SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets 50 / 300 / 300 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg dolutegravir (as sodium), 300 mg lamivudine and 300 mg tenofovir disoproxil fumarate.

Excipient with known effect

Each film-coated tablet contains 145 mg mannitol

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film- coated tablet.

Blue coloured, capsule shaped biconvex film coated tablet, debossed with 'C' on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets is indicated for use alone as a complete regimen for the treatment of human immunodeficiency virus type l (HIV-1) infection in adults and pediatric patients weighing at least 40 kg.

4.2 Posology and method of administration

Posology

Testing prior to initiation and during treatment with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets

Perform pregnancy testing before initiation of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets in adolescents and adults of childbearing potential (see section 4.4 and 4.6).

Prior to or when initiating dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets, test patients for hepatitis B virus (HBV) infection (See section 4.4).
Prior to initiation and during treatment with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets, 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

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

tenofovir disoproxil fumarate (TDF). The recommended dosage regimen of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets in adults and pediatric patients weighing at least 40 kg (88 lbs) is one tablet once daily orally with or without food.

Dosage recommendation with certain concomitant medications

The dolutegravir dose (50 mg) in dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets is insufficient when coadministered with medications listed in Table 1 that may decrease dolutegravir concentrations; the following dolutegravir dosage regimen is recommended.

Table 1. Dosing Recommendations for Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets with Coadministered Medications

Coadministered drug	Dosing recommendation
Efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, carbamazepine, or rifampin	The recommended dolutegravir dosage regimen is 50 mg twice daily. An additional dolutegravir 50-mg tablet, separated by 12 hours from dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets, should be taken.

Not recommended due to lack of dosage adjustment

Because dolutegravir, lamivudine and tenofovir disoproxil fumarate 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 section 4.2).

Pediatric use

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets is a fixed-dose formulation which cannot be adjusted for patients weighing less than 40 kg.

Geriatric use

Clinical trials of individual components of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets 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 disoproxil fumarate tablets 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)

Renal impairment

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets is not recommended for patients with creatinine clearance less than 50 mL per min or patients with end-stage renal disease (ESRD) requiring hemodialysis because dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets is a fixed-dose combination and the dosage of the individual components cannot be adjusted. If a dose reduction of 3TC or TDF, two components of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets, is required for patients with creatinine clearance less than 50 mL per min, then the individual components should be used (See section 4.2 and 5).

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 disoproxil fumarate tablets, has not been studied. Therefore, dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets is not recommended for use in patients with severe hepatic impairment (See section 5).

Method of administration

For oral use only.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- with prior hypersensitivity reaction to dolutegravir lamivudine, or tenofovir disoproxil fumarate (see section 4.4).
- 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).

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 disoproxil fumarate tablets.

Discontinuation of anti-HBV therapy, including 3TC and TDF, two components of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets, may be associated with severe acute exacerbations of hepatitis B. Patients infected with HBV who discontinue dolutegravir, lamivudine, and tenofovir disoproxil fumarate 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 disoproxil fumarate tablets and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters or peeling of the skin, oral blisters or lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, difficulty breathing). Clinical status, including liver aminotransferases, should be monitored and appropriate therapy initiated. Delay in stopping treatment with dolutegravir, lamivudine, and tenofovir disoproxil fumarate 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 disoproxil fumarate tablets (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-fetal toxicity

Preliminary data from an observational study showed that dolutegravir, a component of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets, was associated with increased risk of neural tube defects when administered at the time of conception and in early pregnancy. As there is limited understanding of reported types of neural tube defects associated with dolutegravir use and because the date of conception may not be determined with precision, avoid use of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets 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 dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets, if possible, switch to an alternative regimen.

Perform pregnancy testing before initiation of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets in adolescents and adults of childbearing potential to exclude use of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets during the first trimester of pregnancy (see section 4.2).

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 drug interactions

The concomitant use of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets and other drugs may result in known or potentially significant drug interactions, some of which may lead to (see section 4.3 and 4.5).

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

See table 5 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets; review concomitant medications during therapy with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets; and monitor for the adverse reactions associated with the concomitant drugs.

New onset or worsening renal impairment

TDF, a component of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets, is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of TDF (see section 4.8).

Prior to initiation and during use of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets, on a clinically appropriate schedule, assess serum creatine, estimated creatine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus.

Avoid dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple non-steroidal anti-inflammatory

drugs (NSAIDs) (see section 4.5). Cases of acute renal failure after initiation of high-dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on TDF. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.

Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in patients at risk of renal dysfunction.

Bone loss and mineralization defects

Bone mineral density

In clinical trials in HIV-1 infected adults, TDF, a component of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets, was associated with slightly greater decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving TDF.

Clinical trials evaluating TDF in pediatric subjects were conducted. Under normal circumstances, BMD increases rapidly in pediatric patients. In HIV-1 infected subjects aged 2 years to less than 18 years, bone effects were similar to those observed in adult subjects and suggest increased bone turnover. Total body BMD gain was less in the TDF-treated HIV-1 infected pediatric subjects as compared to the control groups. Similar trends were observed in HBV-infected subjects 12 years to less than 18 years of age. In all pediatric trials, normal skeletal growth (height) was not affected for the duration of the clinical trials.

The effects of TDF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk in adults and pediatric subjects 2 years and older are unknown. The long-term effect of lower spine and total body BMD on skeletal growth in pediatric patients, and in particular, the effects of long-duration exposure in younger children is unknown.

Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained. Assessment of BMD should be considered for adult and pediatric patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. If bone abnormalities are suspected, appropriate consultation should be obtained.

Mineralization defects

Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of TDF (see section 4.8). Arthralgias and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving TDF-containing products (see section 4.4).

Immune reconstitution syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic

infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

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

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 3TC and TDF, two components of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets, alone or in combination with other antiretrovirals. Treatment with dolutegravir, lamivudine, and tenofovir disoproxil fumarate 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).

Risk of hepatic decompensation when used with interferon- and ribavirin-based regimens

Patients receiving interferon alfa with or without ribavirin and 3TC, a component of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets, should be closely monitored for treatment associated toxicities, especially hepatic decompensation. Discontinuation of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child Pugh greater than 6).

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, 3TC, a component of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets, should be used with caution. Treatment with dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur (see section 4.8).

