634mm

450mm

34mm

34mm

Dolutegravir 50 mg, Lamivudine 300 mg and Tenofovir disoproxil fumarate 300 mg (equivalent to 245 mg of tenofovir disoproxil) Tablets

7579

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Dolutegravir 50 mg, Lamivudine 300 mg and Tenofovir disoproxil fumarate 300 mg (equivalent to 245 mg of tenofovir disoproxil) 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
Equivalent to Tenofovir Disoproxil ....300 mg
Lactose monohydrate ....140 mg
Mannitol 157mg

3. PHARMACEUTICAL FORM: Film Coated Tablets
White coloured, biconvex modified capsule shaped beveled edge film coated tablets debossed with 'L160' on one side and plain on the other side

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets is indicated for treatment of HIV-1 infection alone as a complete regimen in adults and paediatric patients weighing 40 kg and greater.

4.2 Posology and method of administration
Recommended Dosage for Adult and Pediatric Patients Weighing at Least 40 kg (88 lbs)
Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets is a three-drug fixed-dose combination product containing 50 mg of dolutegravir (DTG), 300 mg of lamivudine (3TC), and 300 mg of tenofovir disoproxil fumarate (TDF). The recommended dosage of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets in HIV-1-infected adults is one tablet taken orally once daily. Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets should be taken orally once daily with or without food in adults and paediatric patients weighing at least 40 kg (88 lbs) and creatinine clearance greater than or equal to 50 mL per minute.

Missed dose
If the patient misses a dose of dolutegravir-lamivudine-tenofovir disoproxil, the patient should take the medication as soon as possible, providing the next dose is not due within 4 hours. If the next dose is due within 4 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.

Testing Prior to Initiation of Dolutegravir, Lamivudine and Tenofovir Disoproxil fumarate Tablets
Prior to initiation of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets, patients should be tested for hepatitis B virus infection.
Estimated creatinine clearance, urine glucose, and urine protein should be assessed before initiating dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets therapy and should be monitored during therapy in all patients.
Perform pregnancy testing before initiation of dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets in adolescents and adults of childbearing potential (see section 4.4).

Not Recommended in Renal Impairment
Because dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets is a fixed-dose combination tablet and cannot be dose adjusted, it is not recommended for patients with impaired renal function (creatinine clearance less than 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis.

Not Recommended in Moderate to Severe Hepatic Impairment
Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C) [see section 4.4].

4.3 Contraindications
Dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets in patients:
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Co-administration with dofetilide is contraindicated (see section 4.5).

4.4 Special warnings and precautions for use
Dolutegravir-Lamivudine-Tenofovir disoproxil:
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.

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 mycobacterial infections, and Pneumocystis jirovecii pneumonia. 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 reconstitution, 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 observed in some hepatitis B and/or C co-infected patients at the start of dolutegravir therapy. Monitoring of liver biochemistries 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 dolutegravir-based therapy in hepatitis B co-infected patients (see section 4.8).
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.

Opportunistic infections
Patients should be advised that dolutegravir-lamivudine-tenofovir disoproxol 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.

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

Lamivudine and Tenofovir disoproxil:
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.

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 unknown. 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.

Dolutegravir:
Integrase class resistance of particular concern
The decision to use 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 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 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 was explored in two large randomized and blinded studies, GEMINI 1 and GEMINI 2 (see section 5.1). This regimen 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.

Lamivudine:
Lamivudine is not recommended for use as monotherapy.

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 (see section 4.2).

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.

Opportunistic infections: Patients receiving lamivudine, or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with associated HIV diseases.

