WARNING:

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with other antiretrovirals (see section 4.4).

ENVUTEG is not indicated for the treatment of chronic hepatitis B virus (HBV) infections. Safety and efficacy of ENVUTEG has not been established in patients co-infected with HBV and HIV.

POST-TREATMENT EXACERBATIONS OF HEPATITIS B

Severe acute exacerbations of hepatitis B virus (HBV) have been reported in HBV and HIV co-infected patients who have discontinued products containing lamivudine (3TC) and/or tenofovir disoproxil fumarate (TDF) and may occur with discontinuation of ENVUTEG. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in HBV and HIV co-infected patients who discontinue ENVUTEG. If appropriate, initiation of anti-hepatitis B therapy may be warranted (see section 4.4).

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

ENVUTEG Film coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **ENVUTEG** film coated tablet contains:

Lamivudine	300 mg,
Tenofovir alafenamide	25 mg
Dolutegravir sodium (equivalent to dolutegravir)	50 mg.

Contains sugar: mannitol 131,40 mg and lactose monohydrate 60 mg per tablet.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film coated tablets

White to off white, film coated, capsule shaped, biconvex, bevelled edge tablet debossed with **M** on one side of the tablet and **LD** on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ENVUTEG is indicated for use alone as a complete regimen for the treatment of human immunodeficiency virus type I (HIV-1) infection in adults and children weighing at least 40 kg.

Limitation of Use: **ENVUTEG** alone is not recommended in patients with resistance-associated integrase substitutions or clinically suspected integrase strand transfer

inhibitor resistance because the dose of **ENVUTEG** is insufficient in these subpopulations. See the full prescribing information for dolutegravir.

4.2 Posology and method of administration

Posology

Therapy should be initiated by a medical practitioner experienced in the management of HIV infection.

Testing Prior to Initiation and During Treatment with ENVUTEG:

Perform pregnancy testing before initiation of **ENVUTEG** in adolescents and adults of childbearing potential (see section 4.4).

Prior to or when initiating **ENVUTEG**, test patients for hepatitis B virus (HBV) infection (see section 4.4).

Prior to initiation and during treatment with **ENVUTEG**, 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 section 4.4).

Recommended Dosage:

ENVUTEG is a fixed-dose combination medicine containing 50 mg of dolutegravir, 300 mg of lamivudine (3TC), and 25 mg of tenofovir alafenamide (TAF). The recommended dosage regimen of **ENVUTEG** in adults and children weighing at least 40 kg is one tablet once daily orally with or without food.

Special populations

Dosage Adjustment for special population

Because **ENVUTEG** is a fixed-dose combination formulation and cannot be dose adjusted, it is not recommended in patients requiring dosage adjustment.

Paediatric Use

ENVUTEG tablets should only be administered to paediatric patients with a body weight of at least 40 kg because they are a fixed-dose combination that cannot be adjusted. The safety and efficacy have been established for the individual components in this weight group.

Elderly Use

Clinical trials of individual components of **ENVUTEG** did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. Caution should be exercised in the administration of **ENVUTEG** in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see section 5.1).

Renal Impairment

ENVUTEG tablets are not recommended for patients with severe renal impairment (estimated creatinine clearance below 30 mL) because **ENVUTEG** is a fixed-dose combination and the dosage of the individual components cannot be adjusted. No dosage adjustment of **ENVUTEG** tablets is recommended in patients with mild or

moderate renal impairment (estimated creatinine clearance greater than or equal to 30 mL per minute).

Hepatic Impairment

No dosage adjustment of **ENVUTEG** tablets is recommended in patients with mild (Child-Pugh Class A) hepatic impairment. The effect of moderate or severe hepatic impairment (Child-Pugh Class B or C) on the pharmacokinetics of dolutegravir, lamivudine and tenofovir alafenamide has not been studied.

Therefore, **ENVUTEG** tablets are not recommended for use in patients with severe hepatic impairment (see sections 4.3 and 5.1).

4.3 Contraindications

- Known hypersensitivity to lamivudine, tenofovir alafenamide, dolutegravir, or any of the excipients of **ENVUTEG** (listed in section 6.1)**.**
- Patients 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 (see section 4.5).
- Pregnancy and lactation (see section 4.6).
- Co-administration with metformin, adefovir, pilsicainide or didanosine
- Woman of childbearing age
- Patients younger than 18 years
- Moderate and severe hepatic impairment
- Uncontrolled renal failure

4.4 Special warnings and precautions for use

Metabolic abnormalities

Combination antiretroviral therapy, including **ENVUTEG** has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia.

Lipodystrophy

Combination antiretroviral therapy, including **ENVUTEG**, has also been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat, enlargement (buffalo hump), peripheral wasting, facial wasting and breast enlargement in HIV patients.

A higher risk of lipodystrophy has been associated with individual factors such as older age, and with medicine related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Fasting serum lipids and blood glucose levels should be monitored. Lipid disorders should be managed as clinically appropriate. Patients with evidence of lipodystrophy should also have a thorough cardiovascular risk assessment.

Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART). Typically, such reaction

presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, atypical mycobacterial infections, cytomegalovirus retinitis, *pneumocystis jerovecii* and cryptococcal meningitis. Appropriate treatment of the opportunistic disease should be instituted or continued, and ART continued. Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS.
Autoimmune disorders (such as Graves' disease, Guillain-Barre Syndrome, Polymyositi) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

***Osteonecrosis*:**

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (cART) including components of **ENVUTEG**. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness, or difficulty in movement.

Mitochondrial dysfunction:

Nucleoside and nucleotide analogues as contained in **ENVUTEG** have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or postnatally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactataemia, hyperlipidaemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs of symptoms.

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 **ENVUTEG**.

Discontinuation of anti-HBV therapy, including 3TC and TAF, two components of **ENVUTEG**, 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 **ENVUTEG** and other suspect medicines 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 oedema, hepatitis, eosinophilia, angioedema, difficulty breathing). Clinical status, including liver aminotransferases, should be monitored and appropriate therapy initiated. Delay in stopping treatment with **ENVUTEG** or other suspect medicines 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 **ENVUTEG** (see section 4.8). 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-Foetal Toxicity

Preliminary data from an observational study showed that dolutegravir, a component of **ENVUTEG**, 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 **ENVUTEG** at the time of conception through the first trimester of pregnancy (see section 4.6).

