

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dolutegravir, Lamivudine and Tenofovir Alafenamide Tablets 50 MG, 300 MG and 25 MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film coated tablet contains:

Dolutegravir Sodium, IH equivalent to Dolutegravir.....50 mg Lamivudine USP... 300 mg

Tenofovir alafenamide fumarate, IH equivalent to Tenofovir alafenamide... 25 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

Testing Prior to Initiation and During Treatment with Dolutegravir, Lamivudine and Tenofovir Alafenamide Tablets

Perform pregnancy testing before initiation of dolutegravir, lamivudine and tenofovir alafenamide tablets in adolescents and adults of childbearing potential [see Special warnings and precautions for use (4.4), Fertility, pregnancy, and lactation (4.6)].

Prior to or when initiating dolutegravir, lamivudine and tenofovir alafenamide tablets, test patients for hepatitis B virus (HBV) infection [see Special warnings and precautions for use (4.4)].

Prior to initiation and during treatment with dolutegravir, lamivudine and tenofovir alafenamide tablets, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus [see Special warnings and precautions for use (4.4)].

Posology

Dolutegravir, lamivudine and tenofovir alafenamide tablets is a fixed-dose combination product containing 50 mg of dolutegravir, 300 mg of lamivudine (3TC), 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).

Not Recommended in Patients with Severe Renal Impairment

Because dolutegravir, lamivudine and tenofovir alafenamide tablets is a fixed-dose combination formulation and cannot be dose adjusted, it is not recommended in patients requiring dosage adjustment, patients with creatinine clearance less than 50 mL per min, or patients with end-stage renal disease (ESRD) requiring hemodialysis [see Special warnings and precautions for use (4.4)].

Not Recommended in Patients with Severe Hepatic Impairment

Dolutegravir, lamivudine and tenofovir alafenamide tablets is not recommended in patients with severe hepatic impairment (Child-Pugh Score C) [see Special warnings and precautions for use (4.4)]

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

Severe Acute Exacerbation of Hepatitis B in Patients with HBV Infection

All patients should be tested for the presence of chronic hepatitis B virus (HBV) before or when initiating dolutegravir, lamivudine and tenofovir alafenamide tablets.

Discontinuation of anti-HBV therapy, including lamivudine and TAF, two components of dolutegravir, lamivudine and tenofovir alafenamide tablets, may be associated with severe acute exacerbations of hepatitis B. Patients infected with HBV who discontinue dolutegravir, lamivudine 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, resumption of anti-hepatitis B therapy may be warranted.

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, lamivudine 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 with dolutegravir, lamivudine and tenofovir alafenamide tablets or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction.

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

Embryo-Fetal Toxicity

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

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

Adolescents and adults of childbearing potential should be counseled on the consistent use of effective contraception.

Dolutegravir, lamivudine 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, lamivudine 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, lamivudine and tenofovir alafenamide tablets and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs.

See Table 1 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, lamivudine and tenofovir alafenamide tablets; review concomitant medications during therapy with dolutegravir, lamivudine and tenofovir alafenamide tablets; and monitor for the adverse reactions associated with the concomitant drugs.

New Onset or Worsening Renal Impairment

Postmarketing cases of renal impairment, including acute renal failure, proximal renal tubulopathy (PRT), and Fanconi syndrome have been reported with TAF-containing products; while most of these cases were characterized by potential confounders that may have contributed to the reported renal events, it is also possible these factors may have predisposed patients to tenofovir-related adverse events. Dolutegravir, lamivudine and tenofovir alafenamide tablets is not recommended in patients with estimated creatinine clearance below 50 mL per

minute.

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

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

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including the components of dolutegravir, lamivudine 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, Guillain-Barré syndrome, and autoimmune hepatitis) 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 lamivudine, a component of dolutegravir, lamivudine and tenofovir alafenamide tablets, and TDF, another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with dolutegravir, lamivudine 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).

Pancreatitis

In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, lamivudine, a component of dolutegravir, lamivudine and tenofovir alafenamide tablets, should be used with caution. Treatment with dolutegravir, lamivudine and tenofovir alafenamide tablets should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur.

Pediatric Use

The safety and effectiveness of dolutegravir, lamivudine and tenofovir alafenamide tablets for the treatment of HIV-1 infection in pediatric patients weighing at least 25 kg was established through studies with the individual components. Dolutegravir, lamivudine and tenofovir alafenamide tablets is a fixed-dose combination product which cannot be adjusted for pediatric patients weighing less than 25 kg.

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.
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. 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.

Hepatic Impairment

No dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh Score A or B). The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir, a component of dolutegravir, lamivudine and tenofovir alafenamide tablets, has not been studied. Therefore, dolutegravir, lamivudine and tenofovir alafenamide tablets is not recommended for use in patients with severe hepatic impairment.

Females and Males of Reproductive Potential

In adolescents and adults of childbearing potential currently on dolutegravir, lamivudine 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, lamivudine and tenofovir alafenamide tablets and discuss with the patient if an alternative treatment should be.

Pregnancy Testing

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

Contraception

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

4.5 Interaction with other medicinal products and other forms of interaction

Effect of Dolutegravir, Lamivudine, or TAF on the Pharmacokinetics of Other Agents **Dolutegravir**

In vitro, dolutegravir inhibited the renal organic cation transporters, OCT2 (IC₅₀ = 1.93 microM) and multidrug and toxin extrusion transporter (MATE)1 (IC₅₀ = 6.34 microM). In vivo, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2 and potentially MATE1. Dolutegravir may increase plasma concentrations of drugs eliminated via OCT2 or MATE1 (dofetilide, dalfampridine, and metformin, Table 1).

