Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

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

2. Qualitative and quantitative composition

Each film coated tablet contains:
Dolutegravir sodium equivalent to 50 mg of Dolutegravir,
Lamivudine 300 mg,
Tenofovir Alafenamide 25 mg equivalent to 28 mg of Tenofovir Alafenamide Fumarate.
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet.
White to off white colored, oval shaped, biconvex, film coated tablets, debossed with 'DL' on one side and plain on the other side.

4. Clinical particulars

4.1 Therapeutic indications

Dolutegravir, lamivudine and tenofovir alafenamide tablets, a three-drug combination of dolutegravir (integrase strand transfer inhibitor [INSTI]), lamivudine, and tenofovir alafenamide (TAF), both HIV nucleoside analog reverse transcriptase inhibitors (NRTIs), is indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 25 kg

4.2 Posology and method of administration

Pregnancy Testing: Pregnancy testing is recommended before initiation of dolutegravir, lamivudine and tenofovir alafenamide tablets in adolescents and adults of childbearing potential.

Posology

Dolutegravir, lamivudine and tenofovir alafenamide tablets is a three-drug fixed-dose combination product containing 50 mg of dolutegravir, 300 mg of lamivudine, and 25 mg of tenofovir alafenamide (TAF). The recommended dosage of dolutegravir, lamivudine and tenofovir alafenamide tablets is one tablet taken orally once daily with or without food in adults and pediatric patients weighing at least 25 kg (55 lbs).

Dosing Recommendations for Dolutegravir, Lamivudine and Tenofovir Alafenamide Tablets with Coadministered Medications

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir and/or Concomitant Drug	Clinical Comment
HIV-1 Antiviral Agents		
Non-nucleoside reverse transcriptase inhibitor: Etravirine[a]	↓ Dolutegravir	Use of dolutegravir, lamivudine and tenofovir alafenamide tablets with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or

Non-nucleoside reverse transcriptase inhibitor: Efavirenz[a]	↓ Dolutegravir	If coadministration with efavirenz is necessary, an additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, lamivudine and tenofovir alafenamide
Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓ Dolutegravir	Avoid coadministration with dolutegravir, lamivudine and tenofovir alafenamide tablets because there are insufficient data to make dosing
Protease inhibitor: Fosamprenavir/ritonavir[a] Tipranavir/ritonavir[a]	↓ Dolutegravir ↓ Dolutegravir ↓ TAF	If coadministration with fosamprenavir/ritonavir is necessary, an additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, lamivudine and tenofovir alafenamide tablets. Coadministration is not recommended
Other Agents		
Dofetilide	↑ Dofetilide	Coadministration is contraindicated with dolutegravir, lamivudine and tenofovir alafenamide tablets
Carbamazepine[a]	↓ Dolutegravir ↓ TAF	Consider alternative anticonvulsant. If coadministration is necessary, an additional 50- mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, lamivudine and
Oxcarbazepine Phenytoin Phenobarbital	↓ Dolutegravir ↓ TAF	Avoid coadministration with dolutegravir, lamivudine and tenofovir alafenamide tablets because there are insufficient data to make dosing
St. John's wort (*Hypericum perforatum*)	↓ TAF	Coadministration is not recommended with dolutegravir, lamivudine and tenofovir alafenamide tablets.
Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing antacids[a] or laxatives Sucralfate	↓ Dolutegravir	Administer dolutegravir, lamivudine and tenofovir alafenamide tablets 2 hours before or 6 hours after taking medications containing polyvalent cations.
Oral calcium or iron supplements, including multivitamins containing calcium or iron*	↓ Dolutegravir	Administer dolutegravir, lamivudine and tenofovir alafenamide tablets 2 hours before or 6 hours after taking supplements containing calcium or iron. Alternatively, dolutegravir and supplements containing calcium or iron can be taken together with food.
Potassium channel blocker: Dalfampridine	↓ Dalfampridine	Elevated levels of dalfampridine increase the risk of seizures. The potential benefits of taking dalfampridine concurrently with dolutegravir, lamivudine and tenofovir alafenamide tablets should be considered against the risk of seizures
Metformin	↑ Metformin	Refer to the prescribing information of metformin for assessing the benefit and risk of concomitant use with metformin.
Rifampin[a]	↓ Dolutegravir ↓ TAF	Coadministration is not recommended with dolutegravir, lamivudine and tenofovir alafenamide tablets.

Rifabutin Rifapentine	↓ TAF	Coadministration is not recommended with dolutegravir, lamivudine and tenofovir alafenamide tablets.

Missed dose

Instruct patients that if they miss a dose of dolutegravir, lamivudine and tenofovir alafenamide tablets, to take it as soon as they remember. Advise patients not to double their next dose or take more than the prescribed dose

Geriatric Use

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

TAF: In clinical trials of a TAF-containing regimen, 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.