Sodium

This medicinal product also contains less than 23 mg sodium per dosage unit, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of dolutegravir, 3TC, or TDF 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)l (IC50 = 6.34 microM). *In vivo*, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2 and potentially MATEl. Dolutegravir may increase plasma concentrations of drugs eliminated via OCT2 or MATE1 (dofetilide and metformin, Table 5) (see section 4.3 and 4.5).

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: cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2Cl9, CYP2D6, CYP3A, uridine diphosphate (UDP)-glucuronosyl transferase 1A1 (UGTlAl), 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, 3TC, or TDF

Dolutegravir

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

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

Etravirine significantly reduced plasma concentrations of dolutegravir, but the effect of etravirine was mitigated by coadministration of lopinavir/ritonavir or darunavir/ritonavir, and is expected to be mitigated by atazanavir/ritonavir (Table 5) (see section 4.5 and 5).

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

Significant drug interactions for dolutegravir, 3TC, or TDF

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

Dolutegravir

Table 2 provides clinical recommendations as a result of drug interactions with dolutegravir. These recommendations are based on either drug interaction trials or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy. (see section 5).

Table 2. Established and Other Potentially Significant Drug Interactions for Dolutegravir: Alterations in Dose or Regimen May Be Recommended Based on drug Interaction Trials or Predicted Interactions

Concomitant Drug Class: Drug Name	**Effect on Concentration of Dolutegravir and/or Concomitant Drug**	**Clinical Comment**
HIV-1 antiviral agents		
Non-nucleoside reverse transcriptase inhibitor: Etravirine[a]	↓Dolutegravir	Use of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir is not recommended.
Non-nucleoside reverse transcriptase inhibitor: Efavirenz[a]	↓Dolutegravir	An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets. (see section 4.2)

Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓Dolutegravir	Avoid coadministration with dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets because there are insufficient data to make dosing recommendations.
Protease inhibitor: Fosamprenavir/ritonavir[a] Tipranavir/ritonavir[a]	↓Dolutegravir	An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets. (see section 4.3).
Other Agents		
Dofetilide	↑Dofetilide	Coadministration is contraindicated with dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets (see section 4.2)
Carbamazepine[a]	↓Dolutegravir	An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets. (see section 4.2).
Oxcarbazepine Phenytoin Phenobarbital St. John's wort *(Hypericum perforatum)*	↓Dolutegravir	Avoid coadministration with dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets because there are insufficient data to make dosing recommendations.
Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing antacids[a] or laxatives Sucralfate Buffered medications	↓Dolutegravir	Administer dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets 2 hours before or 6 hours after taking medications containing polyvalent cations.
Oral calcium or iron supplements, including multivitamins containing calcium or iron[a]	↓Dolutegravir	Administer dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets 2 hours before or 6 hours after taking supplements containing calcium or iron. Alternatively, dolutegravir and supplements containing calcium or iron can be taken together with food.
Metformin	↑Metformin	Refer to the prescribing information of metformin for assessing the benefit and risk of concomitant use with metformin.
Rifampin[a]	↓Dolutegravir	An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets. (see section 4.2).

[a] See section 5, table 7 and 8 for magnitude of interaction.

TDF

Table 3 provides a listing of established or clinically significant drug interactions. The drug interactions described are based on studies conducted with TDF (see section 5)

Table 3. Established and significant[a] drug interactions for TDF: alteration in dose or regimen may be recommended based on drug interaction trials

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
NRTI: didanosine	↑ didanosine	Patients receiving TDF, a component of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets, and didanosine should be monitored closely for didanosine-associated adverse reactions. Discontinue didanosine in patients who develop didanosine-associated adverse

		reactions. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis, and neuropathy. Suppression of CD4+ cell counts has been observed in patients receiving TDF with didanosine 400 mg daily. In patients weighing greater than 60 kg, reduce the didanosine dose to 250 mg when it is coadministered with TDF. In patients weighing less than 60 kg, reduce the didanosine dose to 200 mg when it is coadministered with TDF. When coadministered, tenofovir disoproxil fumarate and Videx®- EC may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat).
HIV-1 Protease Inhibitors: atazanavir lopinavir/ritonavir atazanavir/ritonavir darunavir/ritonavir	↓ atazanavir ↑ tenofovir	When coadministered with dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets, atazanavir 300 mg should be given with ritonavir 100 mg. Monitor patients receiving dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets concomitantly with lopinavir/ritonavir, ritonavir-boosted atazanavir, or ritonavir-boosted darunavir for TDF-associated adverse reactions. Discontinue dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets in patients who develop TDF-associated adverse reactions.
Hepatitis C Antiviral Agents: sofosbuvir/velpatasvir sofosbuvir/velpatasvir/ voxilaprevir ledipasvir/sofosbuvir	↑ tenofovir	Monitor patients receiving dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets concomitantly with EPCLUSA® (sofosbuvir/velpatasvir) or VOSEVI® (sofosbuvir/velpatasvir/voxilaprevir) for adverse reactions associated with TDF. Monitor patients receiving dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets concomitantly with HARVONI® (ledipasvir/sofosbuvir) without an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination for adverse reactions associated with TDF. In patients receiving dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets concomitantly with HARVONI® and an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination, consider an alternative HCV or antiretroviral therapy, as the safety of increased tenofovir concentrations in this setting has not been established. If coadministration is necessary, monitor for adverse reactions associated with TDF.

a. This table is not all inclusive.
b. ↑=Increase, ↓=Decrease

Drugs affecting renal function

Tenofovir is primarily eliminated by the kidneys (see section 5). Coadministration of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets with drugs that are eliminated by active tubular secretion may increase serum concentrations of tenofovir and/or coadministered drug. Some examples 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). Drugs that decrease renal function may increase concentration of tenofovir.

Do not administer dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets with HEPSERA (adefovir dipivoxil).

Drugs inhibiting organic cation transporters

3TC, a component of dolutegravir, lamivudine, and tenofovir disoproxil fumarate 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) ((see section 5). No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of 3TC.

Sorbitol

Coadministration 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).

