1.3 Product Information

1.3.1 Summary of product characteristics (SmPC)

Summary of product characteristics of Dolutegravir, Lamivudine & Tenofovir Disoproxil Fumarate 50/300/300 mg Tablets is enclosed overleaf.

SUMMARY OF PRODUCT CHARACTERISTICS

DOLUTEGRAVIR (AS SODIUM)/ LAMIVUDINE/ TENOFOVIR DISOPROXIL FUMARATE 50 MG/300 MG/300 MG

1. NAME OF THE MEDICINAL PRODUCT

Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film Coated Tablet Contains:
Dolutegravir Sodium equivalent to Dolutegravir……50 mg
Lamivudine USP…….……...300 mg
Tenofovir Disoproxil Fumarate.....300 mg, which is equivalent to 245 mg of Tenofovir Disoproxil

For full list of excipients, see section **6.1**

3. PHARMACEUTICAL FORM

Film coated Tablets

4. CLINICAL PARTICULARS[1,2,3,4,5]

4.1 Therapeutic indications[1, 2]

Dolutegravir/lamivudine/tenofovir disoproxil fumarate 50/300/300 mg) are indicated for the treatment of human immunodeficiency virus (HIV) infection in adults and adolescents (aged 12 years and above) weighing at least 30 kg.

Consideration should be given to official treatment guidelines for HIV-1 infection, e.g. those by WHO.

For use of antiretroviral agents for post-exposure prophylaxis the most recent official guidelines, e.g. those by WHO should be consulted.

4.2 Posology and method of administration[1, 2]

Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets should be prescribed by a health care provider experienced in the management of HIV infection.

Dose

Adults
The dose of Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets is one tablet once daily.

Adolescents weighing at least 30 kg
The dose in adolescents weighing at least 30 kg with HIV-1 infection not resistant to integrase inhibitors is one tablet of Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets once daily. There is insufficient information on the use of dolutegravir in adolescents with HIV-1 infection resistant to integrase inhibitors.

Children
Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets should not be used in children weighing less than 30 kg since appropriate dose adjustments cannot be achieved with this product. Separate formulations containing lower amounts of dolutegravir, tenofovir disoproxil or lamivudine are required.

Elderly
Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets should be administered with caution to elderly patients.

Renal impairment

- *Mild renal impairment (creatinine clearance 50-80 mL/minute):*

No dose adjustment is required in patients with mild renal impairment.

- *Moderate or severe renal impairment (creatinine clearance <50 mL/minute):*

Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets is not recommended for use in patients with creatinine clearance < 50 ml/minute, as appropriate dose adjustments are not possible. For these patients, separate formulations of dolutegravir, lamivudine and tenofovir disoproxil should be used.

Hepatic impairment

No dose adjustment is needed for patients with mild or moderate hepatic impairment (Child-Pugh grade A or B). No data are available for dolutegravir in patients with severe hepatic impairment (Child-Pugh grade C); therefore, Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets should be used with caution in these patients.

Discontinuation of therapy
If Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets is discontinued in patients co-infected with HIV and hepatitis B virus (HBV), these patients should be closely monitored for evidence of exacerbation of hepatitis.

Missed dose
If the patient misses a dose of Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets, the patient should take it as soon as possible, provided the next dose is not due within 12 hours. If the next dose is due within 12 hours, the patient should not take the missed dose and take the next dose at the usual time.

Dose adjustments
Where discontinuation of therapy with one of the components of Dolutegravir/lamivudine/tenofovir disoproxil fumarate 50/300/300 mg is indicated or where dose modification is necessary, separate preparations of dolutegravir, lamivudine and tenofovir disoproxil should be used. Please refer to the individual summary of product characteristics for these medicinal products.

When the patient's HIV-1 infection is known or suspected to be resistant to integrase inhibitors, additional doses of dolutegravir are necessary. Please refer to the summary of product characteristics of dolutegravir for further information.

Method of administration

Oral use.

It is recommended that Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets be swallowed whole with water.
Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets can usually be taken with food or between meals.

If the HIV-1 is resistant to integrase inhibitors, Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets should preferably be taken with food to increase absorption (particularly in patients with Q148 mutations).

4.3 Contraindications[3,4,5]

- Hypersensitivity to dolutegravir, lamivudine, tenofovir disoproxil or to any of the excipients listed in section **6.1.**
- Medicinal products with narrow therapeutic windows that are substrates of organic cation transporter 2 (OCT2), including but not limited to fampridine (also known as dalfampridine (see section **4.5**)

Please see section **4.4** and **4.5** for further information on drugs that are not recommended with Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets due to individual components.

4.4 Special warnings and precautions for use[3,4,5]

Safety and efficacy of the individual active ingredients in various antiretroviral combination regimens with similar dosages as contained in Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets have been established in reported clinical studies for the treatment of HIV patients. However, safety and efficacy of the fixed-drug combination as in Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets for the treatment of HIV have not been established in clinical studies. The complete package inserts of the other medicines used in this combination should be consulted before initiation of therapy.

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.

Dolutegravir, Lamivudine and Tenofovir disoproxil fumarate

Immune Reactivation Syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterium infections, and *Pneumocystis jirovecii* pneumonia (often referred to as PCP). Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the

reported time to onset is more variable and these events can occur many months after initiation of treatment.

Liver biochemistry elevations consistent with immune reconstitution syndrome were reported in some hepatitis B and/or C co-infected patients at the start of dolutegravir therapy. Monitoring of liver biochemistry parameters is recommended in patients with hepatitis B and/or C co-infection. Particular diligence should be applied in initiating or maintaining effective hepatitis B therapy (referring to treatment guidelines) when starting therapy with dolutegravir in hepatitis B co-infected patients (see section **4.8**).

Opportunistic infections

Patients should be advised that dolutegravir, lamivudine or any other antiretroviral therapy does not cure HIV infection and that they may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

Mitochondrial dysfunction following exposure in utero

Nucleoside and nucleotide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or post-natally to nucleoside analogues; these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactatemia, hyperlipasemia). These events have often been transitory. Late-onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently not known. These findings should be considered for any child exposed *in utero* to nucleoside and nucleotide analogues, who presents with severe clinical findings of unknown etiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Osteonecrosis

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

Liver disease

Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Triple nucleoside therapy

There have been reports of a high rate of virological failure and of emergence of resistance at an early stage when lamivudine was combined with tenofovir disoproxil fumarate and abacavir as well as with tenofovir disoproxil fumarate and didanosine as a once daily regimen.

Dolutegravir

Integrase class resistance of particular concern

The decision to use Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets which contains dolutegravir, in the presence of integrase class resistance should take into account that the activity of dolutegravir is considerably compromised for viral strains harbouring Q148+≥2 secondary mutations from G140A/C/S, E138A/K/T, L74I (see section **5.1**). To what extent dolutegravir provides added efficacy in the presence of such integrase class resistance is uncertain (see section **5.2**).

Hypersensitivity reactions

Hypersensitivity reactions have been reported with dolutegravir, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including severe liver reactions. Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets and other suspect medicinal products should be discontinued immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by raised liver enzymes, fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, eosinophilia, angioedema). Clinical status including liver aminotransferases and bilirubin should be monitored. Delay in stopping treatment with Dolutegravir (sodium)/lamivudine/tenofovir

disoproxil fumarate 50mg/300mg/300mg tablets or other suspect active substances after the onset of hypersensitivity may result in a life-threatening allergic reaction.

Drug interactions
Factors that decrease dolutegravir exposure should be avoided in the presence of integrase class resistance. This includes co-administration with medicinal products that reduce dolutegravir exposure (e.g. magnesium/ aluminium-containing antacid, iron and calcium supplements, multivitamins and inducing agents, etravirine (without boosted protease inhibitors), tipranavir/ritonavir, rifampicin, St. John's wort and certain anti-epileptic medicinal products) (see section **4.5**).

Dolutegravir increased metformin concentrations. A dose adjustment of metformin should be considered when starting and stopping co-administration of dolutegravir with metformin, to maintain glycaemic control (see section **4.5**). Metformin is eliminated renally and, therefore, it is of importance to monitor renal function when co-treated with dolutegravir. This combination may increase the risk for lactic acidosis in patients with moderate renal impairment [stage 3a creatinine clearance (CrCl) 45– 59 mL/min] and a cautious approach is recommended. Reduction of the metformin dose should be highly considered.

Lamivudine and dolutegravir
The two-drug regimen of dolutegravir 50 mg once daily and lamivudine 300 mg once daily is only suitable for the treatment of HIV-1 infection where there is no known or suspected resistance to the integrase inhibitor class, or to lamivudine.

<u>Lamivudine</u>

Renal impairment
In patients with moderate to severe renal impairment, the terminal plasma half-life of lamivudine is increased due to decreased clearance, therefore the dose should be adjusted.

Pancreatitis
Cases of pancreatitis have been reported rarely. However it is not clear whether these cases were due to the antiretroviral treatment or to the underlying HIV disease. Treatment with Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur.

Liver disease
If lamivudine is discontinued in patients co-infected with hepatitis B virus, periodic monitoring of liver function tests and markers of HBV replication is recommended, as withdrawal of lamivudine may result in an acute exacerbation of hepatitis.

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy, and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered (see section **4.8**).

If lamivudine is discontinued in patients co-infected with hepatitis B virus, periodic monitoring of liver function tests and markers of HBV replication is recommended, as withdrawal of lamivudine may result in an acute exacerbation of hepatitis.

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy, and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered (see **section 4.8**).

Paediatric population
Lower rates of virologic suppression and more frequent viral resistance have been reported in children receiving the oral solution of lamivudine as compared to those receiving the tablet formulation. Whenever possible in children, lamivudine as tablet formulation should preferably be used.

Drug Interactions
Lamivudine should not be taken with any other medicinal products containing lamivudine or medicinal products containing emtricitabine (see section **4.5**).

The combination of lamivudine with cladribine is not-recommended (see section **4.5**).

Tenofovir disoproxil fumarate

Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets are not indicated for the treatment of chronic hepatitis B infection. The safety and efficacy of Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets have not been established for the treatment of patients co-infected with HBV and HIV.

Renal and bone effects in adult population

Renal effects in adult population

Tenofovir is principally eliminated via the kidney. Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil in clinical practice (see section **4.8**).

Renal monitoring

It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy with tenofovir disoproxil and renal function (creatinine clearance and serum phosphate) is also monitored after two to four weeks of treatment, after three months of treatment and every three to six months thereafter in patients without renal risk factors. In patients at risk for renal impairment, a more frequent monitoring of renal function is required.

Renal management

If serum phosphate is < 1.5 mg/dL (0.48 mmol/L) or creatinine clearance is decreased to < 50 mL/min in any adult patient receiving tenofovir disoproxil, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations. Consideration should also be given to interrupting treatment with tenofovir disoproxil in adult patients with creatinine clearance decreased to < 50 mL/min or decreases in serum phosphate to < 1.0 mg/dL (0.32 mmol/L). Interrupting treatment with tenofovir disoproxil should also be considered in case of progressive decline of renal function when no other cause has been identified.