Renal impairment

Dolutegravir, lamivudine and tenofovir alafenamide tablets is not recommended for patients with creatinine clearance less than 30 mL per min because dolutegravir, lamivudine and tenofovir alafenamide tablets is a fixed-dose combination and the dosage of the individual components cannot be adjusted. If a dose reduction of lamivudine, a component of dolutegravir, lamivudine and tenofovir alafenamide tablets, is required for patients with creatinine clearance less than 30 mL per min, then the individual components should be used [see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)].

Patients with a creatinine clearance between 30 and 49 mL per min receiving dolutegravir, lamivudine and tenofovir alafenamide tablets may experience a 1.6- to 3.3-fold higher lamivudine exposure (AUC) than patients with a creatinine clearance ≥50 mL per min. There are no safety data from randomized, controlled trials comparing dolutegravir, lamivudine and tenofovir alafenamide tablets to the individual components in patients with a creatinine clearance between 30 and 49 mL per min who received dose-adjusted lamivudine. In the original lamivudine registrational trials in combination with zidovudine, higher lamivudine exposures were associated with higher rates of hematologic toxicities (neutropenia and anemia), although discontinuations due to neutropenia or anemia each occurred in <1% of subjects. Patients with a sustained creatinine clearance between 30 and 49 mL per min who receive dolutegravir, lamivudine and tenofovir alafenamide tablets should be monitored for hematologic toxicities. If new or worsening

neutropenia or anemia develop, dose adjustment of lamivudine, per lamivudine prescribing information, is recommended. If lamivudine dose adjustment is indicated, dolutegravir, lamivudine and tenofovir alafenamide tablets should be discontinued and the individual components should be used to construct the treatment regimen.

There is inadequate information to recommend appropriate dosing of dolutegravir, lamivudine and tenofovir alafenamide in patients requiring dialysis.

4.3 Contraindications

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

with prior hypersensitivity reaction to dolutegravir, lamivudine, or tenofovir alafenamide.

receiving dofetilide due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events with concomitant use of dolutegravir

4.4 Special warnings and precautions for use

Hepatotoxicity

Hepatic adverse events have been reported in patients receiving a dolutegravir-containing regimen. Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of dolutegravir, emtricitabine and tenofovir alafenamide tablets. In some cases, the elevations in transaminases were consistent with immune reconstitution syndrome or hepatitis B reactivation particularly in the setting where anti-hepatitis therapy was withdrawn. Cases of hepatic toxicity, including elevated serum liver biochemistries, hepatitis, and acute liver failure have been reported in patients receiving a dolutegravir-containing regimen without pre-existing hepatic disease or other identifiable risk factors. Drug-induced liver injury leading to liver transplant has been reported with fixed-dose abacavir, dolutegravir, and lamivudine. Monitoring for hepatotoxicity is recommended.

Hypersensitivity Reactions

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

patients who have experienced a previous hypersensitivity reaction to dolutegravir.

Embryo-Fetal Toxicity

An observational study showed an association between dolutegravir, a component of dolutegravir, emtricitabine and tenofovir alafenamide tablets, and an increased risk of neural tube defects when dolutegravir, emtricitabine and tenofovir alafenamide tablets were administered at the time of conception and in early pregnancy. As there is limited understanding of reported types of neural tube defects associated with dolutegravir use and because the date of conception may not be determined with precision, an alternative treatment to dolutegravir, emtricitabine and tenofovir alafenamide tablets should be considered at the time of conception through the first trimester of pregnancy.

Perform pregnancy testing before initiation of dolutegravir, emtricitabine and tenofovir alafenamide tablets in adolescents and adults of childbearing potential to exclude use of dolutegravir, emtricitabine and tenofovir alafenamide tablets during the first trimester of pregnancy. Initiation of dolutegravir, emtricitabine and tenofovir alafenamide tablets is not recommended in adolescents and adults actively trying to become pregnant unless there is no suitable alternative.

Counsel adolescents and adults of childbearing potential to consistently use effective contraception.

In adolescents and adults of childbearing potential currently on dolutegravir, emtricitabine and tenofovir alafenamide tablets who are actively trying to become pregnant, or if pregnancy is confirmed in the first trimester, assess the risks and benefits of continuing dolutegravir, emtricitabine and tenofovir alafenamide tablets versus switching to another antiretroviral regimen and consider switching to an alternative regimen.

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

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

The concomitant use of dolutegravir, emtricitabine and tenofovir alafenamide tablets and other drugs may result in known or potentially significant drug interactions, some of which may lead to :

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

For concomitant drugs for which the interaction can be mitigated, please see Table 3 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with dolutegravir, emtricitabine and tenofovir alafenamide tablets; review concomitant medications during therapy with dolutegravir, emtricitabine and tenofovir alafenamide tablets; and monitor for the adverse reactions associated with the concomitant drugs.

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.

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

Immune Reconstitution Syndrome

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

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

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. Dolutegravir, emtricitabine and tenofovir alafenamide tablets are not recommended in patients with estimated creatinine clearance below 30 mL per minute because data in this population are insufficient.

