFACTA

200 mg/50 mg/25 mg film-coated tablet

Formulation: Antiretroviral (Direct Acting Antivirals)

Each film-coated tablet contains:
Emtricitabine....................................... 200 mg
Dolutegravir Sodium
equivalent to Dolutegravir........................50 mg
Tenofovir Alafenamide hemifumarate
equivalent to Tenofovir Alafenamide..........25 mg

Description;
White to off white, capsule shaped film coated tablets, debossed with "T 47" on one side and "H" on other side.

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

EMTRICITABINE, DOLUTEGRAVIR and TENOFOVIR ALAFENAMIDE tablets 200 mg/50 mg/25 mg, for oral use

WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

See full prescribing information for complete boxed warning.

- **Emtricitabine, Dolutegravir and Tenofovir alafenamide is not approved for the treatment of chronichepatitis B virus (HBV) infection. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine (FTC) and/or tenofovir alafenamide (TDF), and may occur with discontinuation of Emtricitabine, Dolutegravir and Tenofovir alafenamide. Hepatic function should be monitored closely in these patients. If appropriate, initiation of anti-hepatitis B therapy may be warranted. (5.1)**

RECENT MAJOR CHANGES

Dosage and Administration, Pediatric Patients (2.2)
Indications and Usage (1)
Dosage and Administration, Recommended Dosage (2.2)
Warnings and Precautions, Bone Loss and Mineralization Defects *[removed]*
Boxed Warning, Lactic Acidosis/Severe Hepatomegaly with Steatosis *[removed]*
Warnings and Precautions, Lactic Acidosis/Severe Hepatomegaly with Steatosis (5.4)
Warnings and Precautions, Fat Redistribution *[removed]*

INDICATIONS AND USAGE

Emtricitabine, Dolutegravir and tenofovir alafenamide is a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI) plus nucleoside analog HIV-1 reverse transcriptase inhibitors indicated for the treatment of HIV-1 infection in adults.(1)

Limitations of Use:

- Use of emtricitabine, dolutegravir and tenofovir alafenamide in integrase strand transfer inhibitor (INSTI) experienced patients should be guided by the number and type of baseline INSTI substitutions. The efficacy of dolutegravir 50 mg twice daily is reduced in patients with an INSTI-resistance Q148 substitution plus 2 or more additional INSTI-resistance substitutions including T66A, L74I/M, E138A/K/T, G140S/A/C, Y143R/C/H, E157Q, G163S/E/K/Q, or G193E/R. (12.4).
- Emtricitabine, Dolutegravir and tenofovir alafenamide is not indicated for use as pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk.

DOSAGE AND ADMINISTRATION

- Recommended dose in HIV-1 uninfected adults: One tablet (containing 200 mg/50 mg/300 mg of emtricitabine, dolutegravir and tenofovir alafenamide) once daily taken orally with or without food. (2)
- Recommended dose in renally impaired HIV-uninfected individuals: Do not use emtricitabine, dolutegravir and tenofovir alafenamide in HIV-uninfected individuals, if CrCl is below 60 mL/min. If a decrease in CrCl is observed in uninfected individuals while using emtricitabine, dolutegravir and tenofovir alafenamide for PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use.(2)
- Testing: Prior to initiation of emtricitabine, dolutegravir and tenofovir alafenamide, patients should be tested for hepatitis B virus infection, and estimated creatinine clearance, urine glucose and urine protein should be obtained. (2.1)
- **Recommended dosage: One tablet taken once daily with or without food in patients with body weight at least 25 kg and a creatinine clearance greater than or equal to 30 mL per minute. (2.2)**
- **Renal impairment: Emtricitabine, Dolutegravir and tenofovir alafenamide is not recommended in patients with estimated creatinine clearance below 30 mL per minute. (2.3)**

DOSAGE FORMS AND STRENGTHS

Tablets: containing 200 mg of emtricitabine, 50 mg of dolutegravir and 25 mg of tenofovir alafenamide (3)

CONTRAINDICATIONS

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

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 emtricitabine, dolutegravir and tenofovir alafenamide 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. (5.1)
- Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of emtricitabine, dolutegravir and tenofovir alafenamide. Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with emtricitabine, dolutegravir and tenofovir alafenamide is recommended in patients with underlying hepatic disease such as hepatitis B or C. (5.2)
- Redistribution/accumulation of body fat and immune reconstitution syndrome have been reported in patients treated with combination antiretroviral therapy. (5.3, 5.4)
- Immune reconstitution syndrome: May necessitate further evaluation and treatment.(5.2)
- New onset or worsening renal impairment: Assess creatinine clearance, urine glucose, and urine protein in all patients before initiating emtricitabine, dolutegravir and tenofovir alafenamide therapy and monitor during therapy. Monitor serum phosphorus in patients with chronic kidney disease. (5.3)
- Lactic acidosis/severe hepatomegaly with steatosis: Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.4)

ADVERSE REACTIONS

- The most common adverse reactions of moderate to severe intensity and incidence at least 2% (in those receiving emtricitabine, dolutegravir and tenofovir alafenamide in any one adult trial) are insomnia, fatigue, and headache. (6.1)
- Most common adverse reaction (incidence greater than or equal to 10%, all grades) is nausea. (6.1)

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

DRUG INTERACTIONS

- Drugs that are metabolic inducers may decrease the plasma concentrations of dolutegravir. (7.2, 7.3)
- Emtricitabine, Dolutegravir and tenofovir alafenamide should be taken 2 hours before or 6 hours after taking cation-containing antacids or laxatives, sucralfate, oral supplements containing iron or calcium, or buffered medications. Alternatively, emtricitabine, dolutegravir and tenofovir alafenamide and supplements containing calcium or iron can be taken together with food. (7.3)
- Consult the Full Prescribing Information prior to and during treatment for potential drug interactions. (7, 12.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Emtricitabine, Dolutegravir and tenofovir alafenamide should be used during pregnancy only if the potential benefit justifies the potential risk. (8.1)
- Lactation: Breastfeeding is not recommended. (8.2)
- Lactation: Women infected with HIV should be instructed not to breastfeed, due to the potential for HIV transmission. (8.2)
- Pediatrics: Not recommended for patients weighing less than 25 kg.(8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION:

WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

Emtricitabine, Dolutegravir and Tenofovir alafenamide is not approved for the treatment of chronic hepatitis B virus (HBV) infection, and the safety and efficacy of emtricitabine and tenofovir alafenamide have not been established in patients coinfected with human immunodeficiency virus-1 (HIV-1) and HBV. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine (FTC) and/or tenofovir disproxil fumarate (TDF), and may occur with discontinuation of emtricitabine and tenofovir alafenamide.

Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue emtricitabine, dolutegravir and tenofovir alafenamide. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

Emtricitabine, Dolutegravir and tenofovir alafenamide is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults.

Limitations of Use:

- Use of emtricitabine, dolutegravir and tenofovir alafenamide in integrase strand transfer inhibitor (INSTI)-experienced patients should be guided by the number and type of baseline INSTI substitutions. The efficacy of dolutegravir 50 mg twice daily is reduced in patients with an INSTI-resistance Q148 substitution plus 2 or more additional INSTI-resistance substitutions, including T66A, L74I/M, E138A/K/T, G140S/A/C, Y143R/C/H, E157Q, G163S/E/K/Q, or G193E/R *[see Microbiology (12.4)]*.
- Emtricitabine, dolutegravir and tenofovir alafenamide is not indicated for use as pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk.

2 DOSAGE AND ADMINISTRATION

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

Prior to initiation of emtricitabine, dolutegravir and tenofovir alafenamide, patients should be tested for hepatitis B virus infection *[see Warnings and Precautions (5.1)]*.

Estimated creatinine clearance, urine glucose, and urine protein should be assessed before initiating Emtricitabine, Dolutegravir and tenofovir alafenamide therapy and should be monitored during therapy in all patients *[see Warnings and Precautions (5.3)]*.

2.2 Recommended Dosage

The recommended dosage of emtricitabine, dolutegravir and tenofovir alafenamide is one tablet taken orally once daily with or without food in adults and pediatric patients with body weight at least 25 kg and creatinine clearance greater than or equal to 30 mL per minute *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

2.3 Not Recommended in Patients with Severe Renal Impairment

Emtricitabine, Dolutegravir and tenofovir alafenamide is not recommended in patients with estimated creatinine clearance below 30 mL per minute *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)]*.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

Emtricitabine, Dolutegravir and tenofovir alafenamide is contraindicated in patients:

- with previous hypersensitivity reaction to dolutegravir *[see Warnings and Precautions (5.1)]*.
- receiving dofetilide due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events *[see Drug Interactions (7)]*.

5 WARNINGS AND PRECAUTIONS

Dolutegravir

5.1 Hypersensitivity Reactions

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

5.2 Effects on Serum Liver Biochemistries in Patients with Hepatitis B or C Co-infection

Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of dolutegravir [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. Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with dolutegravir are recommended in patients with underlying hepatic disease such as hepatitis B or C.

5.3 Fat Redistribution

Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

5.4 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including dolutegravir. 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.

Emtricitabine and Tenofovir Alafenamide

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

Patients with HIV-1 should be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy [see Dosage and Administration (2.1)]. Emtricitabine and tenofovir alafenamide is not approved for the treatment of chronic HBV infection, and the safety and efficacy of emtricitabine and tenofovir alafenamide have not been established in patients coinfected with HIV-1 and HBV.

Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing FTC and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of emtricitabine and tenofovir alafenamide. Patients coinfected with HIV-1 and HBV who discontinue emtricitabine and tenofovir alafenamide should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, initiation of anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis, since post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

5.2 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including FTC, a component of emtricitabine and tenofovir alafenamide. During the initial phase of combination antiretroviral treatment, patients whose immune system responds 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.

5.3 New Onset or Worsening Renal Impairment

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir prodrugs in both animal toxicology studies and human trials. In clinical trials of FTC+TAF with cobicistat (COBI) plus elvitegravir (EVG), there have been no cases of Fanconi syndrome or Proximal Renal Tubulopathy (PRT). In clinical trials of FTC+TAF with EVG+COBI in treatment-naïve subjects and in virally suppressed subjects switched to FTC+TAF with EVG+COBI with eGFRs greater than 50 mL per minute, renal serious adverse events or discontinuations due to renal adverse reactions were encountered in less than 1% of participants treated with FTC+TAF with EVG+COBI. In a study of virally suppressed subjects with baseline eGFRs between 30 and 69 mL per minute treated with FTC+TAF with EVG+COBI for a median duration of 43 weeks, FTC+TAF with EVG+COBI was permanently discontinued due to worsening renal function in two of 80 (3%) subjects with a baseline eGFR between 30 and 50 mL per minute [see Adverse Reactions (6.1)]. Emtricitabine and tenofovir alafenamide 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.