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

Perform pregnancy testing before initiation of **ENVUTEG** in adolescents and adults of childbearing potential to exclude use of **ENVUTEG** during the first trimester of pregnancy (see section 4.6).

Advise adolescents and adults of childbearing potential to consistently use effective contraception (see section 4.6).

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

The concomitant use of **ENVUTEG** and other medicines may result in known or potentially significant interactions, some of which may lead to (see sections 4.3 and 4.5):

- Loss of therapeutic effect of **ENVUTEG** and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of

concomitant medicines.

See Table 4 for steps to prevent or manage these possible and known significant medicine interactions, including dosing recommendations. Consider the potential for medicine interactions prior to and during therapy with **ENVUTEG**; review concomitant medications during therapy with **ENVUTEG**; and monitor for the adverse reactions associated with the concomitant medicines.

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 TAF with emtricitabine (FTC), elvitegravir (EVG), and cobicistat (COBI), there have been no cases of Fanconi syndrome or Proximal Renal Tubulopathy (PRT), and renal serious adverse events or discontinuations due to renal adverse reactions were encountered in less than 1 % of participants with eGFRs greater than 50 mL/minute who received TAF. **ENVUTEG** 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 medicines including non-steroidal anti-inflammatory medicines are at increased risk of developing renal-related adverse reactions.

Prior to initiation and during treatment with **ENVUTEG**, 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 **ENVUTEG** in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

Lactic Acidosis and Severe Hepatomegaly with Steatosis

Use of **ENVUTEG** can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction.

Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue, and weight loss.

In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/ℓ) and the serum bicarbonate and respond as follows:

- Lactate 2-5 mmol/ℓ with minimum symptoms: switch to medicines that are less likely to cause lactic acidosis.
- Lactate 5-10 mmol/ℓ with symptoms and/or with reduced standard bicarbonate: Stop NRTIs and change treatment option. Once lactate has settled, use medicines that are less likely to cause lactic acidosis. Exclude other causes, (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis and hyperthyroidism.
- Lactate > 10 mmol/ℓ: STOP all therapy (80 % mortality).

The above lactate values may not be applicable to paediatric patients.

Caution should be exercised when administering **ENVUTEG** to patients with known risk

factors for liver disease.

Treatment with **ENVUTEG** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Pancreatitis

Pancreatitis has been observed in some patients receiving **ENVUTEG**.

Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of **ENVUTEG** until diagnosis of pancreatitis is excluded.

Opportunistic infections:

Patients receiving **ENVUTEG** should be advised that they may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by healthcare professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

The risk of HIV transmission to others:

Patients should be advised that current antiretroviral therapy, including **ENVUTEG**, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination.

Appropriate precautions should continue to be employed.

Bone mineral density:

Decreases in bone mineral density of spine and changes in bone biomarkers from baseline are significantly greater with tenofovir disoproxil fumarate as contained in **ENVUTEG**. Decreases in bone mineral density of the hip are significantly greater. Clinically relevant bone fractures are reported. If bone abnormalities are suspected, then appropriate consultation should be obtained. Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk of osteopenia.

Paediatric use:

Safety and effectiveness in paediatric patients and patients < 18 years of age have not been established.

Elderly use:

Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Excipient warnings:

Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, total lactase deficiency, or glucose-galactose malabsorption or fructose intolerance should not take **ENVUTEG**.

4.5 Interaction with other medicines and other forms of interaction

Effect of Dolutegravir on the Pharmacokinetics of Other Medicines

Dolutegravir: *In vitro*, dolutegravir inhibited the renal organic cation transporters, OCT2 (IC_{50} = 1,93 microM) and multidrug and toxin extrusion transporter (MATE)l (IC_{50} = 6,34 microM). *In vivo*, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2 and potentially MATEl. Dolutegravir may increase plasma concentrations of medicines eliminated via OCT2 or MATEl (dofetilide and metformin, Table 1) (see section 4.3).

In vitro, dolutegravir inhibited the basolateral renal transporters, organic anion transporter (OAT)1 (IC_{50} = 2,12 microM) and OAT3 (IC_{50} = 1,97 microM). However, in vivo, dolutegravir did not alter the plasma concentrations of tenofovir or para-amino hippurate, substrates of OATl and OAT3.

In vitro, dolutegravir did not inhibit (IC_{50} greater than 50 microM) the following: cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2Cl9, 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 interaction trials, dolutegravir is not expected to affect the pharmacokinetics of medicines that are substrates of these enzymes or transporters.

Effect of Other Medicines on the Pharmacokinetics of Dolutegravir, 3TC, 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.

Medicines that induce those enzymes and transporters may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir.

Co-administration of dolutegravir and other medicines that inhibit these enzymes may increase dolutegravir plasma concentration.

Etravirine significantly reduced plasma concentrations of dolutegravir, but the effect of etravirine was mitigated by coadministration of lopinavir/ritonavir or darunavir/ritonavir and is expected to be mitigated by atazanavir/ritonavir (Table 1) (see section 5.1).

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

TAF: TAF is a substrate of P-gp, BCRP, OATP1B1, and OATP1B3. Medicines that strongly affect P-gp and BCRP activity may lead to changes in TAF absorption (see Table 6). Medicines 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 **ENVUTEG** and development of resistance. Co-administration of **ENVUTEG** with other medicines 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 interactions for Dolutegravir, 3TC, or TAF

There were no interaction trials conducted with fixed-dose **ENVUTEG**.

ENVUTEG is intended as a complete regimen.

Dolutegravir and TAF: Table 1 provides clinical recommendations as a result of interactions with dolutegravir and/or TAF. These recommendations are based on either interaction trials or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy (see section 5.1).