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

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

Lactic Acidosis and Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including emtricitabine, a component of dolutegravir, emtricitabine and tenofovir alafenamide tablets, and tenofovir DF, another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with dolutegravir, emtricitabine and tenofovir alafenamide tablets should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

4.5 Interaction with other medicinal products and other forms of interaction

Effect of Dolutegravir on the Pharmacokinetics of Other Agents

In vitro, dolutegravir inhibited the renal organic cation transporters, OCT2 (IC_{50} = 1.93 µM) and multidrug and toxin extrusion transporter (MATE) 1 (IC_{50} = 6.34 µM). *In vivo*, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2 and potentially MATE 1. Dolutegravir may increase plasma concentrations of drugs eliminated via OCT2 or MATE 1 (dofetilide and metformin, Table 1) (see section 4.8).

In vitro, dolutegravir inhibited the basolateral renal transporters, organic anion transporter (OAT) 1 (IC_{50} = 2.12 µM) and OAT3 (IC_{50} = 1.97 µM).

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 µM) 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.

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 1) (see section 5.2).

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

Based on drug interaction trial results, the following drugs can be coadministered with dolutegravir without a dose adjustment: atazanavir/ritonavir, darunavir/ritonavir, daclatasvir, elbasvir/grazoprevir, methadone, midazolam, omeprazole, oral contraceptives containing norgestimate and ethinyl estradiol, prednisone, rifabutin, rilpivirine, sofosbuvir/velpatasvir, and Tenofovir (Table 1) (see section 5.2).

Emtricitabine and Tenofovir Alafenamide: TAF, one component of dolutegravir, emtricitabine and tenofovir alafenamide tablets, is a substrate of P-gp, BCRP, OATP1B1, and OATP1B3. Drugs that strongly affect P-gp and BCRP activity may lead to changes in TAF absorption (see Table 3). Drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentration of TAF, which may lead to loss of therapeutic effect of dolutegravir, emtricitabine and tenofovir alafenamide tablets and development of resistance.

Coadministration of dolutegravir, emtricitabine and tenofovir alafenamide tablets with other drugs that inhibit P-gp and BCRP may increase the absorption and plasma concentration of TAF.

TAF is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or UGT1A1. TAF is a weak inhibitor of CYP3A *in vitro*. TAF is not an inhibitor or inducer of CYP3A *in vivo*.
Based on drug interaction studies conducted with the components of emtricitabine and tenofovir alafenamide, no clinically significant drug interactions have been either observed or are expected when emtricitabine and tenofovir alafenamide is combined with the following antiretroviral agents: atazanavir with ritonavir or cobicistat, darunavir with ritonavir or cobicistat, dolutegravir, efavirenz, ledipasvir, lopinavir/ritonavir, maraviroc, nevirapine, raltegravir, rilpivirine, and sofosbuvir. No clinically significant drug interactions have been either observed or are expected when emtricitabine and tenofovir alafenamide is combined with the following drugs: buprenorphine, itraconazole, ketoconazole, lorazepam, methadone, midazolam, naloxone, norbuprenorphine, norgestimate/ethinyl estradiol, and sertraline.

Established and Other Potentially Significant Drug Interactions

There were no drug-drug interaction trials conducted with the dolutegravir, lamivudine, and tenofovir disoproxil fumarate fixed-dose combination tablets.

Table 1 provides clinical recommendations as a result of drug interactions with Dolutegravir, emtricitabine and tenofovir alafenamide. 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 section 5.2).

Table 1. Established and Other Potentially Significant Drug Interactions for Dolutegravir, Emtricitabine and Tenofovir Alafenamide: Alterations in Dose or Regimen May Be Recommended Based on drug Interaction Trials or Predicted Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, TAF and/or Concomitant Drug	Clinical Comment

Antiarrhythmic: Dofetilide	↑ Dolutegravir	Coadministration is contraindicated with dolutegravir, emtricitabine and tenofovir alafenamide tablets *[see Contraindications (4)]*.
Antimycobacterials: Rifabutin Rifampin Rifapentine	↓ TAF	Coadministration of dolutegravir, emtricitabine and tenofovir alafenamide tables with rifabutin, rifampin, or rifapentine is not recommended.
Non-nucleoside reverse Transcriptase inhibitor: Etravirine[a]	↓ Dolutegravir	Use of dolutegravir, emtricitabine and tenofovir alafenamide tablets with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir is not recommended.
Non-nucleoside reverse transcriptase inhibitor: Efavirenz[a]	↓ Dolutegravir	Adjust dose of dolutegravir to 50 mg twice daily. An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, emtricitabine and tenofovir alafenamide tablets.
Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓ Dolutegravir	Avoid coadministration with dolutegravir, emtricitabine and tenofovir alafenamide tablets because there are insufficient data to make dosing recommendations.
Protease inhibitor: Fosamprenavir/ritonavir[a]	↓ Dolutegravir	Adjust dolutegravir dose to 50 mg twice daily. An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, emtricitabine and tenofovir alafenamide tablets.
Other Agents		
Carbamazepine[a]	↓ Dolutegravir	An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, emtricitabine and tenofovir alafenamide tablets; however, use with dolutegravir, emtricitabine and tenofovir alafenamide tablets is not recommended because of the TAF component.
Carbamazepine Oxcarbazepine Phenytoin Phenobarbital	↓ Dolutegravir ↓ TAF	Consider alternative anticonvulsant.
St. John's wort	↓ Dolutegravir	Coadministration of dolutegravir,