Pancreatitis: Cases of pancreatitis have occurred rarely. However, it is not clear whether these cases were due to the antiretroviral treatment or to the underlying HIV disease. Treatment with lamivudine should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur.
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.
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 (see Zeffix SPC).
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: In a study performed in paediatric patients (see section 5.1 ARROW study), lower rates of virologic suppression and more frequent viral resistance were 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:
General
HIV antibody testing should be offered to all HBV infected patients before initiating tenofovir disoproxil therapy (see below Co-infection with HIV-1 and hepatitis B).
HIV-1
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.
Chronic hepatitis B
Patients must be advised that tenofovir disoproxil has not been proven to prevent the risk of transmission of HBV to others through sexual contact or contamination with blood. Appropriate precautions must continue to be used.
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. Co-administration of tenofovir disoproxil and didanosine results in a 40-60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions (see section 4.5). 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.

Triple therapy with nucleosides/nucleotides
There have been reports of a high rate of virological failure and of emergence of resistance at an early stage in HIV patients when tenofovir disoproxil was combined with lamivudine and abacavir as well as with lamivudine and didanosine as a once-daily regimen.

Renal and bone effects in adult population
Renal effects
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 (see section 4.8, proximal tubulopathy). 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 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 tenofovir disoproxil and 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 tenofovir disoproxil 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). In patients with renal risk factors, the co-administration of tenofovir disoproxil with a boosted protease inhibitor should be carefully evaluated.
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).

Renal impairment
Renal safety with tenofovir disoproxil has only been studied to a very limited degree in adult patients with impaired renal function (creatinine clearance < 80 ml/min).

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 (see sections 4.2 and 5.2).

Bone effects
In HIV infected patients, in a 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 observed 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 studies (prospective and cross-sectional), the most pronounced decreases in BMD were seen in patients treated with tenofovir disoproxil as part of a regimen containing a boosted protease inhibitor. Alternative treatment regimens should be considered for patients with osteoporosis that are at a high risk for fractures.
Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy (see section 4.8).
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 clinical study GS-US-104-0352 (see sections 4.8 and 5.1).

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 (see section 4.8, proximal tubulopathy). 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 (see section 4.2). 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 (see section 5.1).
If bone abnormalities are detected or suspected in paediatric patients, consultation with an endocrinologist and/or nephrologist should be obtained.

Liver disease
Safety and efficacy data are very limited in liver transplant patients.
There are limited 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, see above Exacerbations of hepatitis.

Use with certain hepatitis C virus antiviral agents
Co-administration of tenofovir disoproxil with ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir has been shown 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.

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.
Tenofovir disoproxil 245 mg film-coated tablets contain lactose monohydrate. Consequently, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction
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 (see Table 1). Co-administration of dolutegravir and other medicinal products that inhibit these enzymes may increase dolutegravir plasma concentration (see Table 1).
The absorption of dolutegravir is reduced by certain anti-acid agents (see Table 1).

Effect of dolutegravir on the pharmacokinetics of other agents
In vivo, dolutegravir did not have an effect on midazolam, a CYP3A4 probe. Based on 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 (for more information see section 5.2).
In vitro, dolutegravir inhibited 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. dofetilide, metformin) (see Table 1 and section 4.3).
In vitro, dolutegravir 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 studied in vivo. Dolutegravir may increase plasma concentrations of medicinal products in which excretion is dependent upon OAT3.
Established and theoretical interactions with selected antiretrovirals and non-antiretroviral medicinal products are listed in Table 1.

Interaction table
Interactions between dolutegravir and co-administered medicinal products are listed in Table 1 (increase is indicated as "↑", decrease as "↓", no change as "—", area under the concentration versus time curve as "AUC", maximum observed concentration as "Cmax", concentration at end of dosing interval as "Cτ").