Drugs without clinically significant interactions with dolutegravir

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Preliminary data from an observational study has identified a possible increased risk of neural tube defects when dolutegravir, a component of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets, is administered at the time of conception compared with non-dolutegravir-containing antiretroviral regimens. As defects related to closure of the neural tube occur from conception through the first 6 weeks of gestation, embryos exposed to dolutegravir from the time of conception through the first 6 weeks of gestation are at potential risk. In addition, 2 of the 4 birth defects (encephalocele and iniencephaly), which have been observed with dolutegravir use, although often termed neural tube defects, may occur post-neural tube closure, the time period of which may be later than 6 weeks of gestation, but within the first trimester. Due to the limited understanding of the types of reported neural tube defects associated with dolutegravir use and because the date of conception may not be determined with precision, avoid use of dolutegravir at the time of conception through the first trimester of pregnancy. No neural tube defects have been reported in infants born to mothers who have started dolutegravir after the first trimester of pregnancy.

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

There are insufficient human data on the use of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets during pregnancy to definitively assess a drug-associated risk for birth defects and miscarriage. Available data from the Antiretroviral Pregnancy Registry (APR) show no difference in rate of overall birth defects for lamivudine or tenofovir disoproxil fumarate compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The 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.

Breast-feeding

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 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. 3TC and TDF have been shown to be present in human breast milk. It is not known if 3TC or TDF affect milk production or have 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 disoproxil fumarate tablets.

Women of childbearing potential

Perform pregnancy testing in adolescents and adults of childbearing potential before initiation of ddolutegravir, lamivudine and tenofovir disoproxil fumarate tablets.

Adolescents and adults of childbearing potential should avoid use of ddolutegravir, lamivudine and tenofovir disoproxil fumarate tablets at the time of conception through the first trimester of pregnancy because of the potential risk of neural tube defects (see section 4.6).

Advise adolescents and adults of childbearing potential who are taking ddolutegravir, lamivudine and tenofovir disoproxil fumarate tablets to consistently use effective contraception.

Fertility

There are no data on dolutegravir, lamivudine and tenofovir disoproxil fumarate effects on human male or female fertility.

4.7 Effects on ability to drive and use machines

Dolutegravir, lamivudine and tenofovir disoproxil fumarate has no or negligible influence on ability to drive and use machines.

4.8 Undesirable effects

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

- Exacerbation of Hepatitis B (see section 4.4).
- Hypersensitivity Reactions (see section 4.4).
- New Onset or Worsening Renal Impairment (see section 4.4).
- Bone Loss and Mineralization Defects (see section 4.4).
- Immune Reconstitution Syndrome (see section 4.4).
- Lactic Acidosis and Severe Hepatomegaly with Steatosis (see section 4.4).
- Hepatic Decompensation in Patients Co-infected with HIV-1 and Hepatitis C (see section 4.4).
- Pancreatitis (see section 4.4).

Clinical trials experience

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

Treatment-naïve subjects

In SINGLE, 833 adult subjects were randomized and received at least one dose of either dolutegravir 50 mg with fixed-dose abacavir sulfate 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 sulfate and lamivudine and 14% in subjects receiving fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate once daily.

Treatment-emergent adverse reactions (ARs) of moderate to severe intensity observed in at least 2% of subjects in either treatment arm of SINGLE are provided in Table 4.

Table 4. 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 Sulfate and Lamivudine Once Daily (n = 414)	Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate Once Daily (n = 419)
Psychiatric		
Insomnia	3%	3%
Depression	1%	2%
Abnormal dreams	<1%	2%
Nervous System		
Dizziness	<1%	5%
Headache	2%	2%
Gastrointestinal		
Nausea	<1%	3%
Diarrhea	<1%	2%
General Disorders		
Fatigue	2%	2%
Skin and Subcutaneous Tissue		
Rash[a]	<1%	6%
Ear and Labyrinth		
Vertigo	0	2%

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

In addition, Grade 1 insomnia was reported by 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

In an international, multicenter, double-blind trial (ING111762, SAILING), 719 HIV-1-infected, antiretroviral treatment-experienced adults were randomized and received either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily with investigator-selected background regimen consisting of up to 2 agents, including at least one fully active agent. At 48 weeks, the rates of adverse events leading to discontinuation were 3% in subjects receiving

dolutegravir 50 mg once daily + background regimen and 4% in subjects receiving raltegravir 400 mg twice daily + background regimen.

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

Less common adverse reactions observed in treatment-naïve and treatment-experienced trials:

The following ARs occurred in less than 2% of treatment-naïve or treatment-experienced subjects receiving dolutegravir in a combination regimen in any one trial. These events have been included because of their seriousness and assessment of potential causal relationship.

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

Hepatobiliary disorders: Hepatitis.

Musculoskeletal disorders: Myositis.

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

Renal and urinary disorders: Renal impairment.

Skin and subcutaneous tissue disorders: Pruritus.

Treatment-experienced, integrase strand transfer inhibitor-naïve subjects:

Laboratory abnormalities observed in SAILING were generally similar compared with observations seen in the treatment-naïve trials.

Hepatitis B and/or hepatitis C virus co-infection:

In Phase 3 trials, subjects with hepatitis B and/or C virus co-infection were permitted to enroll provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal. Overall, the safety profile in subjects with hepatitis B and/or C virus co-infection was similar to that observed in subjects without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or C virus co-infection for all treatment groups. Grades 2 to 4 ALT abnormalities in hepatitis B and/or C co-infected compared with HIV mono-infected subjects receiving dolutegravir were observed in 18% vs. 3% with the 50 mg once-daily dose. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C at the start of therapy with dolutegravir, particularly in the setting where anti-hepatitis therapy was withdrawn (see section 4.4).

Changes in serum creatinine:

Dolutegravir has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function (see section 5). Increases in serum creatinine occurred within the first 4 weeks of treatment and remained stable through 96 weeks. In treatment-naïve subjects, a mean change from baseline of 0.15 mg per dL (range: -0.32 mg per dL to 0.65 mg per dL) was observed after 96 weeks of treatment. Creatinine increases were comparable by background NRTIs and were similar in treatment-experienced subjects.

Clinical trials experience in pediatric subjects:

IMPAACT P1093 is an ongoing multicenter, open-label, non-comparative trial of approximately 160 HIV-1-infected pediatric subjects aged 4 weeks to less than 18 years, of which 46 treatment-experienced, INSTI-naïve subjects aged 6 to less than 18 years have been enrolled (see section 4.2 and 5.1).

