1.3.1 Package Insert /Summary Of Product Characteristics Pack Insert & Summary Of Product Characteristics is enclosed.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg tenofovir disoproxil fumarate (TDF) equivalent to 245 mg of tenofovir disoproxil or 136 mg of tenofovir, 300 mg lamivudine and 50 mg Dolutegravir (as Sodium)

Each film-coated tablet contains 68 mg lactose, 125 mg of mannitol and 5.981 mg of sodium

For full list of excipients see section 6.1

3. PHARMACEUTICAL FORM

White to off white capsule shaped, biconvex, film coated tablets debossed with 'TLD' on one side and breakline on the other side.

The break-line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg is a fixed dose combination of Tenofovir disoproxil fumarate, Lamivudine and Dolutegravir. It is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents weighing 40 kg or greater.

The choice of Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg to treat antiretroviral experienced patients with HIV-1 infection should be based on individual viral resistance testing and/or the treatment history of the patient.

4.2 Posology and method of administration

Therapy should be prescribed by a physician experienced in the management of HIV-1 infection.

Adults and adolescents weighing at least 40 kg
The recommended dose of Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg is one tablet taken orally once daily with or without food.

Special populations

Children:
Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg is not recommended for use in children below 10 years of age due to a lack of data on safety and efficacy.

Elderly:
Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg should be administered with caution to elderly patients.

Dose adjustments
Where discontinuation of therapy with one of the components of Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg is indicated or where dose modification is necessary, separate preparations of Tenofovir disoproxil fumarate, Lamivudine and Dolutegravir are available. Please refer to the Summary of Product Characteristics for these medicinal products.

If Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg is co-administered with Efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, carbamazepine, or rifampin the dolutegravir dosage regimen is recommended 50 mg twice daily. An additional dolutegravir 50-mg tablet, separated by 12 hours from Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg, should be taken.

Renal impairment
Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg is not recommended for patients with renal impairment (estimated creatinine clearance below 50 mL/min). Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg is a fixed-dose combination tablets and cannot be dose adjusted.

Hepatic impairment:
For Dolutegravir no clinically important pharmacokinetic differences between subjects with moderate hepatic impairment and matching healthy subjects were observed. 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.

Method of administration
Oral use.

It is recommended that Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg be swallowed whole with water.

It is recommended that Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg be taken with or without food.

4.3 Contraindications

Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg is contraindicated in patients with clinically significant hypersensitivity to Tenofovir disoproxil fumarate, Lamivudine and Dolutegravir or to any of the excipients contained in the formulation.

Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg are contraindicated in patients:

- with prior hypersensitivity reaction to tenofovir disoproxil fumarate or lamivudine, dolutegravir. 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 Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg 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 Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction.

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

4.4 Special warnings and precautions for use

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. See full prescribing information for lamivudine and tenofovir disoproxil fumarate. Treatment with Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg 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. Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg are not approved for the treatment of chronic HBV infection, and the safety and efficacy of Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg have not been established in patients coinfected with HBV and HIV-1.

Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg should not be administered with HEPSERA® (adefovir dipivoxil).

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 Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg (see section 4.8). See full prescribing information for dolutegravir. In some cases the elevations in transaminases were consistent with immune reconstitution syndrome or hepatitis B reactivation particularly in the setting where anti-hepatitis therapy was withdrawn. Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg are recommended in patients with underlying hepatic disease such as hepatitis B or C.

Post treatment Exacerbations of Hepatitis: Clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine or tenofovir disoproxil fumarate. See full prescribing information for lamivudine and 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. See full prescribing information for lamivudine.

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. Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg 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 Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg 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, Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg should be used with caution. Treatment with Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg 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 Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg, patients with estimated creatinine clearance below 50 mL/min should not receive Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg.

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 Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg. 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 Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg and periodically during Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg therapy.

Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg 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 Disoproxil Fumarate. 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 Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg should be closely monitored for treatment associated toxicities, especially hepatic decompensation. See Summary of Product Characteristics for these medicinal products for lamivudine. Discontinuation of Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg 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
Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg contains fixed doses of an integrase strand transfer inhibitor (dolutegravir) and 2 nucleoside analogue reverse transcriptase inhibitors (lamivudine and tenofovir disoproxil fumarate); concomitant administration of Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg 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, bone mineral density 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 bone mineral density 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.

The effects of tenofovir disoproxil fumarate-associated changes in bone mineral density and biochemical markers on long-term bone health and future fracture risk are unknown. Assessment of bone mineral density 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. 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 Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg. 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.

Opportunistic infections
Patients receiving Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by healthcare providers experienced in the treatment of patients with HIV associated diseases.

Transmission of HIV
While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Elderly patients
Elderly patients are more likely to have decreased renal function; therefore caution should be exercised when treating elderly patients with tenofovir disoproxil.

Excipients
Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption may experience symptoms of intolerance when using it.

Each tablet also contains 5.981 mg of sodium which is less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other agents on 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 (see table below).

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.

Effects of dolutegravir on other agents

In vitro, dolutegravir inhibited the renal organic cation transporters, OCT2 (IC50 = 1.93 μM) and multidrug and toxin extrusion transporter (MATE) 1 (IC_{50} = 6.34 μM). In vivo, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2 and potentially MATE1. Dolutegravir may increase plasma concentrations of drugs eliminated via OCT2 or MATE1 (dofetilide and metformin, see table below).

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.

Established and Other Potentially Significant Drug Interactions

There were no drug-drug interaction trials conducted with the Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir 300mg/300mg/50mg fixed-dose combination tablets.

Below table 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.

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	↓Dolutegravir	Use of Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir is not recommended.
Non-nucleoside reverse transcriptase inhibitor: Efavirenz	↓Dolutegravir	Adjust dolutegravir dose to 50 mg twice daily. An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg.
Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓Dolutegravir	Avoid coadministration with Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg because there are insufficient data to make dosing recommendations.
Protease inhibitor: Fosamprenavir/ritonavir Tipranavir/ritonavir	↓Dolutegravir	Adjust dolutegravir dose to 50 mg twice daily. An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg.

Other Agents		
Carbamazepine	↓Dolutegravir	Adjust dolutegravir dose to 50 mg twice daily. An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg.
Oxcarbazepine Phenytoin Phenobarbital St. John's wort (*Hypericum perforatum*)	↓Dolutegravir	Avoid coadministration with Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg because there are insufficient data to make dosing recommendations.
Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing antacidsa or laxatives Sucralfate Buffered medications	↓Dolutegravir	Administer Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg 2 hours before or 6 hours after taking medications containing polyvalent cations.
Oral calcium or iron supplements, including multivitamins containing calcium or iron	↓Dolutegravir	Administer Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg 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 Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg. When stopping Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg, the metformin dose may require an adjustment. Monitoring of blood glucose when initiating concomitant use and after withdrawal of Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg is recommended.
Rifampin	↓Dolutegravir	Adjust dolutegravir dose to 50 mg twice daily. An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg.

Didanosine
Coadministration of Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg 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. 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 Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg. Data are not available to recommend a dose adjustment of didanosine for adult of pediatric patients weighing less than 60 kg. When coadministered, Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg 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. When coadministered with Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg 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. 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 Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg concomitantly with lopinavir/ritonavir, ritonavir-boosted atazanavir, or ritonavir-boosted darunavir should be monitored for tenofovir disoproxil fumarate-associated adverse reactions. Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg should be discontinued in patients who develop tenofovir disoproxil fumarate-associated adverse reactions.

Hepatitis C Antiviral Agents
Coadministration of Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg and ledipasvir/sofosbuvir (HARVONI) or sofosbuvir/velpatasvir (EPCLUSA) has been shown to increase tenofovir exposure.

In patients receiving Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg concomitantly with sofosbuvir/velpatasvir, monitor for adverse reactions associated with tenofovir disoproxil fumarate.

In patients receiving Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg 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 Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg concomitantly with ledispasvir/sofosbuvir and an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination, consider an alternative HCV or antiretroviral therapy, as the safety of increased tenofovir concentrations in this setting has not been established. If coadministration is necessary, monitor for adverse reactions associated with tenofovir disoproxil fumarate.

Drugs Affecting Renal Function
Since tenofovir is primarily eliminated by the kidneys, coadministration of Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg 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.

There were no drug-drug interaction trials conducted with the Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir 300mg/300mg/50mg fixed-dose combination tablets. Hence, drug interaction with tenofovir disoproxil fumarate, dolutegravir and lamivudine as single components are presented below;

No clinically significant drug interactions are expected between dolutegravir and lamivudine.