In vitro, dolutegravir inhibited the basolateral renal transporters, organic anion transporter (OAT)1 (IC₅₀ = 2.12 microM) and OAT3 (IC₅₀ = 1.97 microM). However, in vivo, dolutegravir did not alter the plasma concentrations of tenofovir or para-amino hippurate, substrates of OAT1 and OAT3.

In vitro, dolutegravir did not inhibit (IC₅₀ greater than 50 microM) the following: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, 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, Lamivudine, or TAF

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.

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

TAF

TAF 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 6). 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, lamivudine and tenofovir alafenamide tablets and development of resistance. Coadministration of dolutegravir, lamivudine 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.

Significant Drug Interactions for Dolutegravir, Lamivudine, or TAF

There were no drug-drug interaction trials conducted with fixed-dose dolutegravir, lamivudine and tenofovir alafenamide tablets. Dolutegravir, lamivudine and tenofovir alafenamide tablets is intended as a complete regimen.

Dolutegravir and TAF

Table 1 provides clinical recommendations as a result of drug interactions with dolutegravir and/or TAF. 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 and TAF: 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 and/or Concomitant Drug	Clinical Comment
<i>HIV-1 Antiviral Agents</i>		
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	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 tablets.
Non-nucleoside reverse transcriptase inhibitor: Nevirapine	Dolutegravir	Avoid coadministration with dolutegravir, lamivudine and tenofovir alafenamide tablets because there are insufficient data to make dosing recommendations.
Protease inhibitor: Fosamprenavir/ritonavir Tipranavir/ritonavir	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 with dolutegravir, lamivudine and tenofovir alafenamide tablets.
<i>Other Agents</i>		
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 tenofovir alafenamide tablets.
Oxcarbazepine Phenytoin Phenobarbital	Dolutegravir TAF	Avoid coadministration with dolutegravir, lamivudine and tenofovir alafenamide tablets because there are insufficient data to make dosing recommendations.
St. John's wort (<i>Hypericum perforatum</i>)	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 Buffered medications	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 in these patients.
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.

^aSee Clinical Pharmacology for magnitude of interaction.

Lamivudine

Drugs Inhibiting Organic Cation Transporters

Lamivudine, a component of dolutegravir, lamivudine and tenofovir alafenamide tablets, is predominantly eliminated in the urine by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system (e.g., trimethoprim). No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

Sorbitol

Co administration of single doses of lamivudine and sorbitol resulted in a sorbitol dose-dependent reduction in lamivudine. When possible, avoid use of sorbitol-containing

medicines with lamivudine.

Drugs without Clinically Significant Interactions with Dolutegravir or TAF

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.

TAF

Based on drug interaction studies conducted with TAF, 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.

Drugs Affecting Renal Function with TAF

Because tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of TAF 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

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk Summary

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

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

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 and miscarriage 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. Oral administration of lamivudine to pregnant rabbits during organogenesis resulted in embryoletality at systemic exposure (AUC) similar to the recommended clinical dose; however, no adverse development effects were observed with oral administration of lamivudine to pregnant rats during organogenesis at plasma concentrations (C_{max}) 35 times the recommended clinical dose. No adverse developmental effects were observed when TAF was administered during the period of organogenesis at exposure equal to or 53 times (rats and rabbits, respectively) the TAF exposure at the recommended daily dose of TAF.

Data

Human Data

Dolutegravir

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

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

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

Based on prospective reports to the APR of 842 exposures to dolutegravir during pregnancy resulting in live births (including 512 exposed in the first trimester), the prevalence of defects in live births was 3.3% (95% CI: 1.9% to 5.3%) following first-trimester exposure to dolutegravir-containing regimens

and 4.8% (95% CI: 2.8% to 7.8%) following second-/third-trimester exposure to dolutegravir-containing regimens. In the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP), the background birth defect rate was 2.7%.

Lamivudine

Based on prospective reports from the APR of over 11,000 exposures to lamivudine during pregnancy resulting in live births (including over 4,500 exposed in the first trimester), there was no difference between the overall risk of birth defects for lamivudine compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of defects in live births was 3.1% (95% CI: 2.6% to 3.6%) following first trimester exposure to lamivudine-containing regimens and 2.8% (95% CI: 2.5%, 3.3%) following second/third trimester exposure to lamivudine-containing regimens.

Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical trials conducted in South Africa. The trials assessed pharmacokinetics in 16 women at 36 weeks gestation using 150 mg lamivudine twice daily with zidovudine, 10 women at 38 weeks gestation using 150 mg lamivudine twice daily with zidovudine, and 10 women at 38 weeks gestation using lamivudine 300 mg twice daily without other antiretrovirals. These trials were not designed or powered to provide efficacy information.

Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, amniotic fluid specimens were collected following natural rupture of membranes and confirmed that lamivudine crosses the placenta in humans. Based on limited data at delivery, median (range) amniotic fluid concentrations of lamivudine were 3.9 (1.2 to 12.8)-fold greater compared with paired maternal serum concentration (n = 8).

TAF

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

Animal Data

Dolutegravir

Dolutegravir was administered orally at up to 1,000 mg per kg daily to pregnant rats and rabbits on gestation Days 6 to 17 and 6 to 18, respectively, and to rats on gestation Day 6 to lactation/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).