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

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

3TC

Pancreatitis: Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced pediatric subjects receiving 3TC alone or in combination with other antiretroviral agents. In an open-label dose-escalation trial (NUCA2002), 14 subjects (14%) developed pancreatitis while receiving monotherapy with 3TC. Three of these subjects died of complications of pancreatitis. In a second open-label trial (NUCA2005), 12 subjects (18%) developed pancreatitis. In Trial ACTG300, pancreatitis was not observed in 236 subjects randomized to 3TC plus zidovudine. Pancreatitis was observed in 1 subject in this trial who received open-label 3TC in combination with zidovudine and ritonavir following discontinuation of didanosine monotherapy (see section 4.4).

TDF

Adverse Reactions from Clinical Trials Experience in HIV-1 Infected Adults: More than 12,000 subjects have been treated with TDF alone or in combination with other antiretroviral medicinal products for periods of 28 days to 215 weeks in clinical trials and expanded access programs. More than 1,500 subjects have received TDF 300 mg once daily in clinical trials; over 11,000 subjects have received TDF in expanded access programs.

The most common adverse reactions (incidence greater than or equal to 10%, Grades 2 to 4) identified from any of the 3 large controlled clinical trials include rash, diarrhea, headache, pain, depression, asthenia, and nausea.

Changes in bone mineral density

In HIV-1 infected adult subjects in Study 903, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in subjects receiving TDF + 3TC + efavirenz (-2.2% ± 3.9) compared with subjects receiving stavudine + 3TC + efavirenz (-1.0% ± 4.6) through 144 weeks. Changes in BMD at the hip were similar between the two treatment groups (-2.8% ± 3.5 in the TDF vs. -2.4% ± 4.5 in the stavudine group). In both groups, the majority of the reduction in BMD occurred in the first 24 to 48 weeks of the trial and this reduction was sustained through Week 144. Twenty-eight percent of TDF-treated subjects vs. 21% of the stavudine-treated subjects lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 subjects in the TDF group and 6 subjects in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C telopeptide, and urinary N telopeptide) and higher serum parathyroid hormone levels and 1,25 Vitamin D levels in the TDF group relative to the stavudine group; however, except for bone-specific alkaline phosphatase, these changes resulted in values that remained within the normal range (see section 4.4).

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 disoproxil fumarate 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

3TC

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 (see section 4.4), posttreatment exacerbations of hepatitis B (see section 4.4).

Hypersensitivity: anaphylaxis, urticaria

Musculoskeletal: muscle weakness, CPK elevation, rhabdomyolysis

Skin: alopecia, pruritus

TDF

Immune system disorders: allergic reaction, including angioedema

Metabolism and nutrition disorders: lactic acidosis, hypokalemia, hypophosphatemia

Respiratory, thoracic, and mediastinal disorders: dyspnea

Gastrointestinal disorders: pancreatitis, increased amylase, abdominal pain

Hepatobiliary disorders: hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT)

Skin and subcutaneous tissue disorders: rash

Musculoskeletal and connective tissue disorders: rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy

Renal and Urinary Disorders: acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria

General disorders and administration site conditions: asthenia

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia

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 local reporting system.

4.9 Overdose

There is no known specific treatment for overdose with dolutegravir, lamivudine and tenofovir disoproxil fumarate 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.

TDF

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of TDF, a 4-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Dolutegravir, 3TC, and TDF are HIV-1 antiviral agents

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 IC_{50} 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.

TDF: TDF is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. TDF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate, an obligate chain terminator. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Pharmacodynamic effects

Effects on electrocardiogram:

A thorough QT trial has been conducted for dolutegravir. Neither the effects of 3TC nor TDF as single entities or the fixed-dose dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets on the QT interval have 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 post dose.

Effects on renal function:

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

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. EC_{50} values were in the range of 0.003 to 15 microM (1 microM = 0.23 mcg per mL). The median EC_{50} 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 EC_{50} 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.

TDF: The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC_{50} (50% effective concentration) values for tenofovir were in the range of 0.04 microM to 8.5 microM. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values ranged from 0.5 μM to 2.2 μM) and strain-specific activity against HIV-2 (EC_{50} values ranged from 1.6 μM to 5.5 μM).

Antiviral activity in combination with other antiviral agents

Neither dolutegravir nor 3TC were antagonistic to all tested anti-HIV agents.

Resistance in cell culture

Dolutegravir: 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.

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).

TDF: HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R substitution in reverse transcriptase and showed a 2- to 4-fold reduction in susceptibility to tenofovir. In addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in low-level reduced susceptibility to tenofovir. K65R substitutions developed in some subjects failing a TDF regimen.

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.

Cross-resistance

Dolutegravir: The single INSTI-resistance substitutions T66K, I151L, and S153Y conferred a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.3-fold to 3.6-fold from reference). Combinations of multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148, and substitutions at E138/G140/Q148 showed a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.5-fold to 21-fold from reference). In HIV-2 mutants, combinations of substitutions A153G/N155H/S163G and E92Q/T97A/N155H/S163D conferred 4-fold decreases in dolutegravir susceptibility, and E92Q/N155H and G140S/Q148R showed 8.5-fold and 17-fold decreases in dolutegravir susceptibility, respectively.

3TC: Cross-resistance among certain reverse transcriptase inhibitors has been observed. 3TC-resistant 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.

TDF: Cross-resistance among certain reverse transcriptase inhibitors has been recognized. The K65R and K70E substitutions selected by tenofovir are also selected in some HIV-1 infected subjects treated with abacavir or didanosine. HIV-1 isolates with the K65R also show reduced susceptibility to emtricitabine and 3TC. HIV-1 isolates from subjects (N=20) whose HIV-1 expressed a mean of 3 zidovudine-associated reverse transcriptase substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N), showed a 3.1-fold decrease in the susceptibility to tenofovir.

Subjects whose virus expressed an L74V substitution without zidovudine resistance associated substitutions (N=8) had reduced response to TDF. Limited data are available for patients whose virus expressed a Y115F substitution (N=3), Q151M substitution (N=2), or T69 insertion (N=4), all of whom had a reduced response.

Clinical efficacy and safety

Adult subjects

Treatment-naïve subjects

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

Week 144 (open-label-phase analysis which followed the Week 96 double-blind phase) outcomes for SINGLE are provided in Table 5.

