1. NAME OF THE MEDICINAL PRODUCT

Dolutegravir, Emtricitabine and Tenofovir Alafenamide Tablets 50mg/200mg/25 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains Dolutegravir 50 mg equivalent to 52.60 mg of Dolutegravir sodium, Emtricitabine 200 mg and Tenofovir alafenamide 25 mg equivalent to 28.043 mg of Tenofovir alafenamide hemifumarate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet

Description: White to off white, capsule shaped film coated tablets, debossed with "T47" on one side and "H" on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dolutegravir, Emtricitabine and Tenofovir alafenamide is indicated, in combination with:

- other antiretroviral agents, for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 Kg.
- other antiretroviral agents other than protease inhibitors that require a CYP3A inhibitor, for the treatment of HIV-1 infection in pediatric patients weighing at least 25 Kg and less than 35 Kg.

4.2 Posology and method of administration

Testing Prior to Initiation of Treatment

- Perform pregnancy testing before initiation of treatment in adolescents and adults of childbearing potential.
- Prior to initiation of treatment, patients should be tested for hepatitis B virus infection.
- Estimated creatinine clearance, urine glucose, and urine protein should be assessed before initiating therapy and should be monitored during therapy in all patients

Dosage Recommendation

The recommended dosage is one tablet taken orally once daily with or without food in adults

and pediatric patients with body weight at least 35 Kg and creatinine clearance greater than or equal to 30 mL per minute.

For specific dosing recommendations for coadministered third agents, refer to their respective prescribing information. The safety and effectiveness of this combination 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.

Not Recommended in Patients with Severe Renal Impairment

Dolutegravir, Emtricitabine and Tenofovir alafenamide combination is not recommended in patients with estimated creatinine clearance below 30 mL per minute.

4.3 Contraindications

Dolutegravir, emtricitabine and tenofovir alafenamide tablets are 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

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.

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

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. 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 abacavir, dolutegravir, and lamivudine combination. Monitoring for hepatotoxicity is recommended.

Patients with HIV-1 should be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy. Dolutegravir, emtricitabine and tenofovir alafenamide tablets is not approved for the treatment of chronic HBV infection, and the safety and efficacy of this combination 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 this emtricitabine and tenofovir alafenamide should be closely monitored with both clinical and laboratory follow-ups 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.

Embryo-Fetal Toxicity

Preliminary data from an observational study showed that dolutegravir was associated with increased risk of neural tube defects when administered at the time of conception and in early pregnancy. As there is limited understanding of reported types of neural tube defects associated with dolutegravir use and because the date of conception may not be determined with precision, avoid use of dolutegravir at the time of conception through the first trimester of pregnancy.

If there are plans to become pregnant or if pregnancy is confirmed within the first trimester while on dolutegravir, if possible, switch to an alternative regimen. Perform pregnancy testing

before initiation of dolutegravir in adolescents and adults of childbearing potential to exclude use of dolutegravir during the first trimester of pregnancy. Advise adolescents and adults of childbearing potential to consistently use effective contraception.

Immune Reconstitution Syndrome

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

Lactic Acidosis and Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues, including emtricitabine 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).

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. This combination 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 this combination 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 FTC and TAF in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

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

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

- Loss of therapeutic effect of dolutegravir 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 5 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; review concomitant medications during therapy with dolutegravir; and monitor for the adverse reactions associated with the concomitant drugs.

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 = 1.93 mM) and multidrug and toxin extrusion transporter 50 (MATE) 1 (IC = 6.34 mM). Invivo, 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 1).

In vitro, dolutegravir inhibited the basolateral renal transporters, organic anion transporter

(OAT) 1 (IC = 2.12 mM) and OAT3 (IC = 1.97 mM). 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 greater than 50 mM) the following: cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, 50 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.

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).

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

Established and Other Potentially Significant Drug Interactions

Table 1 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.