Lamivudine

Lamivudine was administered orally to pregnant rats (at 90, 600, and 4,000 mg per kg per day) and rabbits (at 90, 300, and 1,000 mg per kg per day and at 15, 40, and 90 mg

per kg per day) during organogenesis (on gestation Days 7 through 16 [rat] and 8 through 20 [rabbit]). No evidence of fetal malformations due to lamivudine was observed in rats and rabbits at doses producing plasma concentrations (C_{max}) approximately 35 times higher than human exposure at the recommended daily dose. Evidence of early embryoletality was seen in the rabbit at system exposures (AUC) similar to those observed in humans, but there was no indication of this effect in the rat at plasma concentrations (C_{max}) 35 times higher than human exposure at the recommended daily dose. Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. In the fertility/pre-and postnatal development study in rats, lamivudine was administered orally at doses of 180, 900, and 4,000 mg per kg per day (from prior to mating through postnatal Day 20). In the study, development of the offspring, including fertility and reproductive performance, was not affected by maternal administration of lamivudine.

TAF

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 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 TAF.

Lactation

Risk Summary

The Centers for Disease Control and Prevention recommends that HIV-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. It is not known whether dolutegravir or TAF 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. Lamivudine has been shown to be present in human breast milk. It is not known if lamivudine affects milk production or has effects on the breastfed infant. Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving dolutegravir, lamivudine and tenofovir alafenamide tablets.

Data

Animal Data

Dolutegravir

Dolutegravir was the primary drug-related component excreted into the milk of lactating rats following a single oral dose of 50 mg per kg on lactation Day 10, with milk

concentrations of up to approximately 1.3 times that of maternal plasma concentrations observed 8 hours postdose.

TAF

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

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

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

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 in Adult Subjects

As per literature data, 833 subjects were randomized and received at least one dose of either dolutegravir 50 mg with fixed-dose abacavir and lamivudine once daily or fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate once daily (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 50 mg once daily + fixed-dose abacavir and lamivudine and 14% in subjects receiving fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate once daily.

Treatment-emergent adverse reactions of moderate to severe intensity observed in at least 2% of subjects in either treatment arm are provided in Table 2.

Table 2: Treatment-Emergent Adverse Reactions of at Least Moderate Intensity (Grades 2 to 4) and at Least 2% Frequency in Treatment-Naïve Subjects in SINGLE Trial (Week 144 Analysis)

System	Organ	Class/Preferred Term	Dolutegravir 50 mg + Abacavir and Lamivudine Once Daily (n = 414)	Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate Once Daily (n = 419)
Psychiatric	Insomnia	Depression	3%	3%
		Abnormal dreams	1%	2%
			< 1%	2%
Nervous System	Dizziness		< 1%	5%
		Headache	2%	2%

Gastrointestinal	< 1%	3%
Nausea Diarrhea	< 1%	2%
General Disorders	2%	2%
Fatigue		
Skin and Subcutaneous Tissue	< 1%	6%
Rash ^a		
Ear and Labyrinth	0	2%
Vertigo		

^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 7% and 4% of subjects receiving dolutegravir and fixed-dose efavirenz, emtricitabine, and tenofovir disoproxil fumarate, respectively. These events were not treatment limiting.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects

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

Less Common Adverse Reactions Observed in Clinical Trials

As per literature data, the following adverse reactions occurred in less than 2% of subjects receiving dolutegravir in a combination regimen in any one trial. These events have been included because of their seriousness and assessment of potential causal relationship.

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

Hepatobiliary Disorders: Hepatitis.

Musculoskeletal Disorders: Myositis.

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

Renal and Urinary Disorders: Renal impairment.

Skin and Subcutaneous Tissue Disorders: Pruritus.

Laboratory Abnormalities

Treatment-Naïve Subjects

Selected laboratory abnormalities (Grades 2 to 4) with a worsening grade from baseline and representing the worst-grade toxicity in at least 2% of subjects are presented in Table 3. The mean change from baseline observed for selected lipid values is presented in Table 4.

Table 3: Selected Laboratory Abnormalities (Grades 2 to 4) in Treatment-Naïve Subjects (Week

144 Analysis)

Laboratory Parameter Preferred Term	Dolutegravir 50 mg + Abacavir and Lamivudine Once Daily (n = 414)	Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate Once Daily (n = 419)
ALT Grade 2 (> 2.5 to 5.0 x ULN) Grade 3 to 4 (> 5.0 x ULN)	3% 1%	5% < 1%
AST Grade 2 (> 2.5 to 5.0 x ULN) Grade 3 to 4 (> 5.0 x ULN)	3% 1%	4% 3%
Total Bilirubin Grade 2 (1.6 to 2.5 x ULN) Grade 3 to 4 (> 2.5 x ULN)	< 1% < 1%	< 1% < 1%
Creatine kinase Grade 2 (6.0 to 9.9 x ULN) Grade 3 to 4 ($\geq$ 10.0 x ULN)	5% 7%	3% 8%
Hyperglycemia Grade 2 (126 to 250 mg/dL) Grade 3 (> 250 mg/dL)	9% 2%	6% < 1%
Lipase Grade 2 (> 1.5 to 3.0 x ULN) Grade 3 to 4 (> 3.0 x ULN)	11% 5%	11% 4%
Total neutrophils Grade 2 (0.75 to 0.99 x 10) Grade 3 to 4 (< 0.75 x 10)	4% 3%	5% 3%

Table 4: Mean Change from Baseline in Fasted Lipid Values in Treatment-Naïve Subjects (Week 144 Analysis^a)

Laboratory Parameter Preferred Term	Dolutegravir 50 mg + Abacavir and Lamivudine Once Daily (n = 414)	Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate Once Daily (n = 419)
Cholesterol (mg/dL)	24.0	26.7
HDL cholesterol (mg/dL)	5.4	7.2
LDL cholesterol (mg/dL)	16.0	14.6
Triglycerides (mg/dL)	13.6	31.9

^aSubjects on lipid-lowering agents at baseline were excluded from these analyses (19 subjects in each arm in SINGLE: dolutegravir + fixed-dose abacavir and lamivudine n = 30 and fixed-dose 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 (dolutegravir + fixed-dose abacavir and lamivudine n = 36 and fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate n = 36).