Table 5. Virologic Outcomes of Randomized Treatment in SINGLE at 144 Weeks (Snapshot Algorithm)

	Dolutegravir 50 mg + Abacavir Sulfate and Lamivudine Once Daily (n = 414)	**Efavirenz, Emtricitabine, and Tenofovir DF Once Daily (n = 419)**
HIV-1 RNA <50 copies/mL	71%	63%
Treatment difference[a]	8.3% (95% CI: 2.0% 14.6%)[d]	
Virologic nonresponse	10%	7%
Data in window not <50 copies/mL	4%	<1%
Discontinued for lack of efficacy	3%	3%
Discontinued for other reasons while not suppressed	3%	4%
Changes in ART regimen	0	0
No virologic data	18%	30%
Reasons		
Discontinued study/study drug due to adverse event or death[b]	4%	14%
Discontinued study/study drug for other reasons[c]	12%	13%
Missing data during window but on study	2%	3%
Proportion (%) of Subjects with HIV-1 RNA <50 copies/mL by Baseline Category		
Plasma viral load (copies/mL)		
≤100,000	73%	64%
>100,000	69%	61%

Gender		
Male	72%	66%
Female	69%	48%
Race		
White	72%	71%
African-American/African Heritage/Other	71%	47%

[a] Adjusted for pre-specified stratification factors.
[b] Includes subjects who discontinued due to an adverse event or death at any time point if this resulted in no virologic data on treatment during the analysis window.
[c] Other includes reasons such as withdrew consent, loss to follow-up, moved, and protocol deviation.
[d] The primary endpoint was assessed at Week 48 and the virologic success rate was 88% in the group receiving dolutegravir and 81% in the fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate group, with a treatment difference of 7.4% and 95% CI of (2.5%, 12.3%).

Treatment differences were maintained across baseline characteristics including baseline viral load, CD4+ cell count, age, gender, and race. The adjusted mean changes in CD4+ cell counts from baseline were 378 cells per mm^3 in the group receiving dolutegravir + fixed-dose abacavir sulfate and lamivudine and 332 cells per mm^3 for the fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate group at 144 weeks. The adjusted difference between treatment arms and 95% CI was 46.9 cells per mm^3 (15.6 cells per mm^3, 78.2 cells per mm^3) (adjusted for pre-specified stratification factors: baseline HIV-1 RNA, and baseline CD4+ cell count).

Treatment-experienced, integrase strand transfer inhibitor-naïve subjects

In SAILING, there were 715 subjects included in the efficacy and safety analyses. At Week 48, 71% of subjects randomized to dolutegravir plus background regimen versus 64% of subjects randomized to raltegravir plus background regimen had HIV-1 RNA less than 50 copies per mL (treatment difference and 95% CI: 7.4% [0.7%, 14.2%]).

Pediatric subjects

The efficacy of the individual components of ddolutegravir, lamivudine and tenofovir disoproxil fumarate tablets for the treatment of HIV-1 infection was evaluated in pediatric patients enrolled in the IMPAACT P1093 trial (NCT01302847) or the ARROW trial (NCT02028676), as summarized below.

- Dolutegravir, in combination with other antiretroviral drugs was evaluated in treatment-experienced, INSTI-naïve, HIV-1–infected subjects aged 6 to less than 18 years in a 48-week open-label, multicenter, dose-finding clinical trial, IMPAACT P1093. Subjects aged 12 to less than 18 years were enrolled in Cohort I and subjects aged 6 to less than 12 years were enrolled in Cohort IIA. At 48 weeks, 61% (14/23) of subjects aged 12 to less than 18 years treated with dolutegravir once daily plus optimized background therapy achieved virologic response defined as HIV-1 RNA less than 50 copies per mL. Across both cohorts, virologic suppression at Week 48 was achieved in 67% (16/24) of subjects weighing at least 40 kg.

- Lamivudine once daily, with abacavir and a third antiretroviral drug, was evaluated in a randomized, multicenter trial (ARROW) in HIV-1–infected, treatment-naïve subjects. Subjects randomized to once-daily dosing (n = 336) and who weighed at least 25 kg received lamivudine 300 mg and abacavir 600 mg, as either the single entities or as fixed-dose abacavir sulfate and lamivudine. At Week 96, 67% of subjects receiving abacavir and lamivudine once-daily in combination with a third antiretroviral drug, had HIV-1 RNA less than 80 copies per mL.

5.2 Pharmacokinetic properties

The mean systemic exposures of dolutegravir, lamivudine and tenofovir disoproxil fumarate

from the combination tablets (50 mg/300 mg/300 mg) were similar to that from TIVICAY tablets of ViiV USA (containing dolutegravir 50 mg), EPIVIR tablets of ViiV USA (containing lamivudine 300 mg), and VIREAD tablets of Gilead Sciences, Inc. USA (containing tenofovir disoproxil fumarate 300 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 (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 [^{14}C] 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. Dolutegravir steady-state pharmacokinetic parameter estimates in HIV-1-infected adults

Parameter	50 mg Once Daily Geometric Mean (%CV)
$AUC_{(0-24)}$ (mcg•h/mL)	53.6 (27)
C_{max} (mcg/mL)	3.67 (20)
C_{min} (mcg/mL)	1.11 (46)

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

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).

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 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 3TC is recovered as unchanged drug 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 ($t_{½}$) ranged from 5 to 7 hours. In HIV-1-infected subjects, total clearance was 398.5 ± 69.1 mL per min (mean ± SD).

TDF

The pharmacokinetic properties of TDF are summarized in Table 7. Following oral administration of TDF, maximum tenofovir serum concentrations are achieved in 1.0 ± 0.4 hour. Less than 0.7% of tenofovir binds to human plasma proteins *in vitro* and the binding is independent of concentration over the range of 0.01 to 25 µg/mL. Approximately 70 to 80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of TDF, the terminal elimination half-life of tenofovir is approximately 17 hours.

Table 7. Single Dose Pharmacokinetic Parameters for Tenofovir in Adults[a]

	Tenofovir
Fasted Oral Bioavailability[b] (%)	25 (NC to 45.0)
Plasma Terminal Elimination Half-Life[b] (hr)	17 (12.0 to 25.7)
C_{max}[c] (mcg/mL)	0.30±0.09
AUC[c] (mcg·hr/mL)	2.29±0.69
CL/F[c] (mL/min)	1043±115
CL_{renal}[c] (mL/min)	243±33

a. NC=Not calculated
b. Median (range)
c. Mean (± SD)

Effects of food on oral absorption of dolutegravir, lamivudine and tenofovir disoproxil fumarate

The effect of food on dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets has not been evaluated. Based on cross trial comparisons, no clinically significant effect of food on the pharmacokinetics of dolutegravir, lamivudine, and tenofovir is anticipated, hence dolutegravir, lamivudine, and tenofovir disoproxil fumarate 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.