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

5.4 Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including emtricitabine, a component of emtricitabine and tenofovir alafenamide, and tenofovir DF, another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with emtricitabine and tenofovir alafenamide 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

Dolutegravir

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

- Hypersensitivity reactions *[see Warnings and Precautions (5.1)]*.
- Effects on serum liver biochemistries in patients with hepatitis B or C co-infection *[see Warnings and Precautions (5.2)]*.
- Fat Redistribution *[see Warnings and Precautions (5.3)]*.
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.4)]*.

6.1 Clinical Trials Experience

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

Clinical Trials Experience in Adult Subjects

Treatment-Naïve Subjects: The safety assessment of dolutegravir in HIV-1-infected treatment-naïve subjects is based on the analyses of data from 2 international, multicenter, double-blind trials, SPRING-2 (ING113086) and SINGLE (ING114467) and data from the international, multicenter, open-label FLAMINGO (ING114915) trial.

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 abacavir sulfate and lamivudine [EPZICOM®] or emtricitabine/tenofovir [TRUVADA®]). There were 808 subjects included in the efficacy and safety analyses. Through 96 weeks, the rate of adverse events leading to discontinuation was 2% in both treatment arms.

In SINGLE, 833 subjects were randomized and received at least 1 dose of either dolutegravir50 mg with fixed-dose abacavir sulfate and lamivudine (EPZICOM) once daily or fixed-dose efavirenz/emtricitabine/tenofovir (ATRIPLA®) once daily (study treatment was blinded through Week 96 and open-label from Week 96 through Week 144). Through 144 weeks, the rates of adverse events leading to discontinuation were 4% in subjects receiving dolutegravir 50 mg once daily + EPZICOM and 14% in subjects receiving ATRIPLA once daily.

Treatment-emergent adverse drug reactions (ADRs) of moderate to severe intensity observed in at least 2% of subjects in either treatment arm in SPRING-2 and SINGLE trials are provided in Table 1. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 1. Treatment-Emergent Adverse Drug Reactions of at Least Moderate Intensity (Grades 2 to 4) and at Least 2% Frequency in Treatment-Naïve Subjects in SPRING-2 (Week 96 Analysis) and SINGLE Trials (Week 144 Analysis)

	SPRING-2		SINGLE	
System Organ Class/ Preferred Term	Dolutegravir 50 mg Once Daily + 2 NRTIs (n = 403)	Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)	Dolutegravir 50 mg + EPZICOM Once Daily (n = 414)	ATRIPLA Once Daily (n = 419)
Psychiatric				
Insomnia	<1%	<1%	3%	3%
Depression	<1%	<1%	1%	2%
Abnormal dreams	<1%	<1%	<1%	2%
Nervous System				
Dizziness	<1%	<1%	<1%	5%
Headache	<1%	<1%	2%	2%
Gastrointestinal				
Nausea	1%	1%	<1%	3%
Diarrhea	<1%	<1%	<1%	2%
Skin and Subcutaneous Tissue				
Rash [a]	0	<1%	<1%	6%
General Disorders				
Fatigue	<1%	<1%	2%	2%
Ear and Labyrinth				
Vertigo	0	<1%	0	2%

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

In addition, Grade 1 insomnia was reported by 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 ATRIPLA, respectively. These events were not treatment limiting.

In a multicenter, open-label trial (FLAMINGO), 243 subjects received dolutegravir 50 mg once daily versus 242 subjects who received darunavir 800 mg/ritonavir 100 mg once daily, both in combination with investigator-selected NRTI background regimen (either EPZICOM or emtricitabine and tenofovir disoproxil fumarate). There were 484 subjects included in the efficacy and safety analyses. Through 96 weeks, the rates of adverse events leading to discontinuation were 3% in subjects receiving dolutegravir and 6% in subjects receiving darunavir/ritonavir. The ADRs observed in FLAMINGO were generally consistent with those seen in SPRING-2 and SINGLE.

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 ADR 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.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Subjects: In a multicenter, open-label, single-arm trial (ING112574, VIKING-3), 183 HIV-1-infected, antiretroviral treatment-experienced adults with virological failure and current or historical evidence of raltegravir and/or elvitegravir resistance received dolutegravir 50 mg twice daily with the current failing background regimen for 7 days and with optimized background therapy from Day 8. The rate of adverse events leading to discontinuation was 4% of subjects at Week 48.

Treatment-emergent ADRs in VIKING-3 were generally similar compared with observations with the 50-mg once-daily dose in adult Phase 3 trials.

Less Common Adverse Reactions Observed in Treatment-Naïve and Treatment-Experienced Trials: The following ADRs 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 2. The mean change from baseline observed for selected lipid values is presented in Table 3. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

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

	SPRING-2		SINGLE	
Laboratory Parameter Preferred Term	Dolutegravir 50 mg Once Daily + 2 NRTIs (n = 403)	Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)	Dolutegravir 50 mg + EPZICOM Once Daily (n = 414)	ATRIPLA Once Daily (n = 419)
ALT				
Grade 2 (>2.5-5 x ULN)	4%	4%	3%	5%
Grade 3 to 4 (>5 x ULN)	2%	2%	1%	<1%
AST				
Grade 2 (>2.5-5 x ULN)	5%	3%	3%	4%
Grade 3 to 4 (>5 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 (6-9.9 x ULN)	2%	5%	5%	3%
Grade 3 to 4 (≥10 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 x ULN)	7%	7%	11%	11%
Grade 3 to 4 (>3 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%

ULN = Upper limit of normal.

Table 3. 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])

	SPRING-2		SINGLE	
Laboratory Parameter Preferred Term	Dolutegravir 50 mg Once Daily + 2 NRTIs (n = 403)	Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)	Dolutegravir 50 mg + EPZICOM Once Daily (n = 414)	ATRIPLA 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

[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 + EPZICOM n = 30 and ATRIPLA n = 27). Ninety-four subjects initiated a lipid-lowering agent post-baseline; their last fasted on treatment values (prior to starting the agent) were used regardless if they discontinued the agent (SPRING-2: Dolutegravir n = 9, raltegravir n = 13; SINGLE: Dolutegravir + EPZICOM n = 36 and ATRIPLA: n = 36).

Laboratory abnormalities observed in the FLAMINGO trial were generally consistent with observations in SPRING-2 and SINGLE.

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.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Subjects: The most common treatment-emergent laboratory abnormalities (greater than 5% for Grades 2 to 4 combined) observed in VIKING-3 at Week 48 were elevated ALT (9%), AST (8%), cholesterol (10%), creatine kinase (6%), hyperglycemia (14%), and lipase (10%). Two percent (4 of 183) of subjects had a Grade 3 to 4 treatment-emergent hematology laboratory abnormality, with neutropenia (2% [3 of 183]) being the most frequently reported.

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 (5.2)]*.

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

Clinical Trials Experience in Pediatric Subjects

IMPAACT P1093 is an ongoing multicenter, open-label, non-comparative trial of approximately 160 HIV-1-infected pediatric subjects aged 4 weeks to less than 18 years, of which 46 treatment-experienced, INSTI-naïve subjects aged 6 to less than 18 years have been enrolled *[see Use in Specific Populations (8.4), Clinical Studies (14.2)]*.

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

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

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.

Musculoskeletal

Arthralgia, myalgia.

Emtricitabine and Tenofovir Alafenamide

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

- Severe Acute Exacerbations of Hepatitis B *[see Boxed Warning and Warnings and Precautions (5.1)]*.
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.2)]*.
- New Onset or Worsening Renal Impairment *[see Warnings and Precautions (5.3)]*.
- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[see Warnings and Precautions (5.4)]*

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 drug given in the same or different combination therapy) and may not reflect the rates observed in practice.

Adverse Reactions in Clinical Trials of FTC+TAF with EVG+COBI in Treatment-Naïve Adults with HIV-1 Infection

In pooled 48-week trials of antiretroviral treatment-naïve HIV-1 infected adult subjects, the most common adverse reaction in subjects treated with FTC+TAF with EVG+COBI (N=866) (incidence greater than or equal to 10%, all grades) was nausea (10%). In this treatment group, 0.9% of subjects discontinued FTC+TAF with EVG+COBI due to adverse events during the 48-week treatment period [see Clinical Studies (14)]. The safety profile was similar in virologically-suppressed adults with HIV-1 infection who were switched to FTC+TAF with EVG+COBI (N=799). Antiretroviral treatment-naïve adult subjects treated with FTC+TAF with EVG+COBI experienced mean increases of 30 mg/dL of total cholesterol, 15 mg/dL of LDL cholesterol, 7 mg/dL of HDL cholesterol and 29 mg/dL of triglycerides after 48 weeks of use.

Renal Laboratory Tests

In two 48-week trials in antiretroviral treatment-naïve HIV-1 infected adults treated with FTC+TAF with EVG+COBI (N=866) with a median baseline eGFR of 115 mL per minute, mean serum creatinine increased by 0.1 mg per dL from baseline to Week 48. Median urine protein-to-creatinine ratio (UPCR) was 44 mg per gram at baseline and at Week 48. In a 48-week trial in virologically-suppressed TDF-treated adults who switched to FTC+TAF with EVG+COBI (N=959) with a mean baseline eGFR of 112 mL per minute, mean serum creatinine was similar to baseline and median UPCR was 61 mg per gram at baseline and 46 mg per gram at Week 48. In a 24-week trial in adults with renal impairment (baseline eGFR 30 to 69 mL per minute) who received FTC+TAF with EVG+COBI (N=248), mean serum creatinine was 1.5 mg per dL at both baseline and Week 24. Median UPCR was 161 mg per gram at baseline and 93 mg per gram at Week 24.

Bone Mineral Density Effects

In the pooled analysis of two 48-week trials of antiretroviral treatment-naïve HIV-1 infected adult subjects, bone mineral density (BMD) from baseline to Week 48 was assessed by dual-energy X-ray absorptiometry (DXA). Mean BMD decreased from baseline to Week 48 –1.30% with FTC+TAF with EVG+COBI at the lumbar spine and –0.66% at the total hip. BMD declines of 5% or greater at the lumbar spine were experienced by 10% of FTC+TAF with EVG+COBI subjects. BMD declines of 7% or greater at the femoral neck were experienced by 7% of FTC+TAF with EVG+COBI subjects. The long-term clinical significance of these BMD changes is not known. Fractures (excluding fingers and toes) were reported in 7 (0.8%) subjects in the FTC+TAF with EVG+COBI group.

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

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

In 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=23; cohort 2) who received FTC+TAF with EVG+COBI through 24 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 of adults.