Interactions between dolutegravir and co-administered medicinal products are listed in the following table (increase is indicated as ↑, decrease as ↓, no change as ↔, area under the concentration versus time curve as AUC, maximum observed concentration as C_{max}, concentration at end of dosing interval as C_{τ}).

Drug interactions

Medicines by therapeutic area	Interaction Changes shown as geometric mean	Recommendations on co-administration
Antimicrobials		
Antiretrovirals		
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Etravirine without boosted protease inhibitors	Dolutegravir ↓ AUC ↓ 71%; Cmax ↓ 52%; Cτ ↓ 88% Etravirine ↔ (induction of UGT1A1 and CYP3A enzymes)	Etravirine decreased plasma dolutegravir concentration. The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with etravirine without boosted protease inhibitors. In paediatric patients the weight-based once-daily dose should be given twice daily. When used with etravirine for infection resistant to integrase inhibitors, dolutegravir should be co-administered with atazanavir/ritonavir, or darunavir/ritonavir, or lopinavir/ritonavir
Lopinavir/ritonavir + etravirine	Dolutegravir ↔ AUC ↑ 11%; Cmax ↑ 7%; Cτ ↑ 28% LPV ↔ RTV ↔	No dose adjustment is necessary.
Darunavir/ritonavir + etravirine	Dolutegravir ↓ AUC ↓ 25%; Cmax ↓ 12%; Cτ ↓ 36% DRV ↔ RTV ↔	No dose adjustment is necessary
Efavirenz	Dolutegravir ↓ AUC ↓ 57%; Cmax ↓ 39%; Cτ ↓ 75% Efavirenz ↔ (historical controls) (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with efavirenz. In paediatric patients the weight-based once-daily dose should be given twice daily. For infection resistant to integrase inhibitors, alternative combinations that do not include efavirenz should be considered.
Nevirapine	Dolutegravir ↓ (Not studied, a similar reduction in exposure as observed with	The recommended adult dose of dolutegravir is 50 mg twice daily when given with nevirapine. In

Medicines by therapeutic area	Interaction Changes shown as geometric mean	Recommendations on co-administration
	efavirenz is expected, due to induction)	paediatric patients the weight-based once-daily dose should be given twice daily. For infection resistant to integrase inhibitors, alternative combinations that do not include nevirapine should be considered.
Rilpivirine	Dolutegravir ↔ AUC ↑ 12%; Cmax ↑ 13%; Cτ ↑ 22% Rilpivirine ↔	No dose adjustment is necessary.
Nucleoside reverse transcriptase inhibitors (NRTI)		
Tenofovir disoproxil	Dolutegravir ↔ AUC ↑ 1%; Cmax ↓ 3%; Cτ ↓8% Tenofovir ↔	No dose adjustment is necessary.
Protease inhibitors (PIs)		
Atazanavir	Dolutegravir ↑ AUC ↑ 91%; Cmax ↑ 50%; Cτ ↑ 180% Atazanavir ↔ (historical controls) (inhibition of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary. The dose of dolutegravir should not exceed 50 mg twice daily in combination with atazanavir because data are not available.
Atazanavir/ritonavir	Dolutegravir ↑ AUC ↑ 62%; Cmax ↑ 34%; Cτ ↑ 121% Atazanavir ↔ Ritonavir ↔ (inhibition of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary. The dose of dolutegravir should not exceed 50 mg twice daily in combination with atazanavir because data are not available.
Tipranavir/ritonavir	Dolutegravir ↓ AUC ↓ 59%; Cmax ↓ 47%; Cτ ↓ 76% (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with tipranavir/ritonavir. In paediatric patients the weight-based once daily dose should be given twice daily. For infection resistant to integrase inhibitors, alternative combinations that do not include nevirapine should be considered.
Fosamprenavir/ ritonavir	Dolutegravir ↓ AUC ↓ 35%; Cmax ↓ 24%; Cτ ↓ 49% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary in the absence of integrase class resistance. For infection resistant to integrase inhibitors, alternative combinations that do not include fosamprenavir/ritonavir should be considered.
Darunavir/ritonavir	Dolutegravir ↓ AUC ↓ 22%; Cmax ↓ 11%; C24hours ↓ 38%	No dose adjustment is necessary.

Medicines by therapeutic area	Interaction Changes shown as geometric mean	Recommendations on co-administration
	(induction of UGT1A1 and CYP3A enzymes)	
Lopinavir/ritonavir	Dolutegravir ↔ AUC ↓ 4%; Cmax ↔ 0%; C24hours ↓ 6%	No dose adjustment is necessary.
Antivirals against hepatitis C		
Boceprevir	Dolutegravir ↔ AUC ↑ 7%; Cmax ↑ 5%; Cτ ↑ 8% Boceprevir ↔ (historical controls)	No dose adjustment is necessary.
Daclatasvir	Dolutegravir ↔ AUC ↑ 33%; Cmax ↑ 29%; Cτ ↑ 45% Daclatasvir ↔	No dose adjustment is necessary.
Elbasvir/grazoprevir Glecaprevir/pibrentasvir Ledipasvir/sofosbuvir Ombitasvir/paritaprevir Ombitasvir/paritaprevir/dasabuvir Simeprevir Sofosbuvir Sofosbuvir/velpatasvir Sofosbuvir/velpatasvir/ voxilaprevir	Dolutegravir ↔ (Not studied)	No dose adjustment is necessary.
Antibiotics		
Rifampicin	Dolutegravir ↓ AUC ↓ 54%; Cmax ↓ 43%; Cτ ↓72% (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with rifampicin. In paediatric patients the weight-based once daily dose should be given twice daily. For infection resistant to integrase inhibitors, co-administration of dolutegravir and rifampicin should be avoided.
Rifabutin	Dolutegravir ↔ AUC ↓ 5%; Cmax ↑ 16%; Cτ ↓ 30% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Antifungals		
Fluconazole Itraconazole Ketoconazole Posaconazole Voriconazole	Dolutegravir ↔ (Not studied)	No dose adjustment is necessary. Based on data from other CYP3A4 inhibitors, a marked increase is not expected.
Antiepileptics		
Carbamazepine	Dolutegravir ↓ AUC ↓ 49%; Cmax ↓ 33%; Cτ ↓ 73%	The recommended adult dose of dolutegravir is 50 mg twice daily when given with carbamazepine. In paediatric patients the weight-

Medicines by therapeutic area	Interaction Changes shown as geometric mean	Recommendations on co-administration
		based once-daily dose should be given twice daily. Alternatives to carbamazepine should be used in patients with infection resistant to integrase inhibitors.
Oxcarbazepine Phenytoin Phenobarbital	Dolutegravir ↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a reduction in exposure similar to carbamazepine is expected)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with these enzyme inducers. In paediatric patients the weight-based once-daily dose should be given twice daily. Alternatives to these medicines that are not enzyme inducers should be used in patients with infection resistant to integrase inhibitors.
Antiarrhythmics		
Dofetilide	Dofetilide ↑ (Not studied, potential increase via inhibition of OCT2 transporter)	Dolutegravir and dofetilide co-administration is contraindicated due to potential life-threatening toxicity caused by high dofetilide concentration.
Antacids and supplements		
Magnesium- or aluminium-containing antacid	Dolutegravir ↓ AUC ↓ 74%; Cmax ↓ 72% (Complex binding to polyvalent ions)	Magnesium- or aluminium-containing antacid should be taken well separated in time from dolutegravir (minimum 2 hours after or 6 hours before).
Calcium supplements	Dolutegravir ↓ AUC ↓ 39%; Cmax ↓ 37%; C24hours ↓ 39% (Complex binding to polyvalent ions)	Calcium supplements, iron supplements or multivitamins should be taken well separated in time from the administration of dolutegravir (minimum 2 hours after or 6 hours before).
Iron supplements	Dolutegravir ↓ AUC ↓ 54%; Cmax ↓ 57%; C24hours ↓ 56% (Complex binding to polyvalent ions)	
Multivitamins	Dolutegravir ↓ AUC ↓ 33%; Cmax ↓ 35% C24hours ↓ 32% (Complex binding to polyvalent ions)	
Antidiabetics		
Metformin	Co-administered with dolutegravir 50 mg once daily: Metformin ↑ AUC ↑ 79%; Cmax ↑ 66% Co-administered with dolutegravir 50 mg twice daily:	A dose adjustment of metformin should be considered when starting and stopping co-administration of dolutegravir with metformin, to maintain glycaemic control. In patients