Table 1: Drug interactions:

Medicinal products by therapeutic areas	Interaction Geometric mean change (%)	Recommendations concerning co-administration
HIV-1 Antiviral Agents		
Non-nucleoside Reverse Transcriptase Inhibitors		
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 decreased plasma dolutegravir concentration. The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with etravirine without boosted protease inhibitors. In paediatric patients the weight-based once daily dose should be administered twice daily. Dolutegravir should not be used with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir in INI-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 studied, a similar reduction in exposure as observed 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		
Tenofovir	Dolutegravir — AUC ↑ 1% C_{max} ↓ 3% Cτ ↓ 8% Tenofovir —	No dose adjustment is necessary.
Protease Inhibitors		
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 — Ritonavir — (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.
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 paediatric patients the weight-based once daily dose should be administered twice daily. In the presence of integrase class resistance this combination should be avoided (see section 4.4).
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.
Nelfinavir	Dolutegravir — (Not studied)	No dose adjustment is necessary.
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		
Boceprevir	Dolutegravir — AUC ↑ 7% C_{max} ↑ 5% Cτ ↑ 8% Boceprevir — (historical controls)	No dose adjustment is necessary.
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		
Antiarrhythmics		
Dofetilide	Dofetilide ↑ (Not studied, potential increase via inhibition of OCT2 transporter)	Dolutegravir and dofetilide co-administration is contraindicated due to potential life-threatening toxicity caused by high dofetilide concentration (see section 4.3).
Anticonvulsants		
Carbamazepine	Dolutegravir ↓ AUC ↓ 49% C_{max} ↓ 33% Cτ ↓ 73%	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with carbamazepine. In paediatric patients 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 studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a similar reduction in exposure as observed 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 studied)	No dose adjustment is necessary. Based on data from other CYP3A4 inhibitors, a marked increase is not expected.
Herbal products		
St. John's wort	Dolutegravir ↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a similar reduction in exposure as observed 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 (minimum 2 hours after or 6 hours 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 (minimum 2 hours after or 6 hours 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 50mg once daily: Metformin AUC ↑ 79% C_{max} ↑ 66% When co-administered with dolutegravir 50mg twice daily: Metformin AUC ↑ 145 % C_{max} ↑ 111%	A dose adjustment of metformin should be considered 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 (section 4.4).
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 paediatric patients the weight-based once daily dose should be administered twice daily. 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 contraceptives		
Ethinyl estradiol (EE) and Norelgestromin (NGMN)	Dolutegravir — EE — AUC ↑ 3% C_{max} ↓ 1% NGMN — AUC ↓ 2% C_{max} ↓ 11%	Dolutegravir had no pharmacodynamic effect on Luteinizing Hormone (LH), Follicle 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 of either agent.

Paediatric population
Interaction studies have only been performed in adults.

Lamivudine:
Interaction studies have only been performed in adults.
The likelihood of metabolic interactions is low due to limited metabolism and plasma protein binding and almost complete renal clearance.
Administration of trimethoprim/sulfamethoxazole 160 mg/800 mg 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 (see section 4.2). Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole. When concomitant administration 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 shown 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 %) was observed 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).
Due to similarities, Lamivudine should not be administered concomitantly with other cytidine analogues, such as emtricitabine. Moreover, Lamivudine should not be taken with any other medicinal products containing lamivudine (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 lamivudine 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. PIs) unlikely.
Coadministration of sorbitol solution (3.2 g, 10.2 g, 13.4 g) with a single 300 mg dose of lamivudine oral solution 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 coadministration of Lamivudine with medicinal products containing sorbitol or other osmotic acting poly-alcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol). Consider more frequent monitoring of HIV-1 viral load when chronic coadministration cannot be avoided.

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

Concomitant use not recommended
Tenofovir disoproxil fumarate should not be administered concomitantly with other medicinal products containing tenofovir disoproxil or tenofovir alafenamide.
Tenofovir disoproxil fumarate should not be administered concomitantly with adefovir dipivoxil.
Didanosine
Co-administration of tenofovir disoproxil and didanosine is not recommended (see section 4.4 and Table 2).

Renally eliminated medicinal products
Since tenofovir is primarily eliminated by the kidneys, co-administration of tenofovir disoproxil 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 and/or the co-administered medicinal products.
Use of tenofovir disoproxil should be avoided with concurrent or recent use of a nephrotoxic medicinal product. 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 interactions
Interactions between tenofovir disoproxil and other medicinal products are listed in Table 2 below (increase is indicated as " ", decrease as " ", no change as " ", twice daily as "b.i.d.", and once daily as "q.d.").