Hepatitis B and/or Hepatitis C Virus Co-infection

As per literature data, 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. 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

As per literature data, 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

As per literature data, there is an ongoing multicenter, open-label, non-comparative trial of HIV-1-infected pediatric subjects aged 4 weeks to less than 18 years.

The safety analysis based on subjects (n = 75) who received the recommended dose (determined by weight and age) through Week 24 showed that 11% of subjects experienced drug-related clinical adverse reactions. The only Grade 1 to 2 drug-related clinical adverse reactions reported by more than one subject was immune reconstitution inflammatory syndrome (IRIS) (n = 2). There were no Grade 3 or 4 drug-related adverse reactions reported. No adverse reactions led to discontinuation.

As per literature data the Grade 3 or 4 laboratory abnormalities reported in more than one subject were decreased neutrophil count (n = 11), decreased blood bicarbonate (n = 4), decreased hemoglobin (n = 3), increased lipase (n = 2), and increased blood potassium (n = 2). These laboratory events were not considered to be drug-related. Median laboratory values were similar at baseline and Week 24.

Changes in median serum creatinine were similar to those observed in adults.

Lamivudine

Pancreatitis

As per literature data, pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced pediatric subjects receiving lamivudine alone or in combination with other antiretroviral agents. In an open-label dose-escalation trial, 14 subjects (14%) developed pancreatitis while receiving monotherapy with lamivudine. Three of these subjects died of complications of pancreatitis. In a second open-label trial, 12 subjects (18%) developed pancreatitis. In Trial, pancreatitis was not observed in 236 subjects randomized to lamivudine plus zidovudine. Pancreatitis was observed in 1 subject in this trial who received open-label lamivudine in combination with zidovudine and ritonavir following discontinuation of didanosine monotherapy.

TAF

Adverse Reactions in Clinical Trials of TAF Compared to TDF in Treatment-Naïve Adults with HIV-1 Infection.

As per literature data the safety profile of TAF (n = 866) compared to TDF (n = 867), each with emtricitabine (FTC), elvitegravir (EVG), and cobicistat (COBI), was assessed in antiretroviral treatment-naïve HIV-1 infected adults in the pooled analysis of two randomized trials (Studies

104 and 111). Adverse reactions reported in subjects treated with the TAF-containing regimen (incidence greater than or equal to 5 %, all grades) occurred at a similar rate in subjects treated with the TDF-containing regimen. The most common adverse reaction was nausea. During the 48-week treatment period, 0.9% of subjects discontinued the TAF-containing regimen due to adverse events. Subjects treated with the TAF-containing regimen 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. The safety profile was similar in virologically-suppressed adults with HIV-1 infection who were switched from a TDF-containing regimen to TAF with FTC, EVG, and COBI (N = 799).

Renal Laboratory Tests

As per literature data, in two 48-week trials in antiretroviral treatment-naïve HIV-1 infected adults treated with TAF and FTC, EVG, and 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 TAF with FTC, EVG, and COBI (N=959) with a mean baseline eGFR of 112 mL per minute, mean serum creatinine was similar to baseline at Week 48; median UPCR was 61 mg per gram at baseline and 46 mg per gram at Week 48. Across these trials, renal serious adverse events or discontinuations due to renal adverse reactions were encountered in less than 1% of participants treated with TAF and FTC, EVG, and COBI.

As per literature data, in a 24-week trial in adults with renal impairment (baseline eGFR 30 to 69 mL per minute) who received TAF with FTC, EVG, and 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. TAF with FTC, EVG, and COBI was permanently discontinued due to worsening renal function in two of 80 (3%) subjects.

Bone Mineral Density Effects

As per literature data in the pooled analysis of antiretroviral treatment-naïve trials (Studies 104 and 111), bone mineral density (BMD) from baseline to Week 48 was assessed by dual-energy X-ray absorptiometry (DXA). With the TAF-containing regimen, mean BMD decreased from baseline to Week 48 by -1.30% 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 subjects receiving the TAF-containing regimen. BMD declines of 7% or greater at the femoral neck were experienced by 7% of subjects receiving the TAF containing regimen. The long-term clinical significance of these BMD changes is not known.

As per literature data in 799 virologically-suppressed TDF-treated adult subjects who switched to TAF with FTC, EVG, and 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 subjects receiving the TAF-containing regimen. BMD declines of 7% or greater at the femoral neck were experienced by 1% of subjects receiving the TAF-containing regimen.

Adverse Reactions in Clinical Trials in Pediatric Subjects with HIV-1 Infection Pediatric Subjects Weighing at Least 25 kg

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

count observed in cohort 2 the safety of this combination was similar to that in adults.

Bone Mineral Density Effects

Cohort 1: Treatment-Naïve Adolescents (12 to Less Than 18 Years; at least 35 kg)

As per literature data among the subjects in cohort 1 receiving TAF with FTC, EVG, and 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)

As per literature data among the subjects in cohort 2 receiving TAF with FTC, EVG, and COBI, mean BMD increased from baseline to Week 48, +3.9% at the lumbar spine and +4.2% for TBLH. Mean changes from baseline BMD Z-scores were -0.24 for lumbar spine and 0.19 for TBLH at Week 48. Six subjects had significant (at least 4%) lumbar spine BMD loss at Week 48 and 2 subjects also had at least 4% TBLH BMD loss at Week 48.