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

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of Dolutegravir and/or Concomitant Medicine**	**Clinical Comment**
HIV-1 Antiviral Medicines		
Non-nucleoside reverse transcriptase inhibitor: Etravirine[a]	↓ Dolutegravir	Use of **ENVUTEG** with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir is not recommended.
Non-nucleoside reverse transcriptase inhibitor: Efavirenz[a]	↓ Dolutegravir	If co-administration with efavirenz is necessary, an additional 50 mg dose of dolutegravir should be taken, separated by 12 hours from **ENVUTEG**.

Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓ Dolutegravir	Avoid co-administration with **ENVUTEG** because there is insufficient data to make dosing recommendations.
Protease inhibitor: Fosamprenavir/ ritonavir[a]	↓ Dolutegravir	If co-administration with fosamprenavir/ ritonavir is necessary, an additional 50 mg dose of dolutegravir should be taken, separated by 12 hours from **ENVUTEG**. Co-administration is not recommended with **ENVUTEG**.
Tipranavir/ ritonavir[a]	↓ Dolutegravir ↓ TAF	
Other Agents		
Dofetilide	↑ Dofetilide	Co-administration is contraindicated with **ENVUTEG** (see section 4.2).
Carbamazepine[a]	↓Dolutegravir ↓ TAF	Consider alternative anticonvulsant. If co-administration is necessary, an additional 50 mg dose of dolutegravir should be taken, separated by 12 hours from **ENVUTEG**.
Oxcarbazepine Phenytoin Phenobarbitone	↓ Dolutegravir ↓ TAF	Avoid co-administration with **ENVUTEG** because there are insufficient data to make dosing recommendations.
St. John's wort (Hypericum perforatum)	↓ TAF	Co-administration is not Recommended with **ENVUTEG**.

Medicines containing polyvalent cations (e.g., Mg or Al): Cation-containing antacids[a] or laxatives Sucralfate Buffered medicines	↓ Dolutegravir	Administer **ENVUTEG** 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 **ENVUTEG** 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	Co-administration of dolutegravir as in **ENVUTEG** increased metformin plasma concentration. Metformin is contraindicated in patients taking **ENVUTEG**
Rifampicin[a]	↓ Dolutegravir ↓ TAF	Co-administration is not recommended with **ENVUTEG**. A supplement dose of 50 mg is required in patients taking rifampicin and doutegravir
Rifabutin Rifapentine	↓ TAF	Co-administration is not recommended with **ENVUTEG**.

[a] See section 5.1 for magnitude of interactions.

3TC: *Medicines Inhibiting Organic Cation Transporters:* 3TC, a component of

ENVUTEG, is predominantly eliminated in the urine by active organic cationic secretion. The possibility of interactions with other medicines 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) (see section 5.1). No data are available regarding interactions with other medicines that have renal clearance mechanisms similar to that of 3TC.

Sorbitol: Co-administration of single doses of lamivudine and sorbitol resulted in a sorbitol dose dependent reduction in 3TC. When possible, avoid use of sorbitol-containing medicines with 3TC (see section 5.1).

Medicines without Clinically Significant Interactions with Dolutegravir or TAF

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

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

TAF: Based on 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 medicines: buprenorphine, itraconazole, ketoconazole, lorazepam, methadone, midazolam, naloxone, norbuprenorphine, norgestimate/ethinyl estradiol, and sertraline.

Medicines Affecting Renal Function with TAF

Because tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, co-administration of TAF with medicines that reduce renal function or compete for active tubular secretion may increase concentrations of tenofovir and other renally eliminated medicines and this may increase the risk of adverse reactions. Some examples of medicines that are eliminated by active tubular secretion include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs (see section 4.4).

4.6 Fertility, pregnancy, and lactation

Women of childbearing potential /Contraception in males and females

Pregnancy Testing: Perform pregnancy testing in adolescents and adults of childbearing potential before initiation of **ENVUTEG**.

Contraception: Adolescents and adults of childbearing potential should avoid use of **ENVUTEG** at the time of conception through the first trimester of pregnancy because of the potential risk of neural tube defects.

Advise adolescents and adults of childbearing potential who are taking **ENVUTEG** to consistently use effective contraception.

Pregnancy

ENVUTEG is contraindicated in pregnancy and lactation. Neural tube defects have been noted in an observational study in humans, where DTG-based regimens were used at the time of conception and early pregnancy (see section 4.3).

Tenofovir, dolutegravir and lamivudine were shown to cross the placenta in reproductive toxicity studies in animals. Late onset neurological disorders, including seizures, have been observed in children who have been exposed to nucleoside analogues such as tenofovir and lamivudine, (see Mitochondrial Dysfunction under section 4.4). **ENVUTEG** should not be prescribed in women who plan to become pregnant. Woman of child-bearing age should not use **ENVUTEG** unless they are reliably using highly effective contraception. Treatment with **ENVUTEG** should not be initiated without a medically supervised negative pregnancy test. This test should be repeated at frequent intervals during treatment with **ENVUTEG**, and especially in the event that pregnancy is suspected.

If there are plans to become pregnant or if pregnancy is confirmed while on dolutegravir during the first trimester, the patient must be switched to an alternative regimen.

Lactation

Mothers breastfeeding their infants should not use **ENVUTEG**. Lamivudine is excreted in human milk at similar concentrations to those found in serum; tenofovir is excreted in breast milk and it is not known whether dolutegravir is excreted in human milk.

4.7 Effects on ability to drive and use machines

ENVUTEG cause dizziness and fatigue which may affect the ability to drive and use machines. Patients should ensure that they do not engage in driving or using machines until they know how **ENVUTEG** affects them.

4.8 Undesirable effects

Adverse reactions identified in an analysis of pooled data from clinical studies are listed below by system organ class and by frequency.