Co-administration and risk of renal toxicity

Use of Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets (due to tenofovir disoproxil), should be avoided with concurrent or recent use of a nephrotoxic medicinal product (e.g. aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2). If concomitant use of Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets nephrotoxic agents is unavoidable, renal function should be monitored weekly.

Cases of acute renal failure after initiation of high dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) have been reported in patients treated with tenofovir disoproxil and with risk factors for renal dysfunction. If Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets is co-administered with an NSAID, renal function should be monitored adequately.

A higher risk of renal impairment has been reported in patients receiving tenofovir disoproxil in combination with a ritonavir or cobicistat boosted protease inhibitor. A close monitoring of renal function is required in these patients (see section **4.5**).

Tenofovir disoproxil has not been clinically evaluated in patients receiving medicinal products which are secreted by the same renal pathway, including the transport proteins human organic anion transporter (hOAT) 1 and 3 or MRP 4 (e.g. cidofovir, a known nephrotoxic medicinal product). These renal transport proteins may be responsible for tubular secretion and in part, renal elimination of tenofovir and cidofovir. Consequently, the pharmacokinetics of these medicinal products which are secreted by the same renal pathway including transport proteins hOAT 1 and 3 or MRP 4, might be modified if they are co-administered. Unless clearly necessary, concomitant use of these medicinal products which are secreted by the same renal pathway is not recommended, but if such use is unavoidable, renal function should be monitored weekly (see section **4.5**).

Adult patients with creatinine clearance < 50 ml/min, including haemodialysis patients:

There are limited data on the safety and efficacy of tenofovir disoproxil in patients with impaired renal function. Therefore, tenofovir disoproxil should only be used if the potential benefits of treatment are considered to outweigh the potential risks. In patients with severe renal impairment (creatinine clearance < 30 ml/min) and in patients who require haemodialysis use of tenofovir disoproxil is not recommended. If no alternative treatment is available, the dosing interval must be adjusted and renal function should be closely monitored.

Bone effects

Bone abnormalities such as osteomalacia which can manifest as persistent or worsening bone pain and, which can infrequently contribute to fractures may be associated with tenofovir disoproxil-induced proximal renal tubulopathy (see section **4.8**).

Tenofovir disoproxil may also cause a reduction in bone mineral density (BMD). In HIV infected patients, in a reported 144-week controlled clinical study that compared tenofovir disoproxil with stavudine in combination with lamivudine and efavirenz in antiretroviral-naïve adult patients, small decreases in bone mineral density (BMD) of the hip and spine were reported in both treatment groups. Decreases in BMD of spine and changes in bone biomarkers from baseline were significantly greater in the tenofovir disoproxil treatment group at 144 weeks. Decreases in BMD of hip were significantly greater in this group until 96 weeks. However, there was no increased risk of fractures or evidence for clinically relevant bone abnormalities over 144 weeks.

In other reported clinical studies, the most pronounced decreases in BMD were reported in patients treated with tenofovir disoproxil as part of a regimen containing a boosted protease

inhibitor. Alternative treatment regimens other should be considered for patients with osteoporosis that are at a high risk for fractures.

If bone abnormalities are suspected or detected, then appropriate consultation should be obtained.

Renal and bone effects in paediatric population

There are uncertainties associated with the long term effects of bone and renal toxicity. Moreover, the reversibility of renal toxicity cannot be fully ascertained. Therefore, a multidisciplinary approach is recommended to adequately weigh on a case by case basis the benefit/risk balance of treatment, decide the appropriate monitoring during treatment (including decision for treatment withdrawal) and consider the need for supplementation.

Renal effects
Renal adverse reactions consistent with proximal renal tubulopathy have been reported in HIV-1 infected paediatric patients aged 2 to < 12 years in a reported clinical study with tenofovir disoproxil.

Renal monitoring
Renal function (creatinine clearance and serum phosphate) should be evaluated prior to treatment, and monitored during treatment as in adults (see above).

Renal management
If serum phosphate is confirmed to be < 3.0 mg/dL (0.96 mmol/L) in any paediatric patient receiving tenofovir disoproxil, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations. If renal abnormalities are suspected or detected then consultation with a nephrologist should be obtained to consider interruption of tenofovir disoproxil treatment. Interrupting treatment with tenofovir disoproxil should also be considered in case of progressive decline of renal function when no other cause has been identified.

Co-administration and risk of renal toxicity
The same recommendations apply as in adults (see above).

Renal impairment
The use of tenofovir disoproxil is not recommended in paediatric patients with renal impairment. Tenofovir disoproxil should not be initiated in paediatric patients with renal impairment and should be discontinued in paediatric patients who develop renal impairment during tenofovir disoproxil therapy.

Bone effects
Tenofovir disoproxil may cause a reduction in BMD. The effects of tenofovir disoproxil-associated changes in BMD on long-term bone health and future fracture risk are currently unknown. If bone abnormalities are detected or suspected in paediatric patients, consultation with an endocrinologist and/or nephrologist should be obtained.

Liver disease
Reported safety and efficacy data are very limited in liver transplant patients.

There are limited reported data on the safety and efficacy of tenofovir disoproxil in HBV infected patients with decompensated liver disease and who have a Child-Pugh-Turcotte (CPT) score > 9. These patients may be at higher risk of experiencing serious hepatic or renal adverse reactions. Therefore, hepatobiliary and renal parameters should be closely monitored in this patient population.

Exacerbations of hepatitis
Flares on treatment: Spontaneous exacerbations in chronic hepatitis B are relatively common and are characterised by transient increases in serum ALT. After initiating antiviral therapy, serum ALT may increase in some patients (see section **4.8**). In patients with compensated liver disease, these increases in serum ALT are generally not accompanied by an increase in serum bilirubin concentrations or hepatic decompensation. Patients with cirrhosis may be at a higher risk for hepatic decompensation following hepatitis exacerbation, and therefore should be monitored closely during therapy.

Flares after treatment discontinuation: Acute exacerbation of hepatitis has also been reported in patients who have discontinued hepatitis B therapy. Post-treatment exacerbations are usually associated with rising HBV DNA, and the majority appears to be self-limited. However, severe exacerbations, including fatalities, have been reported. Hepatic function should be monitored at repeated intervals with both clinical and laboratory follow-up for at least 6 months after discontinuation of hepatitis B therapy. If appropriate, resumption of hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Liver flares are especially serious, and sometimes fatal in patients with decompensated liver disease.

Co-infection with hepatitis C or D

There are no data on the efficacy of tenofovir in patients co-infected with hepatitis C or D virus.

Co-infection with HIV-1 and hepatitis B
Due to the risk of development of HIV resistance, tenofovir disoproxil should only be used as part of an appropriate antiretroviral combination regimen in HIV/HBV co-infected patients. Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered. However, it should be noted that increases of ALT can be part of HBV clearance during therapy with tenofovir.

Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets are not indicated for the treatment of chronic hepatitis B infection. The safety and efficacy of Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets have not been established for the treatment of patients co-infected with HBV and HIV.

Use with certain hepatitis C virus antiviral agents
Co-administration of tenofovir disoproxil with ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir has been reported to increase plasma concentrations of tenofovir, especially when used together with an HIV regimen containing tenofovir disoproxil and a pharmacokinetic enhancer (ritonavir or cobicistat). The safety of tenofovir disoproxil in the setting of ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with co-administration of ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir with tenofovir disoproxil given in conjunction with a boosted HIV protease inhibitor (e.g. atazanavir or darunavir) should be considered, particularly in patients at increased risk of renal dysfunction. Patients receiving ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir concomitantly with tenofovir disoproxil and a boosted HIV protease inhibitor should be monitored for adverse reactions related to tenofovir disoproxil.

Co-administration of other medicinal products
- Tenofovir disoproxil should not be administered concomitantly with other medicinal products containing tenofovir disoproxil or tenofovir alafenamide.
- Tenofovir disoproxil should not be administered concomitantly with adefovir dipivoxil.
- Co-administration of tenofovir disoproxil and didanosine is not recommended.

Elderly

Tenofovir disoproxil has not been studied in patients over the age of 65. Elderly patients are more likely to have decreased renal function; therefore caution should be exercised when treating elderly patients with Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets as this medicine contains tenofovir disoproxil.

Excipients

Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets contains less than 1 mmol sodium (23 mg) per tablet, that is to say is essentially 'sodium free'.

Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets contains mannitol. It may have mild laxative effect.

4.5 Interaction with other medicinal products and other forms of interaction[3,4,5]

No drug interaction studies have been reported using this fixed-dose combination (FDC). Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets contain dolutegravir, lamivudine and tenofovir; therefore any interactions identified for these individually may occur with this FDC.

Interactions relevant to Dolutegravir

Effect of other agents on the pharmacokinetics of dolutegravir

All factors that decrease dolutegravir exposure should be avoided in the presence of integrase class resistance. Dolutegravir is eliminated mainly through metabolism by UGT1A1. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP; therefore medicinal products that induce those enzymes may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir. Co-administration of dolutegravir and other medicinal products that inhibit these enzymes may increase dolutegravir plasma concentration.

The absorption of dolutegravir is reduced by certain anti-acid agents.

Effect of dolutegravir on the pharmacokinetics of other agents

In vivo, dolutegravir did not reportedly have an effect on midazolam, a CYP3A4 probe. Based on reported *in vivo* and/or *in vitro* data, dolutegravir is not expected to affect the pharmacokinetics of medicinal products that are substrates of any major enzyme or transporter such as CYP3A4, CYP2C9 and P-gp (see section **5.2**).

In vitro, dolutegravir has been reported to inhibit the renal organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter (MATE) 1. *In vivo*, a 10-14% decrease of creatinine clearance (secretory fraction is dependent on OCT2 and MATE-1 transport) was

observed in patients. *In vivo*, dolutegravir may increase plasma concentrations of medicinal products in which excretion is dependent upon OCT2 or MATE-1 (e.g. fampridine [also known as dalfampridine], metformin).

In vitro, dolutegravir reportedly inhibited the renal uptake transporters, organic anion transporters (OAT1) and OAT3. Based on the lack of effect on the *in vivo* pharmacokinetics of the OAT substrate tenofovir, *in vivo* inhibition of OAT1 is unlikely. Inhibition of OAT3 has not been reported *in vivo*. Dolutegravir may increase plasma concentrations of medical products in which excretion is dependent upon OAT3.

Reported and theoretical interactions with selected antiretrovirals and non-antiretroviral medicinal products are listed in **Table** below (increased exposure is indicated as "↑", decreased exposure 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 "Cτ"). The table should not be considered exhaustive but is representative of the classes studied.