Bone Mineral Density Effects

Cohort 1: Treatment-naïve adolescents (12 to less than 18 years; at least 35kg)

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

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

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

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=23) 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 Week 24. The mean baseline and mean change from baseline in CD4+ cell count and in CD4% from Week 2 to Week 24 are presented in Table 4. All subjects maintained their CD4+ cell counts above 400 cells/mm³ *[see Use in Specific Populations (8.4)]*.

Table 4. Mean Change in CD4+ Count and Percentage from Baseline to Week 24 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
CD4+ Cell Count (cells/mm³)	966 (201.7)[a]	-162	-125	-162	-150
CD4%	40 (5.3)[a]	+0.5	-0.1	-0.8	-1.5

[a] Mean (SD)

7 DRUG INTERACTIONS

Dolutegravir

7.1 Effect of Dolutegravir on the Pharmacokinetics of Other Agents

In vitro, dolutegravir inhibited the renal organic cation transporters, OCT2 (IC_{50} = 1.93 microM) and multidrug and toxin extrusion transporter (MATE) 1 (IC_{50} = 6.34 microM). *In vivo*, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2 and potentially MATE1. Dolutegravir may increase plasma concentrations of drugs eliminated via OCT2 or MATE1 (dofetilide and metformin, Table 6) *[see Contraindications (4), Drug Interactions (7.3)]*.

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

In vitro, dolutegravir did not inhibit (IC_{50} greater than 50 microM) the following: cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate (UDP)-glucuronosyl transferase 1A1 (UGT1A1), UGT2B7, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, multidrug resistance protein (MRP)2, or MRP4. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6, or CYP3A4. Based on these data and the results of drug interaction trials, dolutegravir is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters.

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

7.2 Effect of Other Agents on the Pharmacokinetics of Dolutegravir

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

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

Etravirine significantly reduced plasma concentrations of dolutegravir, but the effect of etravirine was mitigated by coadministration of lopinavir/ritonavir or darunavir/ritonavir, and is expected to be mitigated by atazanavir/ritonavir (Table 6) *[see Drug Interactions (7.3), Clinical Pharmacology (12.3)]*.

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

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

7.3 Established and Other Potentially Significant Drug Interactions

Table 5 provides clinical recommendations as a result of drug interactions with dolutegravir. These recommendations are based on either drug interaction trials or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy. *[See Dosage and Administration (2), Clinical Pharmacology (12.3).]*

Table 5. Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Trials or Predicted Interactions *[see Dosage and Administration (2)]*

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir and/or Concomitant Drug	Clinical Comment
HIV-1 Antiviral Agents		
Non-nucleoside reverse transcriptase inhibitor: Etravirine[a]	↓Dolutegravir	Use of dolutegravir with etravirine without coadministration of atazanavir/ritonavir, darunavir/ ritonavir, or lopinavir/ritonavir is not recommended.
Non-nucleoside reverse transcriptase inhibitor: Efavirenz[a]	↓Dolutegravir	Adjust dose of dolutegravir tablets to 50 mg twice daily for treatment-naïve and treatment-experienced, INSTI-naïve adult patients. In pediatric patients, increase the weight-based dose to twice daily. Use alternative combinations that do not include metabolic inducers where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[b]
Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓Dolutegravir	Avoid coadministration with nevirapine because there are insufficient data to make dosing recommendations.
Protease inhibitor: Fosamprenavir/ritonavir[a] Tipranavir/ritonavir[a]	↓Dolutegravir	Adjust dose of dolutegravir tablets to 50 mg twice daily for treatment-naïve and treatment-experienced, INSTI-naïve adult patients. In pediatric patients, increase the weight-based dose to twice daily. Use alternative combinations that do not include metabolic inducers where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[b]
Other Agents		
Carbamazepine[a]	↓Dolutegravir	Adjust dose of dolutegravir tablets to 50 mg twice daily in treatment-naïve or treatment-experienced, INSTI-naïve adult patients. In pediatric patients, increase the weight-based dose to twice daily. Use alternative treatment that does not include carbamazepine where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[b]
Oxcarbazepine Phenytoin Phenobarbital St. John's wort *(Hypericum perforatum)*	↓Dolutegravir	Avoid coadministration with dolutegravir 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 tablets 2 hours before or 6 hours after taking medications containing polyvalent cations.
Oral calcium or iron supplements, including multivitamins containing calcium or iron[a]	↓Dolutegravir	Administer dolutegravir tablets 2 hours before or 6 hours after taking supplements containing calcium or iron. Alternatively, dolutegravir and supplements containing calcium or iron can be taken together with food.
Metformin	↑Metformin	With concomitant use, limit the total daily dose of metformin to 1,000 mg either when starting metformin or dolutegravir. When stopping dolutegravir, the metformin dose may require an adjustment. Monitoring of blood glucose when initiating concomitant use and after withdrawal of dolutegravir is recommended.
Rifampin[a]	↓Dolutegravir	Adjust dose of dolutegravir tablets to 50 mg twice daily for treatment-naïve and treatment-experienced, INSTI-naïve adult patients. In pediatric patients, increase the weight-based dose to twice daily (Table 2). Use alternatives to rifampin where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[b]

[a] *See Clinical Pharmacology (12.3) Table 12 or Table 13 for magnitude of interaction.*

[b] The lower dolutegravir exposures observed in INSTI-experienced patients (with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance *[see Microbiology (12.4)]*) upon coadministration with certain inducers may result in loss of therapeutic effect and development of resistance to Dolutegravir or other coadministered antiretroviral agents.

Emtricitabine and Tenofovir Alafenamide

7.1 Potential for Other Drugs to Affect One or More Components of Emtricitabine and Tenofovir Alafenamide

TAF, a component of emtricitabine and tenofovir alafenamide, 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 2). 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 emtricitabine and tenofovir alafenamide and development of resistance. Coadministration of emtricitabine and tenofovir alafenamide 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*.

7.2 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 (5.3)]*.

7.3 Established and Other Potentially Significant Interactions

Table 6 provides a listing of established or potentially clinically significant drug interactions with recommended steps to prevent or manage the drug interaction (the table is not all inclusive). The drug interactions described are based on studies conducted with either emtricitabine and tenofovir alafenamide, the components of emtricitabine and tenofovir alafenamide (emtricitabine and tenofovir alafenamide) as individual agents, or are predicted drug interactions that may occur with emtricitabine and tenofovir alafenamide. For magnitude of interaction, *[see Clinical Pharmacology (12.3)]*.

Table 6. Established and Other Potentially Significant[a] Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Antiretroviral Agents: Protease Inhibitors (PI)		
tipranavir/ritonavir	↓TAF	Coadministration with emtricitabine and tenofovir alafenamide is not recommended.
Other Agents		
Anticonvulsants: carbamazepine oxcarbazepine phenobarbital phenytoin	↓TAF	Coadministration with emtricitabine and tenofovir alafenamide is not recommended.
Herbal Products: St. John's wort (Hypericum perforatum)	↓TAF	Coadministration of emtricitabine and tenofovir alafenamide with St. John's wort is not recommended.

[a] This table is not all inclusive.

[b] ↓= Decrease

7.4 Drugs without Clinically Significant Interactions with Emtricitabine and Tenofovir Alafenamide

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.

8 USE IN SPECIFIC POPULATIONS

Dolutegravir

8.1 Pregnancy

Risk Summary

There are insufficient human data on the use of dolutegravir during pregnancy to inform a drug-associated risk of birth defects and miscarriage. Given the limited number of pregnancies exposed to dolutegravir-based regimens reported to the APR, no definitive conclusions can be drawn on the safety of dolutegravir in pregnancy, and continued monitoring is ongoing through the APR. The background rate for major birth defects in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) is 2.7%. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15% to 20%. In animal reproduction studies, no evidence of adverse developmental outcomes was observed with dolutegravir [see Data]. During organogenesis in the rat and rabbit, systemic exposures (AUC) to dolutegravir were less than (rabbits) and approximately 27 times (rats) the exposure in humans at the maximum recommended human dose (MRHD). In the rat pre/postnatal developmental study, maternal systemic exposure (AUC) to dolutegravir was approximately 27 times the exposure in humans at the MRHD.

Data

Animal Data: Dolutegravir was administered orally at up to 1,000 mg per kg daily to pregnant rats and rabbits on gestation Days 6 to 17 and 6 to 18, respectively, and also to rats on gestation day 6 to lactation/post-partum Day 20. No adverse effects on embryo-fetal (rats and rabbits) or pre/post-natal (rats) development were observed at up to the highest dose tested. During organogenesis systemic exposures (AUC) to dolutegravir in rabbits were less than the exposure in humans at the maximum recommended human dose (MRHD) and in rats were approximately 27 times the exposure in humans at the MRHD. In the rat pre/post-natal development study, decreased body weight of the developing offspring was observed during lactation at a maternally toxic dose (approximately 27 times human exposure at the MRHD).

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. It is not known whether dolutegravir is present in human breast milk, affects human milk production, or has effects on the breastfed infant. When administered to lactating rats, dolutegravir was present in milk *[see Data]*.

Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), and (2) developing viral resistance (in HIV-positive infants), instruct mothers not to breastfeed if they are receiving dolutegravir.

Data

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

8.4 Pediatric Use

The safety, virologic, and immunologic responses in subjects who received dolutegravir were evaluated in 46 treatment-experienced, INSTI-naïve, HIV-1-infected subjects aged 6 to less than 18 years in an open-label, multicenter, dose-finding clinical trial, IMPAACT P1093 *[see Clinical Pharmacology (12.3), Clinical Studies (14.2)]*. Frequency, type, and severity of adverse drug reactions among the 46 pediatric subjects were comparable to those observed in adults *[see Adverse Reactions (6.2)]*. In 17 subjects weighing at least 30 kg, pharmacokinetic parameters of dolutegravir were comparable to adults receiving 50 mg once daily *[see Clinical Pharmacology (12.3)]*.

Safety and efficacy of dolutegravir have not been established in pediatric patients weighing less than 30 kg or in any pediatric patients who are INSTI-experienced.

8.5 Geriatric Use

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

8.6 Hepatic Impairment

No clinically important pharmacokinetic differences between subjects with moderate hepatic impairment and matching healthy subjects were observed. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh Score A or B). The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir has not been studied. Therefore, Dolutegravir is not recommended for use in patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

Dolutegravir plasma concentrations were decreased in subjects with severe renal impairment compared with those in matched healthy controls. However, no dosage adjustment is necessary for treatment-naïve or treatment-experienced and INSTI-naïve patients with mild, moderate, or severe renal impairment or for INSTI-experienced patients (with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance) with mild or moderate renal impairment. Caution is warranted for INSTI-experienced patients (with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance *[see Microbiology (12.4)]*) with severe renal impairment, as the decrease in dolutegravir concentrations may result in loss of therapeutic effect and development of resistance to dolutegravir or other coadministered antiretroviral agents *[see Clinical Pharmacology (12.3)]*. Dolutegravir has not been studied in patients on dialysis.