Tabulated list of adverse reactions

Blood and the lymphatic system disorders	Frequent	Neutropenia
	Frequency unknown	Anaemia
Immune system disorders	Frequent	Allergic reaction, including angioedema
	Less frequent	Hypersensitivity, Immune Reconstitution Syndrome (see section 4.4)

Metabolism and nutrition disorders	Frequent	Hypertriglyceridaemia, hyperglycaemia
	Frequency unknown	Hypophosphataemia, lactic acidosis, hypokalaemia
Psychiatric disorders	Frequent	Insomnia, abnormal dreams, suicidal ideation, attempt, behaviour, or completion. These events were observed primarily in subjects with a pre-existing history of depression or other psychiatric illness
Nervous system disorders	Frequent	Headache, dizziness
Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea
Gastrointestinal disorders	Frequent	Nausea, diarrhoea, vomiting, flatulence, upper abdominal pain, dyspepsia, amylase elevation, lipase elevation
	Less frequent	Abdominal pain, abdominal discomfort
	Frequency unknown	Pancreatitis

Hepatobiliary disorders	Frequent	Hyperbilirubinaemia, increased liver enzymes (including increased AST, increased ALT and/or gamma GT)
	Less frequent	Hepatitis
	Frequency unknown	Hepatic steatosis
Skin and subcutaneous tissue disorders	Frequent	Rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash, skin discolouration
Musculoskeletal, connective tissue and bone disorders	Frequent	Creatine kinase elevation, myositis, arthralgia
	Frequency unknown	Myopathy, osteomalacia, rhabdomyolysis, muscular weakness
Renal and urinary disorders	Frequent	Renal impairment
	Frequency unknown	Increased creatinine, renal insufficiency, renal failure, acute renal failure, Fanconi syndrome, proximal tubulopathy, nephrogenic diabetes insipidus,

		proteinuria, acute tubular necrosis, polyuria, interstitial nephritis
General disorders and administration site conditions	Frequent	Fatigue, pain, asthenia

Description of selected adverse reactions

Changes in laboratory chemistries

Increases in serum creatinine occurred within the first week of treatment with dolutegravir and remained stable through 48 weeks. In treatment naïve patients a mean change from baseline of 9,96 μmol/l (range: -53 μmol/l to 54,8 μmol/l) was observed after 48 weeks of treatment. Creatinine increases were comparable by background NRTIs and were similar in treatment experienced patients. These changes are not considered to be clinically relevant since they do not reflect a change in glomerular filtration rate.

Small increases in total bilirubin (without clinical jaundice) were observed with dolutegravir. These changes are not considered clinically relevant as they likely reflect competition between dolutegravir and unconjugated bilirubin for a common clearance pathway (UGT1A1).

Asymptomatic creatine phosphokinase (CPK) elevations mainly in associate with exercise have also been reported with dolutegravir therapy.

Hepatitis B and/or Hepatitis C Virus Co-infection

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

Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C at the start of therapy with dolutegravir, particularly in the setting where anti-hepatitis therapy was withdrawn (see section 4.4).

Not for use in subjects <40 kg.

Post marketing experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during post marketing use.

Psychiatric disorders:

Frequency unknown: Anxiety

Hepatobiliary disorders:

Frequency unknown: Acute liver failure, hepatotoxicity.

Musculoskeletal disorders:

Frequency unknown: Arthralgia, myalgia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is *important. It allows continued monitoring of the benefit/risk balance of the* medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

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.

3TC: Because a negligible amount of 3TC 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 3TC 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

Pharmacological Classification:

A 20.2.8 Antimicrobial (Chemotherapeutic) Agents. Antiviral Agents.

Pharmacotherapeutic group: Antivirals for systemic use, nucleoside and nucleotide reverse transcriptase inhibitors; ATC code: J05AF13.

5.1 Pharmacodynamic properties

Mechanism of action:

Dolutegravir: Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. Strand transfer biochemical assays using purified HIV-1 integrase and pre-processed substrate DNA resulted in IC50 values of 2,7 nM and 12,6 nM.

3TC: 3TC is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-

TP). The principal mode of action of 3TC-TP is inhibition of HIV-1 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue.

Lamivudine: Lamivudine, a nucleoside reverse transcriptase inhibitor (NRTI), is a selective inhibitor of HIV-1 and HIV-2 replication *in vitro*.

Lamivudine is metabolised intracellularly to the 5'-triphosphate which has an intracellular half-life of 16-19 hours. Lamivudine 5'-triphosphate is a weak inhibitor of the RNA and DNA dependent activities of HIV reverse transcriptase, its mode of action is a chain terminator of HIV reverse transcription.

Reduced *in vitro* sensitivity to lamivudine has been reported for HIV isolates from patients who have received lamivudine therapy.

Lamivudine-resistant HIV-1 mutants are cross-resistant to didanosine and zalcitabine.

In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

Lamivudine does not interfere with cellular deoxynucleotide metabolism and has little effect on mammalian cell and mitochondrial DNA content.

Tenofovir alafenamide: TAF is a phosphonoamidate prodrug of tenofovir (2' deoxyadenosine monophosphate analogue). Plasma exposure to TAF allows for permeation into cells and then TAF is intracellularly converted to tenofovir through hydrolysis by cathepsin A. Tenofovir is subsequently phosphorylated by cellular kinases to the active metabolite tenofovir diphosphate.

Tenofovir diphosphate inhibits HIV-1 replication through incorporation into viral DNA by

the HIV reverse transcriptase, which results in DNA chain-termination.

Tenofovir has activity that is specific to hepatitis B virus and human immunodeficiency virus (HIV-1 and HIV-2). Cell culture studies have shown that both tenofovir and FTC can be fully phosphorylated when combined in cells. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of toxicity to mitochondria in cell culture.

Antiviral activity in cell culture

Dolutegravir: Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean EC_{50} values of 0,5 nM (0,21 ng per mL to 2,1 nM (0,85 ng per mL) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells.
Dolutegravir exhibited antiviral activity against 13 clinically diverse clade B isolates with a mean EC_{50} value of 0,52 nM in a viral integrase susceptibility assay using the integrase coding region from clinical isolates. Dolutegravir demonstrated antiviral activity in cell culture against a panel of HIV-1 clinical isolates (3 in each group of M clades A, B, C, D, E, F and G, and 3 in group O) with EC_{50} values ranging from 0,02 nM to 2,14 nM for HIV-1.
Dolutegravir EC_{50} values against 3 HIV-2 clinical isolates in PBMC assays ranged from 0,09 nM to 0,61 nM.