Medicines by therapeutic area	Interaction Changes shown as geometric mean	Recommendations on co-administration
	Metformin ↑ AUC ↑ 145%; Cmax ↑ 111%	with moderate renal impairment a dose adjustment of metformin should be considered when given with dolutegravir, because the risk of lactic acidosis is increased in patients with moderate renal impairment due to increased metformin concentration.
Contraceptives		
Ethinylestradiol and norelgestromin	Dolutegravir ↔ Ethinylestradiol ↔ AUC ↑ 3%; Cmax ↓ 1% Norelgestromin ↔ AUC ↓ 2%; Cmax ↓ 11%	Dolutegravir had no pharmacodynamic effect on luteinizing hormone, follicle stimulating hormone and progesterone. No dose adjustment of oral contraceptives is necessary when given with dolutegravir.
Corticosteroids		
Prednisone	Dolutegravir ↔ AUC ↑ 11%; Cmax ↑ 6%; Cτ ↑ 17%	No dose adjustment is necessary.
Drug abuse		
Methadone	Dolutegravir ↔ Methadone ↔ AUC ↓ 2%; Cmax ↔ 0%; Cτ ↓ 1%	No dose adjustment is necessary.
Herbal products		
St. John's wort	Dolutegravir ↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a reduction in exposure similar to carbamazepine is expected)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with St. John's wort. In paediatric patients the weight-based once-daily dose should be given twice daily. Alternatives to St. John's wort should be used in patients with infection resistant to integrase inhibitors.

Interactions for tenofovir disoproxil fumarate

Interaction studies have only been performed in adults.

Based on the results of in vitro experiments and the known elimination pathway of tenofovir, the potential for CYP450 mediated interactions involving tenofovir with other medicinal products is low.

Concomitant use not recommended
Tenofovir Disoproxil Fumarate should not be administered with any other medicines containing:
- tenofovir disoproxil fumarate
- tenofovir alafenamide
- adefovir dipivoxil
- didanosine

Renally eliminated medicinal products:
Since tenofovir is primarily eliminated by the kidneys, co-administration of tenofovir disoproxil fumarate with medicines that reduce renal function or compete for active tubular secretion via transport proteins hOAT 1, hOAT 3 or MRP 4 (e.g. cidofovir) may increase serum concentrations of tenofovir, or the co-administered medicines, or both.

Nephrotoxic medicinal products:
Use of tenofovir disoproxil fumarate should be avoided with concurrent use of a nephrotoxic medicinal product. Examples include, but are not limited to, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir and interleukin-2.

Given that tacrolimus can affect renal function, close monitoring is recommended when it is coadministered with tenofovir disoproxil fumarate.

Other interactions:
Interactions between tenofovir disoproxil fumarate and HIV protease inhibitors, as well as antiviral agents other than protease inhibitors, are listed in the table below (increased exposure is indicated as "↑", decreased exposure as "↓", no change as "↔",).

Interactions between tenofovir disoproxil fumarate and other medicinal products

Medicines by therapeutic area (dose in mg)	**Effects on drug levels Mean % change in AUC, C_{max}, C_{min}**	**Recommendations on co-administration**
ANTI-INFECTIVES		
Antiretrovirals		
Protease inhibitors		
Atazanavir (400 mg once daily)	Atazanavir: AUC: ↓ 25% C_{max}: ↓ 21% C_{min}: ↓ 40% Tenofovir: AUC: ↑ 24% C_{max}: ↑ 14% C_{min}: ↑ 22%	If atazanavir and tenofovir are co-administered, atazanavir should be given at a dose 300 mg once daily together with ritonavir 100 mg once daily
Atazanavir/Ritonavir (300 mg/100 mg once daily)	Atazanavir: AUC: ↓ 25% C_{max}: ↓ 28% C_{min}: ↓ 26% Tenofovir: AUC: ↑ 37% C_{max}: ↑ 34% C_{min}: ↑ 29%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir-associated adverse events, including renal disorders. Renal function should be closely monitored
Lopinavir/Ritonavir (400 mg/100 mg twice daily.)	Lopinavir/ritonavir: No significant effect on lopinavir/ritonavir pharmacokinetic parameters. Tenofovir: AUC: ↑ 32% C_{max}: ↔ C_{min}: ↑ 51%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir-associated adverse events, including renal disorders. Renal function should be closely monitored
Darunavir/Ritonavir (300 mg/100 mg twice daily.)	Darunavir: No significant effect on darunavir/ritonavir	No dose adjustment is recommended. The increased exposure of tenofovir could

Medicines by therapeutic area (dose in mg)	Effects on drug levels Mean % change in AUC, C_{max}, C_{min}	Recommendations on co-administration
	pharmacokinetic parameters. Tenofovir: AUC: ↑ 22% C_{min}: ↑ 37%	potentiate tenofovir-associated adverse events, including renal disorders. Renal function should be closely monitored
NRTIs		
Didanosine (400 mg once daily)	Didanosine AUC ↑ 40-60%	The risk of didanosine-related adverse effects (e.g. pancreatitis, lactic acidosis) appear to be increased, and CD4 cells may decrease significantly on coadministration. Also didanosine at 250 mg co-administered with tenofovir with several different antiretroviral combination regimens has been associated with a high rate of virological failure. Co-administration of tenofovir disoproxil fumarate and didanosine is not recommended
Adefovir dipivoxil	AUC: ↔ Cmax: ↔	Tenofovir disoproxil fumarate should not be administered concurrently with adefovir dipivoxil (see section 4.4).
Entecavir (1 mg once daily)	AUC: ↔ Cmax: ↔	No clinically significant pharmacokinetic interactions when tenofovir disoproxil fumarate was co-administered with entecavir.

Studies with other medicines
There were no clinically significant pharmacokinetic interactions when tenofovir disoproxil fumarate was co-administered with emtricitabine, lamivudine, indinavir, efavirenz, saquinavir (ritonavir boosted), methadone, ribavirin, rifampicin, tacrolimus, or the hormonal contraceptive norgestimate/ethinylestradiol.

Interactions for Lamivudine

Interaction studies have only been performed in adults.

The likelihood of metabolic interactions is low due to limited metabolism and plasma protein binding and almost complete renal clearance.

Lamivudine metabolism does not involve CYP3A, making interactions with medicinal products metabolised by this system (e.g. PIs) unlikely.

Sulfamethoxazole/trimethoprim increases plasma concentrations of lamivudine but a clinically significant effect is not expected; the patient should be monitored for lamivudine toxicity in case of marked renal impairment or if high doses of sulfamethoxazole/trimethoprim are used (e.g. for Pneumocystis jirovecii pneumonitis treatment).

Medicinal products, whose main route of elimination is active renal secretion via the organic cationic transport

system, e.g. trimethoprim, may interact with lamivudine. Medicinal products (e.g. ranitidine, cimetidine), which are eliminated only in part by this mechanism, were shown not to interact with lamivudine.

Due to similarities, Lamivudine should not be administered concomitantly with other cytidine analogues, such as emtricitabine. Moreover, Lamivudine should not be taken with any other medicinal products containing lamivudine.

In vitro lamivudine inhibits the intracellular phosphorylation of cladribine leading to a potential risk of cladribine loss of efficacy in case of combination in the clinical setting. Some clinical findings also support a possible interaction between lamivudine and cladribine. Therefore, the concomitant use of lamivudine with cladribine is not recommended.

4.6 Pregnancy and lactation

Pregnancy
There are no adequate and well controlled trials in pregnant women. Reproduction studies with the components of Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg have been performed in animals. Animal reproduction studies are not always predictive of human response. Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg should be used during pregnancy only if the potential benefit outweigh the risks.

Animal Data
Dolutegravir: Reproduction studies performed in rats and rabbits at doses up to 50 times the human dose of 50 mg once daily have revealed no evidence of impaired fertility or harm to the fetus due to dolutegravir.

