SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 50 mg/300 mg/300 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Dolutegravir sodium equivalent to Dolutegravir 50 mg,
Lamivudine USP 300 mg,
Tenofovir Disoproxil Fumarate 300 mg equivalent to tenofovir disoproxil 245 mg.
This medicinal product contains 150.40 mg of lactose monohydrate and 131.38 mg of mannitol.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White colored, oval shaped, biconvex, film coated tablets, debossed with 'LA75' on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets are 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 40 kg or greater.

Limitation of Use:

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets alone are not recommended in patients with resistance-associated integrase substitutions or clinically suspected integrase strand transfer inhibitor resistance because the dose of dolutegravir in dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets is insufficient in these subpopulations. See the dolutegravir prescribing information.

4.2 Posology and method of administration

The therapy should be initiated by a physician experienced in the management of HIV infection.

Posology

Adults and Pediatric Patients Weighing 40 kg (88 lbs) or Greater

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets are a fixed-dose combination product containing 50 mg of dolutegravir, 300 mg of lamivudine, and 300 mg of tenofovir disoproxil fumarate. The recommended dosage regimen of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets in adults and pediatric patients weighing 40 kg (88 lbs) or greater is one tablet once daily.

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 below Table that may decrease dolutegravir concentrations; the following dolutegravir dosage regimen is recommended.

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.

Missed dose

If a patient misses a dose of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets within 12 hours of the time it is usually taken, the patient should take as soon as possible and resume their normal dosing schedule. If a patient misses a dose of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets by more than 12 hours and it is almost time for their next dose, the patient should not take the missed dose and simply resume the usual dosing schedule.

If the patient vomits within 1 hour of taking dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets, another tablet should be taken. If the patient vomits more than 1 hour after taking dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets they do not need to take another dose.

Elderly

No data are available on which to make a dose recommendation for patients 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 5.2).

Renal impairment

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets are not recommended for patients with creatinine clearance less than 50 mL/min because dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets are a fixed-dose combination and the dosage of the individual components cannot be adjusted. If a dose reduction of lamivudine or tenofovir disoproxil fumarate, 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 5.2).

Hepatic impairment

Dolutegravir

No dosage adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh grade A or B). No data are available in patients with severe hepatic impairment (Child-Pugh grade C); therefore dolutegravir should be used with caution in these patients (see section 5.2).

Pregnancy Testing Before Initiation of Dolutegravir

Perform pregnancy testing before initiation of dolutegravir in adolescents and adults of childbearing potential.

Method of administration

Oral use.
Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

4.4 Special warnings and special precautions for use

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 and 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).

Patients with Hepatitis B Virus Co-infection

It is recommended that all patients with HIV-1 be tested for the presence of chronic HBV before initiating antiretroviral therapy. Dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets are not approved for the treatment of chronic HBV infection, and the safety and efficacy of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets have not been established in patients coinfected with HBV and HIV-1.

Dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets should not be administered with HEPSERA® (adefovir dipivoxil) (see section 4.5).

Effects on Serum Liver Biochemistries: 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. Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets are recommended in patients with underlying hepatic disease such as hepatitis B or C.

Posttreatment Exacerbations of Hepatitis: Clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine or tenofovir disoproxil fumarate. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment.

Emergence of lamivudine-Resistant HBV: Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in subjects dually infected with HIV-1 and HBV. Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-1-infected subjects who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

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.

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, 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).

New Onset or Worsening Renal Impairment

Because dose interval adjustment requirement for tenofovir disoproxil fumarate for patients with CrCL below 50 mL/min and dose adjustments of lamivudine cannot be achieved with dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets, patients with estimated creatinine clearance below 50 mL/min should not receive dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets.

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir disoproxil fumarate (see section 4.8).

It is recommended that estimated creatinine clearance be assessed in all patients prior to initiating therapy and as clinically appropriate during therapy with dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets. In patients at risk of renal dysfunction, including patients who have previously experienced renal events while receiving adefovir dipivoxil (HEPSERA), it is recommended that estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein be assessed prior to initiation of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets and periodically during dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets therapy.

Dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets should be avoided 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 tenofovir DF. 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 at-risk patients.

Use with Interferon- and Ribavirin-Based Regimens

Patients receiving interferon alfa with or without ribavirin and 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).

Related Products that are Not Recommended

Dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets contains fixed doses of an INSTI) (dolutegravir) and 2 nucleoside analogue reverse transcriptase inhibitors (lamivudine and tenofovir disoproxil fumarate); concomitant administration of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets with other products containing lamivudine, emtricitabine, tenofovir disoproxil fumarate, or tenofovir alafenamide is not recommended.