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

Concomitant Drug	Effect on	Clinical Comment

Class: Drug Name	Concentration of Dolutegravir and/or Concomitant Drug	
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 lopinavir/ritonavir is not recommended
Non-nucleoside reverse transcriptase inhibitor: Efavirenz[a]	↓Dolutegravir	Adjust dolutegravir dose 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 dolutegravir dose 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		
Dofetilide	↑Dofetilide	Coadministration is contraindicated with dolutegravir, emtricitabine, and tenofovir alafenamide tablets
Carbamazepine[a]	↓Dolutegravir	Adjust dose of dolutegravir 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, emtricitabine, and tenofovir alafenamide tablets because there are insufficient data to make dosing recommendations.
Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing antacids[a] or laxatives Sucralfate Buffered medications	↓Dolutegravir	Administer dolutegravir, emtricitabine, and tenofovir alafenamide tablets 2 hours before or 6 hours after taking medications containing polyvalent cations.
Oral calcium or iron supplements, including multivitamins containing calcium or iron[a]	↓Dolutegravir	Administer dolutegravir, emtricitabine, and tenofovir alafenamide tablets 2 hours before or 6 hours after taking supplements containing calcium or iron. Alternatively, dolutegravir and supplements containing calcium or iron can be taken together with food
Metformin	↑Metformin	With concomitant use, limit the total daily dose of metformin to 1000 mg either when starting metformin or dolutegravir, emtricitabine, and tenofovir alafenamide tablets. When stopping dolutegravir, emtricitabine, and tenofovir alafenamide tablets, the metformin dose may require an adjustment. Monitoring of blood glucose when initiating concomitant use and after withdrawal of dolutegravir, emtricitabine, and tenofovir alafenamide tablets is recommended
Rifampin[a]	↓Dolutegravir	Adjust dolutegravir dose 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 alternatives to rifampin where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[b]

[a] Table 14 or Table 15 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 upon coadministration with certain inducers may result in loss of therapeutic effect and development of resistance to dolutegravir or other coadministered antiretroviral agents.

Drugs without Clinically Significant Interactions with Dolutegravir

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

Potential for Other Drugs to Affect Tenofovir Alafenamide

Tenofovir alafenamide is a substrate of P-glycoprotein (P-gp), BCRP, OATP1B1, and OATP1B3. Drugs that strongly affect P-gp and BCRP activity may lead to changes in tenofovir alafenamide absorption (see Table 2).

Drugs that induce P-gp activity are expected to decrease the absorption of tenofovir alafenamide, resulting in decreased plasma concentrations of tenofovir alafenamide, which may lead to loss of therapeutic effect of tenofovir alafenamide. Coadministration of tenofovir alafenamide with other drugs that inhibit P-gp and BCRP may increase the absorption and plasma concentration of tenofovir alafenamide. Tenofovir alafenamide 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*.

Drugs Affecting Renal Function

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

Established and Other Potentially Significant Interactions

Table 2 provides a listing of established or potentially clinically significant drug interactions with recommended steps to prevent or manage the drug interaction. The drug interactions described are based on studies conducted with FDC of emtricitabine and tenofovir alafenamide

as individual agents, or are predicted drug interactions that may occur with FDC of emtricitabine and tenofovir alafenamide.

Table 2. Established and Other Potentially Significant Drug Interactions[a]

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Antiretroviral Agents: Protease Inhibitors (PI)		
Tipranavir/ Ritonavir	↓ tenofovir alafenamide	Coadministration with TAF is not recommended
Anticonvulsants: carbamazepine[c]* oxcarbazepine* phenobarbital* phenytoin*	↓ tenofovir alafenamide	Consider alternative anticonvulsant
Antimycobacterial: Rifabutin* Rifampin* Rifapentine*	↓ tenofovir alafenamide	Coadministration of tenofovir alafenamide with rifabutin, rifampin or rifapentine is not recommended
Herbal Products: St. John's wort* (Hypericum perforatum)	↓ tenofovir alafenamide	Coadministration of tenofovir alafenamide with St. John's wort is not recommended
a. This table is not all inclusive. b. ↓ = decrease.		

Drugs without Clinically Significant Interactions with Tenofovir alafenamide

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

4.6 Pregnancy and lactation

Pregnancy

Dolutegravir:

Risk Summary: Preliminary data from an observational study has identified a possible increased risk of neural tube defects when dolutegravir is administered at the time of conception compared with non-dolutegravir-containing antiretroviral regimens. As defects

related to closure of the neural tube occur from conception through the first 6 weeks of gestation, embryos exposed to dolutegravir from the time of conception through the first 6 weeks of gestation are at potential risk. In addition, 2 of the 4 birth defects (encephalocele and iniencephaly), which have been observed with dolutegravir use, although often termed neural tube defects, may occur post-neural tube closure, the time period of which may be later than 6 weeks of gestation, but within the first trimester. Due to the limited understanding of the types of reported neural tube defects associated with dolutegravir use and because the date of conception may not be determined with precision, avoid use of dolutegravir at the time of conception through the first trimester of pregnancy. No neural tube defects have been reported in infants born to mothers who have started dolutegravir after the first trimester of pregnancy.