Table: Interactions between dolutegravir and other medicinal products

Medicinal products by therapeutic area	**Interactions geometric mean change (%)**	**Recommendations concerning co-administration**
HIV-1 Antiviral Agents		
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Etravirine without boosted protease inhibitors	Dolutegravir ↓ AUC ↓ 71% C_{max} ↓ 52% Cτ ↓ 88% Etravirine ↔ (induction of UGT1A1 and CYP3A enzymes)	Etravirine without boosted protease inhibitors was reported to decreased plasma dolutegravir concentration. The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with etravirine without boosted protease inhibitors. Dolutegravir should not be used with etravirine without co- administration of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir in integrase inhibitor-resistant patients.
Lopinavir/ritonavir + etravirine	Dolutegravir ↔ AUC ↑ 11% C_{max} ↑ 7% Cτ ↑ 28% LPV ↔ RTV ↔	No dose adjustment is necessary.
Darunavir/ritonavir + etravirine	Dolutegravir ↓ AUC ↓ 25% C_{max} ↓ 12% Cτ ↓ 36% DRV ↔ RTV ↔	No dose adjustment is necessary

Efavirenz	Dolutegravir ↓ AUC ↓ 57% C_{max} ↓ 39% Cτ ↓ 75% Efavirenz ↔ (historical controls) (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with efavirenz. . In paediatric patients the weight-based once daily dose should be administered twice daily. In the presence of integrase class resistance alternative combinations that do not include efavirenz should be considered (see section **4.4**).
Nevirapine	Dolutegravir ↓ (Not reported, a similar reduction in exposure as reported with efavirenz is expected, due to induction)	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with nevirapine. . In paediatric patients the weight-based once daily dose should be administered twice daily. In the presence of integrase class resistance alternative combinations that do not include nevirapine should be considered (see section **4.4**).
Rilpivirine	Dolutegravir ↔ AUC ↑ 12% C_{max} ↑ 13% Cτ ↑ 22% Rilpivirine ↔	No dose adjustment is necessary.
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
Tenofovir	Dolutegravir ↔ AUC ↑ 1% C_{max} ↓ 3% Cτ ↓ 8% Tenofovir ↔	No dose adjustment is necessary.
Protease Inhibitors (PIs)		
Atazanavir	Dolutegravir ↑ AUC ↑ 91% C_{max} ↑ 50% Cτ ↑ 180% Atazanavir ↔ (historical controls) (inhibition of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary. Dolutegravir should not be dosed higher than 50 mg twice daily in combination with atazanavir (see section **5.2**) due to lack of data.
Atazanavir/ritonavir	Dolutegravir ↑ AUC ↑ 62% C_{max} ↑ 34% Cτ ↑ 121% Atazanavir ↔	No dose adjustment is necessary. Dolutegravir should not be dosed higher than 50 mg twice daily in combination with atazanavir (see section **5.2**) due to lack of data.

	Ritonavir ↔ (inhibition of UGT1A1 and CYP3A enzymes)	
Tipranavir/ritonavir (TPV+RTV)	Dolutegravir ↓ AUC ↓ 59% C_{max} ↓ 47% Cτ ↓ 76% (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with tipranavir/ritonavir. In the presence of integrase class resistance this combination should be avoided (see section **5.2**)
Fosamprenavir/ritonavir (FPV+RTV)	Dolutegravir ↓ AUC ↓ 35% C_{max} ↓ 24% Cτ ↓ 49% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary in the absence of integrase class resistance. In the presence of integrase class resistance alternative combinations that do not include fosamprenavir/ritonavir should be considered.
	(Not reported)	
Darunavir/ritonavir	Dolutegravir ↓ AUC ↓ 22% C_{max} ↓ 11% C_{24} ↓ 38% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Lopinavir/ritonavir	Dolutegravir ↔ AUC ↓ 4% C_{max} ↔ 0% C_{24} ↓ 6%	No dose adjustment is necessary.
Other Antiviral agents		
Daclatasvir	Dolutegravir ↔ AUC ↑ 33% C_{max} ↑ 29% Cτ ↑ 45% Daclatasvir ↔	Daclatasvir did not change dolutegravir plasma concentration to a clinically relevant extent. Dolutegravir did not change daclatasvir plasma concentration. No dose adjustment is necessary.
Other agents		
Potassium channel blocker		
Fampridine (also known as dalfampridine)	Fampridine ↑	Co-administration of dolutegravir has the potential to cause seizures due to increased fampridine plasma concentration via inhibition of OCT2 transporter; co-administration has not been reported. Fampridine co-administration with dolutegravir is contraindicated.
Anticonvulsants		
Carbamazepine	Dolutegravir ↓ AUC ↓ 49% C_{max} ↓ 33%	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with carbamazepine. In paediatric patients

	Cτ ↓ 73%	the weight-based once daily dose should be administered twice daily. Alternatives to carbamazepine should be used where possible for INI resistant patients.
Oxcarbazepine Phenytoin Phenobarbital	Dolutegravir ↓ (Not reported, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a similar reduction in exposure as reported with carbamazepine is expected)	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with these metabolic inducers. In paediatric patients the weight-based once daily dose should be administered twice daily. Alternative combinations that do not include these metabolic inducers should be used where possible in INI-resistant patients.
Azole anti-fungal agents		
Ketoconazole Fluconazole Itraconazole Posaconazole Voriconazole	Dolutegravir ↔ (Not reported)	No dose adjustment is necessary. Based on reported data from other CYP3A4 inhibitors, a marked increase is not expected.
Herbal products		
St. John's wort	Dolutegravir ↓ (Not reported, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a similar reduction in exposure as reported with carbamazepine is expected)	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with St. John's wort. In paediatric patients the weight-based once daily dose should be administered twice daily. Alternative combinations that do not include St. John's wort should be used where possible in INI-resistant patients.
Antacids and supplements		
Magnesium/ aluminium-containing antacid	Dolutegravir ↓ AUC ↓ 74% C_{max} ↓ 72% (Complex binding to polyvalent ions)	Magnesium/ aluminium-containing antacid should be taken well separated in time from the administration of **Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets** due to dolutegravir (at least 2 h after or 6 h before).
Calcium supplements	Dolutegravir ↓ AUC ↓ 39% C_{max} ↓ 37% C_{24} ↓ 39% (Complex binding to polyvalent ions)	Calcium supplements, iron supplements or multivitamins should be taken well separated in time from the administration of **Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets** due to dolutegravir (at least 2 h after or 6 h before).
Iron supplements	Dolutegravir ↓ AUC ↓ 54%	

	C_{max} ↓ 57% C_{24} ↓ 56% (Complex binding to polyvalent ions)	
Multivitamin	Dolutegravir ↓ AUC ↓ 33% C_{max} ↓ 35% C_{24} ↓ 32% (Complex binding to polyvalent ions)	
Corticosteroids		
Prednisone	Dolutegravir ↔ AUC ↑ 11% C_{max} ↑ 6% Cτ ↑ 17%	No dose adjustment is necessary.
Antidiabetics		
Metformin	Metformin ↑ When co-administered with dolutegravir 50 mg once daily: Metformin AUC ↑ 79% C_{max} ↑ 66% When co-administered with dolutegravir 50 mg twice daily: Metformin AUC ↑ 145 % C_{max} ↑ 111%	Dose adjustment of metformin should be considererd when starting and stopping coadministration of dolutegravir with metformin, to maintain glycaemic control. In patients with moderate renal impairment a dose adjustment of metformin should be considered when coadministered with dolutegravir, because of the increased risk for lactic acidosis in patients with moderate renal impairment due to increased metformin concentration.
Antimycobacterials		
Rifampicin	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 43% Cτ ↓72% (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with rifampicin in the absence of integrase class resistance. In the presence of integrase class resistance this combination should be avoided (see section **4.4**).
Rifabutin	Dolutegravir ↔ AUC ↓ 5% C_{max} ↑ 16% Cτ ↓ 30% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Oral contraceptive		
Ethinyl estradiol (EE)	Dolutegravir ↔	Dolutegravir had no pharmacodynamic effect on Luteinizing Hormone (LH), Follicle

and Norelgestromin (NGMN)	EE ↔ AUC ↑ 3% C_{max} ↓ 1% NGMN ↔ AUC ↓ 2% C_{max} ↓ 11%	Stimulating Hormone (FSH) and progesterone. No dose adjustment of oral contraceptives is necessary when co-administered with dolutegravir.
Analgesics		
Methadone	Dolutegravir ↔ Methadone ↔ AUC ↓ 2% C_{max} ↔ 0% Cτ ↓ 1%	No dose adjustment is necessary.

Interactions relevant to Lamivudine

Interaction studies with lamivudine have only been reported in adults.

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

Administration of trimethoprim/sulfamethoxazole 160 mg/800 mg reportedly results in a 40% increase in lamivudine exposure, because of the trimethoprim component; the sulfamethoxazole component did not interact. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary. Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole. When concomitant administration of lamivudine and trimethoprim/sulfamethoxazole 160 mg/800 mg is warranted, patients should be monitored clinically.

Co-administration of lamivudine with high doses of co-trimoxazole for the treatment of *Pneumocystis jirovecii* pneumonia (PCP) and toxoplasmosis should be avoided.

The possibility of interactions with other medicinal products administered concurrently should be considered, particularly when the main route of elimination is active renal secretion via the organic cationic transport system e.g. trimethoprim. Other medicinal products (e.g. ranitidine, cimetidine) are eliminated only in part by this mechanism and were reported not to interact with lamivudine. The nucleoside analogues (e.g. didanosine) like zidovudine, are not eliminated by this mechanism and are unlikely to interact with lamivudine.

A modest increase in C_{max} (28 %) has been reported for zidovudine when administered with lamivudine, however overall exposure (AUC) is not significantly altered. Zidovudine has no effect on the pharmacokinetics of lamivudine (see section **5.2**).

As Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets contain lamivudine, this product should not be administered concomitantly with other cytidine analogues, such as emtricitabine. Moreover, Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets should not be taken with any other medicinal products containing lamivudine (see section **4.4**).

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 Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets with cladribine is not recommended (see section **4.4**).

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

Co-administration of sorbitol solution (3.2 g, 10.2 g, 13.4 g) with a single 300 mg dose of lamivudine oral solution reportedly resulted in dose-dependent decreases of 14%, 32%, and 36% in lamivudine exposure (AUC_{∞}) and 28%, 52%, and 55% in the C_{max} of lamivudine in adults. When possible, avoid chronic co-administration of Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets with medicinal products containing sorbitol or other osmotic acting polyalcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol). Consider more frequent monitoring of HIV-1 viral load when chronic co-administration cannot be avoided.

Interactions relevant to Tenofovir disoproxil

Interaction studies have only been reported in adults. Based on the results of reported *in vitro* experiments and the known elimination pathway of tenofovir, the potential for CYP450 mediated interactions involving tenofovir with other medicinal products is low.

<u>Concomitant use not recommended with the following:</u>

The same recommendation will also be applicable to Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets**.**

Tenofovir disoproxil fumarate should not be administered concomitantly with other medicinal products containing tenofovir disoproxil fumarate or tenofovir alafenamide.

Tenofovir disoproxil fumarate should not be administered concomitantly with adefovir dipivoxil.

Didanosine: Co-administration of tenofovir disoproxil fumarate and didanosine is not recommended (see section **4.4**).

Renally eliminated medicinal products: Since tenofovir is primarily eliminated by the kidneys, co- administration of tenofovir disoproxil fumarate with medicinal products 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 medicinal products, or both.

Use of Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets should be avoided with concurrent or recent use of a nephrotoxic medicinal product, due to tenofovir disoproxil. Some examples include, but are not limited to, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2 (see section **4.4**).

Given that tacrolimus can affect renal function, close monitoring is recommended when it is co-administered with tenofovir disoproxil.