Oral administration of dolutegravir to pregnant rats at doses up to 1,000 mg per kg daily, approximately 50 times the 50-mg once-daily human clinical exposure based on AUC, from days 6 to 17 of gestation did not elicit maternal toxicity, developmental toxicity, or teratogenicity.

Oral administration of dolutegravir to pregnant rabbits at doses up to 1,000 mg per kg daily, approximately 0.74 times the 50-mg once-daily human clinical exposure based on AUC, from days 6 to 18 of gestation did not elicit developmental toxicity or teratogenicity. In rabbits, maternal toxicity (decreased food consumption, scant/no feces/urine, suppressed body weight gain) was observed at 1,000 mg per kg.

Lamivudine: Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. Reproduction studies with orally administered lamivudine have been performed in rats and rabbits at doses producing plasma levels up to approximately 32 times the human exposure for a dose of 300 mg. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryolethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at plasma levels up to 32 times those in humans.

Tenofovir Disoproxil Fumarate: Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir.

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

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

Tenofovir Disoproxil Fumarate
Samples of breast milk obtained from five HIV-1 infected mothers in the first post-partum week show that tenofovir is secreted in human milk

Lamivudine
Lamivudine is excreted in human breast milk.

Dolutegravir
Studies in lactating rats and their offspring indicate that dolutegravir was present in rat milk. It is not known whether dolutegravir is excreted in human breast milk.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed Tenofovir disoproxil fumarate and Lamivudine. However, users should be informed that dizziness has been reported during treatment with tenofovir disoproxil fumarate.

Patients should be informed that dolutegravir can cause dizziness. The patient's clinical status and dolutegravir's side effects should be considered for evaluating the patient's ability to drive or operate machinery.

4.8 Undesirable effects

The adverse events for Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg are as follows,

- 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).

Because clinical trials are conducted under widely varying conditions, adverse event 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.

Tenofovir Disoproxil Fumarate, Lamivudine and Dolutegravir

Serious Dolutegravir Hypersensitivity Reactions: In clinical trials, hypersensitivity reactions have occurred with dolutegravir, a component of Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg (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 adverse events of moderate to severe intensity observed in at least 2% of subjects in either treatment arm of SINGLE are provided in below table.

Table: Treatment-Emergent Adverse events 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	<1%	6%
Ear and Labyrinth		
Vertigo	0	2%

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. See full prescribing information for dolutegravir.

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

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

Hepatobiliary Disorders: Hepatitis.

Musculoskeletal Disorders: Myositis.

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

Renal and Urinary Disorders: Renal impairment.

Skin and Subcutaneous Tissue Disorders: Pruritus.

Laboratory Abnormalities: Treatment-Naïve Subjects: Selected laboratory abnormalities (Grades 2 to 4) with a worsening grade from baseline and representing the worst-grade toxicity in at least 2% of subjects in SINGLE are presented in belowTable.

Table. 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 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.

The mean change from baseline observed for selected lipid values is presented in below table.

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

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

*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.

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

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

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

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 Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg.

The adverse reactions with at least a possible relationship to treatment are listed below by body system organ class and absolute frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10) or common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) or rare (≥ 1/10,000 to < 1/1,000).

The following adverse reactions were associated with tenofovir disoproxil fumarate based on clinical study and post-marketing experience.

Metabolism and nutrition disorders:
Very common: hypophosphataemia
Uncommon: hypokalaemia
Rare: lactic acidosis

Nervous system disorders:
Very common: dizziness
Common: headache

Gastrointestinal disorders:
Very common: diarrhoea, vomiting, nausea
Common: abdominal pain, abdominal distension, flatulence
Uncommon: pancreatitis

Hepatobiliary disorders:
Common: increased transaminases
Rare: hepatic steatosis, hepatitis

Skin and subcutaneous tissue disorders:
Very common: rash
Rare: angioedema

Musculoskeletal and connective tissue disorders:
Uncommon: rhabdomyolysis, muscular weakness
Rare: osteomalacia (manifested as bone pain and infrequently contributing to fractures), myopathy

Renal and urinary disorders:
Uncommon: increased creatinine
Rare: acute renal failure, renal failure, acute tubular necrosis, proximal renal tubulopathy (including Fanconi syndrome), nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus

General disorders and administration site conditions:
Very common: asthenia
Common: fatigue

The following adverse reactions were associated with lamivudine based on clinical study and post-marketing experience.

Blood and lymphatic systems disorders
Uncommon: neutropenia, anaemia (both occasionally severe), thrombocytopenia
Very rare: pure red cell aplasia

Metabolism and nutrition disorders
Unknown: lipodystrophy, hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia, lactic acidosis (sometimes fatal), usually associated with severe hepatomegaly and hepatic steatosis

Nervous system disorders
Common: headache, insomnia
Very rare: peripheral neuropathy (paraesthesia)

Respiratory, thoracic and mediastinal disorders
Common: cough, nasal symptoms

Gastrointestinal disorders
Common: nausea, vomiting, abdominal pain or cramps, diarrhoea
Rare: pancreatitis (including fatal cases), elevated serum amylase

Hepatobiliary disorders
Uncommon: transient elevation of liver enzymes (AST, ALT)
Rare: hepatitis

Skin and subcutaneous tissue disorders
Common: Rash, hair loss
Rare: angioedema

Musculoskeletal and connective tissue disorders
Common: arthralgia, muscle disorder
Rare: rhabdomyolysis
Unknown: osteonecrosis

General disorders and administration site disorders:
Common: fatigue, malaise, fever
Unknown: immune reconstitution syndrome

The following adverse reactions were associated with Dolutegravir based on clinical study and post-marketing experience.

Immune system disorders	
Uncommon	hypersensitivity (see section 4.4) immune reactivation syndrome
Psychiatric disorders	
Common	insomnia abnormal dreams depression
Uncommon	suicidal ideation or suicide attempt (particularly in patients with history of depression or psychiatric illness)
Nervous system disorders	
Very common	headache
Common	dizziness
Gastrointestinal disorders	
Very common	nausea diarrhoea
Common	flatulence upper abdominal pain abdominal pain abdominal discomfort
Hepatobiliary disorders	
Uncommon	hepatitis
Skin and subcutaneous tissue disorders	

Common	rash pruritus
Musculoskeletal and connective tissue disorders	
Uncommon	arthralgia myalgia
General disorders	
Common	Fatigue
Investigations	
Common	raised alanine aminotransferase (ALT) and aspartate aminotransferase (AST) raised creatine kinase

Special populations

Pediatric Use

Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg should only be administered to patients with a body weight of at least 40 kg.

Geriatric Use

Clinical trials of tenofovir disoproxil fumarate or dolutegravir, lamivudine did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Patients with Impaired Renal Function

Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg are not recommended for patients with creatinine clearance less than 50 mL per min because Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg 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 Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg, is required for patients with creatinine clearance less than 50 mL per min, then the individual components should be used.

Patients with Impaired Hepatic Function

Dolutegravir

No clinically important pharmacokinetic differences between subjects with moderate hepatic impairment and matching healthy subjects were observed. 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.

4.9 Overdose

There is no known specific treatment for overdose with Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir Tablets 300mg/300mg/50mg. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required.

Tenofovir Disoproxil Fumarate

Symptoms

If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

Management
Tenofovir can be removed by haemodialysis; the median haemodialysis clearance of tenofovir is 134 ml/minute. It is not known whether tenofovir can be removed by peritoneal dialysis

Lamivudine
No specific symptoms or signs have been identified following acute overdose with lamivudine, apart from those listed as undesirable effects.

If overdose occurs the patient should be monitored for evidence of toxicity, and standard supportive treatment applied as necessary. Since lamivudine is dialyzable, continuous haemodialysis could be used in the treatment of overdose, although this has not been studied.

Dolutegravir
Experience of dolutegravir overdosage is limited. Single doses of up to 250 mg in healthy subjects revealed no specific symptoms or signs, apart from those listed as adverse reactions.

There is no specific treatment for dolutegravir overdose. In an overdose, the patient should be treated supportively with appropriate monitoring, as necessary with advice from a national poisons centre, where available. Dialysis is unlikely to remove dolutegravir to any significant extent because it is highly bound to plasma proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action and pharmacodynamic effects
Tenofovir disoproxil is converted *in vivo* to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate. Lamivudine and tenofovir are phosphorylated by cellular enzymes to form lamivudine triphosphate and tenofovir diphosphate, respectively.