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

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

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with dolutegravir at systemic exposures (AUC) less than (rabbits) and approximately 27 times (rats) the exposure in humans at the maximum recommended human dose (MRHD) of dolutegravir.

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

Data analyzed to date from other sources including the APR, clinical trials, and postmarketing

data are insufficient to address the risk of neural tube defects with dolutegravir.

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 to rats on gestation Day 6 to lactation/post-partum Day 20. No adverse effects on embryo-fetal (rats and rabbits) or pre/post-natal (rats) development were observed at up to the highest dose tested. During organogenesis, systemic exposures (AUC) to dolutegravir in rabbits were less than the exposure in humans at the MRHD and in rats were approximately 27 times the exposure in humans at the MRHD. In the rat pre/post-natal development study, decreased body weight of the developing offspring was observed during lactation at a maternally toxic dose (approximately 27 times human exposure at the MRHD).

Emtricitabine and Tenofovir alafenamide:

There are insufficient human data on the use of FTC and TAF during pregnancy to inform a drug-associated risk of birth defects and miscarriage. TAF use in women during pregnancy has not been evaluated; however, 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 15–20%. In animal studies, no adverse developmental effects were observed when the components of FTC and TAF were administered separately during the period of organogenesis at exposures 60 and 108 times (mice and rabbits, respectively) the FTC exposure and at exposure equal to or 53 times (rats and rabbits, respectively) the TAF exposure at the recommended daily dose of FTC and TAF. Likewise, no adverse developmental effects were seen when FTC was administered to mice through lactation at exposures up to approximately 60 times the exposure at the recommended daily dose of FTC and TAF. 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 FTC and TAF.

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

Lactation

Risk Summary: The Centers for Disease Control and Prevention recommend that HIV-1-

infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

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

It is not known if Dolutegravir, FTC and TAF tablets 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 this combination.

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 postdose.

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. 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.

Females and Males of Reproductive Potential

Pregnancy Testing:

Perform pregnancy testing in adolescents and adults of childbearing potential before initiation of this combination therapy.

Contraception:

Adolescents and adults of childbearing potential should avoid use of dolutegravir at the time of

conception through the first trimester of pregnancy because of the potential risk of neural tube defects.

4.7 Effects on ability to drive and use machines

Not Applicable

4.8 Undesirable effects

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

- Hypersensitivity Reactions
- Severe Acute Exacerbation of Hepatitis
- Hepatotoxicity
- Immune Reconstitution Syndrome
- Lactic Acidosis and Severe Hepatomegaly with Steatosis
- New Onset or Worsening Renal Impairment

Clinical Trials Experience

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

Dolutegravir:

Treatment-Naïve Subjects: 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 or emtricitabine/ tenofovir). 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 adult subjects were randomized and received at least 1 dose of either dolutegravir 50 mg with fixed-dose abacavir sulfate and lamivudine once daily (n = 414) or fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate once daily (n = 419) (study

treatment was blinded through Week 96 and open-label from Week 96 through Week 144). Through 144 weeks, the rate of adverse events leading to discontinuation was 4% in subjects receiving dolutegravir + fixed-dose abacavir sulfate and lamivudine and 14% in subjects receiving fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate once daily.

Treatment-emergent adverse reactions (ARs) of moderate to severe intensity observed in at least 2% of subjects in either treatment arm in SPRING-2 and SINGLE trials are provided 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 3. 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 (Week 144 Analysis)

System Organ Class/ Preferred Term	SPRING-2		SINGLE	
	Dolutegravir 50 mg Once Daily + 2 NRTIs (n = 403)	Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)	Dolutegravir + Abacavir Sulfate and Lamivudine Once Daily (n = 414)	Efavirenz/ Emtricitabine/ Tenofovir DF 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%
General Disorders Fatigue	<1%	<1%	2%	2%
Skin and Subcutaneous Tissue Rash[a]	0	<1%	<1%	6%
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 efavirenz/emtricitabine/tenofovir, 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 FDC of abacavir and lamivudine or FDC of emtricitabine and tenofovir). 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 ARs 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 AR of moderate to severe intensity with at least 2% frequency in either treatment group was diarrhea, 2% (6 of 354) in subjects receiving dolutegravir 50 mg once daily + background regimen and 1% (5 of 361) in subjects receiving raltegravir 400 mg twice daily + background regimen.