Change from Baseline in CD4+ cell counts

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

As per literature data cohort 2 evaluated pediatric subjects (N=52) who were virologically-suppressed and who switched from their antiretroviral regimen to TAF with FTC, EVG, and COBI. Although all subjects had HIV-1 RNA < 50 copies/mL, there was a decrease from baseline in CD4+ cell count at Weeks 24 and 48. The mean baseline and mean change from baseline in CD4+ cell count and in CD4% from Week 2 to Week 48 are presented in Table 5. All subjects maintained their CD4+ cell counts above 400 cells/mm³.

Table 5: Mean Change in CD4+ Count and CD4 Percentage from Baseline to Week 48 in Virologically-Suppressed Pediatric Patients from 6 to <12 Years Who Switched to TAF with FTC, EVG, and COBI

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

Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postmarketing use for each of the individual components of dolutegravir, lamivudine 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

Lamivudine

Body as a Whole: redistribution/accumulation of body fat.

Endocrine and Metabolic: hyperglycemia.

General: weakness.

Hemic and Lymphatic: anemia (including pure red cell aplasia and severe anemias progressing on therapy).

Hepatic and Pancreatic: lactic acidosis and hepatic steatosis, post treatment exacerbations of hepatitis B.

Hypersensitivity: anaphylaxis, urticaria.

Musculoskeletal: muscle weakness, CPK elevation, rhabdomyolysis.

Skin: alopecia, pruritus.

TAF

Skin and Subcutaneous Tissue Disorders: angioedema, urticaria, and rash

Renal and Urinary Disorders: acute renal failure, acute tubular necrosis, proximal renal tubulopathy, and Fanconi syndrome

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 Pharmacy and Poisons Board, Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>

4.9 Overdose

There is no known specific treatment for overdose with dolutegravir, lamivudine 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.

Lamivudine

Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event.

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 dolutegravir, lamivudine and tenofovir alafenamide tablets) 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

Effects on Electrocardiogram

A thorough QT trial has been conducted for dolutegravir and TAF. The effects of lamivudine as

a single entity or the fixed-dose dolutegravir, lamivudine and tenofovir alafenamide tablet on the QT interval have not been evaluated.

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.

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.

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, iothexol) or effective renal plasma flow (determined by the clearance of probe drug, para-amino hippurate) compared with the placebo.

5.2 Pharmacokinetic properties

Pharmacokinetics in Adults

Dolutegravir, Lamivudine and Tenofovir Alafenamide Tablets

The mean systemic exposures of dolutegravir, lamivudine and tenofovir alafenamide from the combination tablets (50 mg/300 mg/25 mg) were comparable to that from TIVICAY tablets of ViiV U.S.A. (containing dolutegravir 50 mg), EPIVIR tablets of ViiV U.S.A. (containing lamivudine 300 mg), and DESCovy tablets of Gilead Sciences, Inc. U.S.A. (containing emtricitabine and tenofovir alafenamide 200 mg/25 mg), respectively, when single doses were administered to healthy subjects under fasted and fed conditions.

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-glycoprotein substrate in vitro. The absolute bioavailability of dolutegravir has not been established. Dolutegravir is highly bound (greater than or equal to 98.9%) to human plasma proteins based on in vivo data and binding is independent of plasma concentration of dolutegravir. The apparent volume of distribution (V_d/F) following 50-mg once-daily administration is estimated at 17.4 L based on a population pharmacokinetic analysis.

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

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

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 (Table 6).

Table 6: Dolutegravir Steady-State Pharmacokinetic Parameter Estimates in HIV-1-Infected Adults

Parameter	50 mg Once Daily Geometric Mean (% CV)
AUC _(0 to 24) (mcg•h/mL)	53.6 (27)
C _{max} (mcg/mL)	3.67 (20)
C _{min} (mcg/mL)	1.11 (46)

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 post dose after 16 weeks of treatment. The clinical relevance of this finding has not been established.

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).

Lamivudine

Following oral administration, lamivudine is rapidly absorbed and extensively distributed. After multiple dose oral administration of lamivudine 300 mg once daily for 7 days to 60 healthy subjects, steady-state C_{max} (C_{max,ss}) was 2.04 ± 0.54 mcg per mL (mean ± SD) and the 24 hour steady state AUC (AUC_{24,ss}) was 8.87 ± 1.83 mcg•hour per mL. Binding to plasma protein is low. Approximately 70% of an intravenous dose of lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans sulfoxide metabolite (approximately 5% of an oral dose after 12 hours). In most single-dose trials in HIV-1-infected subjects, HBV-infected subjects, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life (t_{1/2}) ranged from 5 to 7 hours. In HIV-1-infected subjects, total clearance was 398.5 ± 69.1 mL per min (mean± SD).

TAF

The pharmacokinetic (PK) properties of the components of TAF are provided in Table 7. The multiple dose PK parameters of TAF and its metabolite tenofovir are provided in Table 8.

Table 7: Pharmacokinetic Properties of the Components of TAF

x	Tenofovir Alafenamide
Absorption	
T _{max} (h)	1
Effect of high fat meal (relative to fasting) ^a	AUC Ratio = 1.75 (1.64, 1.88) C _{max} Ratio = 0.85 (0.75, 0.95)
Distribution	
% Bound to human plasma proteins	~ 80

Source of protein binding data	<i>Ex vivo</i>
Blood-to-plasma ratio	1.0
Metabolism	
Metabolism	Cathepsin A ^b (PBMCs) CES1 (hepatocytes) CYP3A (minimal)
Elimination	
Major route of elimination	Metabolism (> 80% of oral dose)
t _{1/2} (h) ^c	0.51
% Of dose excreted in urine ^d	< 1
% Of dose excreted in feces ^d	31.7

PBMCs = peripheral blood mononuclear cells; CES1 = carboxylesterase 1

^aValues 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.

^bIn 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.