Bone Effects of Tenofovir Disoproxil Fumarate

Bone Mineral Density: In clinical trials in HIV-1 infected adults, tenofovir disoproxil fumarate 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 tenofovir disoproxil fumarate.

Clinical trials evaluating tenofovir disoproxil fumarate in pediatric and adolescent 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 tenofovir disoproxil fumarate-treated HIV-1 infected pediatric subjects as compared to the control groups. Similar trends were observed in chronic hepatitis B infected adolescent subjects aged 12 years to less than 18 years. In all pediatric trials, skeletal growth (height) appeared to be unaffected. For more information, consult the tenofovir disoproxil fumarate prescribing information.

The effects of tenofovir disoproxil fumarate-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Assessment of BMD should be considered for adults and pediatric patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. 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.

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 tenofovir disoproxil fumarate (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 products containing tenofovir disoproxil fumarate.

Fat Redistribution

Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

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.

Embryo-Fetal Toxicity

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

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

Perform pregnancy testing before initiation of dolutegravir in adolescents and adults of childbearing potential to exclude use of dolutegravir during the first trimester of pregnancy.

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

Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets contain lactose monohydrate. Consequently, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of Dolutegravir on the Pharmacokinetics of Other Agents

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

In vitro, dolutegravir inhibited the basolateral renal transporters, organic anion transporter (OAT) 1 (IC_{50} = 2.12 μM) and OAT3 (IC_{50} = 1.97 μM). However, *in vivo*, dolutegravir did not alter the plasma concentrations of tenofovir or para-amino hippurate, substrates of OAT1 and OAT3.

In vitro, dolutegravir did not inhibit (IC_{50} greater than 50 μM) the following: cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate (UDP)-glucuronosyl transferase 1A1 (UGT1A1), UGT2B7, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, multidrug resistance protein (MRP)2, or MRP4. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6, or CYP3A4. Based on these data and the results of drug interaction trials, dolutegravir is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters.

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

Effect of Other Agents on the Pharmacokinetics of Dolutegravir

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

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

Etravirine significantly reduced plasma concentrations of dolutegravir, but the effect of etravirine was mitigated by coadministration of lopinavir/ritonavir or darunavir/ritonavir, and is expected to be mitigated by atazanavir/ritonavir (Table 1) (see section 5.2).

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

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

Established and Other Potentially Significant Drug Interactions

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

Table 1 provides clinical recommendations as a result of drug interactions with dolutegravir. These recommendations are based on either drug interaction trials or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy (see section 5.2).

Table 1. Established and Other Potentially Significant Drug Interactions for Dolutegravir: 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	Adjust dolutegravir dose to 50 mg twice daily. An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets.
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	Adjust dolutegravir dose to 50 mg twice daily. An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets.
Other Agents		
Carbamazepine[a]	↓Dolutegravir	Adjust dolutegravir dose to 50 mg twice daily. An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets.
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	↓Dolutegravir	Administer dolutegravir, lamivudine, and

supplements, including multivitamins containing calcium or iron[a]		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	With concomitant use, limit the total daily dose of metformin to 1000 mg either when starting metformin or dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets. When stopping dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets, the metformin dose may require an adjustment. Monitoring of blood glucose when initiating concomitant use and after withdrawal of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets is recommended.
Rifampin[a]	↓Dolutegravir	Adjust dolutegravir dose to 50 mg twice daily. An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets.

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

Didanosine

Coadministration of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions. Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions.

When tenofovir disoproxil fumarate was administered with didanosine, C_{max}, and AUC of didanosine increased significantly (see section 5.2). The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis and neuropathy. Suppression of $CD4^+$ cell counts has been observed in patients receiving tenofovir disoproxil fumarate with didanosine 400 mg daily.

In patients weighing greater than 60 kg, the didanosine dose should be reduced to 250 mg once daily when it is coadministered with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets. Data are not available to recommend a dose adjustment of didanosine for adult of pediatric patients weighing less than 60 kg. When coadministered, dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets and didanosine EC may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat).

HIV-1 Protease Inhibitors

Tenofovir disoproxil fumarate decreases the AUC and C_{min} of atazanavir (see section 5.2). When coadministered with dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets should not be coadministered with atazanavir without ritonavir.