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

Virologically Suppressed Subjects: The ARs observed for dolutegravir plus rilpivirine in the Week 48 analysis of pooled data from 2 identical, international, multicenter, open-label trials

(SWORD-1 and SWORD-2) of 513 HIV–1-infected, virologically suppressed subjects switching from their current antiretroviral regimen to dolutegravir plus rilpivirine, were consistent with the AR profiles and severities for the individual components when administered with other antiretroviral agents. There were no ARs (Grades 2 to 4) with an incidence of at least 2% in either treatment arm. The rates of adverse events leading to discontinuation were 4% in subjects receiving dolutegravir plus rilpivirine once daily and less than 1% in subjects who remained on their current antiretroviral regimen.

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

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

Hepatobiliary Disorders: Hepatitis

Musculoskeletal Disorders: Myositis

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

Renal and Urinary Disorders: Renal impairment

Skin and Subcutaneous Tissue Disorders: Pruritus

Laboratory Abnormalities: Treatment-Naïve Subjects: Selected laboratory abnormalities (Grades 2 to 4) with a worsening grade from baseline and representing the worst-grade toxicity in at least 2% of subjects in SINGLE are presented in Table 4. The mean change from baseline observed for selected lipid values is presented in Table 5.

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

Laboratory Abnormality Preferred Term	**SPRING-2**		**SINGLE**	
	Dolutegravir 50 mg Once Daily + 2 NRTIs (n = 403)	**Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)**	**Dolutegravir + Abacavir and Lamivudine Once Daily (n = 414)**	**Efavirenz/ Emtricitabine/ Tenofovir DF Once Daily (n = 419)**

ALT Grade 2 (>2.5 to 5.0 x ULN) Grade 3 to 4 (>5.0 x ULN)	4% 2%	4% 2%	3% 1%	5% <1%
AST Grade 2 (>2.5 to 5.0 x ULN) Grade 3 to 4 (>5.0 x ULN)	5% 3%	3% 2%	3% 1%	4% 3%
Total Bilirubin Grade 2 (1.6 to 2.5 x ULN) Grade 3 to 4 (≥2.5 x ULN)	3% <1%	2% <1%	<1% <1%	<1% <1%
Creatine kinase Grade 2 (6.0 to 9.9 x ULN) Grade 3 to 4 (≥10.0 x ULN)	2% 7%	5% 4%	5% 7%	3% 8%
Hyperglycemia Grade 2 (126 to 250 mg/dL) Grade 3 (>250 mg/dL)	6% <1%	6% 2%	9% 2%	6% <1%
Lipase Grade 2 (>1.5 to 3.0 x ULN) Grade 3 to 4 (>3.0 ULN)	7% 2%	7% 5%	11% 5%	11% 4%
Total neutrophils Grade 2 (0.75 to 0.99 x 10^9) Grade 3 to 4 (<0.75 x 10^9)	4% 2%	3% 2%	4% 3%	5% 3%
ULN = Upper limit of normal				

Table 5. Mean Change from Baseline in Fasted Lipid Values in Treatment-Naïve Subjects in in SPRING-2 (Week 96 Analysis) and SINGLE (Week 144 Analysis[a])

Laboratory Abnormality Preferred Term Lipid	**SPRING-2**		**SINGLE**	
	Dolutegravir 50 mg Once Daily + 2 NRTIs (n = 403)	**Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)**	**Dolutegravir + Abacavir and Lamivudine Once Daily**	**Efavirenz/ Emtricitabine/ Tenofovir DF Once Daily (n = 419)**

			(n = 414)	
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 + FDC of abacavir sulfate and lamivudine n = 30 and FDC of efavirenz/emtricitabine/tenofovir disoproxil fumarate n = 27). Ninety-four subjects initiated a lipid-lowering agent post-baseline; their last fasted on-treatment values (prior to starting the agent) were used regardless if they discontinued the agent (SPRING-2: Dolutegravir n = 9, raltegravir n = 13; SINGLE: Dolutegravir + FDC of abacavir sulfate and lamivudine n = 36 and FDC of efavirenz/ emtricitabine/ tenofovir disoproxil fumarate: 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.

Virologically Suppressed Adults: Laboratory abnormalities observed in SWORD-1 and SWORD-2 were generally similar compared with observations seen in the other Phase 3 trials.