(Hypericum perforatum)	↓ TAF	emtricitabine and tenofovir alafenamide tablets with St. John's wort is not recommended.
Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing antacids[a] or laxatives Sucralfate Buffered medications	↓ Dolutegravir	Administer dolutegravir, emtricitabine and tenofovir alafenamide tablets 2 hours before or 6 hours after taking medications containing polyvalent cations.
Oral calcium or iron supplements, including multivitamins containing calcium or iron[a]	↓ Dolutegravir	Administer dolutegravir, emtricitabine and tenofovir alafenamide tablets 2 hours before or 6 hours after taking supplements containing calcium or iron. Alternatively, dolutegravir, emtricitabine and tenofovir alafenamide tablets and supplements containing calcium or iron can be taken together with food.
Metformin[a]	↑ Metformin	With concomitant use, limit the total daily dose of metformin to 1,000 mg either when starting metformin or dolutegravir, emtricitabine and tenofovir alafenamide tablets. When stopping dolutegravir, emtricitabine and tenofovir alafenamide tablets, the metformin dose may require an adjustment. Monitoring of blood glucose when initiating concomitant use and after withdrawal of dolutegravir, emtricitabine and tenofovir alafenamide tablets is recommended.

[a] *See section 5.2 Table 8 or Table 9 for magnitude of interaction.*

Hepatitis C Antiviral Agents

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. l)].

Drugs Affecting Renal Function

Because FTC and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of dolutegravir, emtricitabine and tenofovir alafenamide tablets with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of FTC, tenofovir, and other renally eliminated drugs and this may increase the risk of adverse reactions. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs

Bone Mineral Density Effects

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

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

4.6 Pregnancy and Lactation

Pregnancy

Data from a birth outcome survillance study has identified an increased risk of neural tube defects when dolutegravir, a component of dolutegravir, emtricitabine and tenofovir alafenamide tablets, is administered at the time of conception compared with non-dolutegravir-containing antiretroviral regimens. As defects related to closure of the neural tube occur from conception through the first 6 weeks of gestation, embryos exposed to dolutegravir from the time of conception through the first 6 weeks of gestation are at potential risk. In addition, 2 of the 5 birth defects (encephalocele and iniencephaly), which have been observed with dolutegravir use, although often termed neural tube defects, may occur post-neural tube closure, the time period of which may be later than 6

weeks of gestation, but within the first trimester. Due to the limited understanding of the types of reported neural tube defects associated with dolutegravir use and because the date of conception may not be determined with precision, an alternative treatment to dolutegravir should be considered at the time of conception through the first trimester of pregnancy. Initiation of dolutegravir is not recommended in adolescents and adults actively trying to become pregnant unless there is no suitable alternative *(see Data)*.

In adolescents and adults of childbearing potential currently on dolutegravir who are actively trying to become pregnant, or if pregnancy is confirmed in the first trimester, assess the risks and benefits of continuing dolutegravir versus switching to another antiretroviral regimen and consider switching to an alternative regimen. Advise pregnant adolescents and adults of the potential risk to the embryo exposed to dolutegravir from the time of conception through the first trimester of pregnancy. A benefit-risk assessment should consider factors such as feasibility of switching, tolerability, ability to maintain viral suppression, and risk of transmission to the infant against the risk of neural tube defects *[see Warnings and Precautions (5.1)]*.

There are insufficient human data on the use of dolutegravir, emtricitabine and tenofovir alafenamide tablets during pregnancy to inform a drug-associated risk of birth defects and miscarriage. Tenofovir alafenamide (TAF) use in women during pregnancy has not been evaluated; however, emtricitabine (FTC) use during pregnancy has been evaluated in a limited number of women as reported to the Antiretroviral Pregnancy Registry (APR). Given the limited number of pregnancies exposed to dolutegravir-based regimens reported to the APR, no definitive conclusions can be drawn on the safety of dolutegravir, emtricitabine and tenofovir alafenamide tablets in pregnancy, and continued monitoring is ongoing through the APR. The background rate for major birth defects in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) is 2.7%. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15% to 20%.

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

Emtricitabine and Tenofovir Alafenamide: In animal studies, no adverse developmental effects were observed when the components of emtricitabine and tenofovir alafenamide were administered separately

during the period of organogenesis at exposures 60 and l08 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.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.

Breast-feeding

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

It is not known if dolutegravir, emtricitabine and tenofovir alafenamide tablets affect milk production or have effects on the breastfed child. Because of the potential for (l) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants) and (3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving dolutegravir, emtricitabine and tenofovir alafenamide tablets.

Dolutegravir: It is not known whether dolutegravir is present in human breast milk, affects human milk production, or has effects on the breastfed infant. When administered to lactating rats, dolutegravir was present in milk [see Data].

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

Fertility

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

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

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

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

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

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

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

4.7 Effects on ability to drive and use machines

Patients should be informed that the product can cause dizziness. The patient's clinical status and side effects of product should be considered when evaluating the patient's ability to drive or operate machinery.