3TC: The antiviral activity of 3TC against HIV-1 was assessed in a number of cell lines including monocytes and PBMCs using standard susceptibility assays. EC50 values were in the range of 0,003 to 15 microM (1 microM = 0,23 mcg per mL). The median

EC50 values of lamivudine were 60 nM (range: 20 to 70 nM), 35 nM (range: 30 to 40 nM), 30 nM (range: 20 to 90 nM), 20 nM (range: 3 to 40 nM), 30 nM (range: 1 to 60 nM), 30 nM (range: 20 to 70 nM), 30 nM (range: 3 to 70 nM), and 30 nM (range: 20 to 90 nM) against HIV-1 clades A-G and group O viruses (n = 3 except n = 2 for clade B) respectively. The EC50 values against HIV-2 isolates (n = 4) ranged from 0,003 to 0,120 microM in PBMCs. 3TC was not antagonistic to all tested anti-HIV agents. Ribavirin (50 microM) used in the treatment of chronic HCV infection decreased the anti-HIV-1 activity of lamivudine by 3,5-fold in MT-4 cells.

Tenofovir alafenamide: The antiviral activity of TAF against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophate cells and CD4-T lymphocytes. The EC_{50} values for TAF ranged from 2,0 to 14,7 nM.

TAF displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including sub-types A, B, C, D, E, F and G (EC_{50} values ranged from 0,10 to 12,0 nM) and strain specific activity against HIV-2 (EC50 values ranged from 0,91 to 2,63 nM).

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

Antiviral activity in combination with other antiviral medicines:

Dolutegravir: The antiviral activity of dolutegravir was not antagonistic when combined

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

Neither dolutegravir nor 3TC were antagonistic to all tested anti-HIV agents. See full prescribing information for dolutegravir and 3TC.

Resistance:

In cell culture: Dolutegravir-resistant viruses were selected in cell culture starting from different wild-type HIV-1 strains and clades. Amino acid substitutions E92Q, G118R, S153F or Y, G193E or R263K emerged in different passages and conferred decreased susceptibility to dolutegravir of up to 4-fold. Passage of mutant viruses containing the Q148R or Q148H substitutions selected for additional substitutions in integrase that conferred decreased susceptibility to dolutegravir (fold-change increase of 13 to 46). The additional integrase substitutions included T97A, E138K, G140S, and M154I. Passage of mutant viruses containing both G140S and Q148H selected for L74M, E92Q, and N155H.

3TC: 3TC-resistant variants of HIV-1 have been selected in cell culture. Genotypic analysis showed that the resistance was predominantly due to a methionine to valine or isoleucine (M184V/I).

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

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

Resistance in vitro:

Isolation from wild type HIV-1: Viruses highly resistant to dolutegravir have not been observed during HIV-1 passage. During wilde type HIV-1 passage in the presence of dolutegravir integrase substitutions observed were S153Y and S153F with FCs ≤ 4,1 for strain IIIB, or E92Q with FC = 3,1 and G193E with FC = 3,2 for strain NL432. Additional passage of wildtype subtype B, C and A/G viruses in the presence of dolutegravir selected for R263K, G118R and S153T.

Anti-HIV activity against resistant strains: Reverse Transcriptase Inhibitor- and Protease Inhibitor-Resistant Strains: Dolutegravir demonstrated equivalent potency against 2 non-nucleoside (NN)-RTI-resistant, 3 nucleoside (N)-RTI-resistant and 2-PI-resistant HIV-1 mutant clones (1 triple and 1 sextuple) compared to the wildtype strain.

Integrase Inhibitor-Resistant HIV-1 Strains: Dolutegravir showed anti-HIV activity (susceptibility) with FC < 5 against 27 and 28 integrase inhibitor -resistant mutant viruses with single substitutions including T66A/I/K, E92Q/V, Y143C/H/R, Q148H/K/R, and N155H

Integrase Inhibitor-Resistant HIV-2 Strains: Site directed mutant HIV-2 viruses were constructed based on subjects infected with HIV-2 and treated with raltegravir who showed virologic failure. Overall, the HIV-2 FCs observed were similar to HIV-1 FCs observed for similar pathway mutations.

Resistant in vivo: Integrase inhibitor naïve patients: No integrase inhibitor (INI) resistant mutations or treatment emergent resistance to the NRTI backbone therapy were isolated with dolutegravir 50 mg once daily in treatment -naïve studies.

Resistance:

In a pooled analysis of patients receiving **ENVUTEG**, sequence analysis was performed on paired baseline and on treatment HBV isolates for patients who either experienced virologic breakthrough (2 consecutive visits with HBV DNA ≥ 69 IU/mL after having been < 69 IU/mL, or 1,0 log 10 or greater increase in HBV DNA from nadir) or patients with HBV DNA ≥ 69 IU/mL at Week 96 or at early discontinuation at or after Week 24. In analyses at Week 48 (N = 20) and Week 96 (N = 72), no amino acid substitutions associated with resistance to **ENVUTEG** were identified in these isolates (genotypic and phenotypic analyses).

Resistance in Clinical Subjects: *Dolutegravir:* No subjects in the treatment arm receiving dolutegravir + fixed-dose abacavir sulfate and lamivudine in SINGLE (treatment-naïve trial) had a detectable decrease in susceptibility to dolutegravir or background NRTIs in the resistance analysis subset (n = 11 with HIV-1 RNA greater than 400 copies per mL at failure or last visit and having resistance data). Two virologic failure subjects in SINGLE had treatment-emergent G/D/E193D and G193G/E integrase substitutions at Week 84 and Week 108, respectively, and 1 subject with 275 copies per mL HIV-1 RNA had a treatment-emergent Q157Q/P integrase substitution detected at Week 24. None of these subjects had a corresponding decrease in dolutegravir susceptibility.

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

Cross-resistance:

The antiviral activity of tenofovir alafenamide was evaluated against a panel of isolates containing nucleos(t)ide reverse transcriptase inhibitor mutations in HepG2 cells. HBV

isolates expressing the rtV173L, rtL180M, and rtM204V/I substitutions associated with resistance to lamivudine remained susceptible to tenofovir alafenamide (< 2 fold change in EC_{50}). HBV isolates expressing the rtL180M. rtM204V plus rtT184G, rtS202G, or rtM250V substitutions associated with resistance to entecavir remained susceptible to tenofovir alafenamide. HBV isolates expressing the rtA181T, rtA181V, or rtN236T single substitutions associated with resistance to adefovir remained susceptible to tenofovir alafenamide; however, the HBV isolate expressing rtA181V plus rtN236T exhibited reduced susceptibility to tenofovir alafenamide (3,7 fold change in EC_{50}). The clinical relevance of these substitutions is not known.