TDF: The pharmacokinetics of tenofovir following a 300 mg single dose of tenofovir disoproxil fumarate have been studied in non-HIV infected subjects with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in subjects with

hepatic impairment compared with unimpaired subjects. No change in tenofovir disoproxil fumarate dosing is required in patients with hepatic impairment.

Renal impairment

Because dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets is a fixed-dose formulation and cannot be dose adjusted, dolutegravir, lamivudine and tenofovir disoproxil fumarate 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).

Gender

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

Race

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

TDF: There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations.

Elderly

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

3TC and TDF: The pharmacokinetics of 3TC or TDF have not been studied in subjects older than 65 years.

Pediatric population

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets should not be administered to pediatric patients weighing less than 40 kg (88 lbs).

Dolutegravir and 3TC: The pharmacokinetics of the combination of dolutegravir and 3TC in pediatric subjects have not been established.

TDF: Steady-state pharmacokinetics of tenofovir were evaluated in 8 HIV-1 infected pediatric subjects (12 to less than 18 years). Mean ± SD C_{max} and AUC_{tau} are 0.38 ± 0.13 mcg/mL and 3.39 ± 1.22 mcg•hr/mL, respectively. Tenofovir exposure achieved in these pediatric subjects receiving oral daily doses of TDF 300 mg was similar to exposures achieved in adults receiving once-daily doses of TDF 300 mg.

Drug interactions studies:

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

Dolutegravir

Dosing or regimens recommendations as a result of established and other potentially significant drug-drug interactions with dolutegravir are provided in Table 2 (see section 4.5).

The effects of dolutegravir on the exposure of coadministered drugs are summarized in Table 8 and the effects of coadministered drugs on the exposure of dolutegravir are summarized in Table 9.

Table 8. 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, 1.05)	0.98 (0.93, 1.04)	0.98 (0.93, 1.03)
Ethinyl estradiol 0.035 mg	50 mg twice daily	15	0.99 (0.91 to 1.08)	1.03 (0.96 to 1.11)	1.02 (0.93 to 1.11)
Grazoprevir 200 mg once daily	50 mg single dose	12	0.64 (0.44, 0.93)	0.81 (0.67, 0.97)	0.86 (0.79, 0.93)
Metformin 500 mg twice daily	50 mg once daily	15[a]	1.66 (1.53 to 1.81)	1.79 (1.65 to 1.93)	–
Metformin 500 mg twice daily	50 mg twice daily	15[a]	2.11 (1.91 to 2.33)	2.45 (2.25 to 2.66)	–
Methadone 16 to 150 mg	50 mg twice daily	11	1.00 (0. 94 to 1.06)	0.98 (0.91 to 1.06)	0.99 (0.91 to 1.07)
Midazolam 3 mg	25 mg once daily	10	–	0.95 (0.79 to 1.15)	–
Norelgestromin 0.25 mg	50 mg twice daily	15	0.89 (0.82 to 0.97)	0.98 (0.91 to 1.04)	0.93 (0.85 to 1.03)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.10 (0.99 to 1.22)	1.06 (0.98 to 1.16)	1.21 (1.07 to 1.38)
Sofosbuvir 400 mg once daily Metabolite (GS-331007)	50 mg once daily	24	0.88 (0.80, 0.98) 1.01 (0.93, 1.10)	0.92 (0.85, 0.99) 0.99 (0.97, 1.01)	NA 0.99 (0.97, 1.01)
Tenofovir disoproxil fumarate 300 mg once daily	50 mg once daily	15	1.09 (0.97 to 1.23)	1.12 (1.01 to 1.24)	1.19 (1.04 to 1.35)
Velpatasvir 100 mg once daily	50 mg once daily	24	0.94 (0.86, 1.02)	0.91 (0.84, 0.98)	0.88 (0.82, 0.94)

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

Table 9. Summary of effect of coadministered drugs on the pharmacokinetics of dolutegravir

Coadministered Drug(s) and Dose(s)	**Dose of Dolutegravir**	**n**	**Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00**		
			C_{max}	**AUC**	**C_τ or C_{24}**
Atazanavir 400 mg once daily	30 mg once daily	12	1.50 (1.40 to 1.59)	1.91 (1.80 to 2.03)	2.80 (2.52 to 3.11)
Atazanavir/ritonavir 300 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 twice daily	50 mg once daily	8	1.07 (1.02 to 1.13)	1.11 (1.02 to 1.20)	1.28 (1.13 to 1.45)
Fosamprenavir/ritonavir 700 mg/100 mg twice daily	50 mg once daily	12	0.76 (0.63 to 0.92)	0.65 (0.54 to 0.78)	0.51 (0.41 to 0.63)
Lopinavir/ritonavir 400 mg/100 mg twice daily	30 mg once daily	15	1.00 (0.94 to 1.07)	0.97 (0.91 to 1.04)	0.94 (0.85 to 1.05)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.13 (1.06 to 1.21)	1.12 (1.05 to 1.19)	1.22 (1.15 to 1.30)
Tenofovir 300 mg once daily	50 mg once daily	15	0.97 (0.87 to 1.08)	1.01 (0.91 to l.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 simultaneous administration (fed)	50 mg single dose	11	1.07 (0.83 to 1.38)	1.09 (0.84 to 1.43)	1.08 (0.81 to 1.42)
Calcium carbonate 1,200 mg 2 h after dolutegravir	50 mg single dose	11	1.00 (0.78 to 1.29)	0.94 (0.72 to 1.23)	0.90 (0.68 to 1.19)
Carbamazepine 300 mg twice daily	50 mg once daily	16[c]	0.67 (0.61 to 0.73)	0.51 (0.48 to 0.55)	0.27 (0.24 to 0.31)
Daclatasvir 60 mg once daily	50 mg once daily	12	1.29 (1.07 to 1.57)	1.33 (1.11 to 1.59)	1.45 (1.25 to 1.68)
Ferrous fumarate 324 mg simultaneous administration (fasted)	50mg single dose	11	0.43 (0.35 to 0.52)	0.46 (0.38 to 0.56)	0.44 (0.36 to 0.54)
Ferrous fumarate 324 mg simultaneous administration (fed)	50 mg single dose	11	1.03 (0.84 to 1.26)	0.98 (0.81 to 1.20)	1.00 (0.81 to 1.23)
Ferrous fumarate 324 mg 2 h after dolutegravir	50 mg single dose	10	0.99 (0.81 to 1.21)	0.95 (0.77 to 1.15)	0.92 (0.74 to 1.13)