4.8 Undesirable effects

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

- Hepatotoxicity [see Warnings and Precautions (4.4)].
- Hypersensitivity Reactions [see Warnings and Precautions (4.4)].
- Severe Acute Exacerbation of Hepatitis B [see Boxed Warning and Warnings and Precautions (4.4)].
- Immune Reconstitution Syndrome [see Warnings and Precautions (4.4)].
- New Onset or Worsening Renal Impairment [see Warnings and Precautions (4.4)].
- Lactic Acidosis and Severe Hepatomegaly with Steatosis [see Warnings and Precautions (4.4)].

Clinical Trials Experience

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

Dolutegravir, Emtricitabine, Tenofovir Alafenamide

Clinical Trials Experience in Adult Subjects

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

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

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

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

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

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

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

Hepatobiliary Disorders: Hepatitis.

Musculoskeletal Disorders: Myositis.

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

Renal and Urinary Disorders: Renal impairment.

Skin and Subcutaneous Tissue Disorders: Pruritus.

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

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

	SPRING-2	
Laboratory Parameter Preferred Term	**Dolutegravir 50 mg Once Daily + 2 NRTIs (n = 403)**	**Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)**
ALT		
Grade 2 (>2.5 to 5.0 x ULN)	4%	4%
Grade 3 to 4 (>5.0 x ULN)	2%	2%
AST		
Grade 2 (>2.5 to 5.0 x ULN)	5%	3%

Grade 3 to 4 (>5.0 x ULN)	3%	2%
Total Bilirubin		
Grade 2 (1.6 to 2.5 x ULN)	3%	2%
Grade 3 to 4 (>2.5 x ULN)	<1%	<1%
Creatine kinase		
Grade 2 (6.0 to 9.9 x ULN)	2%	5%
Grade 3 to 4 (≥10.0 x ULN)	7%	4%
Hyperglycemia		
Grade 2 (126 to 250 mg/dL)	6%	6%
Grade 3 (>250 mg/dL)	<1%	2%
Lipase		
Grade 2 (>1.5 to 3.0 x ULN)	7%	7%
Grade 3 to 4 (>3.0 x ULN)	2%	5%
Total neutrophils		
Grade 2 (0.75 to 0.99 x 10^9)	4%	3%
Grade 3 to 4 (<0.75 x 10^9)	2%	2%

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])

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

[a] Subjects on lipid-lowering agents at baseline were excluded from these analyses (19 subjects in each arm in SPRING-2. Ninety-four subjects initiated a lipid-lowering agent post-baseline; their last fasted on-treatment values (prior to starting the agent) were used regardless if they discontinued the agent (SPRING-2: dolutegravir n = 9, raltegravir n = 13).

Hepatitis B and/or Hepatitis C Virus Co-infection: In Phase 3 trials, subjects with hepatitis B and/or C virus co-infection were permitted to enroll provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal. Overall, the safety profile in subjects with hepatitis B and/or C virus co-infection was similar to that observed in subjects without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or C virus co-infection for all treatment groups. Grades 2 to 4 ALT abnormalities in

hepatitis B and/or C co-infected compared with HIV mono-infected subjects receiving dolutegravir were observed in 18% vs. 3% with the 50-mg once-daily dose and 13% vs. 8% with the 50-mg twice-daily dose. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C at the start of therapy with dolutegravir, particularly in the setting where anti-hepatitis therapy was withdrawn (see section 4.4).

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 section 5.1). 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 section 4.2).

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.

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

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

subjects. BMD declines of 7% or greater at the femoral neck were experienced by 1% of FTC + TAF with EVG + COBI subjects.

Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postmarketing use. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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

Musculoskeletal: Arthralgia, myalgia.

Psychiatric: Anxiety.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

There is known specific treatment for overdose with dolutegravir, emtricitabine and tenofovir alafenamide tablets. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required.

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

Emtricitabine (FTC): Limited clinical experience is available at doses higher than the recommended dose of FTC. In one clinical pharmacology study, single doses of FTC 1,200 mg (6 times the recommended dose of FTC) were administered to 11 subjects. No severe adverse reactions were reported. The effects of higher doses are not known.

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

Tenofovir Alafenamide (TAF): Limited clinical experience is available at doses higher than the recommended dose of TAF. A single dose of 125 mg TAF (5 times the TAF dose in 200 mg/25 mg fixed-dose combination emtricitabine and tenofovir alafenamide) was administered to 48 healthy subjects; no serious adverse reactions were reported. The effects of higher

doses are unknown. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral for systemic use; antivirals for treatment of HIV infections, combinations.

Mechanism of Action

Dolutegravir, emtricitabine and tenofovir alafenamide tablets are a fixed-dose combination of antiretroviral drugs dolutegravir (DTG), emtricitabine (FTC) and tenofovir alafenamide (TAF).