Hepatitis B and/or Hepatitis C Virus Co-infection: In Phase 3 trials, subjects with hepatitis B and/or C virus co-infection were permitted to enroll provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal. Overall, the safety profile in subjects with hepatitis B and/or C virus co-infection was similar to that observed in subjects without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or C virus co-infection for all treatment groups. Grades 2 to 4 ALT abnormalities in hepatitis B and/or C co-infected compared with HIV mono-infected subjects receiving dolutegravir were observed in 18% vs. 3% with the 50 mg once-daily dose and 13% vs. 8% with the 50 mg twice-daily dose. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C at

the start of therapy with dolutegravir, particularly in the setting where anti-hepatitis therapy was withdrawn.

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. 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.

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

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

Emtricitabine and Tenofovir alafenamide

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

In pooled 48-week trials of antiretroviral treatment-naïve HIV-1 infected adult subjects, the most common adverse reaction in subjects treated with Emtricitabine (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 35 Kg)

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 6All subjects maintained their CD4+ cell counts above 400 cells/mm^3.

Table 6. 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

		Mean Change from Baseline			
	Baseline	**Week 2**	**Week 4**	**Week 12**	**Week 24**
CD4+ Cell Count (cells/mm^3)	966 (201.7)[a]	-162	-125	-162	-150
CD4%	40 (5.3)[a]	+0.5%	-0.1%	-0.8%	-1.5%
a. Mean (SD)					

Post-marketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during post-marketing use for each of the individual components of dolutegravir, emtricitabine, and tenofovir alafenamide tablets. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Dolutegravir

Hepatobiliary Disorders: Acute liver failure, hepatotoxicity

Investigations: Weight increased

Musculoskeletal: Arthralgia, myalgia.

Psychiatric: Anxiety

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 the authority ADR reporting tool; search for authority Adverse Reactions Reporting Tool in the Google Play Store.

4.9 Overdose

There is no known specific treatment for overdose with dolutegravir, emtricitabine and tenofovir alafenamide tablets. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required.

Dolutegravir

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

Emtricitabine

Limited clinical experience is available at doses higher than the recommended dose of FTC. In one clinical pharmacology study, single doses of FTC 1200 mg (6 times the FTC dose) 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

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 25 mg) 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 approximately54%.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Pharmacotherapeutic group: Antiretroviral drug

ATC code: J05AX12- Dolutegravir, J05AR17- Emtricitabine and Tenofovir Alafenamide

Mechanism of action

Dolutegravir, emticitabine, and tenofovir alafenamide are HIV-1 antiviral agents.

Dolutegravir

Effects on Electrocardiogram:

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

Effects on Renal Function:

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

of probe drug, para-amino hippurate) compared with the placebo.

Tenofovir alafenamide

Cardiac Electrophysiology

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

5.2 Pharmacokinetics properties

Dolutegravir:

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

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

Parameter	**50 mg Once Daily Geometric Mean (%CV)[a]**	**50 mg Twice Daily Geometric Mean (%CV)[b]**
$AUC_{(0\text{-}24h)}$ (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_{24h} 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.

Effect of Food: 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.

Elimination

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.

Metabolism: Dolutegravir is primarily metabolized via UGT1A1 with some contribution from CYP3A.

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).

Excretion: 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).

The pharmacokinetic (PK) properties of the components of FTC and TAF are provided in Table 8. The multiple dose PK parameters of FTC and TAF and its metabolite tenofovir are provided in Table 9.

Table 2 Pharmacokinetic Properties of the Components of FTC and TAF

	Emtricitabine	Tenofovir alafenamide
Absorption		
T_{max} (h)	3	1
Effect of high fat meal (relative to fasting)[a]	AUC Ratio = 0.91 (0.89, 0.930) C_{max} Ratio = 0.74 (0.69, 0.78)	AUC Ratio = 1.75 (1.64, 1.88) C_{max} Ratio = 0.85 (0.75, 0.95)
Distribution		
% Bound to human plasma proteins	<4	80%
Source of protein binding data	*In vitro*	Ex vivo
Blood-to-plasma ratio	0.6	1.0
Metabolism		
Metabolism[b]	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 3. 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} (mcg per mL)	2.1 (20.2)	0.16 (51.1)	0.02 (26.1)

AUC_{tau} (mcg.h per mL)	11.7 (16.6)	0.21 (71.8)	0.29 (27.4)
C_{trough} (mcg per mL)	0.10 (46.7)	NA	0.01 (28.5)

CV=Coefficient of Variation; NA=Not Applicable

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

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

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

Specific Populations

Pediatric Patients

The pharmacokinetics of dolutegravir in HIV-1-infected children (n = 17) weighing at least 30 kg (dosed by weight bands, receiving either 35 mg or 50 mg) were similar to those observed in HIV-1-infected adults who received dolutegravir 50 mg once daily.