Other reported interactions

Interactions between tenofovir disoproxil fumarate and other medicinal products are listed in **Table below** (increase is indicated as "↑", decrease as "↓", no change as "↔", and once daily as "OD").

Table: Interactions between tenofovir disproxil fumarate and other medicinal products

Drugs by Therapeutic Area (dose in mg)	**Effect on drug levels mean percent change in AUC, C_{max}, C_{min}**	**Recommendations on co-administration**
Anti-infectives		
Anitretrovirals		
Protease Inhibitors (PIs)		
Atazanavir/Ritonavir (300 mg/100 mg OD)	Atazanavir: AUC: ↓ 25% C_{max}: ↓ 28% C_{min}: ↓ 26% Tenofovir: AUC: ↑ 37% C_{max}: ↑ 34%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir adverse events, including renal disorders. Renal function should be closely monitored (see section **4.4**).

	C_{min}: ↑ 29%	
Lopinavir/Ritonavir (400 mg/100 mg twice daily)	Lopinavir/ritonavir: No significant effect on lopinavir/ritonavir Tenofovir: AUC: ↑ 32% C_{max}: ↔ C_{min}: ↑ 51%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir adverse events, including renal disorders. Renal function should be closely monitored (see section **4.4**).
Darunavir/Ritonavir (300 mg/100 mg twice daily)	Darunavir: No significant effect on darunavir/ritonavir Tenofovir: AUC: ↑ 22% C_{min}: ↑ 37%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir adverse events, including renal disorders. Renal function should be closely monitored (see section **4.4**).
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
Didanosine	Co-administration of tenofovir disoproxil and didanosine reportedly results in a 40-60% increase in systemic exposure to didanosine	Co-administration of tenofovir disoproxil, and didanosine is not recommended (see section **4.4**). Increased systemic exposure to didanosine may increase didanosine related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co-administration of tenofovir disoproxil and didanosine at a dose of 400 mg daily has been associated with a significant decrease in CD4 cell count, possibly due to an intracellular interaction increasing phosphorylated (i.e. active) didanosine. A decreased dosage of 250 mg didanosine co-administered with tenofovir disoproxil therapy has been associated with reports of high rates of virological failure within several tested combinations for the treatment of HIV 1 infection
Adefovir dipivoxil	AUC: ↔ C_{max}: ↔	Tenofovir disoproxil should not be administered concurrently with adefovir dipivoxil (see section **4.4**).

Entecavir	AUC: ↔ C_{max}: ↔	No clinically significant pharmacokinetic interactions when tenofovir disoproxil is co-administered with entecavir.
Hepatitis C virus antiviral agents		
Ledipasvir/Sofosbuvir (90 mg/400 mg once daily) + Atazanavir/Ritonavir (300 mg/100 mg once daily) + Emtricitabine/Tenofovir disoproxil fumarate (200 mg/245 mg once daily)[1]	Ledipasvir: AUC: ↑ 96% C_{max}: ↑ 68% C_{min}: ↑ 118% Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 42% Atazanavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 63% Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 45% Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 47% C_{min}: ↑ 47%	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil fumarate, ledipasvir/sofosbuvir and atazanavir/ritonavir may increase adverse reactions related to tenofovir disoproxil fumarate, including renal disorders. The safety of tenofovir disoproxil fumarate when used with ledipasvir/sofosbuvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been reported. The combination should be used with caution with frequent renal monitoring, if other alternatives are not available (see section **4.4**).
Ledipasvir/Sofosbuvir (90 mg/400 mg once daily) + Darunavir/Ritonavir (800 mg/100 mg once daily) + Emtricitabine/Tenofovir disoproxil fumarate (200 mg / 245 mg	Ledipasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Sofosbuvir: AUC: ↓ 27% C_{max}: ↓ 37% GS-331007[2] : AUC: ↔ C_{max}: ↔	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil fumarate, ledipasvir/sofosbuvir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil fumarate, including renal disorders. The safety of tenofovir disoproxil fumarate when used with ledipasvir/sofosbuvir and a pharmacokinetic enhancer (e.g.

once daily)[1]	C_{min}: ↔ Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 48% Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 50% C_{max}: ↑ 64% C_{min}: ↑ 59%	ritonavir or cobicistat) has not been reported. The combination should be used with caution with frequent renal monitoring, if other alternatives are not available (see section **4.4**).
Ledipasvir/Sofosbuvir (90 mg/400 mg once daily) + Efavirenz/Emtricitabine/ Tenofovir disoproxil fumarate (600 mg/200 mg/245 mg once daily)	Ledipasvir: AUC: ↓ 34% C_{max}: ↓ 34% C_{min}: ↓ 34% Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2] : AUC: ↔ C_{max}: ↔ C_{min}: ↔ Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 98% C_{max}: ↑ 79% C_{min}: ↑ 163%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil fumarate, including renal disorders. Renal function should be closely monitored (see section **4.4**).
Ledipasvir/Sofosbuvir	Ledipasvir: AUC: ↔	No dose adjustment is recommended.

(90 mg/400 mg once daily) + Emtricitabine/Rilpivirine/ Tenofovir disoproxil fumarate (200 mg/25 mg/245 mg once daily)	C_{max}: ↔ C_{min}: ↔ Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Rilpivirine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 40% C_{max}: ↔ C_{min}: ↑ 91%	The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil fumarate, including renal disorders. Renal function should be closely monitored (see section **4.4**).
Ledipasvir/Sofosbuvir (90 mg/400 mg once daily) + Dolutegravir (50 mg once daily) + Emtricitabine/Tenofovir disoproxil fumarate (200 mg/245 mg once daily)	Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2] AUC: ↔ C_{max}: ↔ C_{min}: ↔ Ledipasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Dolutegravir AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir:	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil fumarate, including renal disorders. Renal function should be closely monitored (see section **4.4**).

	AUC: ↑ 65% C_{max}: ↑ 61% C_{min}: ↑ 115%	
Sofosbuvir/Velpatasvir (400 mg/100 mg once daily) + Atazanavir/Ritonavir (300 mg q.d./100 mg once daily) + Emtricitabine/Tenofovir disoproxil fumarate (200 mg/245 mg once daily)	Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 42% Velpatasvir: AUC: ↑ 142% C_{max}: ↑ 55% C_{min}: ↑ 301% Atazanavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 39% Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 29% Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 55% C_{min}: ↑ 39%	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil fumarate, sofosbuvir/velpatasvir and atazanavir/ritonavir may increase adverse reactions related to tenofovir disoproxil fumarate, including renal disorders. The safety of tenofovir disoproxil fumarate when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring (see section **4.4**).
Sofosbuvir/Velpatasvir (400 mg/100 mg once daily) + Darunavir/Ritonavir (800 mg q.d./100 mg once daily) + Emtricitabine/Tenofovir disoproxil fumarate (200 mg/245 mg once daily)	Sofosbuvir: AUC: ↓28% Cmax: ↓ 38% GS-331007[2]: AUC: ↔ Cmax: ↔ Cmin: ↔ Velpatasvir: AUC: ↔ C_{max}: ↓ 24% C_{min}: ↔ Darunavir:	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil fumarate, sofosbuvir/velpatasvir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil fumarate, including renal disorders. The safety of tenofovir disoproxil fumarate when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established.

	AUC: ↔ C_{max}: ↔ C_{min}: ↔ Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 39% C_{max}: ↑ 55% C_{min}: ↑ 52%	The combination should be used with caution with frequent renal monitoring (see section **4.4**).
Sofosbuvir/Velpatasvir (400 mg/100 mg once daily) + Lopinavir/Ritonavir (800 mg/200 mg once daily) + Emtricitabine/Tenofovir disoproxil fumarate (200 mg/245 mg once daily)	Sofosbuvir: AUC: ↓ 29% C_{max}: ↓ 41% GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↓ 30% C_{min}: ↑ 63% Lopinavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 42% C_{min}: ↔	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil fumarate, sofosbuvir/velpatasvir and lopinavir/ritonavir may increase adverse reactions related to tenofovir disoproxil fumarate, including renal disorders. The safety of tenofovir disoproxil fumarate when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring (see section **4.4**).

Sofosbuvir/Velpatasvir (400 mg/100 mg once daily) + Raltegravir (400 mg twice daily) + Emtricitabine/Tenofovir disoproxil fumarate (200 mg/245 mg once daily)	Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Raltegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 21% Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 40% C_{max}: ↑ 46% C_{min}: ↑ 70%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil fumarate, including renal disorders. Renal function should be closely monitored (see section **4.4**)
Sofosbuvir/Velpatasvir (400 mg/100 mg once daily) + Efavirenz/Emtricitabine/ Tenofovir disoproxil fumarate (600 mg/200 mg/245 mg once daily)	Sofosbuvir: AUC: ↔ C_{max}: ↑ 38% GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↓ 53% C_{max}: ↓ 47% C_{min}: ↓ 57% Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔	Concomitant administration of sofosbuvir/velpatasvir and efavirenz is expected to decrease plasma concentrations of velpatasvir. Co-administration of sofosbuvir/velpatasvir with efavirenz-containing regimens is not recommended.

	Tenofovir: AUC: ↑ 81% C_{max}: ↑ 77% C_{min}: ↑ 121%	
Sofosbuvir/Velpatasvir (400 mg/100 mg once daily) + Emtricitabine/Rilpivirine/ Tenofovir disoproxil fumarate (200 mg/25 mg/245 mg once daily)	Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Rilpivirine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 40% C_{max}: ↑ 44% C_{min}: ↑ 84%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil fumarate, including renal disorders. Renal function should be closely monitored (see section **4.4**).
Sofosbuvir/Velpatasvir/Voxilaprevir (400 mg/100 mg/100 mg+100 mg q.d.) + Darunavir (800 mg q.d.) + Ritonavir (100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ C_{max}: ↓ 30% C_{min}: N/A GS-3310072: AUC: ↔ C_{max}:↔ C_{min}: N/A Velpatasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Voxilaprevir: AUC: ↑ 143% C_{max}:↑ 72%	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, sofosbuvir/velpatasvir/voxilaprevir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir/voxilaprevir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring.

	C_{min}: ↑ 300% Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 34% Ritonavir: AUC: ↑ 45% C_{max}: ↑ 60% C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 39% Cmax: ↑ 48% Cmin: ↑ 47%	
Sofosbuvir (400 mg once daily) + Efavirenz/Emtricitabine/ Tenofovir disoproxil fumarate (600 mg/200 mg/245 mg once daily)	Sofosbuvir: AUC: ↔ C_{max}: ↓ 19% GS-331007[2]: AUC: ↔ C_{max}: ↓ 23% Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 25% C_{min}: ↔	No dose adjustment is required.

[1]Data reported from simultaneous dosing with ledipasvir/sofosbuvir. Staggered administration (12 h apart) provided similar results.
[2]The predominant circulating metabolite of sofosbuvir.

Other medicinal products

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

4.6 Fertility, pregnancy and lactation[3,4,5]

Women of childbearing potential

Women of childbearing potential (WOCBP) should undergo pregnancy testing before initiation of dolutegravir. WOCBP who are taking dolutegravir should use effective contraception throughout treatment.

Pregnancy

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

Data reported for individual components of the FDC is presented below.