Emtricitabine and Tenofovir Alafenamide

8.1 Pregnancy

Risk Summary

There are insufficient human data on the use of emtricitabine and tenofovir alafenamide during pregnancy to inform a drug-associated risk of birth defects and miscarriage. Tenofovir alafenamide (TAF) use in women during pregnancy has not been evaluated; however, emtricitabine (FTC) use during pregnancy has been evaluated in a limited number of women reported to the APR. Available data from the APR show no difference in the risk of overall major birth defects for FTC (2.4%) 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). The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in the clinically recognized pregnancies in the U.S. general population is 15 to 20%. In animal studies, no adverse developmental effects were observed when the components of emtricitabine and tenofovir alafenamide were administered separately during the period of organogenesis at exposures 60 and 108 times (mice and rabbits, respectively) the FTC exposure and at exposure equal to or 53 times (rats and rabbits, respectively) the TAF exposure at the recommended daily dose of emtricitabine and tenofovir alafenamide *[see Data (8.1)]*. Likewise, no adverse developmental effects were seen when FTC was administered to mice through lactation at exposures up to approximately 60 times the exposure at the recommended daily dose of emtricitabine and tenofovir alafenamide. No adverse effects were observed in the offspring when TDF was administered through lactation at tenofovir exposures of approximately 14 times the exposure at the recommended daily dosage of emtricitabine and tenofovir alafenamide.

Data

Human Data

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

Animal Data

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

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

8.2 Lactation

Risk Summary

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

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

It is not known if emtricitabine and tenofovir alafenamide affects milk production or has effects on the breastfed child. Because of the potential for: 1) HIV transmission (in HIV-negative infants); 2) developing viral resistance (in HIV-positive infants); and 3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving emtricitabine and tenofovir alafenamide *[see Data (8.2)]*.

Data

Human Data

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

Animal Data

Tenofovir Alafenamide: Studies in rats and monkeys have demonstrated that tenofovir is secreted in milk. Tenofovir was excreted into the milk of lactating rats following oral administration of TDF (up to 600 mg/kg/day) at up to approximately 24% of the median plasma concentration in the highest dosed animals at lactation day 11 [see Data (8.1)]. Tenofovir was excreted into the milk of lactating monkeys following a single subcutaneous (30 mg/kg) dose of tenofovir at concentrations up to approximately 4% of plasma concentration, resulting in exposure (AUC) of approximately 20% of plasma exposure.

8.4 Pediatric Use

The safety and effectiveness of emtricitabine and tenofovir alafenamide, in combination with other antiretroviral agents, for the treatment of HIV-1 infection was established in pediatric patients with body weight greater than or equal to 25 kg *[see Indication and Usage (1) and Dosage and Administration (2.2)]*.

Use of emtricitabine and tenofovir alafenamide in pediatric patients between the ages of 12 to less than 18 years weighing at least 35 kg is supported by adequate and well controlled studies of FTC+TAF with EVG+COBI in adults and by an open-label trial in antiretroviral treatment-naïve HIV-1 infected pediatric subjects ages 12 to less than 18 years and weighing at least 35 kg (N=50; cohort 1). The safety and efficacy of FTC+TAF with EVG+COBI in these pediatric subjects was similar to that of HIV-1 infected adults on this regimen *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]*.

Use of emtricitabine and tenofovir alafenamide in pediatric patients weighing at least 25 kg is supported by adequate and well controlled studies of FTC+TAF with EVG+COBI in adults and by an open-label trial in virologically-suppressed pediatric subjects between the ages of 6 to less than 12 years weighing at least 25 kg, in which subjects were switched from their antiretroviral regimen to FTC+TAF with EVG+COBI (N=23; cohort 2). The safety in these subjects through 24 weeks of FTC+TAF with EVG+COBI was similar to that of HIV-1 infected adults on this regimen, with the exception of a decrease in mean change from baseline in CD4+ cell count *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14)]*.

Safety and effectiveness of emtricitabine and tenofovir alafenamide 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)]*.

Safety and effectiveness of emtricitabine and tenofovir alafenamide in pediatric patients less than 25 kg have not been established.

8.5 Geriatric Use

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

Emtricitabine and tenofovir alafenamide is not recommended in patients with severe renal impairment (estimated creatinine clearance below 30 mL per minute). No dosage adjustment of emtricitabine and tenofovir alafenamide is recommended in patients with estimated creatinine clearance greater than or equal to 30 mL per minute *[see Dosage and Administration (2.3) and Clinical Studies (14)]*.

8.7 Hepatic Impairment

No dosage adjustment of emtricitabine and tenofovir alafenamide is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. emtricitabine and tenofovir alafenamide has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Dolutegravir

There is no known specific treatment for overdose with dolutegravir. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required. As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

Emtricitabine and Tenofovir Alafenamide

No data are available on overdose of emtricitabine and tenofovir alafenamide in patients. If overdose occurs, monitor the patient for evidence of toxicity. Treatment of overdose with emtricitabine and tenofovir alafenamide consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient.

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

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

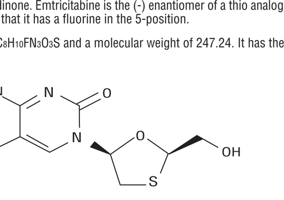
Tenofovir alafenamide (TAF): Limited clinical experience is available at doses higher than the recommended dose of TAF. A single dose of 125 mg TAF (5 times the TAF dose in 200/25 mg emtricitabine and tenofovir alafenamide) was administered to 48 healthy subjects; no serious adverse reactions were reported. The effects of higher doses are unknown. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%.

11 DESCRIPTION

Emtricitabine, Dolutegravir and tenofovir alafenamide tablets is a fixed dose combination tablet for oral administration. Each film coated tablet contains 200 mg of Emtricitabine, 50 mg of Dolutegravir Sodium (equivalent to Dolutegravir) and 25 mg of Tenofovir alafenamide hemifumarate (equivalent to Tenofovir alafenamide). In addition, each tablet contains the following inactive ingredients: Croscarmellose sodium, Magnesium stearate, Mannitol, Microcrystalline cellulose, Povidone, Sodium starch glycolate and Sodium stearyl fumarate. The tablets are coated with opadry II White. which contains polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

Dolutegravir

Emtricitabine, Dolutegravir and tenofovir alafenamide tablets contains dolutegravir, as dolutegravir sodium, an HIV INSTI. The chemical name of dolutegravir sodium is Sodiwn (4R,12aS)-9-«2,4-difluorobenzyl)carbamoyl)-4-methyl-6,8-dioxo-3,4,6,8,12.12a-hexahydro-21-1-pyrido[1'.2':4,5]pyrazino(2,1-bJ[1,3JOXal.in-7-olate. The molecular formula is $C_{20}H_{18}F_2N_3NaO_5$ and the molecular weight is 441.36 g per mol. It has the following structural formula:



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

Emtricitabine

Emtricitabine is a synthetic nucleoside analog of cytidine. Tenofovir alafenamide is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. Both emtricitabine and tenofovir exhibit inhibitory activity against HIV-1 reverse transcriptase.

Emtricitabine: The chemical name of emtricitabine is (2R-cis)-4-Amino-5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-ylJ-2(1H)-pyrimidinone. Emtricitabine 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.

It has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24. It has the following structural formula:

PATIENT INFORMATION

EMTRICITABINE+DOLUTEGRAVIR+TENOFOVIR ALAFENAMIDE Tablets

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

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

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

- **Allergic reactions.** Call your healthcare provider right away if you develop a rash with emtricitabine, dolutegravir and tenofovir alafenamide. **Stop taking emtricitabine, dolutegravir and tenofovir alafenamide tablets and get medical help right away if you:**

o **develop a rash with any of the following signs or symptoms:**

- fever
- generally ill feeling
- extreme tiredness
- muscle or joint aches
- blisters or sores in mouth
- blisters or peeling of the skin
- redness or swelling of the eyes
- swelling of the mouth, face, lips,or tongue
- problems breathing

o **develop any of the following signs or symptoms of liver problems:**

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

o **Worsening of Hepatitis B virus infection. Emtricitabine, Dolutegravir and tenofovir alafenamide is not for use to treat chronic hepatitis B virus (HBV) infection. If you have hepatitis B virus (HBV) infection and take emtricitabine, dolutegravir and tenofovir alafenamide, your HBV may get worse (flare-up) if you stop taking emtricitabine, dolutegravir and tenofovir alafenamide. A "flare-up" is when your HBV infection suddenly returns in a worse way than before.**

- It is not known if emtricitabine, dolutegravir and tenofovir alafenamide is safe and effective in people who have both HIV-1 and HBV infection.
- Do not run out of emtricitabine, dolutegravir and tenofovir alafenamide. Refill your prescription or talk to your healthcare provider before your emtricitabine and tenofovir alafenamide is all gone.
- Do not stop taking emtricitabine, dolutegravir and tenofovir alafenamide without first talking to your healthcare provider.
- If you stop taking emtricitabine, dolutegravir and tenofovir alafenamide, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your HBV infection. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking emtricitabine, dolutegravir and tenofovir alafenamide.

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

What are emtricitabine, dolutegravir and tenofovir alafenamide tablets?

Emtricitabine, Dolutegravir and tenofovir alafenamide tablets are a prescription medicine that is used together with other antiretroviral medicines to treat Human Immunodeficiency Virus (HIV-1) infection in adults and adolescents.

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

It is not known if emtricitabine, dolutegravir and tenofovir alafenamide tablets are safe and effective in children who weigh less than 66 pounds or in children who have received certain types of medicine for HIV-1 infection.

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

Who should not take emtricitabine, dolutegravir and tenofovir alafenamide tablets?

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

- have ever had an allergic reaction to a medicine that contains dolutegravir (dolutegravir, TRIUMEQ®).
- take dofetilide (TIKOSYN®). Taking emtricitabine, dolutegravir and tenofovir alafenamide tablets and dofetilide (TIKOSYN®) can cause side effects that may be serious or life-threatening.

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

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

- have ever had an allergic reaction to emtricitabine, dolutegravir and tenofovir alafenamide tablets.
- have had liver problems, including hepatitis B or C infection.
- have any other medical condition.
- are pregnant or plan to become pregnant. It is not known if emtricitabine, dolutegravir and tenofovir alafenamide will harm your unborn baby. Tell your healthcare provider if you become pregnant while taking emtricitabine, dolutegravir and tenofovir alafenamide.