Lopinavir/ritonavir, atazanavir coadministered with ritonavir, and darunavir coadministered with ritonavir have been shown to increase tenofovir concentrations (see section 5.2). Tenofovir disoproxil fumarate is a substrate of P-glycoprotein (Pgp) and breast cancer

resistance protein (BCRP) transporters. When tenofovir disoproxil fumarate is coadministered with an inhibitor of these transporters, an increase in absorption may be observed. Patients receiving dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets concomitantly with lopinavir/ritonavir, ritonavir-boosted atazanavir, or ritonavir-boosted darunavir should be monitored for tenofovir disoproxil fumarate-associated adverse reactions. Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets should be discontinued in patients who develop tenofovir disoproxil fumarate-associated adverse reactions.

Hepatitis C Antiviral Agents

Coadministration of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets and ledipasvir/sofosbuvir (HARVONI) or sofosbuvir/velpatasvir (EPCLUSA) has been shown to increase tenofovir exposure (see section 5.2).

In patients receiving dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets concomitantly with sofosbuvir/velpatasvir, monitor for adverse reactions associated with tenofovir disoproxil fumarate.

In patients receiving dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets concomitantly with ledipasvir/sofosbuvir without an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination, monitor for adverse reactions associated with tenofovir disoproxil fumarate.

In patients receiving dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets concomitantly with ledispasvir/sofosbuvir without 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 tenofovir disoproxil fumarate.

Drugs Affecting Renal Function

Since tenofovir is primarily eliminated by the kidneys (see section 5.2), coadministration of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to, adefovir dipivoxil, cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate and well controlled trials in pregnant women. Reproduction studies with the components of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets have been performed in animals (see Dolutegravir, Abacavir, and Lamivudine sections below). Animal reproduction studies are not always predictive of human response. Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets should be used during pregnancy only if the potential benefit outweigh the risks.

Dolutegravir: In reproductive toxicity studies in animals, dolutegravir was shown to cross the placenta. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Dolutegravir should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus.

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to dolutegravir during pregnancy.

Risk Summary

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

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

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

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

Data

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

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

Animal Data: Dolutegravir was administered orally at up to 1,000 mg per kg daily to pregnant rats and rabbits on gestation Days 6 to 17 and 6 to 18, respectively, and to rats on gestation dayDay 6 to lactation/post-partum Day 20. No adverse effects on embryo-fetal (rats and rabbits) or pre/post-natal (rats) development were observed at up to the highest dose tested. During organogenesis, systemic exposures (AUC) to dolutegravir in rabbits were less than the exposure in humans at the MRHD and in rats were approximately 27 times the exposure in humans at the MRHD. In the rat pre/post-natal development study, decreased body weight of the developing offspring was observed during lactation at a maternally toxic dose (approximately 27 times human exposure at the MRHD).

Lamivudine: As a general rule, when deciding to use antiretroviral agents for the treatment of HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data as well as the clinical experience in pregnant women should be taken into account.

Animal studies with lamivudine showed an increase in early embryonic deaths in rabbits but not in rats. Placental transfer of lamivudine has been shown to occur in humans.

More than 1000 outcomes from first trimester and more than 1000 outcomes from second and third trimester exposure in pregnant women indicate no malformative and foeto/neonatal effect. Lamivudine can be used during pregnancy if clinically needed. The malformative risk is unlikely in humans based on those data.

For patients co-infected with hepatitis who are being treated with lamivudine and subsequently become pregnant, consideration should be given to the possibility of a recurrence of hepatitis on discontinuation of lamivudine.

Mitochondrial dysfunction: Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in infants exposed *in utero* and/or post-natally to nucleoside analogues.

Tenofovir Disoproxil Fumarate: A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicate no malformations or foetal/neonatal toxicity associated with tenofovir disoproxil fumarate. Animal studies do not indicate reproductive toxicity.

Breast-feeding

It is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, instruct mothers not to breastfeed.

Dolutegravir

It is unknown whether dolutegravir is excreted in human milk. Available toxicological data in animals has shown excretion of dolutegravir in milk. In lactating rats that received a single oral dose of 50 mg/kg at 10 days postpartum, dolutegravir was detected in milk at concentrations typically higher than blood.

Risk Summary

The Centers for Disease Control and Prevention recommends that HIV 1 infected mothers in

the United States 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 (see Data).

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.

Data

Animal Data: Dolutegravir was the primary drug-related component excreted into the milk of lactating rats following a single oral dose of 50 mg per kg on lactation Day 10, with milk concentrations of up to approximately 1.3 times that of maternal plasma concentrations observed 8 hours postdose.

Lamivudine

Following oral administration lamivudine was excreted in breast milk at similar concentrations to those found in serum. Based on more than 200 mother/child pairs treated for HIV, serum concentrations of lamivudine in breastfed infants of mothers treated for HIV are very low (< 4% of maternal serum concentrations) and progressively decrease to undetectable levels when breastfed infants reach 24 weeks of age. There are no data available on the safety of lamivudine when administered to babies less than three months old.