3TC: Cross-resistance among certain reverse transcriptase inhibitors has been observed. 3TCresistant HIV-1 isolate were cross-resistant in cell culture to didanosine (ddI). Cross-resistance is also expected with abacavir and emtricitabine as these select M184V substitutions.

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

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

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 conditions. The mean systemic exposures of dolutegravir and lamivudine 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), and EPIVIR tablets of ViiV U.S.A. (containing lamivudine 300 mg) under fed conditions. Based on cross trial comparison, under fed conditions, the effect of food on the systemic exposure of TAF from the combination tablets is comparable to the effect of food on the systemic exposure of TAF from DESCOVY.

Dolutegravir: Following oral administration of dolutegravir, peak plasma concentrations were observed 2 to 3 hours post dose. With once-daily dosing, pharmacokinetic steady state is achieved within approximately 5 days with average accumulation ratios for AUC, C_{max}, and C24h 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 (Vd/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 faeces. 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 medicine was less than 1 % of the dose. Dolutegravir has a terminal half-life of approximately 14 hours and an apparent clearance (CLIF) 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 5).

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

Parameter	50 mg Once Daily Geometric
$AUC_{(0-24)}$ (mcg•h/mL)	53,6 (27)
C_{max} (mcg/mL)	3,67 (20)
C_{min} (mcg/mL)	1,11 (46)

Cerebrospinal Fluid CCSF): 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.

Polymomhisms 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).

3TC: Following oral administration, 3TC is rapidly absorbed and extensively distributed. After multiple dose oral administration of 3TC 300 mg once daily for 7 days to 60 healthy subjects, steady-state C_{max} ($C_{max,ss}$) was 2,04 ± 0,54 meg 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 3TC is recovered as unchanged medicine in the urine. Metabolism of 3TC 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 (ty2) 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 6. The multiple dose PK parameters of TAF and its metabolite tenofovir are provided in Table 7.

Table 6: Pharmacokinetic properties of the components of TAF

	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	*Ex vivo*
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 faeces[d]	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: TAF (single dose administration of C4C] tenofovir alafenamide).

Table 7: 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	0,21 (71,8)	0,29 (27,4)
C_{trough} (microgram per mL)	NA	0,01 (28,5)

CV = Coefficient of Variation; NA = Not Applicable

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

[b.] From Population PK analysis in two trials of treatment-naive 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: *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.

3TC: The pharmacokinetic properties of 3TC have been determined in adults with impaired hepatic function. Pharmacokinetic parameters were not altered by diminishing hepatic function.

Safety and efficacy of 3TC 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 (see section 4.2)

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 50 mL per min or patients with end-stage renal disease (ESRD) requiring hemodialysis (see section 4.2).

Table 8: Pharmacokinetics of the Components of TAF and a Metabolite (Tenofovir) in HIV Infected Adults with Renal Impairment Compared to Subjects with Normal Renal Function

	AUC_{tau} (microgram·hour per mL) Mean (CV %)		
Creatinine	**≥ 90mL per minute**	**60-89mL per minute (N =**	**30-59 mL per minute**
Tenofovir	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.

Gender: There are no significant or clinically relevant gender 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. *AUC_{last}

Race: There are no significant or clinically relevant racial differences in the pharmacokinetics of dolutegravir, 3TC, or TAF based on the available information that was analyzed for each of the individual components.

Elderly Patients:

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

3TC: The pharmacokinetics of 3TC 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 (see section 4.2).

Paediatric Patients: Dolutegravir, lamivudine and tenofovir alafenamide tablets should not be administered to pediatric patients weighing less than 40 kg.

Dolutegravir and 3TC: The pharmacokinetics of the combination of dolutegravir and 3TC 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 9).

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

Parameter Mean (CV%)	Emtricitabine	Tenofovir Alafenamide	Tenofovir
C_{max} (microgram per	2,3 (22,5)	0,17 (64,4)	0,02 (23,7)
AUC_{tau} (microgram•hour	14,4 (23,9)	0,20[b] (50,0)	0,29[b]
C_{trough} (microgram per	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 paediatric subjects with HIV-1 infection

(N = 24).

[b.] N = 23

Interactions Studies: The interaction trials described were conducted with dolutegravir, 3TC, and/or TDF as single entities; no medicine interaction trials have been conducted using the fixed-dose dolutegravir, lamivudine and tenofovir alafenamide tablets. No clinically significant medicine interactions are expected between dolutegravir and 3TC.

Dolutegravir: Dosing or regimens recommendations as a result of established and other potentially significant interactions with dolutegravir are provided in Table 1 (see section 4.5).

The effects of dolutegravir on the exposure of co-administered medicines are summarized in Table 10 and the effects of co-administered medicines on the exposure of dolutegravir are summarized in Table 11.