Table 4. Dolutegravir Steady-State Pharmacokinetic Parameters in Pediatric Subjects

Weight (n)	**Dose of Dolutegravir**	**Dolutegravir Pharmacokinetic Parameter Estimates Geometric Mean (%CV)**		
≥ 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)

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 11).

Table 5. 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} (mcg per mL)	2.3 (22.5)	0.17 (64.4)	0.02 (23.7)
AUC_{tau} (mcg.h per mL)	14.4 (23.9)	0.20[b] (50.0)	0.29[b] (18.8)
C_{trough} (mcg 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 patients 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 12 years and weighing at least 25 kg (55 lbs) who received FTC+TAF with EVG+COBI were higher (20 to 80% for AUC) than exposures achieved in adults following the administration of this dosage regimen; however, the increase was not considered clinically significant (Table 12)

Table 6. 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} (mcg per mL)	3.4 (27.0)	0.31 (61.2)	0.03 (20.8)
AUC_{tau} (mcg.h per mL)	20.6[b] (18.9)	0.33 (44.8)	0.44 (20.9)
C_{trough} (mcg per mL)	0.11 (24.1)	NA	0.02 (24.9)
CV=Coefficient of Variation; NA=Not Applicable a. From Intensive PK analysis in a trial in virologically suppressed pediatric patients with HIV-1 infection (N=23) b. N = 22			

Geriatric Patients:

Dolutegravir: Population pharmacokinetic analysis 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.

Patients with Hepatic Impairment:

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

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.

HBV/HCV Co-infection:

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

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

Patients with Renal Impairment:

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 C24 of dolutegravir were lower by 40%, 23%, and 43%, respectively, compared with those in matched healthy subjects. 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. Dolutegravir has not been studied in patients requiring dialysis.

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 13)

Table 7. Pharmacokinetics of the Components of TAF and a Metabolite of TAF (Tenofovir) in HIV-Infected Adults with Renal Impairment Compared to Subjects with Normal Renal Function[a]

	AUCtau (mcg.h per mL) **Mean (CV%)**

Creatinine Clearance	≥90 mL per minute (N=18)[b]	60-89 mL per minute (N=14)[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.

Race and Gender

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

Assessment of Drug Interactions:

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 combination of dolutegravir, emtricitabine, and tenofovir alafenamide.

Dolutegravir

Dosing recommendations as a result of established and other potentially significant drug-drug interactions with dolutegravir are provided in the table 14:

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

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	Cτ or C24
Daclatasvir 60 mg once daily	50 mg once daily	12	1.03 (0.84 to 1.25)	0.98 (0.83 to 1.15)	1.06 (0.88 to 1.29)
Elbasvir 50 mg once daily	50 mg single dose	12	0.97 (0.89, 1.05)	0.98 (0.93, 1.04)	0.98 (0.93, 1.03)
Ethinyl estradiol 0.035 mg	50 mg twice daily	15	0.99 (0.91 to 1.08)	1.03 (0.96 to 1.11)	1.02 (0.93 to 1.11)
Grazoprevir 200 mg once daily	50 mg single dose	12	0.64 (0.44, 0.93)	0.81 (0.67, 0.97)	0.86 (0.79, 0.93)
Metformin 500 mg twice daily	50 mg once daily	15 a	1.66 (1.53 to 1.81)	1.79 (1.65 to 1.93)	–
Metformin 500 mg twice	50 mg twice	15	2.11	2.45	–