Dolutegravir
Reported preliminary data from a surveillance study has suggested an increased incidence of neural tube defects (0.9%) in mothers exposed to dolutegravir at the time of conception compared with mothers exposed to non-dolutegravir containing regimens (0.1%). The incidence of neural tube defects in the general population ranges from 0.05-0.1%.

Most neural tube defects occur within the first 4 weeks of embryonic development after conception (approximately 6weeks after the last menstrual period). If a pregnancy is confirmed in the first trimester while on dolutegravir, the benefits and risks of continuing dolutegravir versus switching to another antiretroviral regimen should be discussed with the patient taking the gestational age and the critical time period of neural tube defect development into account.

The reported data analysed from the Antiretroviral Pregnancy Registry do not indicate an increased risk of major birth defects in over 600 women exposed to dolutegravir during pregnancy but are currently insufficient to address the risk of neural tube defects.

No adverse development outcomes, including neural tube defects have been reported in animals (see section **5.3**). Dolutegravir has been reported to cross the placenta in animals.

More than 1000 outcomes from exposure during second and third trimester of pregnancy indicate no evidence of increased risk of foeto/neonatal toxicity. Dolutegravir may be used during the second and third trimester of pregnancy when the expected benefit justifies the potential risk to the foetus.

Lamivudine
Increase in early embryonic deaths have been reported with lamivudine in rabbits but not in rats. Placental transfer of lamivudine has been reported in humans.

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

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

Mitochondrial dysfunction: Nucleoside and nucleotide analogues have been reported to cause a variable degree of mitochondrial damage both in vitro and in vivo. There have been reports of mitochondrial dysfunction in infants exposed in utero and/or post-natally to nucleoside analogues (see section **4.4**).

Tenofovir disoproxil fumarate
A large amount of data on pregnant women (more than 1,000 pregnancy outcomes) report no malformations or foetal/neonatal toxicity associated with tenofovir disoproxil. No reproductive toxicity has been reported in animals. The use of tenofovir disoproxil may be considered during pregnancy, if necessary.

Lactation

As a general rule, it is recommended that HIV-infected women do not breast-feed their infants in order to avoid transmission of HIV to the infant.

Dolutegravir
Dolutegravir is excreted in human milk in small amounts. There is insufficient information on the effects of dolutegravir in neonates/infants.

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

Tenofovir disoproxil fumarate
Tenofovir has been reported to be excreted in human milk at very low levels and exposure of infants through breast milk is considered negligible.

There are no data on the use of this fixed-dose combination (FDC) in pregnancy and lactation.
Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets *should not be used in pregnancy and lactation.*

Fertility

There are limited clinical data with respect to the effect of dolutegravir and tenofovir disoproxil on fertility. Based on limited reported animal studies, dolutegravir, lamivudine and tenofovir disoproxil are not reported to have any effects on male or female fertility.

4.7 Effects on ability to drive and use machines[3,4,5]

The effect on the ability to drive and use machines has not been reported. However, patients should be informed that dizziness has been reported during treatment with dolutegravir and tenofovir disoproxil. The clinical status of the patient and the adverse reaction profile of dolutegravir and tenofovir disoproxil should be borne in mind when considering the use of Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg tablets along with the patient's ability to drive or operate machinery.

4.8 Undesirable effects[3,4,5]

Summary of the safety profile

The most severe adverse reaction with dolutegravir, reported in an individual patient, was a hypersensitivity reaction that included rash and severe liver effects (see section **4.4**). The most commonly seen treatment emergent adverse reactions were nausea (13%), diarrhoea (18%) and headache (13%).

HIV-1 and hepatitis B: In patients receiving tenofovir disoproxil, rare events of renal impairment, renal failure and uncommon events of proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have been reported. Monitoring of renal function is recommended for patients receiving tenofovir disoproxil (see section **4.4**).

HIV-1: Approximately one third of patients can be expected to experience adverse reactions following treatment with tenofovir disoproxil in combination with other antiretroviral agents. These reactions are usually mild to moderate gastrointestinal events. Approximately 1% of tenofovir disoproxil-treated adult patients discontinued treatment due to the gastrointestinal events.

Co-administration of tenofovir disoproxil and didanosine is not recommended as this may result in an increased risk of adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported.

Tabulated list of adverse reactions

The adverse reactions reported below are considered to be at least possibly related to individual component of this FDC during therapy for HIV disease and are presented in **Table below** by body system, organ class and absolute frequency. Frequencies of reported adverse reactions are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

Table: Reported adverse events for Dolutegravir, Lamivudine and Tenofovir Disoproxil

Frequency	Dolutegravir	Lamivudine	Tenofovir Disoproxil
Blood and lymphatic system disorders			
Uncommon:	-	Neutropenia, anaemia (both occasionally severe), thrombocytopenia	-
Very rare:	-	Pure red cell aplasia	-
Immune system disorders			
Uncommon:	Hypersensitivity, immune reconstitution syndrome (see section **4.4**)	-	-
Nervous system disorders			
Very common:	Headache	-	Dizziness
Common:	Dizziness	Headache, insomnia	Headache
Very rare:	-	Peripheral neuropathy (or paraesthesia)	-
Respiratory, thoracic and mediastinal disorders			

Frequency	Dolutegravir	Lamivudine	Tenofovir Disoproxil
Common:		Cough, nasal symptoms	-
Metabolism and nutrition disorders			
Very common:	-	-	Hypophosphataemia*
Uncommon:	-	-	Hypokalaemia*
Rare:	-	-	Lactic acidosis
Very rare:	-	Lactic acidosis	-
Gastrointestinal disorders			
Very common:	Nausea, diarrhea	-	Diarrhoea, vomiting, nausea
Common:	Vomiting, flatulence, upper abdominal pain, abdominal pain, abdominal discomfort	Nausea, vomiting, abdominal pain or cramps, diarrhoea	Abdominal pain, abdominal distension, flatulence
Uncommon:	-	-	Pancreatitis
Rare:	-	Pancreatitis, elevation in serum amylases	-
Hepatobiliary disorders			
Common:	Alanine aminotransferase (ALT) and/or Aspartate aminotransferase (AST) elevations	-	Increased transaminases
Uncommon:	Hepatitis	Transient elevation in liver enzymes [Alanine aminotransferase (ALT) and/or Aspartate aminotransferase (AST)]	-
Rare:	Acute hepatic failure, increased bilirubin	Hepatitis	Heptatic steatosis, hepatitis
Skin and subcutaneous tissue disorders			
Very common:	-	-	Rash
Common:	Rash, pruritus	Rash, alopecia	-
Rare:	-	Angioedema	Angioedema
Musculoskeletal and connective tissue disorders			
Common:	-	Arthralgia, muscle disorders	
Uncommon:	Arthralgia, myalgia		Rhabdomyolysis*,

Frequency	Dolutegravir	Lamivudine	Tenofovir Disoproxil
			muscular weakness[*]
Rare:	-	Rhabdomyolysis	Osteomalacia (manifested as bone pain and infrequently contributing to fractures)[*#], myopathy[*]
General disorders and administration site conditions			
Very common:	-	-	Asthenia
Common:	Fatigue	Fatigue, malaise, fever	Fatigue
Psychiatric disorders			
Common:	Insomnia, abnormal dreams, depression, anxiety	-	-
Uncommon:	Suicidal ideation[#] , suicide attempt[#] [#]particularly in patients with pre-existing history of depression or psychiatric illness	-	-
Renal and urinary disorders			
Uncommon:	-	-	Increased creatinine, proximal renal tubulopathy (including Fanconi syndrome)
Rare	-	-	Acute renal failure, renal failure, acute tubular necrosis, nephritis (including acute interstitial nephritis)[#], nephrogenic diabetes insipidus
Investigations			
Common:	ALT and/or AST elevations, Creatine phosphokinase (CPK) elevations	-	-

[*]Adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil in the absence of this condition.

[#]Adverse reaction listed above was reported from post-marketing data but not from reported randomised controlled clinical studies or the tenofovir disoproxil fumarate expanded access program. The frequency category was reported from a statistical calculation based on the total number of patients exposed to tenofovir disoproxil fumarate.

Paediatric population

Dolutegravir

Based on limited reported data in children and adolescents (aged 4 weeks and above, to less than 18 years, and weighing at least 3 kg), there were no additional types of adverse reactions beyond those reported in the adult population.

Lamivudine

No additional safety issues have been reported in paediatric subjects receiving either once or twice daily dosing compared to adults.

Description of selected adverse reactions with dolutegravir

Immune response syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section **4.4**)

Changes in laboratory biochemistry parameters with dolutegravir

Increases in serum creatinine were reported within the first week of treatment with dolutegravir and remained stable through 48 weeks. A mean change from baseline of 9.96 µmol/L was reported after 48 weeks of treatment. Creatinine increases were comparable by various background regimens. These changes are not considered to be clinically relevant since they do not reflect a change in glomerular filtration rate.

Co-infection with Hepatitis B or C (dolutegravir)

The safety profile in patients co-infected with hepatitis B and/or C was reported to be similar to that reported in patients 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 co-infection for all treatment groups. Liver chemistry elevations consistent with immune reconstitution syndrome were reported in some subjects with hepatitis B and/or C co-infection at the start of dolutegravir therapy, particularly in those whose anti-hepatitis B therapy was withdrawn.

Description of selected adverse reactions reported with tenofovir disoproxil fumarate

- **HIV-1 and hepatitis B:**

Renal impairment
It has been reported that tenofovir disoproxil may cause renal damage, monitoring of renal function during treatment with tenofovir is recommended (see section **4.4**). Proximal renal tubulopathy generally resolved or improved after tenofovir disoproxil discontinuation. However, in some patients, it was reported that declines in creatinine clearance did not completely resolve despite tenofovir disoproxil discontinuation. Patients at risk of renal impairment (such as patients with baseline renal risk factors, advanced HIV disease, or patients receiving concomitant nephrotoxic medications) are at increased risk of experiencing incomplete recovery of renal function despite tenofovir disoproxil discontinuation (see section **4.4**).

- **HIV-1:**

Interaction with didanosine
Co-administration of tenofovir disoproxil and didanosine is not recommended as it reported to result in a 40-60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported.

Osteonecrosis
Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to CART. The frequency of this is unknown (see section **4.4**).

- **Hepatitis B:**

Exacerbations of hepatitis during treatment
In reported studies with nucleoside-naïve patients, on-treatment ALT elevations > 10 times ULN (upper limit of normal) and > 2 times baseline occurred in 2.6% of tenofovir disoproxil-treated patients. ALT elevations had a median time to onset of 8 weeks, resolved with continued treatment, and, in a majority of cases, were associated with a ≥ 2 $\log_{10}$ copies/mL reduction in viral load that preceded or coincided with the ALT elevation. Periodic monitoring of hepatic function is recommended during treatment.

Exacerbations of hepatitis after discontinuation of treatment

In HBV infected patients, clinical and laboratory evidence of exacerbations of hepatitis has been reported after discontinuation of HBV therapy.