  Pregnancy Registry. There is a pregnancy registry for women who take antiretroviral medicines during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.
- are breastfeeding or plan to breastfeed. **Do not breastfeed if you take emtricitabine, dolutegravir and tenofovir alafenamide tablets**.
- you should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby. Talk with your healthcare provider about the best way to feed your baby.

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

Some medicines interact with dolutegravir. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine. You can ask your healthcare provider or pharmacist for a list of medicines that interact with dolutegravir.

Over-the-counter medicines that interact with dolutegravir include:

- St. John's wort (*Hypericum perforatum*). Avoid use of St. John's wort with dolutegravir.
- antacids, laxatives, or other medicines that contain aluminum, magnesium, sucralfate (CARAFATE®), or buffered medicines. Dolutegravir should be taken at least 2 hours before or 6 hours after you take antacids, laxatives, or other medicines that contain aluminum, magnesium, sucralfate (CARAFATE®), or buffered medicines.
- iron or calcium supplements taken by mouth. Supplements containing calcium or iron may be taken at the same time with dolutegravir if taken with food. Otherwise, dolutegravir should be taken at least 2 hours before or 6 hours after you take these medicines.

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

- have kidney problems
- **Do not start a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take emtricitabine, dolutegravir and tenofovir alafenamide tablets with other medicines.

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

- **Take emtricitabine, dolutegravir and tenofovir alafenamide tablets exactly as your healthcare provider tells you to take it.**
- If you miss a dose of emtricitabine, dolutegravir and tenofovir alafenamide tablets, take it as soon as you remember. Do not take 2 doses at the same time or take more than what your healthcare provider tells you to take.
- Stay under the care of a healthcare provider during treatment with emtricitabine, dolutegravir and tenofovir alafenamide tablets.
- Emtricitabine, Dolutegravir and tenofovir alafenamide tablets may be taken with or without food.
- Do not run out of emtricitabine, dolutegravir and tenofovir alafenamide tablets. The virus in your blood may increase and the virus may become harder to treat. When your supply starts to run low, get more from your healthcare provider or pharmacy.
- If you take too much emtricitabine, dolutegravir and tenofovir alafenamide tablets, call your healthcare provider or go to the nearest hospital emergency room right away.
- Take emtricitabine, dolutegravir and tenofovir alafenamide tablets exactly as your healthcare provider tells you to take it. Emtricitabine and tenofovir alafenamide must be taken together with other HIV-1 medicines to treat HIV-1 infection.
- Take emtricitabine, dolutegravir and tenofovir alafenamide tablets 1 time each day with or without food.
- Do not change your dose or stop taking emtricitabine, dolutegravir and tenofovir alafenamide tablets without first talking with your healthcare provider. Stay under a healthcare provider's care during treatment with emtricitabine, dolutegravir and tenofovir alafenamide tablets.
- Do not miss a dose of emtricitabine, dolutegravir and tenofovir alafenamide tablets.

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

- **Emtricitabine, Dolutegravir and tenofovir alafenamide tablets can cause serious side effects including:**
- **See "What is the most important information I should know about emtricitabine, dolutegravir and tenofovir alafenamide tablets?"**
- **Changes in liver tests.** People with a history of hepatitis B or C virus may have an increased risk of developing new or worsening changes in certain liver tests during treatment with emtricitabine, dolutegravir and tenofovir alafenamide tablets. Your healthcare provider may do tests to check your liver function before and during treatment with emtricitabine, dolutegravir and tenofovir alafenamide tablets.
- **Changes in body fat can happen in people who take HIV-1 medicines.** These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the middle of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term health effects of these problems are not known.
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. This inflammation may cause you to have minor symptoms, such as fever, but inflammation can also lead to serious problems. Tell your healthcare provider right away if you start having new symptoms after you start taking emtricitabine, dolutegravir and tenofovir alafenamide tablets.
- **New or worse kidney problems, including kidney failure.** Your healthcare provider should do blood and urine tests to check your kidneys before you start and during treatment with emtricitabine, dolutegravir and tenofovir alafenamide tablets. Your healthcare provider may tell you to stop taking emtricitabine, dolutegravir and tenofovir alafenamide tablets if you develop new or worse kidney problems.
- **Too much lactic acid in your blood (lactic acidosis).** Too much lactic acid is a serious but rare medical emergency that can lead to death. Tell your healthcare provider right away if you get these symptoms: weakness or being more tired than usual, unusual muscle pain, being short of breath or fast breathing, stomach pain with nausea and vomiting, cold or blue hands and feet, feel dizzy or lightheaded, or a fast or abnormal heartbeat.
- **Severe liver problems.** In rare cases, severe liver problems can happen that can lead to death. Tell your healthcare provider right away if you get these symptoms: skin or the white part of your eyes turns yellow, dark "tea-colored" urine, light-colored stools, loss of appetite for several days or longer, nausea, or stomach-area pain.
- **The most common side effects of emtricitabine, dolutegravir and tenofovir alafenamide tablets include:**
  - trouble sleeping
  - tiredness
  - headache
  - nausea

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the possible side effects of emtricitabine, dolutegravir and tenofovir alafenamide tablets. Call your doctor for medical advice about side effects. You may report side effects to FDA at www.fda.gov.ph.

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

- Store emtricitabine, dolutegravir and tenofovir alafenamide tablets below 30°C and protect from moisture.

  Shelf Life: 24 Months.
- Keep the container tightly closed.

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

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

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use emtricitabine, dolutegravir and tenofovir alafenamide tablets for a condition for which it was not prescribed. Do not give emtricitabine, dolutegravir and tenofovir alafenamide tablets to other people, even if they have the same symptoms you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about emtricitabine, dolutegravir and tenofovir alafenamide tablets that is written for health professionals.

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

Active ingredient: dolutegravir sodium, emtricitabine and tenofovir alafenamide.

Inactive ingredients: croscarmellose sodium, magnesium stearate, mannitol, microcrystalline cellulose, povidone, sodium starch glycolate and sodium stearyl fumarate. The tablets are coated with opadry II white which contains polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

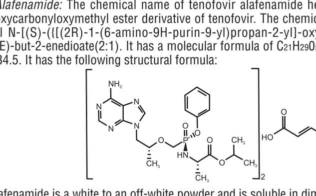
Other brands listed are the registered trademarks of their respective owners and are not trademarks of Hetero Labs Limited.

Manufactured by:
HETERO LABS LIMITED (Unit-III)
Formulation Plot No. 22-110,
Industrial Development Area, Jeedimetla,
Hyderabad, 500 055, Telangana, India

Dimensions: 400 x 950 mm
Colour: Black

Emtricitabine is a white to off-white powder and is freely soluble in water and in methanol. Practically insoluble in methylene chloride.

Tenofovir Alafenamide: The chemical name of tenofovir alafenamide hemifumarate drug substance is the bisisopropoxycarbonyloxymethyl ester derivative of tenofovir. The chemical name of tenofovir alafenamide is propan-2-yl N-[(S)-({[(2R)-1-(6-amino-9H-purin-9-yl)propan-2-yl]-oxy}methyl)(phenoxy)phosphoryl]-L-alaninate,(2E)-but-2-enedioate(2:1). It has a molecular formula of $C_{21}H_{29}O_5N_6O_{10}P$ • $\frac{1}{2}$ $C_4H_4O_4$ and a molecular weight of 534.5. It has the following structural formula:



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

12 CLINICAL PHARMACOLOGY

Dolutegravir

12.1 Mechanism of Action

Dolutegravir is an HIV-1 antiviral agent *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

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

Effects on Electrocardiogram

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

Effects on Renal Function

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

12.3 Pharmacokinetics

The pharmacokinetic properties of dolutegravir have been evaluated in healthy adult subjects and HIV-1-infected adult subjects. Exposure to dolutegravir was generally similar between healthy subjects and HIV-1-infected subjects. The non-linear exposure of dolutegravir following 50 mg twice daily compared with 50 mg once daily in HIV-1-infected subjects (Table 7) was attributed to the use of metabolic inducers in the background antiretroviral regimens of subjects receiving dolutegravir 50 mg twice daily in clinical trials. Dolutegravir was administered without regard to food in these trials.

Table 7. Dolutegravir Steady-State Pharmacokinetic Parameter Estimates in HIV-1- Infected Adults

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

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

Absorption

Following oral administration of dolutegravir, peak plasma concentrations were observed 2 to 3 hours postdose. With once-daily dosing, pharmacokinetic steady state is achieved within approximately 5 days with average accumulation ratios for AUC, C_{max}, and $C_{24\,h}$ ranging from 1.2 to 1.5.

Dolutegravir plasma concentrations increased in a less than dose-proportional manner above 50 mg. Dolutegravir is a P-gp substrate *in vitro*. The absolute bioavailability of dolutegravir has not been established.

Effects of Food on Oral Absorption

Dolutegravir may be taken with or without food. Food increased the extent of absorption and slowed the rate of absorption of dolutegravir. Low-, moderate-, and high-fat meals increased dolutegravir $AUC_{(0-\infty)}$ by 33%, 41%, and 66%; increased C_{max} by 46%, 52%, and 67%; and prolonged T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively.

Distribution

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.

Metabolism and Elimination

Dolutegravir is primarily metabolized via UGT1A1 with some contribution from CYP3A. After a single oral dose of [^{14}C] dolutegravir, 53% of the total oral dose was excreted unchanged in feces. Thirty-one percent of the total oral dose was excreted in urine, represented by an ether glucuronide of dolutegravir (18.9% of total dose), a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose), and its hydrolytic N-dealkylation product (3.6% of total dose). Renal elimination of unchanged drug was low (less than 1% of the dose). 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.

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

Specific Populations

Hepatic Impairment: Dolutegravir is primarily metabolized and eliminated by the liver. In a trial comparing 8 subjects with moderate hepatic impairment (Child-Pugh Score B) with 8 matched healthy controls, exposure of dolutegravir from a single 50-mg dose was similar between the 2 groups. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh Score A or B). The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir has not been studied. Therefore, Dolutegravir is not recommended for use in patients with severe hepatic impairment.

HBV/HCV Co-infection: 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.