daily	daily	a	(1.91 to 2.33)	(2.25 to 2.66)	
Methadone 16 to 150 mg	50 mg twice daily	11	1.00 (0. 94 to 1.06)	0.98 (0.91 to 1.06)	0.99 (0.91 to 1.07)
Midazolam 3 mg	25 mg once daily	10	–	0.95 (0.79 to 1.15)	–
Norelgestromin 0.25 mg	50 mg twice daily	15	0.89 (0.82 to 0.97)	0.98 (0.91 to 1.04)	0.93 (0.85 to 1.03)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.10 (0.99 to 1.22)	1.06 (0.98 to 1.16)	1.21 (1.07 to 1.38)
Sofosbuvir 400 mg once daily Metabolite (GS-331007)	50 mg once daily	24	0.88 (0.80, 0.98) 1.01 (0.93, 1.10)	0.92 (0.85, 0.99) 0.99 (0.97, 1.01)	NA 0.99 (0.97, 1.01)
Tenofovir disoproxil fumarate 300 mg once daily	50 mg once daily	15	1.09 (0.97 to 1.23)	1.12 (1.01 to 1.24)	1.19 (1.04 to 1.35)
Velpatasvir 100 mg once daily	50 mg once daily	24	0.94 (0.86, 1.02)	0.91 (0.84, 0.98)	0.88 (0.82, 0.94)
a The number of subjects represents the maximum number of subjects that were evaluated.					

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

Coadministered Drug(s) and Dose(s)	**Dose of Dolutegravir**	**n**	**Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00**		
			C_{max}	**AUC**	**C_{τ} or C_{24}**
Atazanavir 400 mg once daily	30 mg once daily	12	1.50 (1.40 to 1.59)	1.91 (1.80 to 2.03)	2.80 (2.52 to 3.11)
Atazanavir/ritonavir 300/100 mg once daily	30 mg once daily	12	1.34 (1.25 to 1.42)	1.62 (1.50 to 1.74)	2.21 (1.97 to 2.47)
Darunavir/ritonavir 600/100 mg twice daily	30 mg once daily	15	0.89 (0.83 to 0.97)	0.78 (0.72 to 0.85)	0.62 (0.56 to 0.69)
Efavirenz 600 mg once daily	50 mg once daily	12	0.61 (0.51 to 0.73)	0.43 (0.35 to 0.54)	0.25 (0.18 to 0.34)
Elbasvir/grazoprevir 50/200 mg once daily	50 mg single dose	12	1.22 (1.05, 1.40)	1.16 (1.00, 1.34)	1.14 (0.95, 1.36)
Etravirine 200 mg twice daily	50 mg once daily	16	0.48 (0.43 to 0.54)	0.29 (0.26 to 0.34)	0.12 (0.09 to 0.16)
Etravirine + darunavir/ ritonavir 200 mg + 600/100 mg twice daily	50 mg once daily	9	0.88 (0.78 to 1.00)	0.75 (0.69 to 0.81)	0.63 (0.52 to 0.76)
Etravirine + lopinavir/ ritonavir 200 mg + 400/100 mg twice daily	50 mg once daily	8	1.07 (1.02 to 1.13)	1.11 (1.02 to 1.20)	1.28 (1.13 to 1.45)

Fosamprenavir/ritonavir 700 mg/100 mg twice daily	50 mg once daily	12	0.76 (0.63 to 0.92)	0.65 (0.54 to 0.78)	0.51 (0.41 to 0.63)
Lopinavir/ritonavir 400/100 mg twice daily	30 mg once daily	15	1.00 (0.94 to 1.07)	0.97 (0.91 to 1.04)	0.94 (0.85 to 1.05)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.13 (1.06 to 1.21)	1.12 (1.05 to 1.19)	1.22 (1.15 to 1.30)
Tenofovir 300 mg once daily	50 mg once daily	15	0.97 (0.87 to 1.08)	1.01 (0.91 to 1.11)	0.92 (0.82 to 1.04)
Tipranavir/ritonavir 500/200 mg twice daily	50 mg once daily	14	0.54 (0.50 to 0.57)	0.41 (0.38 to 0.44)	0.24 (0.21 to 0.27)
Antacid (MAALOX) simultaneous administration	50 mg single dose	16	0.28 (0.23 to 0.33)	0.26 (0.22 to 0.32)	0.26 (0.21 to 0.31)
Antacid (MAALOX) 2 h after dolutegravir	50 mg single dose	16	0.82 (0.69 to 0.98)	0.74 (0.62 to 0.90)	0.70 (0.58 to 0.85)
Calcium carbonate 1,200 mg simultaneous administration (fasted)	50 mg single dose	12	0.63 (0.50 to 0.81)	0.61 (0.47 to 0.80)	0.61 (0.47 to 0.80)
Calcium carbonate 1,200 mg simultaneous administration (fed)	50 mg single dose	11	1.07 (0.83 to 1.38)	1.09 (0.84 to 1.43)	1.08 (0.81 to 1.42)
Calcium carbonate 1,200 mg 2 h after dolutegravir	50 mg single dose	11	1.00 (0.78 to 1.29)	0.94 (0.72 to 1.23)	0.90 (0.68 to 1.19)
Carbamazepine 300 mg twice daily	50 mg once daily	16 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)
Rifampina 600 mg once daily	50 mg twice daily	11	0.57 (0.49 to 0.65)	0.46 (0.38 to 0.55)	0.28 (0.23 to 0.34)
Rifampinb 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.