Multivitamin (One-A-Day) simultaneous administration	50 mg single dose	16	0.65 (0.54 to 0.77)	0.67 (0.55 to 0.81)	0.68 (0.56 to 0.82)
Omeprazole 40 mg once daily	50 mg single dose	12	0.92 (0.75 to 1.11)	0.97 (0.78 to 1.20)	0.95 (0.75 to 1.21)
Prednisone 60 mg once daily with taper	50 mg once daily	12	1.06 (0.99 to 1.14)	1.11 (1.03 to 1.20)	1.17 (1.06 to 1.28)
Rifampin[a] 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 agents: Based on *in vitro* study results, 3TC 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 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 drugs 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 (see section 4.4).

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 coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected subjects (see section 4.4).

Sorbitol (excipient): 3TC and sorbitol solutions were coadministered 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 coadministered 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 coadministered 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 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.

Zidovudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-1-infected adult subjects given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg every 12 hours).

TDF: At concentrations substantially higher (~300-fold) than those observed *in vivo,* tenofovir did not inhibit *in vitro* drug metabolism mediated by any of the following human CYP isoforms: CYP3A4, CYP2D6, CYP2C9, or CYP2E1. However, a small (6%) but statistically significant reduction in metabolism of CYP1A substrate was observed. Based on the results of *in vitro* experiments and the known elimination pathway of tenofovir, the potential for CYP mediated interactions involving tenofovir with other medicinal products is low.

TDF has been evaluated in healthy volunteers in combination with other antiretroviral and potential concomitant drugs. Tables 10 and 11 summarize pharmacokinetic effects of coadministered drug on tenofovir pharmacokinetics and effects of TDF on the pharmacokinetics of coadministered drug.

TDF is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters. When TDF is coadministered with an inhibitor of these transporters, an increase in absorption may be observed.

No clinically significant drug interactions have been observed between TDF and efavirenz, methadone, nelfinavir, oral contraceptives, ribavirin, or sofosbuvir.

Table 10. Drug interactions: changes in pharmacokinetic parameters for tenofovir[a] in the presence of the coadministered drug

Coadministered Drug	**Dose of Coadministered Drug (mg)**	**N**	**% Change of Tenofovir Pharmacokinetic Parameters[b] (90% CI)**		
			C_{max}	**AUC**	**C_{min}**
Atazanavir[c]	400 once daily × 14 days	33	↑14 (↑8 to ↑20)	↑24 (↑21 to ↑28)	↑22 (↑15 to ↑30)
Atazanavir/ Ritonavir [c]	300/100 once daily	12	↑34 (↑20 to ↑51)	↑37 (↑30 to ↑45)	↑29 (↑21 to ↑36)
Darunavir/ Ritonavir[d]	300/100 twice daily	12	↑24 (↑8 to ↑42)	↑22 (↑10 to ↑35)	↑37 (↑19 to ↑57)
Indinavir	800 three times daily × 7 days	13	↑14 (↓3 to ↑33)	⇔	⇔
Ledipasvir/ Sofosbuvir[e,f]	90/400 once daily × 10 days	24	↑47 (↑37 to ↑58)	↑35 (↑29 to ↑42)	↑47 (↑38 to ↑57)
Ledipasvir/ Sofosbuvir[e,g]		23	↑64 (↑54 to ↑74)	↑50 (↑42 to ↑59)	↑59 (↑49 to ↑70)
Ledipasvir/ Sofosbuvir[h]	90/400 once daily × 14 days	15	↑79 (↑56 to ↑104)	↑98 (↑77 to ↑123)	↑163 (↑132 to ↑197)
Lopinavir/ Ritonavir	400/100 twice daily × 14 days	24	⇔	↑32 (↑25 to ↑38)	↑51 (↑37 to ↑66)
Saquinavir/	1000/100 twice daily × 14 days	35	⇔	⇔	↑23

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters[b] (90% CI)		
			C_{max}	AUC	C_{min}
Ritonavir					(↑16 to ↑30)
Sofosbuvir[i]	400 single dose	16	↑25 (↑8 to ↑45)	⇔	⇔
Sofosbuvir/ Velpatasvir[j]	400/100 once daily	24	↑44 (↑33 to ↑55)	↑ 40 (↑34 to ↑ 46)	↑84 (↑76 to ↑92)
Sofosbuvir/ Velpatasvir[k]	400/100 once daily	30	↑46 (↑39 to ↑54)	↑40 (↑34 to ↑45)	↑70 (↑61 to ↑79)
Sofosbuvir/ Velpatasvir/ Voxilaprevir[l]	400/100/100 + Voxilaprevir[m] 100 once daily	29	↑48 (↑36 to ↑61)	↑39 (↑32 to ↑46)	↑47 (↑38 to ↑56)
Tacrolimus	0.05 mg/kg twice daily × 7 days	21	↑13 (↑1 to ↑27)	⇔	⇔
Tipranavir/ Ritonavir[n]	500/100 twice daily	22	↓23 (↓32 to ↓13)	↓2 (↓9 to ↑5)	↑7 (↓2 to ↑17)
	750/200 twice daily (23 doses)	20	↓38 (↓46 to ↓29)	↑2 (↓6 to ↑10)	↑14 (↑1 to ↑27)