Tenofovir Disoproxil Fumarate

Tenofovir has been shown to be excreted in human milk. There is insufficient information on the effects of tenofovir in newborns/infants.

Fertility

Dolutegravir

There are no data on the effects of dolutegravir on human male or female fertility. Animal studies indicate no effects of dolutegravir on male or female fertility (see section 5.3).

Pregnancy Testing

Perform pregnancy testing in adolescents and adults of childbearing potential before initiation of dolutegravir.

Contraception

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

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

Lamivudine

Studies in animals showed that lamivudine had no effect on fertility (see section 5.3).

Tenofovir Disoproxil Fumarate

There are limited clinical data with respect to the effect of tenofovir disoproxil fumarate on fertility. Animal studies do not indicate harmful effects of tenofovir disoproxil fumarate on fertility.

4.7 Effects on ability to drive and use machines

Patients should be informed that dizziness has been reported during treatment with components (dolutegravir and tenofovir disoproxil fumarate) of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets. The clinical status of the patient and the adverse reaction profile of dolutegravir should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

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

- Lactic Acidosis and Severe Hepatomegaly with Steatosis (see section 4.4).
- Effects on Serum Liver Biochemistries in Patients with Hepatitis B or C Co-infection (see section 4.4).
- Severe Acute Exacerbation of Hepatitis (see section 4.4).
- Hypersensitivity Reactions (see section 4.4).
- Pancreatitis (see section 4.4).
- New Onset or Worsening Renal Impairment (see section 4.4).
- Hepatic Decompensation in Patients Co-infected with HIV-1 and Hepatitis C (see section 4.4).
- Bone Effects of Tenofovir Disoproxil Fumarate (see section 4.4).
- Fat Redistribution (see section 4.4).
- Immune Reconstitution Syndrome (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.

Dolutegravir, Lamivudine, Tenofovir Disoproxil Fumarate

Serious Dolutegravir Hypersensitivity Reactions: In clinical trials, hypersensitivity reactions have occurred with dolutegravir, a component of dolutegravir, lamivudine, and tenofovir disoproxil fumarate tablets (see section 4.4). These hypersensitivity reactions have been characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury.

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 (n = 414) or fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate once daily (n = 419) (study treatment was blinded through Week 96 and open-label from Week 96 through Week 144). Through 144 weeks, the rate of adverse events leading to discontinuation

was 4% in subjects receiving dolutegravir + fixed-dose abacavir sulfate and lamivudine and 14% in subjects receiving fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate once daily.

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

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

Adverse Reaction	Dolutegravir + 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.

Treatment-Experienced Subjects: SAILING is an international, double-blind trial in INSTI-naïve, antiretroviral treatment-experienced adult subjects. Subjects 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 rate of adverse events leading to discontinuation was consistent with that seen in the overall treatment-naïve patient population.

The ADRs observed in the subset of subjects who received dolutegravir + fixed-dose abacavir sulfate and lamivudine were generally consistent with those seen in the overall treatment-naïve patient population.

Less Common Adverse Reactions Observed in Treatment-Naïve and Treatment-Experienced Trials: The following ADRs 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 preexisting history of depression or other psychiatric illness.

Renal and Urinary Disorders: Renal impairment.

Skin and Subcutaneous Tissue Disorders: Pruritus.

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

Table 3. Selected Laboratory Abnormalities (Grades 2 to 4) in Treatment-Naïve Subjects in SINGLE (Week 144 Analysis)

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

ULN = Upper limit of normal

Table 4. Mean Change from Baseline in Fasted Lipid Values in Treatment-Naïve Subjects in SINGLE (Week 144 Analysis[a])

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

[a] Subjects on lipid-lowering agents at baseline were excluded from these analyses (dolutegravir + fixed-dose abacavir sulfate and lamivudine n = 30 and fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate n = 27). Seventy-two subjects initiated a lipid-lowering agent post-baseline; their last fasted on-treatment values (prior to starting the agent) were used regardless if they discontinued the agent (dolutegravir + fixed-dose abacavir sulfate and lamivudine n = 36 and fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate n = 36).

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

Changes in Serum Creatinine: Dolutegravir has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function (see section 5.1). Increases in serum creatinine occurred within the first 4 weeks of treatment and remained stable through 96 weeks. In treatment-naïve subjects, a mean change from baseline of 0.15 mg per dL (range: -0.32 mg per dL to 0.65 mg per dL) was observed after 96 weeks of treatment. Creatinine increases were comparable by background NRTIs and were similar in treatment-experienced subjects.