Lamivudine, the negative enantiomer of 2'-deoxy-3'-thiacytidine, is a dideoxynucleoside analogue.

Lamivudine triphosphate and tenofovir diphosphate competitively inhibit HIV-1 reverse transcriptase (RT), resulting in DNA chain termination. Both substances are active against HIV-1 and HIV-2, as well as against hepatitis B virus.

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.

Antiviral activity in cell culture for Dolutegravir
The IC_{50} for dolutegravir in various lab-strains using PBMC was 0.5 nM, and when using MT-4 cells it ranged from 0.7 to 2 nM. Similar IC_{50} were seen for clinical isolates without any major difference between subtypes; in a panel of 24 HIV-1 isolates of clades A, B, C, D, E, F and G and group O the mean IC_{50} was 0.2 nM (range 0.02–2.14 nM). The mean IC_{50} for three HIV-2 isolates was 0.18 nM (range 0.09–0.61 nM).

Antiviral activity in combination with other antiviral agents No antagonistic effects were seen in vitro with dolutegravir and other antiretrovirals tested: stavudine, abacavir, efavirenz, nevirapine, lopinavir, amprenavir, enfuvirtide, maraviroc and raltegravir. In addition, no antagonistic effects were seen for dolutegravir and adefovir: ribavirin had no apparent effect on dolutegravir activity.

Effect of human serum In 100% human serum, the mean protein fold shift was 75-fold, resulting in protein adjusted IC90 of 0.064 ug/mL.

Resistance

Tenofovir Disoproxil fumarate
The K65R mutation is selected in vitro when HIV-1 is cultured in the presence of increasing tenofovir concentrations. It may also emerge in vivo upon virological failure of a treatment regimen including tenofovir. K65R reduces tenofovir susceptibility in vitro approximately 2-fold, and has been associated with a lack of response to tenofovir-containing regimens. Clinical studies in treatment-experienced patients have assessed the anti-HIV activity of tenofovir against strains of HIV-1 with thymidine analogue mutations (TAMs), which are not selected for by tenofovir. Patients whose HIV expressed 3 or more TAMs that included either the M41L or L210W mutation showed reduced response to tenofovir disoproxil fumarate.

Lamivudine
HIV-1 resistance to lamivudine involves the development of a M184V amino acid change close to the active site of the viral reverse transcriptase (RT). This variant arises both in vitro and in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy. M184V mutants display greatly reduced susceptibility to lamivudine and show diminished viral replicative capacity in vitro. In vitro studies indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. The clinical relevance of such findings remains, however, not well defined.

In vitro data tend to suggest that the continuation of lamivudine in anti-retroviral regimen despite the development of M184V might provide residual anti-retroviral activity (likely through impaired viral fitness). The clinical relevance of these findings is not established. Indeed, the available clinical data are very limited and preclude any reliable conclusion in the field. In any case, initiation of susceptible NRTI's should always be preferred to maintenance of lamivudine therapy. Therefore, maintaining lamivudine therapy despite emergence of M184V mutation should only be considered in cases where no other active NRTI's are available.

Cross-resistance conferred by the M184V RT is limited within the nucleoside inhibitor class of antiretroviral agents. Zidovudine and stavudine maintain their antiretroviral activities against lamivudine-resistant HIV-1. Abacavir maintains its antiretroviral activities against lamivudineresistant HIV-1 harbouring only the M184V mutation. The M184V RT mutant shows a <4-fold decrease in susceptibility to didanosine; the clinical significance of these findings is unknown. In vitro susceptibility testing has not been standardised and results may vary according to methodological factors.

Lamivudine demonstrates low cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines, and to a variety of bone marrow progenitor cells in vitro.

Dolutegravir
Resistance in vitro Using strain NL432, mutations E92Q (FC 3) and G193E (also FC 3) were selected. The E92Q mutation has been selected in patients with existing raltegravir resistance who were then treated with dolutegravir (listed as a secondary mutation for dolutegravir).

Using clinical isolates of subtype B, C and A/G the integrase substitution R263K and G118R (in C and A/G) R263K was reported from two ART-experienced, integrase-inhibitor-naive patients with subtypes B and C in the clinical program, but without effects on dolutegravir susceptibility in vitro. G118R lowers the susceptibility to dolutegravir in site directed mutants (FC 10), but was not detected in patients receiving dolutegravir in the Phase III program.

Primary mutations for raltegravir/elvitegravir (Q148H/R/K, N155H, Y143R/H/C, E92Q and T66I) do not affect the in vitro susceptibility of dolutegravir as single mutations. When mutations listed as secondary integrase-inhibitor-associated mutations (for raltegravir/elvitegravir) are added to these primary mutations in experiments with site-directed mutants, dolutegravir susceptibility is still unchanged (FC < 2 vs wild type virus), except in

the case of Q148-mutations, where a FC is 5–10 or higher with combinations of certain secondary mutations. The effect by the Q148-mutations (H/R/K) was also verified in passage experiments with site-directed mutants. In serial passage with strain NL432, starting with site-directed mutants harbouring N155H or E92Q, further selection of resistance did not occur (FC unchanged around 1). In contrast, starting with mutants harbouring mutation Q148H (FC 1), a variety of secondary mutations were seen with a consequent increase of FC to values > 10.

A clinically relevant phenotypic cut-off value (FC vs wild type virus) has not been determined; genotypic resistance was a better predictor for outcome.

In an analysis for susceptibility to dolutegravir in raltegravir resistant isolates from raltegravir-experienced patients, dolutegravir has a less than or equal to 10 FC against 94% of the 705 clinical isolates.

Resistance in vivo
In previously untreated patients receiving dolutegravir + 2 NRTIs in clinical studies, resistance did not develop to the integrase inhibitor class or to the NRTI class (n=1118 follow-up of 48–96 weeks).

In patients whose previous antiretroviral treatment had failed who had not received an integrase inhibitor, integrase inhibitor substitutions occurred in 4/354 patients (follow-up 48 weeks) treated with dolutegravir given with an investigator-selected background regimen. Of these four patients, two had a unique R263K integrase substitution, with a maximum FC of 1.93, one had a polymorphic V151V/I integrase substitution, with maximum FC of 0.92, and one had existing integrase mutations and is assumed to have been integrase-inhibitor-experienced or infected with integrase-inhibitor-resistant virus. The R263K mutation was also selected in vitro (see above).

In the presence of integrase-inhibitor class-resistance the following mutations were selected in 32 patients with protocol-defined virological failure (PDVF) through Week 24 and with paired genotypes (all treated with dolutegravir 50 mg twice daily + optimised background agents): L74L/M (n=1), E92Q (n=2), T97A (n=9), E138K/A/T (n=8), G140S (n=2), Y143H (n=1), S147G (n=1), Q148H/K/R (n=4), and N155H (n=1) and E157E/Q (n=1). Treatment-emergent integrase-inhibitor-resistance typically appeared in patients with a history of the Q148-mutation (baseline or historic). Five further subjects experienced PDVF between weeks 24 and 48, and 2 of these 5 had treatment-emergent mutations. Treatment-emergent mutations or mixtures of mutations observed were L74I (n=1), N155H (n=2).

Treatment-emergent mutations in 30 subjects with primary genotypic resistance to integrase inhibitors at screening who were treated with dolutegravir (plus optimised background therapy) were consistent with these findings.

Effects on electrocardiogram
No relevant effects were seen on the QTc interval, with doses exceeding the clinical dose by approximately three-fold.

Clinical efficacy and safety

Tenofovir Disoproxil Fumarate
HIV-1 therapy
In treatment-experienced adult patients the time-weighted average change from baseline in log10 plasma HIV-1 RNA levels the time-weighted average change from baseline in log10 plasma HIV-1 RNA levels (DAVG24) at week 24 was -0.03 log10 copies/ml and -0.61 log10 copies/ml for the placebo and tenofovir disoproxil fumarate 300 mg recipients ($p < 0.0001$). The antiviral response was durable with DAVG at week 48 being -0.57 log10 copies/ml, the proportion of patients with HIV-1 RNA below 400 or 50 copies/ml was 41% and 18% respectively.