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.

^dDosing in mass balance studies: TAF (single dose administration of [14C] tenofovir alafenamide).

Table 8: Multiple Dose PK Parameters of Tenofovir Alafenamide and its Metabolite Tenofovir Following Oral Administration with Food in HIV-Infected Adults

Parameter Mean (CV%)	Tenofovir Alafenamide ^a	Tenofovir ^b
C _{max} (microgram per mL)	0.16 (51.1)	0.02 (26.1)
AUC _{tau} (microgram•hour per mL)	0.21 (71.8)	0.29 (27.4)
C _{trough} (microgram per mL)	NA	0.01 (28.5)

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

^bFrom 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, Lamivudine and Tenofovir Alafenamide

The effect of food on dolutegravir, lamivudine and tenofovir alafenamide tablets has not been evaluated. Based on cross trial comparisons, the pharmacokinetics of dolutegravir, lamivudine and tenofovir alafenamide tablets is not anticipated to be significantly affected by food, hence dolutegravir, lamivudine and tenofovir alafenamide tablets can be administered with or without food.

Specific Populations

Patients with Hepatic Impairment

Dolutegravir

Dolutegravir is primarily metabolized and eliminated by the liver. In a trial comparing 8 subjects with moderate hepatic impairment (Child-Pugh Score B) with 8 matched healthy

controls, exposure of dolutegravir from a single 50 mg dose was similar between the 2 groups. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh Score A or B). The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir has not been studied. Therefore, dolutegravir is not recommended for use in patients with severe hepatic impairment.

Lamivudine

The pharmacokinetic properties of lamivudine have been determined in adults with impaired hepatic function. Pharmacokinetic parameters were not altered by diminishing hepatic function. Safety and efficacy of lamivudine have not been established in the presence of decompensated liver disease.

TAF

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

Patients with Renal Impairment

Because dolutegravir, lamivudine and tenofovir alafenamide tablets is a fixed-dose formulation and cannot be dose adjusted, dolutegravir, lamivudine and tenofovir alafenamide tablets is not recommended in patients with creatinine clearance less than 30 mL per min or patients with end-stage renal disease (ESRD) requiring hemodialysis.

The tenofovir exposure differences in subjects with creatinine clearance range from 30 to ≥ 90 mL per minute were not considered clinically relevant.

Table 9: Pharmacokinetics of the Metabolite (Tenofovir) in HIV Infected Adults with Renal

Impairment Compared to Subjects with Normal Renal Function^a

	AUC _{tau} (microgram·hour per mL) Mean (CV %)		
Creatinine Clearance	≥ 90 mL per minute (N = 18) ^b	60-89 mL per minute (N = 11) ^c	30-59 mL per minute (N = 18)
Tenofovir	0.32 (14.9)	0.46 (31.5)	0.61 (28.4)

^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.

Gender and Race

There are no significant or clinically relevant gender or racial differences in the pharmacokinetics of the individual components (dolutegravir, lamivudine or tenofovir alafenamide) based on the available information that was analyzed for each of the individual components.

Geriatric Patients

Dolutegravir

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

Lamivudine

The pharmacokinetics of lamivudine have not been studied in subjects older than 65 years.

TAF

Population pharmacokinetics analysis of HIV-infected subjects in Phase 2 and Phase 3 trials of TAF with FTC, EVG, and COBI showed that age did not have a clinically relevant effect on exposures of TAF up to 75 years of age.

Pediatric Patients

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

Dolutegravir and Lamivudine

The pharmacokinetics of the combination of dolutegravir and lamivudine in pediatric subjects have not been established.

TAF

Mean exposures of TAF in 24 pediatric subjects aged 12 to less than 18 years who received TAF with FTC, EVG, and COBI were decreased (23% for AUC) 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 10).

Table 10: Multiple Dose PK Parameters of Emtricitabine, Tenofovir Alafenamide and its Metabolite Tenofovir Following Oral Administration of FTC + TAF with EVG + COBI in HIV-Infected Pediatric Subjects Aged 12 to less than 18 Years^a

Parameter Mean (CV%)	Emtricitabine	Tenofovir Alafenamide	Tenofovir
C _{max} (microgram per mL)	2.3 (22.5)	0.17 (64.4)	0.02 (23.7)
AUC _{tau} (microgram•hour per mL)	14.4 (23.9)	0.20 ^b (50.0)	0.29 ^b (18.8)
C _{trough} (microgram per mL)	0.10 ^b (38.9)	NA	0.01 (21.4)

^aFrom Intensive PK analysis in a trial in treatment-naïve pediatric subjects with HIV-1 infection (N = 24).

^b N = 23

The drug interaction trials described were conducted with dolutegravir, lamivudine, and/or TDF as single entities; no drug interaction trials have been conducted using the fixed-dose dolutegravir, lamivudine and tenofovir alafenamide tablets. No clinically significant drug interactions are expected between dolutegravir and lamivudine.

Dolutegravir

Dosing or regimens recommendations as a result of established and other potentially significant drug-drug interactions with dolutegravir are provided in Table 11

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

Table 12.