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

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

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

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

Tenofovir Disoproxil Fumarate: *Clinical Trials in Adult Patients with HIV-1 Infection*: More than 12,000 subjects have been treated with tenofovir disoproxil fumarate alone or in combination with other antiretroviral medicinal products for periods of 28 days to 215 weeks in clinical trials and expanded access programs. A total of 1,544 subjects have received tenofovir disoproxil fumarate 300 mg once daily in clinical trials; over 11,000 subjects have received tenofovir disoproxil fumarate 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 tenofovir disoproxil fumarate + lamivudine + efavirenz (-2.2% ± 3.9) compared with subjects receiving stavudine + lamivudine + 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 tenofovir disoproxil fumarate group 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 tenofovir disoproxil fumarate-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 tenofovir disoproxil fumarate 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 tenofovir disoproxil fumarate 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

Musculoskeletal: arthralgia, myalgia.

Lamivudine

Body as a Whole: Redistribution/accumulation of body fat (see section 4.4).

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.

Tenofovir Disoproxil Fumarate

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.

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.

Lamivudine

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

Tenofovir Disoproxil Fumarate

Limited clinical experience at doses higher than the therapeutic dose of tenofovir disoproxil fumarate 300 mg is available. In Study 901, 600 mg tenofovir disoproxil fumarate was administered to 8 subjects orally for 28 days. No severe adverse reactions were reported. The effects of higher doses are not known.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action

Dolutegravir, lamivudine, and tenofovir disoproxil fumarate are HIV-1 antiviral agents.

Dolutegravir

Effects on Electrocardiogram: A thorough QT trial has been conducted for dolutegravir. Neither the effects of lamivudine nor tenofovir disoproxil fumarate as single entities or the combination of dolutegravir, lamivudine and tenofovir disoproxil fumarate 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 postdose.

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

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.

Lamivudine: Lamivudine 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.

Tenofovir Disoproxil Fumarate: Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate 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.

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 with median EC_{50} values of 0.18 nM (n = 3, range: 0.09 to 0.5 nM), 0.08 nM (n = 5, range: 0.05 to 2.14 nM) 0.12 nM (n = 4, range: 0.05 to 0.51 nM), 0.17 nM (n = 3, range: 0.16 to 0.35 nM), 0.24 nM (n = 3, range: 0.09 to 0.32 nM), 0.17 nM (range: 0.07 to 0.44 nM), 0.2 nM (n = 3, range: 0.02 to 0.87 nM), and 0.42 nM (n = 3, range: 0.41 to 1.79 nM) for clades A, B, C, D, E, F, and G, and group O viruses, respectively. Dolutegravir EC_{50} values against 3 HIV-2 clinical isolates in PBMC assays ranged from 0.09 nM to 0.61 nM.

Lamivudine: The antiviral activity of lamivudine 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. Lamivudine was not antagonistic to all tested anti-HIV agents. Ribavirin (50 microM) used in the treatment of chronic HCV infection decreased the anti-HIV-1 activity of lamivudine by 3.5-fold in MT-4 cells.

Tenofovir Disoproxil Fumarate: 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 μM to 8.5 μM. In drug combination studies, tenofovir was not antagonistic with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir). 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 lamivudine 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.

Lamivudine: Lamivudine-resistant variants of HIV-1 have been selected in cell culture. Genotypic analysis showed that the resistance was due to a specific amino acid substitution in the HIV-1 reverse transcriptase at codon 184 changing the methionine to either valine or isoleucine (M184V/I).

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from subjects. Susceptibility of clinical isolates to lamivudine and zidovudine was monitored in controlled clinical trials. In subjects receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most subjects became phenotypically and genotypically resistant to lamivudine within 12 weeks.

Tenofovir Disoproxil Fumarate: 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.

In Study 903 of treatment-naïve subjects (tenofovir disoproxil fumarate + lamivudine + efavirenz versus stavudine + lamivudine + efavirenz), genotypic analyses of isolates from subjects with virologic failure through Week 144 showed development of efavirenz and lamivudine resistance-associated substitutions to occur most frequently and with no difference between the treatment arms. The K65R substitution occurred in 8/47 (17%) of analyzed patient isolates in the tenofovir disoproxil fumarate arm and in 2/49 (4%) of analyzed patient isolates in the stavudine arm. Of the eight subjects whose virus developed K65R in the tenofovir disoproxil fumarate arm through 144 weeks, seven occurred in the first 48 weeks of treatment and one at Week 96. One patient in the tenofovir disoproxil fumarate arm developed the K70E substitution in the virus. Other substitutions resulting in resistance to tenofovir disoproxil fumarate were not identified in this trial.