In treatment-naïve adult patients the proportion of patients with HIV-1 RNA below 400 copies/ml and 50

copies/ml at 48 weeks of treatment was 80% and 76% respectively in the tenofovir disoproxil fumarate 300 mg arm, compared to 84% and 80% in the stavudine arm. At 144 weeks, the proportion of patients with HIV-1 RNA below 400 copies/ml and 50 copies/ml was 71% and 68% respectively in the tenofovir disoproxil fumarate arm, compared to 64% and 63% in the stavudine arm.

A consistent response to treatment with tenofovir disoproxil fumarate 300 mg was seen regardless of baseline HIV-1 RNA and CD4 count.

Lamivudine
Lamivudine has been investigated in several randomised, prospective clinical trials in combination with other antiretroviral drugs. These studies demonstrate significant decrease in plasma HIV RNA and increase in CD4 cell counts when lamivudine is used in combination with another nucleos(t)ide analogue and third agent of a different therapeutic class, e.g. a non-nucleoside reverse transcriptase inhibitor (NNRTI) ,protease inhibitor (PI) or integrase strand transfer inhibitor (INSTI). In recent studies by intention-to-treat analysis 88% of subjects achieved plasma HIV RNA ≤ 50 copies/ml after 48 weeks of combination antiretroviral treatment.

Dolutegravir
Previously untreated patients
The efficacy of dolutegravir is based on the analyses of 96-week data from two randomised, international, double-blind, active-controlled trials. This is supported by 96-week data from an open-label, randomised and active-controlled study and additional data from the open-label phase of one study to 144 weeks. Throughout the duration of treatment in these studies no cases of treatment-emergent primary resistance to the integrase inhibitors or to nucleoside reverse transcriptase occurred in patients treated with dolutegravir.

In therapy-naïve adult patients with HIV infection who received dolutegravir 50 mg once daily with either abacavir/lamivudine or tenofovir disoproxil/emtricitabine viral load (HIV-1 RNA) was reduced to fewer than 50 copies/ml in 80% of patients after 96 weeks of treatment and was 71% in one study after 144 weeks. Viral suppression was similar or greater than in the comparator groups.

Patients treated previously with regimens that excluded integrase inhibitor
One study involved 719 adult patients with HIV-1 who had previously received antiretroviral therapy. Patients received either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily with investigator-selected background regimen consisting of up to 2 antiretrovirals. After 48 weeks, viral load was reduced to fewer than 50 copies/ml in 71% patients receiving a combination containing dolutegravir compared to 64% of patients receiving a combination containing raltegravir.

Patients in whom treatment that included an integrase inhibitor had failed (with HIV-1 resistant to integrase inhibitors)
One study involved 183 adult patients with HIV-1 whose antiretroviral treatment had failed and whose infection had developed resistance against raltegravir or elvitegravir or both. After 48 weeks of treatment with dolutegravir 50 mg twice daily and optimised background therapy, the viral load was fewer than 50 copies/ml in 63% of patients. Efficacy was lower in patients with Q148 mutation, particularly when accompanied by two or more secondary mutations.

Another study involved 30 adult patients who had HIV-1 infection with primary genotypic resistance to integrase inhibitors. Patients received either dolutegravir 50 mg twice daily or placebo with the current failing regimen for 7 days The primary endpoint at day 8 showed that dolutegravir 50 mg twice daily was superior to placebo, with an adjusted mean treatment difference for the change from baseline in plasma HIV-1 RNA of -1.2 log10 copies/mL. After subsequent treatment of all patients with with dolutegravir 50 mg twice daily and optimised background therapy, 40% of patients had fewer than 50 copies/mL at week 48.

Paediatric population
A study in children and adolescents aged up to 18 years investigated the pharmacokinetics, tolerability and efficacy of dolutegravir given in a dose of around 1 mg/kg daily in combination with other antiretrovirals.

Patients were divided into two cohorts, each including 23 patients (the first cohort included adolescents aged from 12 to 18 years and the second cohort included patients aged from 6 years to 12 years). The viral load after 24 weeks was fewer than 50 copies/ml in 70% of patients in the first cohort and 61% in the second cohort.

5.2 Pharmacokinetic properties

Tenofovir disoproxil
Tenofovir disoproxil fumarate is a water-soluble ester prodrug, which is rapidly converted *in vivo* to tenofovir and formaldehyde. Tenofovir is converted intracellularly to tenofovir monophosphate and to the active component, tenofovir diphosphate.

Absorption
Following oral administration of tenofovir disoproxil to HIV infected patients, tenofovir disoproxil is rapidly absorbed and converted to tenofovir. The oral bioavailability of tenofovir from tenofovir disoproxil in fasted patients was approximately 25%. Administration of tenofovir disoproxil with a high fat meal enhanced the oral bioavailability, with an increase in tenofovir AUC by approximately 40% and C_{max} by approximately 14%.

Distribution
Following intravenous administration the steady-state volume of distribution of tenofovir was estimated to be approximately 800 ml/kg. In vitro protein binding of tenofovir to plasma or serum protein was less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25.0 µg/ml.

Elimination
Tenofovir is primarily excreted by the kidney, both by filtration and an active tubular transport system with approximately 70-80% of the dose excreted unchanged in urine following intravenous administration. Total clearance has been estimated to be approximately 230 ml/h/kg (approximately 300 ml/min).

Renal clearance has been estimated to be approximately 160 ml/h/kg (approximately 210 ml/min), which is in excess of the glomerular filtration rate. This indicates that active tubular secretion is an important part of the elimination of tenofovir. Following oral administration the terminal half-life of tenofovir is approximately 12 to 18 hours.

Studies have established the pathway of active tubular secretion of tenofovir to be influx into proximal tubule cell by the human organic anion transporters (hOAT) 1 and 3 and efflux into the urine by the multidrug resistant protein 4 (MRP 4). In vitro studies have determined that neither tenofovir disoproxil nor tenofovir are substrates for the CYP450 enzymes.

Special populations
Age and gender: Limited data on the pharmacokinetics of tenofovir in women indicate no major gender effect.

Tenofovir exposure achieved in adolescent patients receiving oral daily doses of tenofovir disoproxil 245 mg was similar to exposures achieved in adults receiving once-daily doses of tenofovir disoproxil 245 mg.

Pharmacokinetic studies have not been performed in children or in the elderly (over 65 years). Pharmacokinetics have not been specifically studied in different ethnic groups.

Renal impairment: Pharmacokinetic parameters of tenofovir were determined following administration of a single dose of tenofovir disoproxil 245 mg to 40 non-HIV, non-HBV infected patients with varying degrees of renal impairment defined according to baseline creatinine clearance (CrCl) (normal renal function when CrCl > 80 ml/min; mild with CrCl = 50-79 ml/min; moderate with CrCl = 30-49 ml/min and severe with CrCl = 10-29 ml/min). Compared with patients with normal renal function, the mean (%CV) tenofovir exposure increased from 2.19 (12%) µg·h/ml in subjects with CrCl > 80 ml/min to respectively 3.06 (30%) µg·h/ml, 6.01 (42%) µg·h/ml and 15.99 (45%) µg·h/ml in patients with mild, moderate and severe renal impairment. The dosing

recommendations in patients with renal impairment, with increased dosing interval, are expected to result in higher peak plasma concentrations and lower C_{min} levels in patients with renal impairment compared with patients with normal renal function. The clinical implications of this are unknown.

In patients with end-stage renal disease (ESRD) (CrCl < 10 ml/min) requiring haemodialysis, between dialysis tenofovir concentrations substantially increased over 48 hours achieving a mean C_{max} of 1.03 µg/ml and a mean AUC0-48h of 42.86 µg·h/ml. It is recommended that the dosing interval for tenofovir disoproxil 245 mg is modified in patients with creatinine clearance < 50 ml/min or in patients who already have ESRD and require dialysis (see section 4.2).

The pharmacokinetics of tenofovir in non-haemodialysis patients with creatinine clearance < 10 ml/min and in patients with ESRD managed by peritoneal or other forms of dialysis have not been studied.