Renal Impairment: Renal clearance of unchanged drug is a minor pathway of elimination for dolutegravir. In a trial comparing 8 subjects with severe renal impairment (CrCl less than 30 mL per min) with 8 matched healthy controls, AUC, C_{max}, and C_{24} of dolutegravir were decreased by 40%, 23%, and 43%, respectively, compared with those in matched healthy subjects. The cause of this decrease is unknown. Population pharmacokinetic analysis using data from SAILING and VIKING-3 trials indicated that mild and moderate renal impairment had no clinically relevant effect on the exposure of dolutegravir. No dosage adjustment is necessary for treatment-naïve or treatment-experienced and INSTI-naïve patients with mild, moderate, or severe renal impairment or for INSTI-experienced patients (with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance) with mild or moderate renal impairment. Caution is warranted for INSTI-experienced patients (with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance *[see Microbiology (12.4)]*) with severe renal impairment, as the decrease in dolutegravir concentrations may result in loss of therapeutic effect and development of resistance to dolutegravir or other coadministered antiretroviral agents. Dolutegravir has not been studied in patients requiring dialysis.

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

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

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

Pediatric Patients: The pharmacokinetics of dolutegravir in HIV-1-infected children (n = 17) weighing at least 30 kg were similar to those observed in HIV-1-infected adults who received dolutegravir 50 mg once daily (Table 8) *[see Clinical Studies (14.2)]*.

Table 8. Dolutegravir Steady-State Pharmacokinetic Parameters in Pediatric Subjects

Weight (n)	Dose of Dolutegravir	Dolutegravir Pharmacokinetic Parameter Estimates Geometric Mean (%CV)		
		C_{max} (mcg/mL)	$AUC_{(0-24)}$ (mcg.h/mL)	C_{24} (mcg/mL)
≥40 kg (n = 14)	50 mg once daily	3.89 (43)	50.1(53)	0.99 (66)
≥30 to <40 kg (n = 3)	35 mg once daily	4.40 (54)	64.6 (64)	1.33 (93)

Population pharmacokinetic analyses demonstrate comparable exposures in children, at least 30kg, dosed by weight-bands (35 mg or 50 mg of dolutegravir) to that observed in adults.

Drug Interactions

Drug interaction trials were performed with dolutegravir and other drugs likely to be coadministered or commonly used as probes for pharmacokinetic interactions. As dolutegravir is not expected to affect the pharmacokinetics of other drugs dependent on hepatic metabolism (Table 9) *[see Drug Interactions (7.1)]*, the primary focus of these drug interaction trials was to evaluate the effect of coadministered drug on dolutegravir (Table 10).

Dosing or regimen recommendations as a result of established and other potentially significant drug-drug interactions with dolutegravir are provided in Table 9 *[see Dosage and Administration, Drug Interactions (7.3)]*.

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

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug with/without Dolutegravir No Effect = 1.00		
			C_{max}	AUC	C_τ or C_{24}
Daclatasvir 60 mg once daily	50 mg once daily	12	1.03 (0.84 to 1.25)	0.98 (0.83 to 1.15)	1.06 (0.88 to 1.29)
Ethinyl estradiol 0.035 mg	50 mg twice daily	15	0.99 (0.91 to 1.08)	1.03 (0.96 to 1.11)	1.02 (0.93 to 1.11)
Metformin 500 mg twice daily	50 mg once daily	15[a]	1.66 (1.53 to 1.81)	1.79 (1.65 to 1.93)	-
Metformin 500 mg twice daily	50 mg twice daily	15[b]	2.11 (1.91 to 2.33)	2.45 (2.25 to 2.66)	-
Methadone 16 to 150 mg	50 mg twice daily	11	1.00 (0. 94 to 1.06)	0.98 (0.91 to 1.06)	0.99 (0.91 to 1.07)
Midazolam 3 mg	25 mg once daily	10	-	0.95 (0.79 to 1.15)	-
Norelgestromin 0.25 mg	50 mg twice daily	15	0.89 (0.82 to 0.97)	0.98 (0.91 to 1.04)	0.93 (0.85 to 1.03)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.10 (0.99 to 1.22)	1.06 (0.98 to 1.16)	1.21 (1.07 to 1.38)
Tenofovir disoproxil fumarate 300 mg once daily	50 mg once daily	15	1.09 (0.97 to 1.23)	1.12 (1.01 to 1.24)	1.19 (1.04 to 1.35)

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

Table 10. 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)
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)
Boceprevir 800 mg every 8 hours	50 mg once daily	13	1.05 (0.96 to 1.15)	1.07 (0.95 to 1.20)	1.08 (0.91 to 1.28)
Calcium carbonate 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)

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

12.4 Microbiology

Mechanism of Action

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. 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.

Antiviral Activity in Cell Culture

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.

Antiviral Activity in Combination with Other Antiviral Agents

The antiviral activity of dolutegravir was not antagonistic when combined with the INSTI, raltegravir; non-nucleoside reverse transcriptase inhibitors (NNRTIs), efavirenz or nevirapine; the nucleoside reverse transcriptase inhibitors (NRTIs), abacavir or stavudine; the protease inhibitors (PIs), amprenavir or lopinavir; the CCR5 co-receptor antagonist, maraviroc; or the fusion inhibitor, enfuvirtide. Dolutegravir antiviral activity was not antagonistic when combined with the HBV reverse transcriptase inhibitor, adefovir, or inhibited by the antiviral, ribavirin.

Resistance

Cell Culture: 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.

Treatment-Naïve Subjects: No subjects in the dolutegravir 50-mg once-daily 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. No treatment-emergent primary resistance substitutions were observed in either treatment group in the FLAMINGO trial through Week 96.

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

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Subjects: VIKING-3 examined the efficacy of dolutegravir 50 mg twice daily plus optimized background therapy in subjects with prior or current virologic failure on an INSTI-(elvitegravir or raltegravir) containing regimen.

In VIKING-4 (ING116529), 30 subjects with current virological failure on an INSTI-containing regimen and genotypic evidence of INSTI-resistance substitutions at screening were randomized to receive either dolutegravir 50 mg twice daily or placebo with the current failing regimen for 7 days and then all subjects received open-label dolutegravir plus optimized background regimen from Day 8. Virologic responses at Week 48 by baseline genotypic and phenotypic INSTI-resistance categories and the INSTI resistance-associated substitutions that emerged on dolutegravir treatment in VIKING-4 were consistent with those seen in VIKING-3.

Response by Baseline Genotype

Of the 183 subjects with baseline data, 30% harbored virus with a substitution at Q148, and 33% had no primary INSTI-resistance substitutions (T66A/I/K, E92Q/V, Y143R/C/H, Q148H/R/K, and N155H) at baseline, but had historical genotypic evidence of INSTI-resistance substitutions, phenotypic evidence of elvitegravir or raltegravir resistance, or genotypic evidence of INSTI-resistance substitutions at screening.

Response rates by baseline genotype were analyzed in an "as-treated" analysis at Week 48 (n = 175) (Table 11). The response rate at Week 48 to dolutegravir-containing regimens was 47% (24 of 51) when Q148 substitutions were present at baseline; Q148 was always present with additional INSTI-resistance substitutions (see Table 11). In addition, a diminished virologic response of 40% (6 of 15) was observed when the substitution E157Q or K was present at baseline with other INSTI-resistance substitutions but without a Q148H or R substitution.

Table 11. Response by Baseline Integrase Genotype in Subjects with Prior Experience to an Integrase Strand Transfer Inhibitor in VIKING-3

Baseline Genotype	Week 48 (<50 copies/mL) n = 175
Overall Response	66% (116/175)
No Q148 substitution[a]	74% (92/124)
Q148H/R + G140S/A/C without additional INSTI-resistance substitution[b]	61% (17/28)
Q148H/R + ≥2 INSTI-resistance substitutions[b,c]	29% (6/21)

[a] Includes INSTI-resistance substitutions Y143R/C/H and N155H.
[b] INSTI-resistance substitutions included T66A, L74I/M, E138A/K/T, G140S/A/C, Y143R/C/H, E157Q, G163S/E/K/Q, or G193E/R. Two additional subjects had baseline genotypes of Q148Q/R plus L74L/I/M (virologic failure) and Q148R plus E138K (responder).
[c] The most common pathway with Q148H/R + greater than or equal to 2 INSTI-resistance substitutions had Q148+G140+E138 substitutions (n = 16).

Response by Baseline Phenotype

Response rates by baseline phenotype were analyzed in an as-treated analysis using all subjects with available baseline phenotypes through Week 48 (n = 163) (see Table 12). These baseline phenotypic groups are based on subjects enrolled in VIKING-3 and are not meant to represent definitive clinical susceptibility cut points for dolutegravir. The data are provided to guide clinicians on the likelihood of virologic success based on pretreatment susceptibility to dolutegravir in INSTI-resistant patients.

Table 12. Response by Baseline Dolutegravir Phenotype (Fold-Change from Reference) in Subjects with Prior Experience to an Integrase Strand Transfer Inhibitor in VIKING-3

Baseline Dolutegravir Phenotype (Fold-Change from Reference)	Response at Week 48 (<50 copies/mL) Subset n = 163
Overall Response	64% (104/163)
<3-fold change	72% (83/116)
3- <10-fold change	53% (18/34)
≥10-fold change	23% (3/13)

Integrase Strand Transfer Inhibitor Treatment-Emergent Resistance

There were 50 subjects with virologic failure on the dolutegravir twice-daily regimen in VIKING-3 with HIV-1 RNA greater than 400 copies per mL at the failure timepoint, Week 48 or beyond, or the last timepoint on trial. Thirty-nine subjects with virologic failure had resistance data that were used in the Week 48 analysis. In the Week 48 resistance analysis 85% (33 of 39) of the subjects with virologic failure had treatment-emergent INSTI-resistance substitutions in their isolates. The most common treatment-emergent INSTI-resistance substitution was T97A. Other frequently emergent INSTI-resistance substitutions included L74M, I or V, E138K or A, G140S, Q148H, R or K, M154I, or N155H. Substitutions E92Q, Y143R or C/H, S147G, V151A, and E157E/Q each emerged in 1 to 3 subjects' isolates. At failure, the median dolutegravir fold-change from reference was 61-fold (range: 0.75 to 209) for isolates with emergent INSTI-resistance substitutions (n = 33).

Resistance to one or more background drugs in the dolutegravir twice-daily regimen also emerged in 49% (19 of 39) subjects in the Week 48 resistance analysis.

Cross-Resistance

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.

Emtricitabine and Tenofovir Alafenamide

12.1 Mechanism of Action

Emtricitabine and tenofovir alafenamide is a fixed dose combination of antiretroviral drugs emtricitabine (FTC) and tenofovir alafenamide (TAF) *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In a thorough QT/QTc study in 48 healthy subjects, TAF at the recommended dose or at a dose approximately 5 times the recommended dose, did not affect the QT/QTc interval and did not prolong the PR interval. The effect of the other component of emtricitabine and tenofovir alafenamide, FTC, or the combination of FTC and TAF on the QT interval is not known.