In Study 934 of treatment-naïve subjects (tenofovir disoproxil fumarate + EMTRIVA + efavirenz versus zidovudine (AZT)/lamivudine (3TC) + efavirenz), genotypic analysis performed on HIV-1 isolates from all confirmed virologic failure subjects with greater than 400 copies/mL of HIV–1 RNA at Week 144 or early discontinuation showed development of efavirenz resistance-associated substitutions occurred most frequently and was similar between the two treatment arms. The M184V substitution, associated with resistance to EMTRIVA and lamivudine, was observed in 2/19 analyzed subject isolates in the tenofovir disoproxil fumarate + EMTRIVA group and in 10/29 analyzed subject isolates in the zidovudine/lamivudine group. Through 144 weeks of Study 934, no subjects have developed a detectable K65R substitution in their HIV-1 as analyzed through standard genotypic analysis.

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 El38/G 140/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.

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

Tenofovir Disoproxil Fumarate: 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 this substitution also show reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors the K65R or K70E substitution. HIV-1 isolates from subjects (N = 20) whose HIV-1 expressed a mean of three 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.

In Studies 902 and 907 conducted in treatment-experienced subjects (tenofovir disoproxil fumarate + Standard Background Therapy (SBT) compared to Placebo + SBT), 14/304 (5%) of the tenofovir disoproxil fumarate-treated subjects with virologic failure through Week 96 had greater than 1.4-fold (median 2.7-fold) reduced susceptibility to tenofovir. Genotypic analysis of the baseline and failure isolates showed the development of the K65R substitution in the HIV-1 reverse transcriptase gene.

The virologic response to tenofovir disoproxil fumarate therapy has been evaluated with respect to baseline viral genotype (N = 222) in treatment-experienced subjects participating in Studies 902 and 907. In these clinical trials, 94% of the participants evaluated had baseline HIV-1 isolates expressing at least one NRTI substitution. Virologic responses for subjects in the genotype substudy were similar to the overall trial results.

Several exploratory analyses were conducted to evaluate the effect of specific substitutions and substitutional patterns on virologic outcome. Because of the large number of potential comparisons, statistical testing was not conducted. Varying degrees of cross-resistance of tenofovir disoproxil fumarate to preexisting zidovudine resistance-associated substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N) were observed and appeared to depend on the type and number of specific substitutions. Tenofovir disoproxil fumarate-treated subjects whose HIV-1 expressed three or more zidovudine resistance-associated substitutions that included either the M41L or L210W reverse transcriptase substitution showed reduced responses to tenofovir disoproxil fumarate therapy; however, these responses were still improved compared with placebo. The presence of the D67N, K70R, T215Y/F, or K219Q/E/N substitution did not appear to affect responses to tenofovir disoproxil fumarate therapy. Subjects whose virus expressed an L74V substitution without zidovudine resistance associated substitutions (N = 8) had reduced response to tenofovir disoproxil fumarate. Limited data are available for subjects whose virus expressed a Y115F substitution (N = 3), Q151M substitution (N = 2), or T69 insertion (N = 4), all of whom had a reduced response.

In the protocol defined analyses, virologic response to tenofovir disoproxil fumarate was not reduced in subjects with HIV-1 that expressed the abacavir/emtricitabine/lamivudine resistance-associated M184V substitution. HIV-1 RNA responses among these subjects were durable through Week 48.

Studies 902 and 907 Phenotypic Analyses: Phenotypic analysis of baseline HIV-1 from treatment-experienced subjects (N = 100) demonstrated a correlation between baseline susceptibility to tenofovir disoproxil fumarate and response to tenofovir disoproxil fumarate therapy. Table 5 summarizes the HIV-1 RNA response by baseline tenofovir disoproxil fumarate susceptibility.

Table 5. HIV-1 RNA Response at Week 24 by Baseline Tenofovir Disoproxil Fumarate Susceptibility (Intent-To-Treat)[a]

Baseline Tenofovir Disoproxil Fumarate Susceptibility[b]	Change in HIV-1 RNA[c] (N)
< 1	-0.74 (35)
> 1 and ≤ 3	-0.56 (49)
> 3 and ≤4	-0.3 (7)
> 4	-0.12 (9)

[a] Tenofovir susceptibility was determined by recombinant phenotypic Antivirogram assay (Virco).
[b] Fold change in susceptibility from wild-type.
[c] Average HIV-1 RNA change from baseline through Week 24 ($DAVG_{24}$) in $\log_{10}$ copies/mL.

5.2 Pharmacokinetic properties

Pharmacokinetics in Adults

Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets

Dolutegravir, lamivudine and tenofovir disoproxil fumarate from the combination tablets (50 mg/300 mg/300 mg) were comparable to that from DOLUTEGRAVIR 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.