Paediatric population

HIV-1
Assessment of adverse reactions is based on two reported randomised trials in HIV-1 infected paediatric patients (aged 2 to < 18 years) who received treatment with tenofovir disoproxil or placebo/active comparator in combination with other antiretroviral agents for 48 weeks The adverse reactions reported in paediatric patients who received treatment with tenofovir disoproxil were consistent with those reported in clinical studies of tenofovir disoproxil in adults (see *Tabulated list of adverse reactions*).

Reductions in BMD have been reported in paediatric patients. In HIV-1 infected adolescents, the BMD Z-scores observed in subjects who received tenofovir disoproxil were lower than those reported in subjects who received placebo. In HIV-1 infected children, the BMD Z-scores reported in subjects who switched to tenofovir disoproxil were lower than those reported in subjects who remained on their stavudine- or zidovudine-containing regimen.

In a reported study few paediatric patients exposed to tenofovir disoproxil (median tenofovir disoproxil exposure 312 weeks) were reported to discontinue due to adverse reactions consistent with proximal renal tubulopathy. Few patients had estimated glomerular filtration rate (GFR) values between 70 and 90 mL/min/1.73 m^2. Among them, few patients experienced a clinically meaningful decline in estimated GFR which improved after discontinuation of tenofovir disoproxil.

Elderly
Tenofovir disoproxil has not been studied in patients over the age of 65. Elderly patients are more likely to have decreased renal function, therefore caution should be exercised when treating elderly patients with tenofovir disoproxil (see section **4.4**).

Patients with renal impairment
Since tenofovir disoproxil can cause renal toxicity, close monitoring of renal function is recommended in adult patients with renal impairment treated with tenofovir disoproxil (see section **4.4**).

4.9 Overdose[3,4,5]

Dolutegravir
There is currently limited experience with overdosage in dolutegravir.

Limited experience of single higher doses (up to 250 mg in healthy subjects) reported no specific symptoms or signs, apart from those listed as adverse reactions.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available. There is no specific treatment for an overdose of dolutegravir. If overdose occurs, the patient should be treated supportively with appropriate monitoring, as necessary. As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

Lamivudine

Administration of lamivudine at very high dose levels in reported acute animal studies did not result in any organ toxicity. No specific signs or symptoms have been reported following such overdose. If overdosage occurs the patient should be monitored, and standard supportive treatment applied as required. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdosage, although this has not been reported.

Tenofovir disoproxil fumarate

If overdose occurs the patient must be monitored for evidence of toxicity (see section **4.8**), and standard supportive treatment applied as necessary. Tenofovir can be removed by haemodialysis; the median haemodialysis clearance of tenofovir is 134 mL/min. The elimination of tenofovir by peritoneal dialysis has not been studied.

5. PHARMACOLOGICAL PROPERTIES[3,4,5]

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dolutegravir, lamivudine and tenofovir disoproxil: Direct acting antivirals, Antivirals for treatment of HIV infections, combinations, ATC code: J05AR27.

Mechanism of action and pharmacodynamics effects:

Dolutegravir

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral Deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle.

Antiviral activity of dolutegravir in cell culture: The IC_{50} for dolutegravir in various lab strains was reportedly 0.5 nM, and when using MT-4 cells it ranged from 0.7-2 nM. Similar IC_{50}s

were reported 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} value was 0.2 nM (range 0.02-2.14). The mean IC_{50} for HIV-2 isolates was 0.18 nM (range 0.09-0.61).

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

Effect of dolutegravir on human serum: In 100% human serum, the mean protein fold shift was reported to be 75 fold, resulting in protein adjusted IC_{90} of 0.064 ug/mL.

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

Lamivudine

Lamivudine is a nucleoside analogue which has activity against human immunodeficiency virus (HIV) and hepatitis B virus (HBV). It is metabolised intracellularly to the active moiety, lamivudine 5'- triphosphate. Its main mode of action is as a chain terminator of viral reverse transcription.

Antiviral activity of lamivudine in vitro: The triphosphate has selective inhibitory activity against HIV-1 and HIV-2 replication *in vitro*; it is also active against zidovudine-resistant clinical isolates of HIV. No antagonistic effects *in vitro* has been reported with lamivudine and other anti retrovirals (tested agents: abacavir, didanosine, nevirapine and zidovudine).

Tenofovir disoproxil

Tenofovir disoproxil phosphate is the phosphate salt of the prodrug tenofovir disoproxil. Tenofovir disoproxil is absorbed and converted to the active substance tenofovir, which is a nucleoside monophosphate (nucleotide) analogue. Tenofovir is then converted to the active metabolite, tenofovir diphosphate, an obligate chain terminator, by constitutively expressed cellular enzymes. Tenofovir diphosphate has an intracellular half-life of 10 h in activated and 50 h in resting peripheral blood mononuclear cells (PBMCs). Tenofovir diphosphate inhibits HIV-1 reverse transcriptase and the HBV polymerase by direct binding competition with the natural deoxyribonucleotide substrate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of cellular polymerases α, β, and γ. At

concentrations of up to 300 µmol/L, tenofovir has also reported no effect on the synthesis of mitochondrial DNA or the production of lactic acid in *in vitro* assays.

Antiviral activity of tenofovir disoproxil in vitro: The concentration of tenofovir required for 50% inhibition (EC_{50}) of the wild-type laboratory strain HIV-1IIIB is 1 - 6 µmol/L in lymphoid cell lines and 1.1 µmol/L against primary HIV-1 subtype B isolates in PBMCs. Tenofovir is also active against HIV-1 subtypes A, C, D, E, F, G, and O and against HIVBaL in primary monocyte/macrophage cells. Tenofovir shows activity *in vitro* against HIV-2, with an EC_{50} of 4.9 µmol/L in MT-4 cells.

Resistance

Dolutegravir

In vitro resistance

Serial passage is used to study resistance evolution *in vitro*. When using the lab-strain HIV-1 IIIB during passage over 112 days, mutations selected were reported to appear slowly, with substitutions at positions S153Y and F, resulting in a maximal fold change in susceptibility of 4 (range 2-4). These mutations were not selected in patients treated with dolutegravir in the reported clinical studies. Using strain NL432, mutations E92Q (FC 3) and G193E (also FC 3) were selected. The E92Q mutation has been selected in patients with pre-existing raltegravir resistance who were then treated with dolutegravir (listed as a secondary mutation for dolutegravir).

In further selection experiments reported using clinical isolates of subtype B, mutation R263K was reported in all isolates (after 20 weeks and onwards). In subtype C and A/G, isolates the integrase substitution R263K was selected in one isolate, and G118R in two isolates. R263K was reported from two ART experienced, integrase inhbitor-naïve individual patients with subtypes B and C in the reported studies, but without effects on dolutegravir susceptibility *in vitro*. G118R reportedly lowers the susceptibility to dolutegravir in site directed mutants [fold change (FC) 10], but was not detected in patients receiving dolutegravir in the reported Phase III study.

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 of 5-10 or higher is seen 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, no further selection of resistance was seen (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 versus wild type virus) has not been determined; genotypic resistance was a better predictor for outcome. Raltegravir resistant isolates from raltegravir experienced patients were reportedly analyzed for susceptibility to dolutegravir. Dolutegravir has a less than or equal to 10 FC against 94% of the 705 clinical isolates.

In vivo resistance

In previously untreated patients receiving dolutegravir + 2 NRTIs in reported clinical studies, no development of resistance to the integrase class, or to the NRTI class was reported (follow-up of 48-96 weeks). In previously untreated patients receiving dolutegravir + lamivudine in the reported GEMINI studies through week 48 (n=716), no development of resistance to the integrase class, or to the NRTI class was seen.

In patients with prior failed therapies, but naïve to the integrase class, integrase inhibitor substitutions were reported in very few patients (follow-up 48 weeks) treated with dolutegravir, which was given in combination with an investigator selected background regimen (BR). A unique R263K integrase substitution, with a maximum FC of 1.93, a polymorphic V151V/I integrase substitution, with maximum FC of 0.92, and pre-existing integrase mutations were reported and is assumed to have been integrase experienced or infected with integrase resistant virus by transmission. The R263K mutation was also selected *in vitro*.

In the presence of integrase class-resistance in a reported clinical study, the following mutations were reportedly 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 + optimized background agents): L74L/M, E92Q, T97A, E138K/A/T, G140S, Y143H, S147G, Q148H/K/R and N155H and E157E/Q. Treatment emergent integrase resistance reportedly appeared in patients with a history of the Q148-mutation (baseline or historic). Further 5 subjects were reported to experience PDVF between weeks 24 and 48, and 2 of these 5 had treatment emergent mutations. Treatment-emergent mutations or mixtures of mutations reported were L74I and N155H.

Another reported clinical study examined dolutegravir (plus optimized background therapy) in subjects with primary genotypic resistance to INIs at Screening. Treatment-emergent mutations observed were reported to be consistent with those observed in other reported clinical studies.

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 report 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.

Reported 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 reported 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 lamivudine-resistant 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 reported 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*.

Tenofovir disoproxil fumarate

Strains of HIV-1 with reduced susceptibility to tenofovir and a K65R mutation in reverse transcriptase were reportedly selected *in vitro* and in patients. Tenofovir disoproxil should be avoided in antiretroviral experienced patients with strains harbouring the K65R mutation (see

section **4.4**). In addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in low-level reduced susceptibility to tenofovir.

Reported clinical studies in treatment-experienced patients have assessed the anti-HIV activity of tenofovir disoproxil 245 mg against strains of HIV-1 with resistance to nucleoside inhibitors. Reported results indicate that patients whose HIV expressed 3 or more thymidine-analogue associated mutations (TAMs) that included either the M41L or L210W reverse transcriptase mutation showed reduced response to tenofovir disoproxil 245 mg therapy.

5.2 Pharmacokinetic properties

Pharmacokinetic data reported with individual components of this FDC is as below.

Dolutegravir

Dolutegravir pharmacokinetics (PK) are reported to be similar between healthy and HIV-infected subjects. The PK variability of dolutegravir is low to moderate. In reported phase I studies in healthy subjects, between-subject CV_b% for AUC and C_{max} ranged from ~20 to 40% and Cτ from 30 to 65% across reported studies. The between-subject PK variability of dolutegravir was reported to be higher in HIV-infected subjects than healthy subjects. Within-subject variability (CV_w%) was reported to be lower than between-subject variability.

Absorption

Dolutegravir is rapidly absorbed following oral administration, with median time to maximal serum concentrations (T_{max}) at 2 to 3 h post dose for tablet formulation. Food increases the extent and slowed the rate of absorption of dolutegravir. Bioavailability dolutegravir depends on meal content: low, moderate, and high fat meals increased dolutegravir $AUC_{(0-\infty)}$ by 33%, 41%, and 66%, increased C_{max} by 46%, 52%, and 67%, prolonged T_{max} to 3, 4, and 5 h from 2 h under fasted conditions, respectively. These increases may be clinically relevant in the presence of certain integrase class resistance. The absolute bioavailability of dolutegravir has not been reported.