Tenofovir alafenamide

The effects of coadministered drugs on the exposure of tenofovir alafenamide are shown in Table 16. The effects of tenofovir alafenamide on the exposure of coadministered drugs are shown in Table 17.

Table 10. Drug Interactions: Changes in TAF Pharmacokinetic Parameters in the Presence of the Coadministered Drug[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,	NC

					1.03)	
NC = Not Calculated a. All interaction studies conducted in healthy volunteers. b. Study conducted with FTC/TAF. c. Study conducted with FTC+TAF with EVG+COBI.						

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

Coadministered Drug	**Coadministered Drug(s) Dosage (once daily) (mg)**	**Tenofovir Alafenamide Dosage (once daily) (mg)**	**N**	**Mean Ratio of Coadministered Drug PK Parameters (90% CI); No effect = 1.00**		
				C_{max}	**AUC**	**C_{min}**
Atazanavir	300 +100 ritonavir	10	10	0.98 (0.89, 1.07)	0.99 (0.96, 1.01)	1.00 (0.96, 1.04)
Darunavir	800 +150 cobicistat	25b	11	1.02 (0.96, 1.09)	0.99 (0.92, 1.07)	0.97 (0.82, 1.15)
Darunavir	800 +100 ritonavir	10	10	0.99 (0.91, 1.08)	1.01 (0.96, 1.06)	1.13 (0.95, 1.34)
Dolutegravir	50 mg	10	10	1.15 (1.04, 1.27)	1.02 (0.97, 1.08)	1.05 (0.97, 1.13)
Lopinavir	800 +200 ritonavir	10	10	1.00 (0.95, 1.06)	1.00 (0.92, 1.09)	0.98 (0.85, 1.12)
Midazolam[c]	2.5 (single dose, orally)	25	18	1.02 (0.92, 1.13)	1.13 (1.04, 1.23)	NC
	1 (single dose, intravenous)			0.99 (0.89, 1.11)	1.08 (1.04, 1.14)	NC
Rilpivirine	25	25	16	0.93 (0.87, 0.99)	1.01 (0.96, 1.06)	1.13 (1.04, 1.23)
Sertraline	50 (single dose)	10d	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 FTC/TAF. c. A sensitive CYP3A4 substrate. d. Study conducted with FTC+TAF with EVG+COBI.						

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity:

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-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.

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) 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).

Tenofovir alafenamide: Since tenofovir alafenamide is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice was observed after tenofovir alafenamide administration compared to tenofovir disoproxil fumarate administration, carcinogenicity studies were conducted only with tenofovir disoproxil fumarate. Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate 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 300 mg therapeutic dose of tenofovir disoproxil fumarate for HIV-1 infection. The tenofovir exposure in these studies was approximately 151 times (mice) and 50 times (rat) those observed in humans after administration of tenofovir alafenamide treatment. At the high dose in female mice, liver adenomas were increased at tenofovir exposures approximately 151 times those observed after tenofovir alafenamide administration in humans. In rats, the study was negative for carcinogenic findings.

Mutagenesis:

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

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

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

Impairment of Fertility:

Dolutegravir: 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: 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. 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.

Tenofovir alafenamide: There were no effects on fertility, mating performance or early embryonic development when tenofovir alafenamide was administered to male rats at a dose equivalent to 155 times 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose (Avicel PH 112), Croscarmellose Sodium, USP/NF (Ac-di-sol), Magnesium stearate, Mannitol USP (Mannogem Powder), Sodium starch glycolate Type A, USP/NF (Primogel), Povidone, USP (Kollidon 30), Sodium stearyl fumarate, USP/NF , Purified Water IHS/USP/Ph.Eur, Opadry II white 85F18422, HIS

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30˚C and protect from moisture

6.5 Nature and contents of container

50mg/200mg/25 mg

Container pack: 30's HDPE container and 100's HDPE container

6.6 Special precautions for disposal and other handling

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

7. APPLICANT/MANUFACTURER

7.1 Name and Address of Applicant

Name	:	**M/s. Hetero Labs Limited,**
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7.2 Name and Address of Manufacturer

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