Lamivudine: Following oral administration, lamivudine is rapidly absorbed and extensively distributed. After multiple dose oral administration of lamivudine 300 mg once daily for 7 days to 60 healthy subjects, steady-state C_{max} ($C_{max,ss}$) was 2.04 ± 0.54 mcg per mL (mean ±SD) and the 24 hour steady state AUC ($AUC_{24,ss}$) was 8.87 ± 1.83 mcg•hour per mL. Binding to plasma protein is low. Approximately 70% of an intravenous dose of lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans sulfoxide metabolite

(approximately 5% of an oral dose after 12 hours). In most single-dose trials in HIV-1-infected subjects, HBV-infected subjects, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{½}$) ranged from 5 to 7 hours. In HIV-1-infected subjects, total clearance was 398.5 ± 69.1 mL per min (mean ± SD).

Tenofovir Disoproxil Fumarate: The pharmacokinetic properties of tenofovir disoproxil fumarate are summarized in Table 7. Following oral administration of tenofovir disoproxil fumarate, 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 mcg/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 tenofovir disoproxil fumarate, 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, the pharmacokinetics of dolutegravir, lamivudine, and tenofovir is not anticipated to be significantly affected by food, 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.

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

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

Tenofovir Disoproxil Fumarate: 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 are a fixed-dose tablet and cannot be dose adjusted, dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets are not recommended in patients requiring dosage adjustment or patients with renal impairment (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 Lamivudine: There are no significant or clinically relevant racial differences in the pharmacokinetics of dolutegravir or lamivudine based on the available information that was analyzed for each of the individual components.

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

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

Lamivudine and Tenofovir Disoproxil Fumarate: The pharmacokinetics of lamivudine or tenofovir disoproxil fumarate have not been studied in subjects older than 65 years.

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

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

Tenofovir Disoproxil Fumarate: 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 tenofovir disoproxil fumarate 300 mg was similar to exposures achieved in adults receiving once-daily doses of tenofovir disoproxil fumarate 300 mg.

Assessment of Drug Interactions:

The drug interaction trials described were conducted with dolutegravir, lamivudine, and/or tenofovir disoproxil fumarate as single entities; no drug interaction trials have been conducted using the combination of dolutegravir, lamivudine, and tenofovir disoproxil fumarate. No clinically significant drug interactions are expected between dolutegravir and lamivudine.

Dosing recommendations as a result of established and other potentially significant drug-drug interactions with dolutegravir are provided in see section 4.5.

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% Cl) 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)
Ethinyl estradiol 0.035 mg	50 mg twice daily	15	0.99 (0.91 to 1.08)	1.03 (0.96 to 1.11)	1.02 (0.93 to 1.11)
Metformin 500 mg twice daily	50mg 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)
Tenofovir disoproxil fumarate 300 mg once daily	50 mg once daily	15	1.09 (0.97 to 1 .23)	1.12 (1.01 to 1.24)	1.19 (1.04 to 1.35)

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

Table 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 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)
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)
Boceprevir 800 mg every 8 hours	50 mg once daily	13	1.05 (0.96 to 1.15)	1.07 (0.95 to 1.20)	1.08 (0.91 to 1.28)
Calcium carbonate 1200 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 1200 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 1200 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.

Lamivudine: Interferon Alfa: There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in a trial of 19 healthy male subjects (see section 4.5).

Ribavirin: *In vitro* data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected subjects (see section 4.5).

Trimethoprim/Sulfamethoxazole: Lamivudine 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 lamivudine 300 mg with the fifth dose in a crossover design. Coadministration of TMP/SMX with lamivudine 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 lamivudine renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by coadministration with lamivudine. There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used in treat PCP.

Tenofovir Disoproxil Fumarate: 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.

Tenofovir disoproxil fumarate 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 tenofovir disoproxil fumarate on the pharmacokinetics of coadministered drug. Coadministration of tenofovir disoproxil fumarate with didanosine results in changes in the pharmacokinetics of didanosine that may be of clinical significance. Concomitant dosing of tenofovir Disoproxil fumarate with didanosine significantly increases the C_{max} and AUC of didanosine. When didanosine 250 mg enteric-coated capsules were administered with tenofovir disoproxil fumarate, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions (Table 11). The mechanism of this interaction is unknown.