Distribution

Dolutegravir is highly bound (>99%) to human plasma proteins based on reported *in vitro* data. The apparent volume of distribution is reported to be 17 L to 20 L in HIV-infected patients. Binding of dolutegravir to plasma proteins is independent of dolutegravir concentration. Based on reported studies 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 reported to be increased

at low levels of serum albumin (<35 g/L) as seen in subjects with moderate hepatic impairment. Dolutegravir is present in cerebrospinal fluid (CSF). In treatment-naïve subjects on a stable dolutegravir plus abacavir/lamivudine regimen, dolutegravir concentration in CSF reportedly averaged 18 ng/mL (comparable to unbound plasma concentration, and above the IC_{50}). Dolutegravir is reported to be 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 has been reported to be 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). A total of 53% oral dose is reported to be 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. A total of 32% oral dose is reported to be excreted in the urine represented by ether glucuronide of dolutegravir (18.9% of total dose), N-dealkylation metabolite (3.6% of total dose), and a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose).

Drug interactions

In vitro, dolutegravir reportedly demonstrates 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 Pgp, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, MATE2-K, MRP2 or MRP4. *In vitro*, dolutegravir has not been reported to induce CYP1A2, CYP2B6 or CYP3A4. Based on this reported data, dolutegravir is not expected to affect the pharmacokinetics of medicinal products that are substrates of major enzymes or transporters (see section **4.5**). *In vitro*, dolutegravir was not reported to be a substrate of human OATP 1B1, OATP 1B3 or OCT 1.

Elimination

Dolutegravir has a terminal half-life of approximately 14 h. The apparent oral clearance (CL/F) is reported to be approximately 1 L/h in HIV-infected patients.

Linearity/non-linearity

The linearity of dolutegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of tablet formulations, in general, dolutegravir is reported to be exhibit non-linear pharmacokinetics with less than dose-proportional increases in plasma exposure from 2 to 100 mg; however increase in dolutegravir exposure appears dose

proportional from 25 mg to 50 mg for the tablet formulation. With 50 mg twice daily, the exposure over 24 h was approximately doubled compared to 50 mg OD.

Pharmacokinetic / pharmacodynamic relationship(s)

Dolutegravir monotherapy has been reported to have rapid and dose-dependent antiviral activity in HIV-1 infected subjects, with mean decline in HIV-1 RNA of 2.5 $\log_{10}$ 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.

Increasing the dose from 50 mg twice daily to 100 mg twice daily may increase the effectiveness of dolutegravir in patients with integrase resistance and limited treatment options due to advanced multi class resistance. The proportion of responders (HIV-1 RNA <50 c/mL) at week 24 was predicted to increase around 4-18% in the subjects with Q148 + ≥2 secondary mutations from G140A/C/S, E138A/K/T, L74I. Although these simulated results have not been confirmed in reported clinical studies, this high dose may be considered in the presence of the Q148 + ≥2 secondary mutations from G140A/C/S, E138A/K/T, L74I in patients with overall limited treatment options due to advanced multi class resistance. There is no reported 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.

Pharmacokinetics in special population

Children

The pharmacokinetics of dolutegravir in antiretroviral treatment-experienced HIV-1 infected adolescents (12 to <18 years of age) reported that dolutegravir 50 mg once daily oral dosage resulted in dolutegravir exposure comparable to that reported in adults who received dolutegravir 50 mg orally once daily.

Elderly

Population pharmacokinetic analysis of dolutegravir using data in HIV-1 infected adults reported that there was no clinically relevant effect of age on dolutegravir exposure. Pharmacokinetic data reported for dolutegravir in subjects >65 years of age are limited.

Renal impairment

Renal clearance of unchanged active substance is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of dolutegravir was reported in subjects with severe renal impairment (CLcr <30 mL/min) and matched healthy controls. The exposure to dolutegravir was reported to be decrease 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 metabolized and eliminated by the liver. A single dose of 50 mg of dolutegravir was administered to subjects with moderate hepatic impairment (Child-Pugh class B) and to matched healthy adult controls. While the total dolutegravir concentration in plasma was similar, a 1.5- to 2-fold increase in unbound exposure to dolutegravir was reported in subjects with 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 reported.

Polymorphisms in drug metabolising enzymes
There is no evidence that common polymorphisms in drug metabolising enzymes alter dolutegravir pharmacokinetics to a clinically meaningful extent. In a reported meta-analysis using pharmacogenomics samples collected in reported clinical studies in healthy subjects, subjects with UGT1A1 genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1.

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

Race
Population PK analyses using pooled pharmacokinetic data from reported adult clinical studies revealed no clinically relevant effect of race on the exposure of dolutegravir. The pharmacokinetics of dolutegravir following single dose oral administration to Japanese subjects appear similar to reported parameters in Western (US) subjects.

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

Lamivudine

Absorption

Lamivudine is well absorbed from the gastrointestinal tract, and the bioavailability of oral lamivudine in adults has been reported to be between 80 and 85%. Following oral administration, the mean time (T_{max}) to maximal serum concentrations (C_{max}) is about an h. Based on data derived from a reported study in healthy volunteers, at a therapeutic dose of 150 mg twice daily, mean (CV) steady-state C_{max} and C_{min} of lamivudine in plasma are 1.2 µg/mL (24%) and 0.09 µg/mL (27%), respectively. The mean (CV) AUC over a dosing interval of 12 h is 4.7 µg × h/mL (18%). At a therapeutic dose of 300 mg once daily, the mean (CV) steady-state C_{max}, C_{min} and 24 h AUC are 2.0 µg/mL (26%), 0.04 µg/mL (34%) and 8.9 µg.h/mL (21%), respectively.

Co-administration of lamivudine with food has been reported to result 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.

Co-administration of zidovudine has been reported to result in a 13% increase in zidovudine exposure and a 28 % increase in peak plasma levels. This is not considered to be of significance to patient safety and therefore no dosage adjustments are necessary.

Distribution

From the reported intravenous studies, the mean volume of distribution is 1.3 L/kg. The mean systemic clearance of lamivudine has been reported to be approximately 0.32 L/h/kg, with predominantly renal clearance (> 70%) via the organic cationic transport system.

Lamivudine is reported to exhibit linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin (< 16% - 36% to serum albumin in *in vitro* studies).

Lamivudine penetrates the central nervous system and reaches the cerebro-spinal fluid (CSF). The mean ratio CSF/serum lamivudine concentration 2-4 h after oral administration was reported to be approximately 0.12. The true extent of penetration or relationship with any clinical efficacy is unknown.

Biotransformation

The plasma lamivudine half-life after oral dosing is 18 to 19 hours and the active moiety, intracellular lamivudine triphosphate, has been reported to have a prolonged terminal half-life in the cell (16 to 19 h).

Lamivudine has been reported to predominately cleared unchanged by renal excretion. The likelihood of metabolic interactions of lamivudine with other medicinal products is low due to the small extent of hepatic metabolism (5-10%) and low plasma protein binding.

Elimination
Lamivudine elimination is affected by renal dysfunction.

An interaction with trimethoprim, a constituent of co-trimoxazole, has been reported to causea 40% increase in lamivudine exposure at therapeutic doses. This does not require dose adjustment unless the patient also has renal impairment. Administration of co-trimoxazole with lamivudine in patients with renal impairment should be carefully assessed.

Special populations

Pregnancy

Following oral administration, lamivudine pharmacokinetics in late-pregnancy were reported to be similar to non-pregnant women.

Tenofovir disoproxil fumarate

Tenofovir disoproxil 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 reported to be rapidly absorbed and converted to tenofovir. Administration of multiple doses of tenofovir disoproxil with a meal to HIV infected patients has been reported to result in mean (%CV) tenofovir C_{max}, AUC, and C_{min} values of 326 (36.6%) ng/mL, 3,324 (41.2%) ng h/mL and 64.4 (39.4%) ng/mL, respectively. Maximum tenofovir concentrations are reported in serum within 1 h of dosing in the fasted state and within 2 h when taken with food. The oral bioavailability of tenofovir from tenofovir disoproxil in fasted patients was reported to be approximately 25%. Administration of tenofovir disoproxil with a high fat meal been reported to enhance the oral bioavailability, with an increase in tenofovir AUC by approximately 40% and C_{max} by approximately 14%. Following the first dose of tenofovir disoproxil in fed patients, the median C_{max} in serum reportedly ranged from 213 to 375 ng/mL. However, administration of tenofovir disoproxil with a light meal was not reported to have a significant effect on the pharmacokinetics of tenofovir.

Distribution
Following intravenous administration the steady-state volume of distribution of tenofovir has been reported to be approximately 800 mL/kg. After oral administration of tenofovir disoproxil,

tenofovir is reported to distribute to most tissues with the highest concentrations occurring in the kidney, liver and the intestinal contents (reported preclinical studies). *In vitro* protein binding of tenofovir to plasma or serum protein was reported to be less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 μg/mL.

Biotransformation

Reported *in vitro* studies have determined that neither tenofovir disoproxil nor tenofovir are substrates for the CYP450 enzymes. Moreover, at concentrations substantially higher (approximately 300-fold) than those reported *in vivo*, tenofovir did not inhibit *in vitro* drug metabolism mediated by any of the major human CYP450 isoforms involved in drug biotransformation (CYP3A4, CYP2D6, CYP2C9, CYP2E1, or CYP1A1/2). Tenofovir disoproxil at a concentration of 100 μmol/L had been reported to have no effect on any of the CYP450 isoforms, except CYP1A1/2, where a small (6%) but statistically significant reduction in metabolism of CYP1A1/2 substrate was reported. Based on the reported data, it is unlikely that clinically significant interactions involving tenofovir disoproxil and medicinal products metabolised by CYP450 would occur.

Elimination

Tenofovir is primarily excreted by the kidney by both 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 reported to be approximately 230 mL/h/kg (approximately 300 mL/min). Renal clearance has been reported 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 h. Reported 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).

Linearity/non-linearity

The pharmacokinetics of tenofovir is reported to be independent of tenofovir disoproxil dose over the dose range 75 to 600 mg and was not affected by repeated dosing at any dose level.

Special population

Age

Pharmacokinetic studies have not been reported in the elderly (over 65 years of age).

Gender

Limited reported data on the pharmacokinetics of tenofovir in women indicate no major gender effect.

Ethnicity
Pharmacokinetics has not been specifically reported in different ethnic groups.

Renal impairment
Pharmacokinetic parameters of tenofovir were reported following administration of a single dose of tenofovir disoproxil 245 mg to non-HIV, non-HBV infected adult 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 2,185 (12%) ng × h/mL in subjects with CrCl > 80 mL/min to respectively 3,064 (30%) ng h/mL, 6,009 (42%) ng × h/mL and 15,985 (45%) ng × h/mL in patients with mild, moderate and severe renal impairment.

The pharmacokinetics of tenofovir in non-haemodialysis adult patients with creatinine clearance < 10 mL/min and in patients with ESRD managed by peritoneal or other forms of dialysis have not been studied. The pharmacokinetics of tenofovir in paediatric patients with renal impairment have not been reported. No data are available to make dose recommendations.