[a] Subjects received TDF 300 mg once daily.
[b] Increase = ↑; Decrease = ↓; No Effect = ⇔
[c] Reyataz® (atazanavir) Prescribing Information.
[d] Prezista® (darunavir) Prescribing Information.
[e] Data generated from simultaneous dosing with HARVONI® (ledipasvir/sofosbuvir). Staggered administration (12 hours apart) provided similar results.
[f] Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir DF.
[g] Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir DF.
[h] Study conducted with ATRIPLA® (efavirenz/emtricitabine/tenofovir DF) coadministered with HARVONI® (ledipasvir/sofosbuvir); coadministration with HARVONI® also results in comparable increases in tenofovir exposure when tenofovir DF is administered as COMPLERA® (emtricitabine/rilpivirine/tenofovir DF), or TRUVADA® (emtricitabine/tenofovir DF) + dolutegravir.
[i] Study conducted with ATRIPLA® coadministered with SOVALDI® (sofosbuvir).
[j] Study conducted with COMPLERA® (emtricitabine/rilpivirine/tenofovir DF) coadministered with EPCLUSA® (sofosbuvir/velpatasvir); coadministration with EPCLUSA® also results in comparable increases in tenofovir exposures when TDF is administered as ATRIPLA®, STRIBILD® (cobicistat/elvitegravir/emtricitabine/tenofovir DF), TRUVADA® + atazanavir/ritonavir, or TRUVADA® + darunavir/ritonavir.
[k] Administered as raltegravir + emtricitabine/tenofovir DF.
[l] Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir DF.
[m] Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.
[n] Aptivus® (tipranavir) Prescribing Information.

No effect on the pharmacokinetic parameters of the following coadministered drugs was observed with TDF: abacavir, didanosine (buffered tablets), emtricitabine, entecavir and 3TC.

Table 11. Drug interactions: changes in pharmacokinetic parameters for coadministered drug in the presence of TDF

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters[a] (90% CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	↑12 (↓1 to ↑26)	↔	NA
Atazanavir[b]	400 once daily x 14 days	34	↓21 (↓27 to ↓14)	↓25 (↓30 to ↓19)	↓40 (↓48 to ↓32)
Atazanavir[b]	Atazanavir/Ritonavir	10	↓28	↓25[c]	↓23[c]

	300/100 once daily x 42 days		(↓50 to ↑5)	(↓42 to ↓3)	(↓46 to ↑10)
Darunavir[d]	Darunavir/Ritonavir 300/100 once daily	12	↑16 (↑6 to ↑42)	↑21 (↓5 to ↑54)	↑24 (↓10 to ↑69)
Didanosine[e]	250 once, simultaneously with tenofovir Disoproxil fumarate and a light meal[f]	33	↓20[g] (↓32 to ↓7)	↔[g]	NA
Emtricitabine	200 once daily x 7 days	17	↔	↔	↑20 (↑12 to ↑29)
Entecavir	1 mg once daily x 10 days	28	↔	↑13 (↑11 to ↑15)	↔
Indinavir	800 three times daily x 7 days	12	↓11 (↓30 to ↑12)	↔	↔
Lamivudine	150 twice daily x 7 days	15	↓24 (↓34 to ↓12)	↔	↔
Lopinavir Ritonavir	Lopinavir/Ritonavir 400/100 twice daily X 14 days	24	↔ ↔	↔ ↔	↔ ↔
Saquinavir Ritonavir	Saquinavir/Ritonavir 1000/100 twice daily x 14 days	32	↑22 (↑6 to ↑41) ↔	↑29[h] (↑12 to ↑48) ↔	↑47[h] (↑23 to ↑76) ↑23 (↑3 to ↑46)
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	↔	↔	↔
Tipranavir[i]	Tipranavir/Ritonavir 500/100 twice daily	22	↓7 (↓26 to ↓6)	↓18 (↓25 to ↓9)	↓21 (↓30 to ↓10)
	Tipranavir/Ritonavir 750/200 twice daily (23 doses)	20	↓11 (↓16 to ↓4)	↓9 (↓15 to ↓3)	↓ 12 (↓ 22 to 0)

[a] Increase = ↑; Decrease = ↓; No Effect = ↔; NA = Not Applicable
[b] Reyataz (atazanavir) Prescribing Information
[c] In HIV-infected subjects, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2.3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.
[d] Prezista (darunavir) Prescribing Information
[e] Videx (didanosine) EC Prescribing Information. Subjects received didanosine enteric-coated capsules.
[f] 373 kcal, 8.2 g fat
[g] Compared with didanosine (enteric-coated) 400 mg administered alone under fasting conditions.
[h] Increases in AUC and C_{min} are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir DF and ritonavir-boosted saquinavir are coadministered.
[i] Aptivus (tipranavir) Prescribing Information

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

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.

TDF: Long-term oral carcinogenicity studies of TDF in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.

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 of 35 to 45 times those in humans at the recommended dose for HIV-1 infection.

TDF: TDF was mutagenic in the *in vitro* mouse lymphoma assay and negative in an *in vitro* bacterial mutagenicity test (Ames test). In an *in vivo* mouse micronucleus assay, TDF was negative when administered to male mice.

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).

TDF: There were no effects on fertility, mating performance or early embryonic development when TDF was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats.

Animal toxicology or pharmacology

TDF: Tenofovir and TDF administered in toxicology studies to rats, dogs, and monkeys at exposures (based on AUCs) greater than or equal to 6-fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

Evidence of renal toxicity was noted in 4 animal species. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2 to 20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Mannitol,
Microcrystalline Cellulose,
Sodium Starch Glycolate,
Povidone,
Purified Water,
Croscarmellose Sodium,
Magnesium Stearate,

Film-coating

Polyvinyl Alcohol,
Triacetin,
Talc,
Sodium Lauryl Sulfate,
Titanium dioxide,
FD&C Blue No.2 Al. Lake,
FD&C Blue No.1 Al. Lake
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C (86°F)

6.5 Nature and contents of container

'30's container

HDPE bottle of 30 tablets with desiccant, induction seal, and non-child resistant closure carton containg 30's container: HDPE bottle of 30 tablets with desiccant, induction seal, and non-child resistant closure

90's container

HDPE bottle of 90 tablets with desiccant, induction seal, and non-child resistant closure 90's container: HDPE bottle of 90 tablets with desiccant, induction seal, and non-child resistant closure

180's container

HDPE bottle of 180 tablets with desiccant, induction seal, and non-child resistant closure 180's container: HDPE bottle of 180 tablets with desiccant, induction seal, and non-child resistant closure

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Cipla Ltd., India

8. MARKETING AUTHORISATION NUMBER(S)

[Item to be completed at the time of approval]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[Item to be completed at the time of approval]

10. DATE OF REVISION OF THE TEXT

[Item to be completed at the time of approval]