No clinically significant drug interactions have been observed between tenofovir disoproxil fumarate 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 x 14 days	33	↑14 (↑8 to ↑20)	↑24 (↑21 to ↑28)	↑22 (↑l5 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 x 7 days	13	↑14 (↓3 to ↑33)	↔	↔
Ledipasvir/ Sofosbuvir[e,f]	90/400 once daily x 10 days	24	↑47 (↑37 to ↑58)	↑35 (↑29 to ↑42)	↑47 (↑38 to ↑57)
Ledipasvir/Sofosbuvir[c,g]		23	↑64 (↑54 to ↑74)	↑50 (↑42 to ↑59)	↑59 (↑49 to ↑70)
Ledipasvir/Sofosbuvir[h]	90/400 once daily x 14 days	15	↑79 (↑56 to ↑104)	↑98 (↑77 to ↑123)	↑163 (↑132 to ↑197)
Ledipasvir/Sofosbuvir[i]	90/400 once daily x 10 days	14	↑32 (↑25 to ↑39)	↑ 40 (↑31 to ↑50)	↑91 (↑74 to ↑110)

Lopinavir/Ritonavir	400/100 twice daily x 14 days	24	↔	↑32 (↑25 to ↑38)	↑51 (↑37 to ↑66)
Saquinavir/Ritonavir	1000/100 twice daily x 14 days	35	↔	↔	↑23 (↑16 to ↑30)
Sofosbuvir[j]	400 single dose	16	↑25 (↑8 to ↑45)	↔	↔
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	↑ 13 (↑1 to ↑27)	↔	↔
Tipranavir/ Ritonavir[k]	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 tenofovir disoproxil fumarate 300 mg once daily.
[b] Increase = ↑; Decrease = ↓; No Effect = ↔; NC = Not Calculated
[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) provide 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.
[i] Study conducted with COMPLERA (emtricitabine/rilpivirine/tenofovir DF) coadministered with HARVONI.
[j] Study conducted with ATRIPLA (efavirenz/emtricitabine/tenofovir DF) coadministered with SOVALDI® (sofosbuvir).
[k] Aptivus (tipranavir) Prescribing Information

No effect on the pharmacokinetic parameters of the following coadministered drugs was observed with tenofovir disoproxil fumarate: abacavir, didanosine (buffered tablets), emtricitabine, entecavir and lamivudine.

Table 11. Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Tenofovir Disoproxil Fumarate

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 300/100 once daily x 42 days	10	↓28 (↓50 to ↑5)	↓25[c] (↓42 to ↓3)	↓23[c] (↓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	Lopinavir/Ritonavir 400/100 twice daily X 14 days	24	↔	↔	↔ ↔

Ritonavir			↔	↔	
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

Coadministration of tenofovir disoproxil fumarate with didanosine results in changes in the pharmacokinetics of didanosine that may be of clinical significance. Concomitant dosing of tenofovir disoproxil fumarate with didanosine enteric-coated capsules significantly increases the C_{max}, and AUC of didanosine. When didanosine 250 mg enteric-coated capsules were administered with tenofovir disoproxil fumarate, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions. The mechanism of this interaction is unknown. See section 4.5 regarding use of didanosine with tenofovir disoproxil fumarate.

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

Lamivudine: Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 12 times (mice) and 57 times (rats) the human exposures at the recommended dose of 300 mg.

Tenofovir Disoproxil Fumarate: Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate 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.

Lamivudine: Lamivudine was mutagenic in an L5178Y mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was not mutagenic in a microbial mutagenicity assay, in an *in vitro* cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver.

Tenofovir Disoproxil Fumarate: Tenofovir disoproxil fumarate 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, tenofovir disoproxil fumarate was negative when administered to male mice.

Impairment of Fertility: *Dolutegravir and Lamivudine*: Dolutegravir or lamivudine did not affect male or female fertility in rats at doses associated with exposures approximately 44 or 112 times (respectively) higher than the exposures in humans at the doses of 50 mg and 300 mg (respectively).

Tenofovir Disoproxil Fumarate: There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil fumarate 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 and/or Pharmacology

Tenofovir Disoproxil Fumarate: Tenofovir and tenofovir disoproxil fumarate 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, lactose monohydrate, pregelatinized starch, croscarmellose sodium and sodium stearyl fumarate.

Film-coating

Polyvinyl alcohol, titanium dioxide, macrogol and talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container.
Keep the bottle tightly closed. Do not remove desiccant.

6.5 Nature and contents of container

30's Count: White opaque 100 cc HDPE bottles filled with 1gm silica gel canister closed with 38 mm child resistant closures.

90's Count: White opaque 250 cc HDPE bottles filled with 1gm silica gel canister closed with 53 mm child resistant closures.

6.6 Special precautions for disposal and other handling

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

7. SUPPLIER

Laurus Labs Limited
2nd Floor, Serene Chambers, Road No.-7
Banjara Hills, Hyderabad – 500034.
India

8. DATE OF REVISION OF THE TEXT

Sep 2018