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

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug with/without Dolutegravir No Effect = 1.00		
			C _{max}	AUC	C _τ or C ₂₄
Daclatasvir 60 mg once daily	50 mg once daily	12	1.03 (0.84 to 1.25)	0.98 (0.83 to 1.15)	1.06 (0.88 to 1.29)
Elbasvir 50 mg once daily	50 mg single dose	12	0.97 (0.89 to 1.05)	0.98 (0.93 to 1.04)	0.98 (0.93, 1.03)
Ethinyl estradiol 0.035 mg	50 mg twice daily	15	0.99 (0.91 to 1.08)	1.03 (0.96 to 1.11)	1.02 (0.93 to 1.11)
Grazoprevir 200 mg once daily	50 mg single dose	12	0.64 (0.44, 0.93)	0.81 (0.67, 0.97)	0.86 (0.79, 0.93)
Metformin 500 mg twice daily	50 mg once daily	15 ^a	1.66 (1.53 to 1.81)	1.79 (1.65 to 1.93)	-
Metformin 500 mg twice daily	50 mg twice daily	15 ^a	2.11 (1.91 to 2.33)	2.45 (2.25 to 2.66)	-
Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug with/without Dolutegravir No Effect = 1.00		
			C _{max}	AUC	C _τ or C ₂₄
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 12: 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		
Atazanavir 400 mg once daily	30 mg once daily	12	1.50 (1.40 to 1.59)	1.9 (1.80 to 2.03)	2.80 (2.52 to 3.11)
Atazanavir/ritonavir 300 mg/100 mg once daily	30 mg once daily	12	1.34 (1.25 to 1.42)	1.62 (1.50 to 1.74)	2.21 (1.97 to 2.47)
Darunavir/ritonavir 600 mg/100 mg twice daily	30 mg once daily	15	0.89 (0.83 to 0.97)	0.78 (0.72 to 0.85)	0.62 (0.56 to 0.69)
Efavirenz 600 mg once daily	50 mg once daily	12	0.61 (0.51 to 0.73)	0.43 (0.35 to 0.54)	0.25 (0.18 to 0.34)
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 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	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)
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		
twice daily					
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)
Calcium carbonate 1,200 mg simultaneous	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)

administration (fasted)					
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)
Calciumcarbonate 1,200 mg 2h 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 2h 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	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)
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		
twice daily					
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)
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	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)

simultaneous administration (fed)					
Calciumcarbonate 1,200 mg 2h after single dose	50 mg	11	1.00 (0.78 to 1.29)	0.94 (0.72 to 1.23)	0.90 (0.68 to 1.19)
dolutegravir					
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 2h 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	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)
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		
administration					
Omeprazole 40 mg once daily	50 mg single dose	12	0.92 (0.75 to 1.11)	0.97 (0.78 to 1.20)	0.95 (0.75 to 1.21)
Prednisone 60 mg once daily with taper	50 mg once daily	12	1.06 (0.99 to 1.14)	1.11 (1.03 to 1.20)	1.17 (1.06 to 1.28)
Rifampin ^a 600 mg once daily	50 mg twice daily	11	0.57 (0.49 to 0.65)	0.46 (0.38 to 0.55)	0.28 (0.23 to 0.34)
Rifampin ^b 600 mg once daily	50 mg twice daily	11	1.18 (1.03 to 1.37)	1.33 (1.15 to 1.53)	1.22 (1.01 to 1.48)
Rifabutin 300 mg once daily	50 mg once daily	9	1.16 (0.98 to 1.37)	0.95 (0.82 to 1.10)	0.70 (0.57 to 0.87)

^aThe number of subjects represents the maximum number of subjects that were evaluated.

^bComparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg twice daily.

^cComparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg once daily.

Lamivudine

Effect of Lamivudine on the Pharmacokinetics of Other Agents:

Based on in vitro study results, lamivudine at therapeutic drug exposures is not expected to affect the pharmacokinetics of drugs that are substrates of the following transporters: organic anion transporter polypeptide 1B1/3 (OATP1B1/3), breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), multidrug and toxin extrusion protein 1 (MATE1), MATE2-K, organic cation transporter 1 (OCT1), OCT2, or OCT3.

Effect of Other Agents on the Pharmacokinetics of Lamivudine:

Lamivudine is a substrate of MATE1, MATE2-K, and OCT2 in vitro. Trimethoprim (an inhibitor of these drug transporters) has been shown to increase lamivudine plasma concentrations. This interaction is not considered clinically significant as no dose adjustment of lamivudine is needed.

Lamivudine is a substrate of P-gp and BCRP; however, considering its absolute bioavailability (87%), it is unlikely that these transporters play a significant role in the absorption of lamivudine. Therefore, coadministration of drugs that are inhibitors of these efflux transporters is unlikely to affect the disposition and elimination of lamivudine.

Interferon Alfa:

There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in a trial of 19 healthy male subjects.

Ribavirin:

In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected subjects.

Mannitol (Pearlitol 25 C) USP - 131.400 mg (Excipient):

Lamivudine and mannitol solutions were co administered to 16 healthy adult subjects in an open-label, randomized-sequence, 4-period, crossover trial. Each subject received a single 300 mg dose of lamivudine oral solution alone or co administered with a single dose of 3.2 grams, 10.2 grams, or

13.4 grams of sorbitol in solution. Coadministration of lamivudine with sorbitol resulted in dose-dependent decreases of 20%, 39%, and 44% in the AUC (0-24), 14%, 32%, and 36% in the AUC (∞), and 28%, 52%, and 55% in the C_{max} of lamivudine, respectively.

Trimethoprim/Sulfamethoxazole (TMP/SMX):

Lamivudine and TMP/SMX were co administered to 14 HIV-1-positive subjects in a single-center, open-label, randomized, crossover trial. Each subject received treatment with a single 300 mg dose of lamivudine and TMP 160 mg/SMX 800 mg once a day for 5 days with concomitant administration of lamivudine 300 mg with the fifth dose in a crossover design. Coadministration of TMP/SMX with lamivudine resulted in an increase of 43% $\pm$ 23% (mean $\pm$ SD) in lamivudine AUC ∞ , a decrease of 29% $\pm$ 13% in lamivudine oral clearance, and a decrease of 30% $\pm$ 36% in lamivudine renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by coadministration with lamivudine. There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used in treat PCP.