Hepatic impairment
In a reported study, a single 245 mg dose of tenofovir disoproxil was administered to non-HIV, non-HBV infected adult patients with varying degrees of hepatic impairment defined according to Child-Pugh-Turcotte (CPT) classification. It was reported that tenofovir pharmacokinetics was not substantially altered in subjects with hepatic impairment suggesting that no dose adjustment is required in these subjects. The mean (%CV) tenofovir C_{max} and $AUC_{0-\infty}$ values were 223 (34.8%) ng/mL and 2,050 (50.8%) ng × h/mL, respectively, in normal subjects compared with 289 (46.0%) ng/mL and 2,310 (43.5%) ng × h/mL in subjects with moderate hepatic impairment, and 305 (24.8%) ng/mL and 2,740 (44.0%) ng h/mL in subjects with severe hepatic impairment.

Paediatric population
HIV-1: Steady-state pharmacokinetics of tenofovir were reported in HIV-1 infected adolescent patients (aged 12 to < 18 years) with body weight ≥ 35 kg. Mean (± SD) C_{max} and AUC_{tau} are 0.38 ± 0.13 μg/mL and 3.39 ± 1.22 μg × h/mL, respectively. Tenofovir exposure achieved in adolescent patients receiving oral daily doses of tenofovir disoproxil 245 mg was reported to be similar to exposures reported in adults receiving once-daily doses of tenofovir disoproxil 245 mg.

Pharmacokinetic studies have not been reported with tenofovir disoproxil 245 mg tablets in children under 12 years or with renal impairment.

Intracellular pharmacokinetics
In non-proliferating human peripheral blood mononuclear cells (PBMCs) the half-life of tenofovir diphosphate has been reported to be approximately 50 h, whereas the half-life in phytohaemagglutinin-stimulated PBMCs was reported to be approximately 10 h.

5.3 Preclinical safety

Dolutegravir

Dolutegravir was not reported to be mutagenic or clastogenic using *in vitro* tests in bacteria and cultured mammalian cells, and an *in vivo* rodent micronucleus assay. Dolutegravir was not carcinogenic in long term reported studies in the mouse and rat.

Dolutegravir did not affect male or female fertility in rats at doses up to 1000 mg/kg/day, the highest dose tested (24 times the 50 mg twice daily human clinical exposure based on AUC).

Oral administration of dolutegravir to pregnant rats at doses up to 1000 mg/kg daily from days 6 to 17 of gestation did not elicit maternal toxicity, developmental toxicity or teratogenicity (27 times the 50 mg twice daily human clinical exposure based on AUC).

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, scant/no faeces/urine, suppressed body weight gain) was reported 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 reported in two preweanling deaths at 75 mg/kg/day. Over the preweaning treatment period, mean body weight gain was decreased in this group and the decrease persisted throughout the entire study for females during the postweaning period. The systemic exposure at this dose (based on AUC) to dolutegravir was ~17-20-fold higher than humans at the recommended pediatric exposure. There were no new target organs identified in juveniles compared to adults. In the rat pre/post-natal development reported study, decreased body weight of the developing offspring was reported during lactation at a maternally toxic dose (approximately 27 times human exposure at the maximum recommended human dose).

The effect of prolonged daily treatment with high doses of dolutegravir has been reported in repeat oral dose toxicity studies in rats (up to 26 weeks) and in monkeys (up to 38 weeks). The primary effect 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 (GI) intolerance is considered to be due to local active substance administration, mg/kg or mg/m^2 metrics are appropriate determinates of safety cover for this toxicity. GI 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/m^2 equivalent dose for a clinical dose of 50 mg twice daily.

Lamivudine

Administration of lamivudine in animal toxicity studies at high doses was not reported to be associated with any major organ toxicity. At the highest dosage levels, minor effects on indicators of liver and kidney function were reported together with occasional reductions in liver weight. The clinically relevant effects reported were a reduction in red blood cell count and neutropenia.

Lamivudine was not reported to be mutagenic in bacterial tests but, like many nucleoside analogues, reported activity in an *in vitro* cytogenetic assay and the mouse lymphoma assay. Lamivudine was not reported to be genotoxic *in vivo* 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.

A transplacental reported genotoxicity study conducted in monkeys compared zidovudine alone with the combination of zidovudine and lamivudine at human-equivalent exposures. The reported study demonstrated that foetuses exposed *in utero* to the combination sustained a higher level of nucleoside analogue-DNA incorporation into multiple foetal organs, and reported evidence of more telomere shortening than in those exposed to zidovudine alone. The clinical significance of these reported findings is unknown.

The results of long-term reported carcinogenicity studies in rats and mice did not report any carcinogenic potential relevant for humans.

A fertility reported study in rats has report that lamivudine had no effect on male or female fertility.

Tenofovir disoproxil

Non-clinical safety pharmacology reported studies reveal no special hazard for humans. Findings in reported repeated dose toxicity studies in rats, dogs and monkeys at exposure levels greater than or equal to clinical exposure levels and with possible relevance to clinical use include renal and bone toxicity and a decrease in serum phosphate concentration. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (BMD) (rats and dogs). The bone toxicity in young adult rats and dogs occurred at exposures ≥ 5-fold the exposure in paediatric or adult patients; bone toxicity occurred in juvenile infected monkeys at very high exposures following subcutaneous dosing (≥ 40-fold the exposure in patients). Reported 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 BMD.

Reported genotoxicity studies revealed positive results in the *in vitro* mouse lymphoma assay, equivocal results in one of the strains used in the Ames test, and weakly positive results in an UDS test in primary rat hepatocytes. However, it was negative in an *in vivo* mouse bone marrow micronucleus assay.

Reported oral carcinogenicity studies in rats and mice only revealed a low incidence of duodenal tumours at an extremely high dose in mice. These tumours are unlikely to be of relevance to humans.

Reported reproductive studies in rats and rabbits showed no effects on mating, fertility, pregnancy or foetal parameters. However, tenofovir disoproxil reduced the viability index and weight of pups in peri-postnatal toxicity studies at maternally toxic doses.

The active substance tenofovir disoproxil and its main transformation products are persistent in the environment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium, Magnesium stearate, Mannitol, Microcrystalline cellulose, Povidone, Sodium starch glycolate.
The tablets are film-coated with a coating material containing Macrogol/PEG, Polyvinyl alcohol-part hydrolyzed, Talc, and Titanium dioxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Do not store above 30°C. Protect from moisture

6.5 Nature and contents of container

White, opaque HDPE bottle with either 3g, 5g or 10g silica gel desiccant and closed with a white, opaque polypropylene screw cap.
Pack sizes: 30 and 90 film-coated tablets.

6.6 Instructions for use and handling

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

B4-9713

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

05/04/2019

10. DATE OF REVISION OF THE TEXT

Aug 2023

REFERENCES

1. WHO Summary of Product Characteristics of Dolutegravir/Lamivudine/Tenofovir disoproxil fumarate 50mg/300mg/300mg Tablets, Sun Pharmaceutical Industries Limited, February 2020.
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4. UK Summary of Product Characteristics of Epivir® (Lamivudine 150/300 mg tablets), ViiV Healthcare, UK, August 2021.
5. UK Summary of Product Characteristics of Viread® (Tenofovir disoproxil fumarate 245 mg tablets) Gilead Life Sciences, UK, January 2021.

Black

032 C

151 C

375 C

3305 C

SAP CODE :

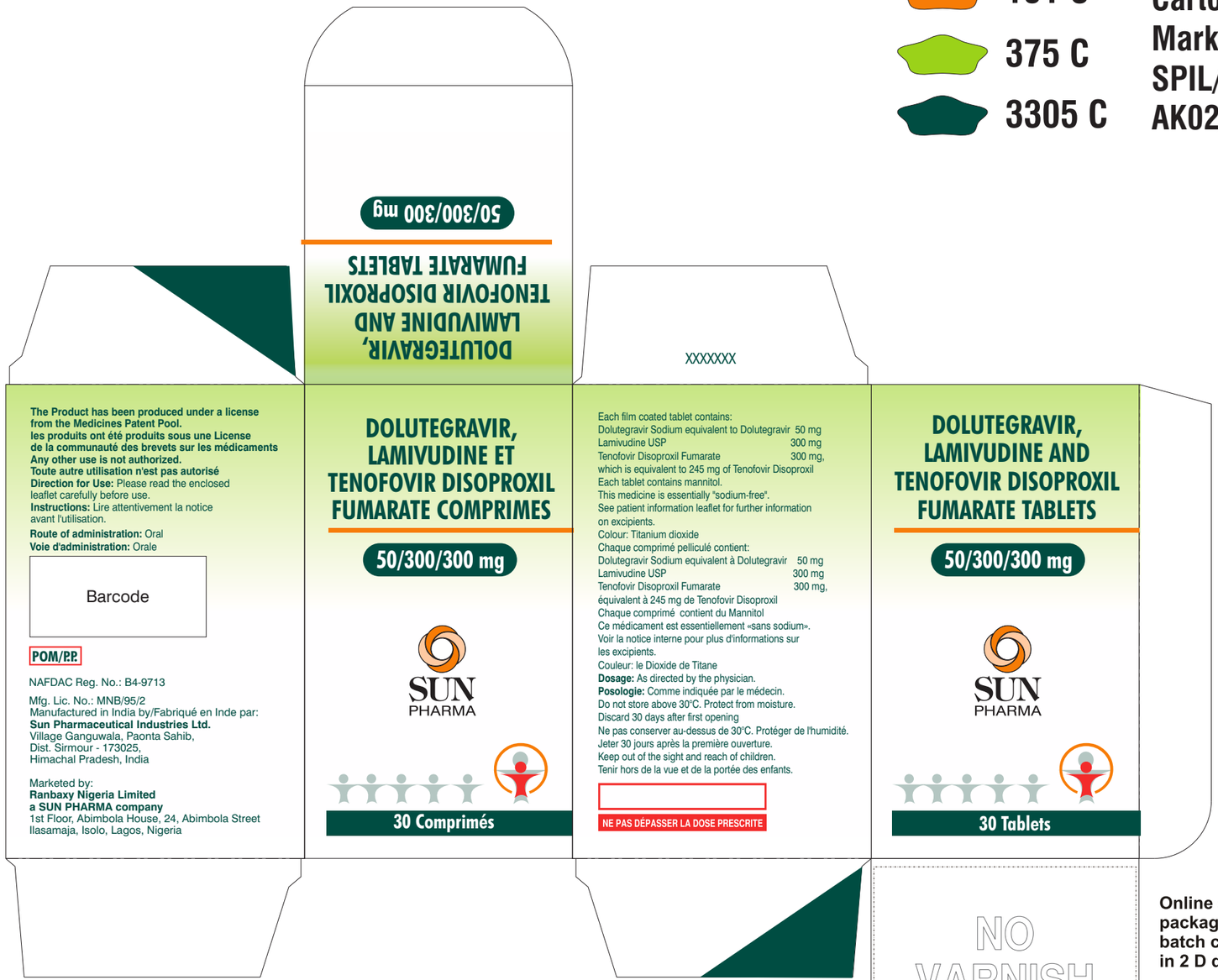
PHARMA CODE:

D+L+T 50+300+300 mg 30's Tabs. CT.

Carton Size : 52 x 58 x 92 mm

Market : Nigeria

SPIL/PKGDEV : AK01/Jul/2020-V01, AK02/Jul/2020-V02



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Exp.:XX/XXXX
S.N.: XXXXXXXXXXXXXX

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