Hepatic impairment
A single 245 mg dose of tenofovir disoproxil was administered to non-HIV, non-HBV infected patients with varying degrees of hepatic impairment defined according to Child-Pugh-Turcotte (CPT) classification. Tenofovir pharmacokinetic parameters were not substantially altered in subjects with hepatic impairment suggesting that no dose adjustment is required in these subjects. The mean (%CV) tenofovir Cmax and $AUC_{0-\infty}$ values were 0.22 (34.8%) µg/ml and 2.05 (50.8%) µg·h/ml, respectively, in normal subjects compared with 0.29 (46.0%) µg/ml and 2.31 (43.5%) µg·h/ml in subjects with moderate hepatic impairment, and 0.31 (24.8%) µg/ml and 2.74 (44.0%) µg·h/ml in subjects with severe hepatic impairment.

Intracellular pharmacokinetics
Tenofovir diphosphate has an intracellular half-life of 10 hours in activated and 50 hours in resting peripheral blood mononuclear cells (PBMCs).

Lamivudine
Absorption and bioavailability
Lamivudine is rapidly absorbed following oral administration. Bioavailabiliy is between 80 and 85%.
Co-administration of lamivudine with food results in a delay of t_{max} and a lower C_{max} (decreased by 47%). However, the extent (based on the AUC) of lamivudine absorbed is not influenced.

Distribution
Intravenous studies with lamivudine showed that the mean apparent volume of distribution is 1.3l/kg. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin (< 36% serum albumin in vitro).

Metabolism
The active moiety, intracellular lamivudine triphosphate, has a prolonged terminal half-life in the cell (16 to 19 hours) compared to the plasma lamivudine half-life (5 to 7 hours). In 60 healthy adult volunteers, lamivudine 300 mg once daily has been demonstrated to be pharmacokinetically equivalent at steady-state to lamivudine 150 mg twice daily with respect to intracellular triphosphate AUC_{24} and C_{max}.

Metabolism of lamivudine is a minor route of elimination. Lamivudine is predominantly cleared unchanged by renal excretion. The likelihood of metabolic drug interactions with lamivudine is low due to the small extent of hepatic metabolism (5 - 10%) and low plasma protein binding.

Elimination
The observed lamivudine half-life of elimination is 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0.32l/h/kg, with predominantly renal clearance (> 70%), including tubular secretion through the organic cationic transport system.

Special populations

Renal impairment: Studies in patients with renal impairment show that lamivudine elimination is affected by renal dysfunction. Dose reduction is recommended for patients with creatinine clearance ≤50 ml/min (see section 4.2).

Dolutegravir
Dolutegravir pharmacokinetics are similar between healthy and HIV-infected subjects. The PK variability of dolutegravir is low to moderate. Following single dose administration of Dolutegravir 50 mg Tablets in healthy volunteers, the mean (± SD) dolutegravir Cmax was 2467 ng/ml (± 665) and the mean (SD) $AUC_{0\text{-}inf}$ was 53704 ng.hour/ml (± 18795) and AUC0-t was 50692 ng.hour/ml (±16877). The mean (± SD) dolutegravir t_{max} was 2.45 (± 1.29) hours.

The linearity of dolutegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of tablets, in general, dolutegravir exhibited non-linear pharmacokinetics with less than dose-proportional increases in plasma exposure from 2 to 100 mg; however, increase in dolutegravir exposure appears dose-dependent from 25 to 50 mg for the tablet formulation. With 50 mg twice daily, the exposure over 24 hours was approximately doubled compared to 50 mg once daily.

Absorption
Dolutegravir is rapidly absorbed following oral administration, with median T_{max} at 2 to 3 hours post dose for tablet formulation.

Food increased the extent and slowed the rate of absorption of dolutegravir. Bioavailability of dolutegravir depends on meal content: low, moderate, and high fat meals increased dolutegravir $AUC_{(0\text{-}\infty)}$ by 33%, 41%, and 66%, increased C_{max} by 46%, 52%, and 67%, prolonged T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively. These increases may be clinically relevant in the presence of certain integrase class resistance. Therefore, it is recommended that patients infected with HIV resistant to integrase inhibitors take dolutegravir with food.

The absolute bioavailability of dolutegravir has not been established.

Distribution
Dolutegravir is highly bound (> 99%) to human plasma proteins based on *in vitro* data. The apparent volume of distribution is 17 to 20 litres in HIV-infected patients, based on a population pharmacokinetic analysis. Binding of dolutegravir to plasma proteins is independent of dolutegravir concentration. Total blood and plasma drug-related radioactivity concentration ratios averaged between 0.441 to 0.535, indicating minimal association of radioactivity with blood cellular components. The unbound fraction of dolutegravir in plasma is increased at low levels of serum albumin (< 35 g/litre) as seen in subjects with moderate hepatic impairment.

Dolutegravir is present in cerebrospinal fluid (CSF). In 13 treatment-naïve patients on a stable dolutegravir plus abacavir/lamivudine regimen, dolutegravir concentration in CSF averaged 18 ng/ml (comparable to unbound plasma concentration, and above the IC_{50}).

Dolutegravir is present in the female and male genital tract. AUC in cervicovaginal fluid, cervical tissue and vaginal tissue were 6–10% of those in corresponding plasma at steady state. AUC in semen was 7% and 17% in rectal tissue of those in corresponding plasma at steady state.

Biotransformation
Dolutegravir is primarily metabolized through glucuronidation via UGT1A1 with a minor CYP3A component. Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged active substance is low (< 1% of the dose). Of the total oral dose, 53% is excreted unchanged in the faeces. It is unknown if all or part of this is due to unabsorbed active substance or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. Excretion in the urine accounts for 33% of the total oral dose as ether glucuronide of dolutegravir (18.9%

of total dose), N-dealkylation metabolite (3.6%), and a metabolite formed by oxidation at the benzylic carbon (3.0%).

Drug interactions
In vitro, dolutegravir demonstrated no direct, or weak inhibition (IC_{50}> 50 μM) of the enzymes cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7, or the transporters P-gp, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, MATE2-K, MRP2 or MRP4. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. Therefore, dolutegravir is not expected to affect the pharmacokinetics of medicines that are substrates of major enzymes or transporters.

In vitro, dolutegravir was not a substrate of human OATP 1B1, OATP 1B3 or OCT 1.

Elimination
Dolutegravir has a terminal half-life of about 14 hours. The apparent oral clearance (CL/F) is approximately 1 litre/hour in HIV-infected patients based on a population pharmacokinetic analysis.

Pharmacokinetic/pharmacodynamic relationship

A dose-ranging trial involving dolutegravir monotherapy found rapid and dose-dependent antiviral activity, with mean decline in HIV-1 RNA of 2.5 log10 at day 11 for 50-mg dose. This antiviral response was maintained for 3 to 4 days after the last dose in the 50 mg group.

PK/PD modelling using pooled data from clinical studies in integrase-inhibitor-resistant patients suggest that increasing the dose from 50 mg twice daily to 100 mg twice daily may increase the effectiveness of dolutegravir in patients with integrase-inhibitor-resistance and limited treatment options due to advanced multi-class resistance. The proportion of responders (HIV-1 RNA < 50 copies/mL) at week 24 was predicted to increase around 4–18% in the subjects with Q148 and two or more secondary mutations from G140A/C/S, E138A/K/T, L74I. Although these simulated results have not been confirmed in clinical trials, this high dose may be considered in the presence of the Q148 and two or more secondary mutations from G140A/C/S, E138A/K/T, L74I in patients with overall limited treatment options due to advanced multi-class resistance. There are no clinical data on the safety or efficacy of the 100 mg twice daily dose. Co-treatment with atazanavir increases the exposure of dolutegravir markedly, and should not be used in combination with this high dose, since safety with the resulting dolutegravir exposure has not been established.

Special populations
Children
The pharmacokinetics of dolutegravir in 10 antiretroviral treatment-experienced HIV-1 infected adolescents (12 up to 18 years of age) found that a dose of dolutegravir 50 mg once daily resulted in dolutegravir exposure comparable to that in adults who received a dose of 50 mg once daily. The pharmacokinetics in 11 children aged 6 to 12 years found that 25 mg once daily in patients weighing at least 20 kg and 35 mg once daily in patients weighing at least 30 kg resulted in dolutegravir exposure comparable to adults. In addition, population PK modelling and simulation analyses showed dosing on a weight-band basis (20, 25, 35, and 50 mg) in children of at least 6 years of age weighing at least 15 kg provides comparable exposure to those in adults (50 mg), with the lowest weight band of 15–20 kg corresponding to 20 mg daily.