Table 10: Summary of Effect of Dolutegravir on the Pharmacokinetics of Co-administered Medicines

Co-administered Medicine(s) and Dose(s)	**Dose of Dolutegravir**	n	**Geometric Mean Ratio (90 % CI) of Pharmacokinetic Parameters of Co-administered Medicine**		
			C_{max}	AUC	C_{τ} 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' 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	15a	1,66 (1,53 to 1,81)	1,79 (1,65 to 1,93)	-
Metformin 500 mg twice daily	50 mg twice daily	15a	2,11 (1,91 to 2,33)	2,45 (2,25 to 2,66)	-
Methadone 16 to 150 mg	50 mg twice daily	11	1,00 (0,94 to 1,06)	0,98 (0,91 to 1,06)	0,99 (0,91 to 1,07)
Midazolam 3 mg	25 mg once daily	10	-	0,95 (0,79 to 1,15)	-
Norelgestromin 0.25 mg	50 mg twice daily	15	0,89 (0,82 to 0,97)	0,98 (0,91 to 1,04)	0,93 (0,85 to 1,03)
Rilpivirine 25 mg once daily	50mg once daily	16	1,10 (0,99 to 1,22)	1,06 (0,98 to 1,16)	1,21 (1,07 to 1,38)
Sofosbuvir 400 mg once daily Metabolite (GS-331007)	50 mg once daily	24	0,88 (0,80, 0,98) 1,01 (0, 93, 1,10)	0,92 (0,85, 0,99) 0,99 (0,97, 1,01)	NA 0,99 (0,97, 1,01)
Tenofovir disoproxil fumarate 300 mg once daily	50 mg once daily	15	1,09 (0,97 to 1,23)	1,12 (1,01 to 1,24)	1,19 (1,04 to 1,35)
Velpatasvir 100 mg once daily	50 mg once daily	24	0,94 (0,86; 1,02)	0,91 (0,84, 0,98)	0,88 (0,82, 0,94)

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

Table 11: Summary of Effect of Co-administered Medicines on the Pharmacokinetics of Dolutegravir

Co-administered Medicine(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90 % CI) of Dolutegravir Pharmacokinetic Parameters		
			C_{max}	AUC	C_τ or C_{24}
Atazanavir 400 mg once daily	30mg 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 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	50 mg once daily	8	1,07 (1,02 to 1,13)	1,11 (1,02 to 1,20)	1,28 (1,13 to 1,45)
Fosamprenavir/ ritonavir 700 mg/100 mg twice daily	50 mg once daily	12	0,76 (0,63 to 0,92)	0,65 (0,54 to 0,78)	0,51 (0,41 to 0,63)
Lopinavir/ ritonavir 400 mg/100 mg twice daily	30 mg once daily	15	1,00 (0,94 to 1,07)	0,97 (0,91 to 1,04)	0,94 (0,85 to 1,05)
Rilpivirine 25 mg once daily	50 mg once daily	16	1,13 (1,06 to 1,21)	1,12 (1,05 to 1,19)	1,22 (1,15 to 1,30)
Tenofovir 300 mg once daily	50 mg once daily	15	0,97 (0,87 to 1,08)	1,01 (0,91 to 1,11)	0,92 (0,82 to 1,04)
Tipranavir/ ritonavir 500 mg/200 mg twice daily	50 mg once daily	14	0,54 (0,50 to 0,57)	0,41 (0,38 to 0,44)	0,24 (0,21 to 0,27)
Antacid (Maalox®) simultaneous administration	50 mg single dose	16	0,28 (0,23 to 0,33)	0,26 (0,22 to 0,32)	0,26 (0,21 to 0,31)

Antacid (Maalox®) 2 h after dolutegravir	50 mg single dose	16	0,82 (0,69 to 0,98)	0,74 (0,62 to 0,90)	0,70 (0,58 to 0,85)
Calcium carbonate 1,200 g simultaneous administration (fasted)	50 mg single dose	12	0,63 (0,50 to 0,81)	0,61 (0,47 to 0,80)	0,61 (047 to 0,80)
Calcium carbonate 1,200 g 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 g 2 h after	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'	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	50mg 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)	092 (0,74 to 1,13)
Multivitamin (One-A- Day®) simultaneous administration	50 mg single dose	16	0,65 (0,54 to 0,77)	0,67 (0,55 to 0,81)	0,68 (0,56 to 0,82)
Omeprazole 40 mg once daily	50 mg single dose	12	0,92 (0,75 to 1,11)	0,97 (0,78 to 1,20)	0,95 (0,75 to 1,21)
Prednisone 60 mg once daily with taper	50 mg once daily	12	1,06 (0,99 to 1,14)	1,11 (1,03 to 1,20)	1,17 (1,06 to 1,28)

Rifampin[a] 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)

[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.

3TC: Effect of 3TC on the Pharmacokinetics of Other medicines: Based on *in vitro* study results, 3TC at therapeutic medicines exposures is not expected to affect the pharmacokinetics of medicines 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 Medicines on the Pharmacokinetics of 3TC: 3TC is a substrate of MATE1, MATE2-K, and OCT2 *in vitro*. Trimethoprim (an inhibitor of these drug transporters) has been shown to increase 3TC plasma concentrations. This interaction is not considered clinically significant as no dose adjustment of 3TC is needed.

3TC 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 3TC. Therefore, coadministration of medicines that are inhibitors of these efflux transporters is unlikely to affect the disposition and elimination of 3TC.

Interferon Alfa: There was no significant pharmacokinetic interaction between 3TC and interferon alfa in a trial of 19 healthy male subjects.

Ribavirin: In vitro data indicate ribavirin reduces phosphorylation of 3TC, 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 3TC (n = 18), stavudine (n = 10), or zidovudine (n = 6) were co-administered as part of a multi-drug regimen to HIV-1/HCV co-infected subjects.

Sorbitol (Excipient): 3TC and sorbitol 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 3TC 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 3TC with sorbitol resulted in dose-dependent decreases of 20 %, 39 %, and 44 % in the $AUC_{(0-24)}$, 14 %, 32 %, and 36 % in the $AUC_{(\infty)}$, and 28%, 52%, and 55% in the C_{max} of 3TC, respectively.

Trimethoprim/Sulfamethoxazole: 3TC and TMP/SMX were co-administered to 14 HIV-1-positive subjects in a single-centre, 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 3TC 300 mg with the fifth dose in a crossover design. Coadministration of TMP/SMX with 3TC resulted in an increase of 43 % ± 23 % (mean ± SD) in lamivudine AUC_{∞}, a decrease of 29 % ± 13 % in lamivudine oral clearance, and a decrease of 30 % ± 36 % in 3TC renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by coadministration with lamivudine. There is no information regarding the effect on 3TC pharmacokinetics of higher doses of TMP/SMX such as those used in treat PCP.