Dolutegravir

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

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

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

5.2 Pharmacokinetic properties

Pharmacokinetics in Adults

Dolutegravir, Emtricitabine and Tenofovir Alafenamide: Dolutegravir, emtricitabine and tenofovir alafenamide from the combination tablets (50 mg/200 mg/25 mg) were comparable to that from TIVICAY® tablets of ViiV

U.S.A. (containing dolutegravir 50 mg) and DESCOVY® tablets of Gilead Sciences, Inc. U.S.A. (containing emtricitabine 200 mg and tenofovir alafenamide 25 mg), respectively, when single doses were administered to healthy subjects under fasted and fed conditions.

Absorption, Distribution, Metabolism, and Excretion: *Dolutegravir*: Following oral administration of dolutegravir, peak plasma concentrations were observed 2 to 3 hours postdose. With once-daily dosing, pharmacokinetic steady-state is achieved within approximately 5 days with average accumulation ratios for AUC, C_{max}, and C_{24h} ranging from 1.2 to 1.5. Dolutegravir is a P-gp substrate *in vitro*. The absolute bioavailability of dolutegravir has not been established. Dolutegravir may be taken with or without food. Food increased the extent of absorption and slowed the rate of absorption of dolutegravir. Low-, moderate-, and high-fat meals increased dolutegravir $AUC_{(0-\infty)}$ by 33%, 41%, and 66%; increased C_{max} by 46%, 52%, and 67%; and prolonged T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively. Dolutegravir is highly bound (greater than or equal to 98.9%) to human plasma proteins based on *in vivo* data and binding is independent of plasma concentration of dolutegravir. The apparent volume of distribution (Vd/F) following 50 mg once-daily administration is estimated at 17.4 L based on a population pharmacokinetic analysis.

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

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

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

The pharmacokinetic properties of dolutegravir have been evaluated in healthy adult subjects and HIV-1-infected adult subjects. Exposure to dolutegravir was generally similar between healthy subjects and HIV-1-infected subjects. The non-linear exposure of dolutegravir following 50 mg twice daily compared with 50 mg once daily in HIV-1-infected subjects (Table 4) was attributed to the use of metabolic inducers in the background antiretroviral regimens of subjects receiving dolutegravir 50 mg twice daily

in clinical trials. Dolutegravir was administered without regard to food in these trials.

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

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

[a] Based on population pharmacokinetic analyses using data from SPRING-1 and SPRING-2.

[b] Based on population pharmacokinetic analyses using data from VIKING (ING112961) and VIKING-3

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

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

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

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

PBMCs = peripheral blood mononuclear cells; CES1 = carboxylesterase 1

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

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

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

d. Dosing in mass balance studies: FTC (single dose administration of [^{14}C] emtricitabine after multiple dosing of emtricitabine for 10 days); TAF (single dose administration of [^{14}C] tenofovir alafenamide).

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

Parameter Mean	Emtricitabine[a]	Tenofovir Alafenamide[b]	Tenofovir[c]
C_{max} (microgram per	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	0.10 (46.7)	NA	0.01 (28.5)

CV = Coefficient of Variation; NA = Not Applicable

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

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

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

Effects of Food on Oral Absorption of Dolutegravir, Emtricitabine and Tenofovir Alafenamide: The pharmacokinetics of dolutegravir, emtricitabine and tenofovir are not affected by food, hence dolutegravir, emtricitabine and tenofovir alafenamide tablets can be administered with or without food.

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

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

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

Renal Impairment: Dolutegravir, emtricitabine and tenofovir alafenamide tablets are not recommended for patients with severe renal impairment (estimated creatinine clearance below 30 mL per min) because dolutegravir, emtricitabine and tenofovir alafenamide tablets are a fixed-dose combination and the dosage of the individual components cannot be adjusted (see section 4.2).

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

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

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

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

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

Emtricitabine and Tenofovir Alafenamide: Pharmacokinetics of FTC and TAF have not been fully evaluated in the elderly (65 years of age and older). Population pharmacokinetics analysis of HIV-infected subjects in Phase 2 and Phase 3 trials of FTC + TAF and EVG + COBI showed that age did not have a clinically relevant effect on exposures of TAF up to 75 years of age.

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

Dolutegravir: The pharmacokinetics of dolutegravir in HIV-1-infected children (n = 14) weighing at least 40 kg were similar to those observed in HIV-1-infected adults who received dolutegravir 50 mg once daily (Table 9)

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)

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

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

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

Dosing or regimen recommendations as a result of established and other potentially significant drug-drug interactions with dolutegravir.