Elderly
Population pharmacokinetic analysis of dolutegravir using data in HIV-1 infected adults showed that there was no clinically relevant effect of age on dolutegravir exposure.

Pharmacokinetic data for dolutegravir in subjects aged over 65 years are limited.

Renal impairment
Renal clearance of unchanged active substance is a minor pathway of elimination for dolutegravir. Pharmacokinetics of dolutegravir were studied in adults with severe renal impairment (creatinine clearance less than 30 ml/minute) and matched healthy controls. The exposure to dolutegravir was decreased by approximately 40% in subjects with severe renal impairment. The mechanism for the decrease is unknown. No dosage adjustment is considered necessary for patients with renal impairment. Dolutegravir has not been studied in patients on dialysis.

Hepatic impairment
Dolutegravir is primarily metabolised and eliminated by the liver. When a single dose of 50 mg of dolutegravir was given to 8 subjects with moderate hepatic impairment (Child-Pugh class B) and to 8 matched healthy adult controls the total dolutegravir concentration in plasma was similar. However, there was a 1.5- to 2-fold increase in unbound dolutegravir in moderate hepatic impairment compared to healthy controls. No dosage adjustment is considered necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of dolutegravir has not been studied.

Polymorphisms in drug metabolising enzymes
Common polymorphisms in drug metabolising enzymes have not been found to alter dolutegravir pharmacokinetics to a clinically meaningful extent. In a meta-analysis using pharmacogenomics, subjects with UGT1A1 genotypes had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1.

Gender
Population PK analyses using pooled pharmacokinetic data from adult trials revealed no clinically relevant effect of gender on the exposure of dolutegravir.

Race
Population PK analyses using pooled pharmacokinetic data from adult trials revealed no clinically relevant effect of race on the exposure of dolutegravir.

Co-infection with Hepatitis B or C
Population pharmacokinetic analysis indicated that hepatitis C virus co-infection had no clinically relevant effect on the exposure to dolutegravir. There are limited data on subjects with hepatitis B co-infection.

5.3 Preclinical safety data

Tenofovir disoproxil
Preclinical studies conducted in rats, dogs and monkeys revealed target organ effects in gastrointestinal tract, kidney, bone and a decrease in serum phosphate concentration. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (rats and dogs). Findings in the rat and monkey studies indicated that there was a substance-related decrease in intestinal absorption of phosphate with potential secondary reduction in bone mineral density. However, no conclusion could be drawn on the mechanism(s) underlying these toxicities. Reproductive studies were conducted in rats and rabbits. There were no effects on mating or fertility parameters or on any pregnancy or foetal parameter. There were no gross foetal alterations of soft or skeletal tissues.

Tenofovir disoproxil reduced the viability index and weight of pups in peripost natal toxicity studies. Genotoxicity studies have shown that tenofovir disoproxil was negative in the in vivo mouse bone marrow micronucleus assay but was positive for inducing forward mutations in the in vitro L5178Y mouse lymphoma cell assay in the presence or absence of S9 metabolic activation. Tenofovir disoproxil was positive in the Ames test (strain TA 1535) in two out of three studies, once in the presence of S9 mix (6.2- to 6.8-fold increase) and

once without S9 mix. Tenofovir disoproxil was also weakly positive in an in vivo / in vitro unscheduled DNA synthesis test in primary rat hepatocytes.

Tenofovir disoproxil did not show any carcinogenic potential in a long-term oral carcinogenicity study in rats. A long-term oral carcinogenicity study in mice showed a low incidence of duodenal tumours, considered likely related to high local concentrations of tenofovir disoproxil in the gastrointestinal tract at a dose of 600 mg/kg/day. While the mechanism of tumour formation is uncertain, the findings are unlikely to be of relevance to humans.

Lamivudine

Non-clinical data on lamivudine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, carcinogenic potential and toxicity to reproduction and development. Lamivudine was not mutagenic in bacterial tests, but showed activity in an in vitro cytogenetic assay and the mouse lymphoma assay. Lamivudine was not genotoxic in vitro at doses that gave plasma concentrations around 40-50 times higher than the anticipated clinical plasma levels. As the in vitro mutagenic activity of lamivudine could not be confirmed in in vivo tests, it is concluded that lamivudine should not represent a genotoxic hazard to patients undergoing treatment.

Dolutegravir

Dolutegravir was not mutagenic or clastogenic in bacteria and cultured mammalian cells, and an *in vivo* rodent micronucleus assay. Dolutegravir was not carcinogenic in long-term studies in the mouse and rat.

Dolutegravir did not affect male or female fertility in rats at doses up to 24 times the 50 mg twice daily human clinical exposure based on AUC. Oral administration of dolutegravir to pregnant rats at doses up to 27 times the 50 mg twice daily human clinical exposure based on AUC from days 6 to 17 of gestation did not cause maternal toxicity, developmental toxicity or teratogenicity.

Oral administration of dolutegravir to pregnant rabbits at doses up to 1000 mg/kg daily from days 6 to 18 of gestation did not elicit developmental toxicity or teratogenicity (0.40 times the 50 mg twice daily human clinical exposure based on AUC). In rabbits, maternal toxicity (decreased food consumption, reduced urine or feaces, suppressed bodyweight gain) was observed at 1000 mg/kg (0.40 times the 50 mg twice daily human clinical exposure based on AUC).

In a juvenile toxicity study in rats, dolutegravir administration resulted in two pre-weanling deaths at 75 mg/kg daily. Over the pre-weaning period, mean bodyweight gain was decreased and the decrease persisted throughout the entire study for females during the post-weaning period. The systemic exposure at this dose (based on AUC) to dolutegravir was about 17 to 20-fold higher than in humans at the recommended paediatric exposure. No new target organs were identified in juveniles compared to adults. In the rat prenatal and postnatal development study, decreased bodyweight of the developing offspring was observed during lactation at a maternally toxic dose (about 27 times human exposure at the maximum recommended dose).

The primary effect of dolutegravir of prolonged daily treatment (up to 26 weeks in rats and up to 38 weeks in monkeys) with high doses of dolutegravir was gastrointestinal intolerance or irritation in rats and monkeys at doses that produce systemic exposures approximately 21 and 0.82 times the 50 mg twice daily human clinical exposure based on AUC, respectively. Because gastrointestinal intolerance is considered to be due to local effects of the active substance, comparison based on bodyweight or on body surface area is appropriate for this toxicity. Gastrointestinal intolerance in monkeys occurred at 15 times the human mg/kg equivalent dose (based on a 50-kg human), and 5 times the human mg/m2 equivalent dose for a clinical dose of 50 mg twice daily.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Core tablet:

Microcrystalline cellulose, Sodium Starch Glycolate, crospovidone, povidone, lactose, croscarmellose sodium, pregelatinised starch, Colloidal Silicon Dioxide, mannitol, sodium stearyl fumarate, magnesium stearate

Film coat:
Polyvinyl alcohol (partly hydrolysed), macrogol/PEG, titanium dioxide 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. Keep out of the reach and sight of children.

6.5 Nature and contents of container

28 Tablets packed in 100 cc, white opaque HDPE container closed with 38mm white opaque polypropylene ribbed screw cap with liner (containing 3 g molecular sieve canister).

30 Tablets packed in 100 cc, white opaque HDPE container closed with 38mm white opaque polypropylene ribbed screw cap with liner (containing 3 g molecular sieve canister).

56 Tablets packed in 150 cc, white opaque HDPE container closed with 38mm white opaque polypropylene ribbed screw cap with liner (containing 3 g molecular sieve canister).

60 Tablets packed in 150 cc, white opaque HDPE container closed with 38mm white opaque polypropylene ribbed screw cap with liner (containing 3 g molecular sieve canister).

84 Tablets packed in 250 cc, white opaque HDPE container closed with 53mm white opaque polypropylene ribbed screw cap with liner (containing 3 g molecular sieve canister).

90 Tablets packed in 250 cc, white opaque HDPE container closed with 53mm white opaque polypropylene ribbed screw cap with liner (containing 3 g molecular sieve canister).

6.6 Special precautions for disposal.

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

7. APPLICANT/SUPPLIER

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8. WHO PREQUALIFICATION REFERENCE NUMBER

Not Applicable

9. DATE OF PREQUALIFICATION

Not Applicable

10. DATE OF REVISION OF THE TEXT:

None