TAF: The effects of co-administered medicines on the exposure of TAF are shown in Table 12 and the effects of TAF on the exposure of co-administered medicines are shown in Table 13 *(these studies were conducted with FTC and/or TAF. For information regarding clinical recommendations, see section 4.5)*

Metformin: Concentrations may be increased by **ENVUTEG.** Metformin is contraindicated in patients taking **ENVUTEG** (see section 4.3)

Table 12: Interactions: Changes in TAF Pharmacokinetic Parameters in the Presence of Co-administered Medicine(s)[a]

				Mean Ratio of TAF PK Parameters (90 % CI);

Co-administered Medicine	Co-administered Medicine(s) Dosage (once daily) (mg)	Tenofovir Alafenamide Dosage (once daily) (mg)	N	C_{max}	AUC	C_{min}
Atazanavir	300 (+ 100 ritonavir)	10	10	1,77 (1,28, 2,44)	1,91 (1,55, 2,35)	NC
Cobicistat	150	8	12	2,83 (2,20, 3,65)	2,65 (2,29, 3,07)	NC
Darunavir	800 (+ 150 cobicistat)	25[b]	11	0,93 (0,72, 1,21)	0,98 (0,80, 1,19)	NC
Darunavir	800 (+ 100 ritonavir)	10	10	1,42 (0,96, 2,09)	1,06 (0,84, 1,35)	NC
Dolutegravir	50	10	10	1,24 (0,88, 1,74)	1,19 (0,96, 1,48)	NC
Efavirenz	600	40[b]	11	0,78 (0,58, 1,05)	0,86 (0,72, 1,02)	NC

Lopinavir	800 (+ 200 ritonavir)	10	10	2,19 (1,72, 2,79)	1,47 (1,17, 1,85)	NC
Rilpivirine	25	25	17	1,01 (0,84, 1,22)	1,01 (0,94, 1,09)	NC
Sertraline	50 (dosed as a single dose)	10[c]	19	1,00 (0,86, 1,16)	0,96 (0,89, 1,03)	NC

NC = Not Calculated

[a.] All interaction studies conducted in healthy volunteers.

[b.] Study conducted with DESCOVY (FTC/TAF).

[c.] Study conducted with FTC + TAF with EVG + COBI.

Table 13: Interactions: Changes in PK Parameters for Co-administered Medicine in the Presence of FTC and/or TAF[a]

Co-administered Medicine	Co-administered Medicine Dosage	Tenofovir Alafenamide Dosage (once daily) (mg)	N	Mean Ratio of Co-administered		
				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	50mg	10	10	1,15 (1,04, 1,27)	1,02 (0,97, 1,08)	1,05 (0,97, 1,13)
Lopinavir	800 + 200 ritonavir	10	10	1,00 (0,95, 1,06)	1,00 (0,92, 1,09)	0,98 (0,85, 1,12)
Midazolam[c]	2.5 (single dose, orally)	25	18	1,02 (0,92, 1,13)	1,13 (1,04, 1,23)	NC
	1 (single dose, intravenous)			0,99 (0,89, 1,11)	1,08 (1,04, 1,14)	NC
Rilpivirine	25	25	16	0,93 (0,87, 0,99)	1,01 (0,96, 1,06)	1,13 (1,04, 1,23)

Sertraline	50 (single dose)	10[d]	19	1,14 (0,94, 1,38)	0,93 (0,77, 1,13)	NC

NC = Not Calculated

[a.] All interaction studies conducted in healthy volunteers.

[b.] Study conducted with DESCOVY (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

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 medicine-related neoplasms were observed at the highest doses tested, resulting in dolutegravir AUC exposures approximately 14 times higher than those in humans at the recommended dose of 50 mg twice daily. In rats, no increases in the incidence of medicine-related neoplasms were observed at the highest dose tested, resulting in dolutegravir AUC exposures 10 times and 15 times higher in males and females, respectively, than those in humans at the recommended dose of 50 mg twice daily.

3TC: Long-term carcinogenicity studies with 3TC 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.

3TC: 3TC was mutagenic in an L5178Y mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. 3TC 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. 3TC showed no evidence of *in vivo* genotoxic

activity in the rat at oral doses of up to 2000 mg per kg, producing plasma levels of35 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 3TC:* Dolutegravir or 3TC 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 doses of 50 mg and 300 mg (respectively).

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.

Animal Toxicology and/or Pharmacology

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

6 PHARMACUETICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium

Lactose monohydrate

Magnesium stearate

Mannitol

Microcrystalline cellulose

Povidone

Sodium starch glycolate

Opadry II White

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 30 ºC.

Store in the original container.

Keep the bottle tightly closed.

Store all medicines out of reach of children

Do not use after the expiry date state on the carton/label

Return all unused medicines to the pharmacist

Do not dispose of unused medicine in drains or sewerage systems.

6.5 Nature and contents of container

The product is presented in the following marketable packs:

30's Bottle Pack (with 4 g Molecular Sieve):

Pack Type	**Configuration**	**Primary packaging components**
HDPE Bottle Pack (with desiccant)	30's count with 4 g desiccant	**Container:** Bottle HDPE 75 ml 38 mm Blue round (HWT) TP **Closure:** Closure 38 mm Blue screw with SG100 SP. **Desiccant:** 2 g Molecular Sieve Canister - SC **Desiccant:** 2 g Molecular sieve sachet GDT2 Reel clariant

30's and 28's Bottle Pack (with 2 g Molecular Sieve):

Pack Type	**Configuration**	**Primary packaging components**
HDPE Bottle Pack (with desiccant)	30's count with 2 g desiccant	**Container:** Bottle HDPE 60 cc (60 ml) 38 mm Blue round (12 g) TP **Closure:** Closure 38 mm Blue screw with SG100 SP. **Desiccant:** 2 g Molecular Sieve Canister

HDPE Bottle Pack (with desiccant)	28's count with 2 g desiccant	**Container:** Bottle HDPE 60 cc (60 ml) 38 mm Blue round (12 g) TP **Closure:** Closure 38 mm Blue screw with SG100 SP. **Desiccant:** 2 g Molecular Sieve Canister

6.6 Special precautions for disposal

No special precautions are required.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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Isando

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Republic of South Africa

8 REGISTRATION NUMBER

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10 DATE OF REVISION OF THE TEXT