12.3 Pharmacokinetics

Absorption, Distribution, Metabolism, and Excretion

The pharmacokinetic (PK) properties of the components of emtricitabine and tenofovir alafenamide are provided in Table 13. The multiple dose PK parameters of FTC and TAF and its metabolite tenofovir are provided in Table 14.

Table 13. Pharmacokinetic Properties of the Components of emtricitabine and tenofovir alafenamide

	Emtricitabine	Tenofovir Alafenamide
Absorption		
T_{max} (h)	3	1
Effect of high fat meal (relative to fasting)[a]	AUC Ratio = 0.91 (0.89, 0.93) C_{max} Ratio = 0.74 (0.69, 0.78)	AUC Ratio = 1.75 (1.64, 1.88) C_{max} Ratio= 0.85 (0.75, 0.95)
Distribution		
% Bound to human plasma proteins	<4	~80
Source of protein binding data	*In vitro*	Ex vitro
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
% 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 150-180 hours within PBMCs.
d. Dosing in mass balance studies: FTC (single dose administration of [^{14}C] emtricitabine after multiple dosing of emtricitabine for ten days); TAF (single dose administration of [^{14}C] tenofovir alafenamide).

Table 14. Multiple Dose PK Parameters of Emtricitabine, Tenofovir Alafenamide and its Metabolite Tenofovir Following Oral Administration with Food in HIV-Infected Adults

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

CV = Coefficient of Variation; NA=Not Applicable

a. From Intensive PK analysis in a phase 2 trial in HIV infected adults treated with FTC+TAF and EVG+COBI.
b. From Population PK analysis in two trials of treatment-naïve adults with HIV-1 infection treated with FTC+TAF with EVG+COBI (N=539).
c. From Population PK analysis in two trials of treatment-naïve adults with HIV-1 infection treated with FTC+TAF with EVG+COBI (N=841).

Specific Populations

Patients with Renal Impairment

The pharmacokinetics of FTC+TAF combined with EVG+COBI in HIV infected subjects with renal impairment (eGFR 30 to 69 mL per minute by Cockcroft-Gault method) were evaluated in a subset of virologically-suppressed subjects in an open-label trial (Table 15).

Table 15. Pharmacokinetics of the Components of Emtricitabine and tenofovir alafenamide and a Metabolite of TAF (Tenofovir) in HIV-Infected Adults with Renal Impairment Compared to Subjects with Normal Renal Functiona

Creatinine Clearance	AUC_{tau} (microgram·hour per mL) Mean (CV%)		
	≥90 mL per minute (N=18)[b]	60-89 mL per minute (N=11)[c]	30-59 mL per minute (N=18)
Emtricitabine	11.4 (11.9)	17.6 (18.2)	23.0 (23.6)
Tenofovir Alafenamide*	0.23 (47.2)	0.24 (45.6)	0.26 (58.8)
Tenofovir	0.32 (14.9)	0.46 (31.5)	0.61 (28.4)

*AUC_{last}
a. Trial in HIV infected adults with renal impairment treated with FTC+TAF with EVG+COBI.
b. From a phase 2 trial in HIV-infected adults with normal renal function treated with FTC+TAF with EVG+COBI.
c. These subjects had an eGFR ranging from 60 to 69 mL per minute.

Patients with Hepatic Impairment

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

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

Hepatitis B and/or Hepatitis C Virus Coinfection

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

Pediatric Patients

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 16).

Table 16 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

Exposures of FTC and TAF achieved in 23 pediatric subjects between the ages of 6 to less than 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 17) *[see Use in Specific Populations (8.4)]*.12 years and weighing at least 25 kg (55 lbs) who received FTC+TAF with EVG+COBI were

Table 17. 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[b] (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

Geriatric Patients

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)]*.

Race

Based on population pharmacokinetic analyses, no dosage adjustment is recommended based on race.

Gender

Based on population pharmacokinetic analyses, no dosage adjustment is recommended based on gender.

Drug Interaction Studies

The effects of coadministered drugs on the exposure of TAF are shown in Table 18 and the effects of emtricitabine and tenofovir alafenamide or its components on the exposure of coadministered drugs are shown in Table 19 [these studies were conducted with emtricitabine and tenofovir alafenamide or the components of emtricitabine and tenofovir alafenamide (FTC or TAF) administered alone]. For information regarding clinical recommendations, *see Drug Interactions (7)*.

Table 18 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 (0.84, 1.22)	1.01 (0.94, 1.09)	NC
Sertraline	50 (dosed as a single dose)	10[c]	19	1.00 (0.86, 1.16)	0.96 (0.89, 1.03)	NC

NC=Not Calculated
a. All intraction 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 19. Drug Interactions: Changes in PK Parameters for Coadministered Drug in the Presence of emtricitabine and tenofovir alafenamide or the Individual Components[a]

Coadministered Drug	Coadministered Drug 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)
Midazolamc	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

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

Tenofovir Alafenamide: TAF is a phosphonoamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analog). Plasma exposure to TAF allows for permeation into cells and then TAF is intracellularly converted to tenofovir through hydrolysis by cathepsin A. Tenofovir is subsequently phosphorylated by cellular kinases to the active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV-1 replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination.

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

Antiviral Activity in Cell Culture

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

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

Tenofovir Alafenamide: The antiviral activity of TAF against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells and CD4-T lymphocytes. The EC_{50} values for TAF ranged from 2.0 to 14.7 nM.

TAF displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including sub-types A, B, C, D, E, F, and G (EC_{50} values ranged from 0.10 to 12 nM) and strain specific activity against HIV-2 (EC_{50} values ranged from 0.91 to 2.63 nM).

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

Resistance

In Cell Culture

Emtricitabine: HIV-1 isolates with reduced susceptibility to FTC were selected in cell culture and in subjects treated with FTC. Reduced susceptibility to FTC was associated with M184V or I substitutions in HIV-1 RT.

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

In Clinical Trials

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

One subject was identified with emergent resistance to FTC (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

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

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

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

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

13 NONCLINICAL TOXICOLOGY

Dolutegravir

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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-fold 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-fold and 15-fold higher in males and females, respectively, than those in humans at the recommended dose of 50 mg twice daily.

Mutagenesis

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

Impairment of Fertility

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 at the recommended dose of 50 mg twice daily.

Emtricitabine and Tenofovir Alafenamide

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Emtricitabine:

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

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

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

Tenofovir Alafenamide

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

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

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

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

Dolutegravir

The efficacy of dolutegravir is based on analyses of data from 3 trials, SPRING-2 (ING113086), SINGLE (ING114467), and FLAMINGO (ING114915), in treatment-naïve, HIV-1-infected subjects (n = 2,125); one trial, SAILING (ING111762), in treatment-experienced, INSTI-naïve HIV-1-infected subjects (n = 715); and from VIKING-3 (ING112574) trial in INSTI-experienced HIV-1-infected subjects (n = 183). The use of dolutegravir in pediatric patients aged 6 years and older is based on evaluation of safety, pharmacokinetics, and efficacy in a multicenter, open-label trial in subjects without INSTI resistance.

14.1 Adult Subjects

Treatment-Naïve Subjects

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

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

Outcomes for SPRING-2 (Week 96 analysis) and SINGLE (Week 144 open-label phase analysis which followed the Week 96 double-blind phase) are provided in Table 20. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 20. Virologic Outcomes of Randomized Treatment in SPRING-2 at Week 96 and SINGLE at Week 144 (Snapshot Algorithm)

	SPRING-2 Week 96		SINGLE Week 144	
	Dolutegravir 50 mg Once Daily + 2NRTIs (n = 403)	Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)	Dolutegravir 50 mg + EPZICOM Once Daily (n = 414)	ATRIPLA Once Daily (n = 419)
HIV-1 RNA <50 copies/mL	82%	78%	71%	63%
Treatment differencea	4.9% (95% CI: -0.6%, 10.3%)[d]		8.3% (95% CI: 2.0%, 14.6%)[e]	
Virologic nonresponse	5%	10%	10%	7%
Data in window not <50 copies/mL	1%	3%	4%	1%
Discontinued for lack of efficacy	2%	3%	3%	3%
Discontinued for other reasons while not suppressed	<1%	3%	3%	4%
Change in ART regimen	<1%	<1%	0	0
No virologic data Reasons	12%	12%	18%	30%
Discontinued study/study drug due to adverse event or death[b]	2%	2%	4%	14%
Discontinued study/study drug for other reasons[c]	8%	9%	12%	13%
Missing data during window but on study	2%	<1	2%	3%
Proportion (%) of Subjects with HIV-1 RNA <50 copies/mL by Baseline Category				
Plasma viral load (copies/mL)				
≤100,000	84%	83%	73%	64%
>100,000	79%	63%	69%	61%
Gender				
Male	84%	79%	72%	66%
Female	70%	68%	69%	48%
Race				
White	83%	78%	72%	71%
African American/African Heritage/Other	77%	75%	71%	47%

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%).
e The primary endpoint was assessed at Week 48 and the virologic success rate was 88% in the group receiving dolutegravir and 81% in the ATRIPLA group, with a treatment difference of 7.4% and 95% CI of (2.5%, 12.3%).
SPRING-2: Virologic outcomes were also comparable across baseline characteristics including CD4+ cell count, age, and use of EPZICOM or emtricitabine and tenofovir disoproxil fumarate as NRTI background regimen. The median change in CD4+ cell counts from baseline were 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.

SINGLE: Treatment differences were maintained across baseline characteristics including baseline viral load, CD4+ cell count, age, gender, and race.

The adjusted mean changes in CD4+ cell counts from baseline were 378 cells per mm^3 in the group receiving dolutegravir + EPZICOM and 332 cells per mm^3 for the ATRIPLA group at 144 weeks. The adjusted difference between treatment arms and 95% CI was 46.9 cells per mm^3 (15.6 cells per mm^3, 78.2 cells per mm^3) (adjusted for pre-specified stratification factors: baseline HIV-1 RNA, and baseline CD4+ cell count).