Table 7. 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		
			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)	–

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug with/without Dolutegravir		
			C_{max}	AUC	C_τ or C_{24}
Metformin 500 mg twice daily	50 mg twice daily	15[a]	2.11 (1.91 to 2.33)	2.45 (2.25 to 2.66)	–
Methadone 16 to 150 mg	50 mg twice daily	11	1.00 (0. 94 to 1.06)	0.98 (0.91 to 1.06)	0.99 (0.91 to 1.07)
Midazolam 3 mg	25 mg once daily	10	–	0.95 (0.79 to 1.15)	–
Norelgestromin 0.25 mg	50 mg twice daily	15	0.89 (0.82 to 0.97)	0.98 (0.91 to 1.04)	0.93 (0.85 to 1.03)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.10 (0.99 to 1.22)	1.06 (0.98 to 1.16)	1.21 (1.07 to 1.38)
Tenofovir disoproxil fumarate 300 mg once daily	50 mg once daily	15	1.09 (0.97 to 1.23)	1.12 (1.01 to 1.24)	1.19 (1.04 to 1.35)

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

Table 8. 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		
			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 mg/100 mg twice daily	50 mg once daily	9	0.88 (0.78 to 1.00)	0.75 (0.69 to 0.81)	0.63 (0.52 to 0.76)
Etravirine + lopinavir/ritonavir 200 mg + 400 mg/100 mg twice daily	50 mg once daily	8	1.07 (1.02 to 1.13)	1.11 (1.02 to 1.20)	1.28 (1.13 to 1.45)

Fosamprenavir/ritonavir 700 mg/100 mg twice daily	50 mg once daily	12	0.76 (0.63 to 0.92)	0.65 (0.54 to 0.78)	0.51 (0.41 to 0.63)
Lopinavir/ritonavir 400 mg/100 mg twice daily	30 mg once daily	15	1.00 (0.94 to 1.07)	0.97 (0.91 to 1.04)	0.94 (0.85 to 1.05)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.13 (1.06 to 1.21)	1.12 (1.05 to 1.19)	1.22 (1.15 to 1.30)
Tenofovir 300 mg once daily	50 mg once daily	15	0.97 (0.87 to 1.08)	1.01 (0.91 to 1.11)	0.92 (0.82 to 1.04)
Tipranavir/ritonavir 500 mg/200 mg twice daily	50 mg once daily	14	0.54 (0.50 to 0.57)	0.41 (0.38 to 0.44)	0.24 (0.21 to 0.27)
Antacid (MAALOX®) simultaneous administration	50 mg single dose	16	0.28 (0.23 to 0.33)	0.26 (0.22 to 0.32)	0.26 (0.21 to 0.31)
Antacid (MAALOX) 2 h after dolutegravir	50 mg single dose	16	0.82 (0.69 to 0.98)	0.74 (0.62 to 0.90)	0.70 (0.58 to 0.85)
Boceprevir 800 mg every 8 hours	50 mg once daily	13	1.05 (0.96 to 1.15)	1.07 (0.95 to 1.20)	1.08 (0.91 to 1.28)
Calcium carbonate 1,200 mg simultaneous administration (fasted)	50 mg single dose	12	0.63 (0.50 to 0.81)	0.61 (0.47 to 0.80)	0.61 (0.47 to 0.80)
Calcium carbonate 1,200 mg simultaneous administration (fed)	50 mg single dose	11	1.07 (0.83 to 1.38)	1.09 (0.84 to 1.43)	1.08 (0.81 to 1.42)
Calcium carbonate 1,200 mg 2 h after dolutegravir	50 mg single dose	11	1.00 (0.78 to 1.29)	0.94 (0.72 to 1.23)	0.90 (0.68 to 1.19)
Carbamazepine 300 mg twice daily	50 mg once daily	16[c]	0.67 (0.61 to 0.73)	0.51 (0.48 to 0.55)	0.27 (0.24 to 0.31)
Daclatasvir 60 mg once daily	50 mg once daily	12	1.29 (1.07 to 1.57)	1.33 (1.11 to 1.59)	1.45 (1.25 to 1.68)
Ferrous fumarate 324 mg simultaneous administration (fasted)	50 mg single dose	11	0.43 (0.35 to 0.52)	0.46 (0.38 to 0.56)	0.44 (0.36 to 0.54)
Ferrous fumarate 324 mg simultaneous administration (fed)	50 mg single dose	11	1.03 (0.84 to 1.26)	0.98 (0.81 to 1.20)	1.00 (0.81 to 1.23)
Ferrous fumarate 324 mg 2 h after dolutegravir	50 mg single dose	10	0.99 (0.81 to 1.21)	0.95 (0.77 to 1.15)	0.92 (0.74 to 1.13)
Multivitamin (One-A-Day®) simultaneous administration	50 mg single dose	16	0.65 (0.54 to 0.77)	0.67 (0.55 to 0.81)	0.68 (0.56 to 0.82)
Omeprazole 40 mg once daily	50 mg single dose	12	0.92 (0.75 to 1.11)	0.97 (0.78 to 1.20)	0.95 (0.75 to 1.21)
Prednisone 60 mg once daily with taper	50 mg once daily	12	1.06 (0.99 to 1.14)	1.11 (1.03 to 1.20)	1.17 (1.06 to 1.28)
Rifampin[a]	50 mg	11	0.57	0.46	0.28

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

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

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

Table 9. Drug Interactions: Changes in TAF Pharmacokinetic Parameters in the Presence of Coadministered Drug(s)[a]