TAF

The effects of co administered drugs on the exposure of TAF are shown in Table 13 and the effects of TAF on the exposure of co administered drugs are shown in Table 14 these studies were conducted with FTC and/or TAF. For information regarding clinical recommendations.

Table 13: Drug Interactions: Changes in TAF Pharmacokinetic Parameters in the Presence of Coadministered Drug(s)^a

Coadministered Drug	Coadministered Drug(s) Dosage (once daily) (mg)	Tenofovir Alafenamide Dosage (once daily) (mg)	N	Mean Ratio of TAF PK Parameters (90% CI); No effect = 1.00		
				C _{max}	AUC	C _{min}
Atazanavir	300 (+ 100 ritonavir)	10	10	1.77 (1.28, 2.44)	1.91 (1.55, 2.35)	NC
Cobicistat	150	8	12	2.83 (2.20, 3.65)	2.65 (2.29, 3.07)	NC
Darunavir	800 (+ 150 cobicistat)	25 ^b	11	0.93 (0.72, 1.21)	0.98 (0.80, 1.19)	NC
Darunavir	800 (+ 100 ritonavir)	10	10	1.42 (0.96, 2.09)	1.06 (0.84, 1.35)	NC
Dolutegravir	50	10	10	1.24 (0.88, 1.74)	1.19 (0.96, 1.48)	NC
Efavirenz	600	40 ^b	11	0.78 (0.58, 1.05)	0.86 (0.72, 1.02)	C
Lopinavir	800 (+ 200 ritonavir)	10	10	2.19 (1.72, 2.79)	1.47 (1.17, 1.85)	NC
Rilpivirine	25	25	17	1.01 (0.84, 1.22)	1.01 (0.94, 1.09)	NC
Sertraline	50 (dosed as a single dose)	10 ^c	19	1.00 (0.86, 1.16)	0.96 (0.89, 1.03)	NC

Table 14: Drug Interactions: Changes in PK Parameters for Co administered Drug in the Presence of FTC and/or TAFa

Co administered Drug	Coadministered Drug Dosage (once daily) (mg)	Tenofovir Alafenamide Dosage (once daily) (mg)	N	Mean Ratio of Co administered Drug PK Parameters (90% CI); No effect = 1.00		
				C _{max}	AUC	C _{min}
Atazanavir	300 + 100 ritonavir	10	10	0.98 (0.89, 1.07)	0.99 (0.96, 1.01)	1.00 (0.96, 1.04)
Darunavir	800 + 150 cobicistat	25 ^b	11	1.02 (0.96, 1.09)	0.99 (0.92, 1.07)	0.97 (0.82, 1.15)
Darunavir	800 + 100 ritonavir	10	10	0.99 (0.91, 1.08)	1.01 (0.96, 1.06)	1.13 (0.95, 1.34)
Dolutegravir	50 mg	10	10	1.15 (1.04, 1.27)	1.02 (0.97, 1.08)	1.05 (0.97, 1.13)
Lopinavir	800 + 200 ritonavir	10	10	1.00 (0.95, 1.06)	1.00 (0.92, 1.09)	0.98 (0.85, 1.12)
Midazolam ^c	2.5 (single dose, orally)	25	18	1.02 (0.92, 1.13)	1.13 (1.04, 1.23)	NC
	1 (single dose, intravenous)			0.99 (0.89, 1.11)	1.08 (1.04, 1.14)	NC
Rilpivirine	25	25	16	0.93 (0.87, 0.99)	1.01 (0.96, 1.06)	1.13 (1.04, 1.23)

Sertraline	50 (single dose)	d 10	19	1.14 (0.94, 1.38)	0.93 (0.77, 1.13)	NC
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NC = Not Calculated

^aAll interaction studies conducted in healthy volunteers.

^bStudy conducted with FTC/TAF.

^cA sensitive CYP3A4 substrate.

^dStudy conducted with FTC + TAF with EVG + COBI

5.3 Preclinical safety data

Carcinogenesis

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 maximum recommended dose. 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 maximum recommended dose.

Lamivudine

Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) the human exposures at the recommended dose of 300 mg.

TAF

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

As per literature data, lamivudine was mutagenic in a mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was not mutagenic in a microbial mutagenicity assay, in an in vitro cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver. Lamivudine showed no evidence of in vivo genotoxic activity in the rat at oral doses of up to 2000 mg per kg, producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV-1 infection.
TAF

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

Dolutegravir and Lamivudine

Dolutegravir or lamivudine did not affect male or female fertility in rats at doses associated with exposures approximately 44 or 112 times (respectively) higher than the exposures in humans at the maximum recommended doses.
TAF

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol USP
Microcrystalline Cellulose NF
Sodium Starch Glycolate NF
Povidone USP
Lactose monohydrate NF
Croscarmellose sodium NF
Magnesium stearate NF
Colloidal Silicon Dioxide NF
Opadry II white

6.2 Incompatibilities

Not Known

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store in a cool dry place below 30°C. protect from light.
Keep all medicines out of reach of children

6.5 Nature and contents of container

1. HDPE Pack of 30's
2. HDPE Pack of 90's

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Lupin Ltd Kalpataru Inspire
3rd Floor, Off Western Express Highway Santacruz (East)
Mumbai 400055, India

Manufactured at –

Lupin Ltd Kalpataru Inspire
3rd Floor, Off Western Express Highway Santacruz (East)
Mumbai 400055, India

8. MARKETING AUTHORISATION NUMBER(S) –

H2026/CTD12201/24556

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION--

APRIL 2026

10. DATE OF REVISION OF THE TEXT

December 2027