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

FLAMINGO: In FLAMINGO, 485 subjects were randomized and received at least 1 dose of either dolutegravir 50 mg once daily (n = 243) or darunavir + ritonavir 800 mg/100 mg once daily (n = 242), both in combination with investigator-selected NRTI background regimen (either fixed-dose abacavir and lamivudine [EPZICOM] or fixed-dose emtricitabine/tenofovir disoproxil fumarate [TRUVADA]). There were 484 subjects included in the efficacy and safety analyses. At baseline, the median age of subjects was 34 years, 15% female, 28% non-white, 10% had hepatitis B and/or C virus co-infection, 3% were CDC Class C (AIDS), 25% had HIV-1 RNA greater than 100,000 copies per mL, and 35% had CD4+ cell count less than 350 cells per mm^3; these characteristics were similar between treatment groups. Overall response rates by Snapshot algorithm through Week 96 were 80% for dolutegravir and 68% for darunavir/ritonavir. The proportion of subjects who were non-responders (HIV-1 RNA greater than or equal to 50 copies per mL) at Week 96 was 8% and 12% in the arms receiving dolutegravir and darunavir + ritonavir, respectively; no virologic data were available for 12% and 21% for subjects treated with dolutegravir and darunavir + ritonavir, respectively. The adjusted overall response rate difference in proportion and 95% CI was 12.4% (4.7%, 20.2%). No treatment-emergent primary resistance substitutions were observed in either treatment group.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects

In the international, multicenter, double-blind trial (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 1 fully active agent. There were 715 subjects included in the efficacy and safety analyses. At baseline, the median age was 43 years, 32% were female, 50% non-white, 16% had hepatitis B and/or C virus co-infection, 46% were CDC Class C (AIDS), 20% had HIV-1 RNA greater than 100,000 copies per mL, and 72% had CD4+ cell count less than 350 cells per mm^3; these characteristics were similar between treatment groups. All subjects had at least 2-class antiretroviral treatment resistance, and 49% of subjects had at least 3-class antiretroviral treatment resistance at baseline. Week 48 outcomes for SAILING are shown in Table 21.

Table 21. Virologic Outcomes of Randomized Treatment in SAILING at 48 Weeks (Snapshot Algorithm)

	Dolutegravir 50 mg Once Daily + BR[a] (n = 354)	Raltegravir 400 mg Twice Daily + BR[a] (n = 361)
HIV-1 RNA <50 copies/mL	71	64%
Adjusted[b] treatment difference	7.4% (95% CI: 0.7%, 14.2%)	
Virologic nonresponse	20%	28%
No virologic data		
Reasons	9%	9%
Discontinued study/study drug due to adverse event or death	3%	4%
Discontinued study/study drug for other reasons[c]	5%	4%
Missing data during window but on study	2%	1%
Proportion (%) with HIV-1 RNA <50 copies/mL by Baseline Category		
Plasma viral load (copies/mL)		
≤50,000 copies/mL	75%	71%
>50,000 copies/mL	62%	47%
Background regimen		
No darunavir use	67%	60%
Darunavir use with primary PI substitutions	85%	67%
Darunavir use without primary PI substitutions	69%	70%
Gender		
Male	70%	66%
Female	74%	60%
Race		
White	75%	71%
African-American/African Heritage/Other	67%	57%

a BR = Background regimen. Background regimen was restricted to less than or equal to 2 antiretroviral treatments with at least 1 fully active agent.
b Adjusted for pre-specified stratification factors.
c Other includes reasons such as withdrew consent, loss to follow-up, moved, and protocol deviation.

Treatment differences were maintained across the baseline characteristics including CD4+ cell count and age.

The mean changes in CD4+ cell counts from baseline were 162 cells per mm^3 in the group receiving dolutegravir and 153 cells per mm^3 in the raltegravir group.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Subjects

VIKING-3 examined the effect of dolutegravir 50 mg twice daily over 7 days of functional monotherapy, followed by optimized background therapy (OBT) with continued treatment of dolutegravir 50 mg twice daily.

In the multicenter, open-label, single-arm VIKING-3 trial, 183 HIV-1-infected, antiretroviral treatment-experienced adults with virological failure and current or historical evidence of raltegravir and/or elvitegravir resistance received dolutegravir 50 mg twice daily with the current failing background regimen for 7 days, then received dolutegravir with OBT from Day 8. A total of 183 subjects enrolled: 133 subjects with INSTI resistance at screening and 50 subjects with only historical evidence of resistance (and not at screening). At baseline, median age of subjects was 48 years; 23% were female, 29% non-white, and 20% had hepatitis B and/or C virus coinfection. Median baseline CD4+ cell count was 140 cells per mm^3, median duration of prior antiretroviral treatment was 13 years, and 56% were CDC Class C. Subjects showed multiple-class antiretroviral treatment resistance at baseline: 79% had greater than or equal to 2 NRTI, 75% greater than or equal to 1 NNRTI, and 71% greater than or equal to 2 PI major substitutions; 62% had non-R5 virus.

Mean reduction from baseline in HIV-1 RNA at Day 8 (primary endpoint) was 1.4 $\log_{10}$ (95% CI: 1.3 $\log_{10}$, 1.5 $\log_{10}$). Response at Week 48 was affected by baseline INSTI substitutions *[see Microbiology (12.4)]*.

After the functional monotherapy phase, subjects had the opportunity to re-optimize their background regimen when possible. Week 48 virologic outcomes for VIKING-3 are shown in Table 22.

Table 22. Virologic Outcomes of Treatment of VIKING-3 at 48 Weeks (Snapshot Algorithm)

	Dolutegravir 50 mg Twice Daily + OBT (n = 183)
HIV-1 RNA <50 copies/mL	63%
Virologic nonresponse	32%
No virologic data	
Reasons	3%
Discontinued study/study drug due to adverse event or death	
Proportion (%) with HIV-1 RNA <50 copies/mL by Baseline Category	
Gender	
Male	63%
Female	64%
Race	
White	63%
African-American/African Heritage/Other	64%

Subjects harboring virus with Q148 and with additional Q148-associated secondary substitutions also had a reduced response at Week 48 in a stepwise fashion [see Microbiology (12.4)].

The median change in CD4+ cell count from baseline was 80 cells per mm^3 at Week 48.

14.2 Pediatric Subjects

IMPAACT P1093 is a Phase 1/2, 48-week, multicenter, open-label trial to evaluate the pharmacokinetic parameters, safety, tolerability, and efficacy of dolutegravir in combination treatment regimens in HIV-1-infected infants, children, and adolescents. Subjects were stratified by age, enrolling adolescents first (Cohort 1: aged 12 to less than 18 years) and then younger children (Cohort 2A: aged 6 to less than 12 years). All subjects received a weight-based dose of Dolutegravir [see Dosage and Administration].

These 46 subjects had a mean age of 12 years (range: 6 to 17), were 54% female and 52% black. At baseline, mean plasma HIV-1 RNA was 4.6 $\log_{10}$ copies per mL, median CD4+ cell count was 639 cells per mm^3 (range: 9 to 1,700), and median CD4+% was 23% (range: 1% to 44%). Overall, 39% had baseline plasma HIV-1 RNA greater than 50,000 copies per mL and 33% had a CDC HIV clinical classification of category C. Most subjects had previously used at least 1 NNRTI (50%) or 1 PI (70%).

At Week 24, the proportion of subjects with HIV-1 RNA less than 50 copies per mL in Cohort 1 and Cohort 2A was 70% (16/23) and 61% (14/23), respectively. At Week 48, the proportion of subjects from Cohort 1 with HIV-1 RNA less than 50 copies per mL was 61% (14/23). Virologic outcomes were also evaluated based on body weight. Across both cohorts, virologic suppression (HIV-1 RNA less than 50 copies per mL) at Week 24 was achieved in 75% (18/24) of subjects weighing at least 40 kg and 55% (6/11) of subjects in the 30 to less than 40 kg weight-band. At Week 48, 63% (12/19) of the subjects in Cohort 1 weighing at least 40 kg were virologically suppressed.

The median CD4+ cell count increase from baseline to Week 48 was 84 cells per mm^3 in Cohort 1. For Cohort 2A, the median CD4+ cell count increase from baseline to Week 24 was 209 cells per mm^3.

Emtricitabine and Tenofovir Alafenamide

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

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 23 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, 100% of subjects remained virologically suppressed at Week 24. From a mean (SD) baseline CD4+ cell count of 966 (201.7), the mean change from baseline in CD4+ cell count was -150 cells/mm^3 and the mean (SD) change in CD4+% was -1.5% (3.7%) at Week 24. All subjects maintained CD4+ cell counts above 400 cells/mm^3 *[see Adverse Reactions (6.1) and Use in Specific Populations (8.4)]*.

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

16 HOW SUPPLIED/STORAGE AND HANDLING

HDPE white opaque colour plastic bottle with child resistant white opaque polypropylene plastic cap with pulp liner x 30's (Box of 30's).

Storage Conditions:

Store at temperatures not exceeding 30°C.

- Keep container tightly closed.

17 PATIENT COUNSELING INFORMATION

Dolutegravir

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

Drug Interactions

Dolutegravir is contraindicated with dofetilide because interactions between these drugs can result in potentially life-threatening adverse events *[see Contraindications (4)]*.

Hypersensitivity Reactions

Advise patients to immediately contact their healthcare provider if they develop rash. Instruct patients to immediately stop taking dolutegravir 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 (5.1)]*.

Effects on Serum Liver Biochemistries in Patients with Hepatitis B or C Co-infection

Advise patients that it is recommended to have laboratory testing before and during therapy as patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of dolutegravir *[see Warnings and Precautions (5.2)]*.

Fat Redistribution

Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time *[see Warnings and Precautions (5.3)]*.

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 is started *[see Warnings and Precautions (5.4)]*.

Lactation

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

Missed Dosage

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

Emtricitabine and Tenofovir Alafenamide

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

Post-treatment Acute Exacerbation of Hepatitis B in Patients with HBV Coinfection

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued products containing FTC and/or TDF, and may likewise occur with discontinuation of emtricitabine and tenofovir alafenamide *[see Warnings and Precautions (5.1)]*. Advise the patient to not discontinue emtricitabine and tenofovir alafenamide without first informing their healthcare provider.

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any symptoms of infection, as in some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started *[see Warnings and Precautions (5.2)]*.

New Onset or Worsening Renal Impairment

Advise patients to avoid taking emtricitabine and tenofovir alafenamide with concurrent or recent use of nephrotoxic agents. Renal impairment, including cases of acute renal failure, has been reported in association with the use of tenofovir prodrugs *[see Warnings and Precautions (5.3)]*.

Lactic Acidosis and Severe Hepatomegaly

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with use of drugs similar to emtricitabine and tenofovir alafenamide. Advise patients that they should stop emtricitabine and tenofovir alafenamide if they develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity *[see Warnings and Precautions (5.4)]*.

Missed Dosage

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

Lactation

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

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Caution: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription

ADR REPORTING STATEMENT: For suspected adverse drug reaction report to the FDA: www.fda.gov.ph
Please seek medical attention immediately at the first sign of any adverse drug reaction.

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Registration Number: DR-XY48349
Date of First Authorization: Oct/2022
Date of Revision of Package Insert: Oct/2022