Coadministered Drug	**Coadministered Drug(s) Dosage (once daily)**	**Tenofovir Alafenamide**	**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	1.91 (1.55	NC
Cobicistat	150	8	12	2.83 (2.20	2.65 (2.29	NC
Darunavir	800 (+ 150 cobicistat)	25[b]	11	0.93 (0.72	0.98 (0.80	NC
Darunavir	800 (+ 100 ritonavir)	10	10	1.42 (0.96	1.06 (0.84	NC
Efavirenz	600	40[b]	11	0.78 (0.58	0.86 (0.72	NC
Lopinavir	800 (+ 200 ritonavir)	10	10	2.19 (1.72	1.47 (1.17	NC
Rilpivirine	25	25	17	1.01 (0.84	1.01 (0.94	NC
Sertraline	50 (dosed as a single dose)	10[c]	19	1.00 (0.86	0.96 (0.89	NC

NC=Not Calculated
a. All interaction studies conducted in healthy volunteers.
b. Study conducted with emtricitabine and tenofovir alafenamide (FTC/TAF).
c. Study conducted with FTC + TAF with EVG + COBI.

Table 10. 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):		
				Cmax	AUC	Cmin
Atazanavir	300 + 100 ritonavir	10	10	0.98 (0.89,	0.99 (0.96,	1.00 (0.96,
Darunavir	800 + 150 cobicistat	25[b]	11	1.02 (0.96,	0.99 (0.92,	0.97 (0.82,
Darunavir	800 + 100 ritonavir	10	10	0.99 (0.91	1.01 (0.96	1.13 (0.95
Dolutegravir	50 mg	10	10	1.15 (1.04,	1.02 (0.97,	1.05 (0.97,
Lopinavir	800 + 200 ritonavir	10	10	1.00 (0.95,	1.00 (0.92,	0.98 (0.85,
Midazolam[c]	2.5 (single dose, orally)	25	18	1.02 (0.92,	1.13 (1.04,	NC
	1 (single dose, intravenous)			0.99 (0.89,	1.08 (1.04,	NC
Rilpivirine	25	25	16	0.93 (0.87	1.01 (0.96	1.13 (1.04
Sertraline	50 (dosed as a single dose)	10[d]	19	1.14 (0.94,	0.93 (0.77,	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.

5.3 Preclinical safety data

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

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

alafenamide) or in rats at doses up to 600 mg per kg per day (28 times the human systemic exposure at the recommended dose in emtricitabine and tenofovir alafenamide).

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

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

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

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

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

Animal Toxicology and/or Pharmacology

Tenofovir Alafenamide: Minimal to slight infiltration of mononuclear cells in the posterior uvea was observed in dogs with similar severity after 3 and 9 month administration of TAF; reversibility was seen after a 3 month recovery period. No eye toxicity was observed in the dog at systemic exposures of 5 (TAF) and 15 (tenofovir) times the exposure seen in humans with the recommended daily TAF dose in emtricitabine and tenofovir alafenamide.

6. Pharmaceutical Particulars

6.1 List of Excipients

Tablet core

Mannitol, microcrystalline cellulose, sodium starch glycolate, povidone, croscarmellose sodium, Magnesium stearate and purified water.

Film-coating

Polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350 and talc.

6.2 Incompatibilities

Not applicable

6.3 Shelf-Life

24 months

6.4 Special Precautions for storage

Do not store above 30°C.

Keep the bottle tightly closed. Do not remove desiccant.

6.5 Nature and Content of container

30's Count (Regular pack heavy weight bottle): White opaque 60 cc HDPE bottles filled with 3 gm silica gel canister and 9 gm/yard polyester closed with 33 mm- 400 ARGUS child resistant closures with TEKNIPLEX HS 123 induction sealing wad.

30's Count (Alternate pack medium weight bottle): White opaque 60 cc HDPE bottles filled with 3 gm silica gel canister and 9 gm/yard polyester closed with 33 mm- 400 ARGUS child resistant closures with TEKNIPLEX HS 123 induction sealing wad.

90's Count (Regular pack heavy weight bottle): White opaque 120 cc HDPE bottles filled with Cansorb IT 3 gm silica gel canister and 9 gm/yard polyester closed with 38 mm- 400 ARGUS child resistant closures with TEKNIPLEX HS 123 induction sealing wad.

90's Count (Alternate pack medium weight bottle): White opaque 120 cc HDPE bottles filled with Cansorb IT 3 gm silica gel canister and 9 gm/yard polyester closed with 38 mm- 400 ARGUS child resistant closures with TEKNIPLEX HS 123 induction sealing wad.

180's Count: White opaque 200 cc HDPE bottles filled with Cansorb IT 3 gm silica gel canister and 9 gm/yard polyester closed with 38 mm- 400 ARGUS child resistant closures with TEKNIPLEX HS 123 induction sealing wad.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7. Marketing Authorization Holder

Laurus Labs Limited, (Unit-2),

Plot No:19, 20 & 21,Western Sector, APSEZ,

Atchutapuram Mandal,

Visakhapatnam-District-531011,
Andhra Pradesh, India.

8. **Marketing Authorization Number**
   CTD10906
9. **Date of first authorization/renewal of the authorization**
   12/09/2023
10. **Date of revision of the text**
    10/05/2025