Table 2: Interactions between tenofovir disoproxil and other medicinal products

Medicinal product by therapeutic areas (dose in mg)	Effects on drug levels Mean percent change in AUC, Cmax, Cmin	Recommendation concerning co-administration with 245 mg tenofovir disoproxil
ANTI-INFECTIVES		
Antiretrovirals		
Protease inhibitors		
Atazanavir/Ritonavir (300 q.d./100 q.d./300 q.d.)	Atazanavir: AUC: ↓ 25% Cmax: ↓ 28% Cmin: ↓ 26% Tenofovir: AUC: ↑ 37% Cmax: ↑ 34% Cmin: ↑ 29%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir-associated adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
Lopinavir/Ritonavir (400 b.i.d./100 b.i.d./300 q.d.)	Lopinavir/ritonavir: No significant effect on lopinavir/ritonavir PK parameters. Tenofovir: AUC: ↑ 32% Cmax: — Cmin: ↑ 51%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir-associated adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
Darunavir/Ritonavir (300/100 b.i.d./300 q.d.)	Darunavir: No significant effect on darunavir/ritonavir PK parameters. Tenofovir: AUC: ↑ 22% Cmin: ↑ 37%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir-associated adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
NRTIs		
Didanosine	Co-administration of tenofovir disoproxil and didanosine results in a 40-60% increase in systemic exposure to didanosine that may increase the risk for 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.	Co-administration of tenofovir disoproxil and didanosine is not recommended (see section 4.4).
Adefovir dipivoxil	AUC: — Cmax: —	Tenofovir disoproxil should not be administered concurrently with adefovir dipivoxil (see section 4.4).
Entecavir	AUC: — Cmax: —	No clinically significant pharmacokinetic interactions when tenofovir disoproxil was co-administered with entecavir.
Hepatitis C virus antiviral agents		
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Atazanavir/Ritonavir (300 mg q.d./100 mg q.d.) + Emtricitabine/ Tenofovir disoproxil (200 mg/245 mg q.d.)1	Ledipasvir: AUC: ↑96% Cmax: ↑68% Cmin: ↑118% Sofosbuvir: AUC: — Cmax: — GS-3310072: AUC: — Cmax: — Cmin: ↑42% Atazanavir: AUC: — Cmax: — Cmin: ↑63% Ritonavir: AUC: — Cmax: — min: ↑45% Emtricitabine: AUC: — Cmax: — Cmin: — Tenofovir: AUC: — Cmax: ↑47% Cmin: ↑47%	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, ledipasvir/sofosbuvir and atazanavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with ledipasvir/sofosbuvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. 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 q.d.) + Darunavir/Ritonavir (800 mg q.d./100 mg q.d.) Emtricitabine/ Tenofovir disoproxil (200 mg/245 mg q.d.)1	Ledipasvir: AUC: — Cmax: — Cmin: — Sofosbuvir: AUC: ↓27% Cmax: ↓37% GS-3310072: AUC: — Cmax: — Cmin: — Darunavir: AUC: — Cmax: — Cmin: — Ritonavir: AUC: — Cmax: — Cmin: ↑48% Emtricitabine: AUC: — Cmax: — Cmin: — Tenofovir: AUC: ↑50% Cmax: ↑64% Cmin: ↑59%	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, ledipasvir/sofosbuvir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with ledipasvir/sofosbuvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. 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 q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Ledipasvir: AUC: ↓34% Cmax: ↓34% Cmin: ↓34% Sofosbuvir: AUC: — Cmax: — GS-3310072: AUC: — Cmax: — Cmin: — Efavirenz: AUC: — Cmax: — Cmin: — Emtricitabine: AUC: — Cmax: — Cmin: — Tenofovir: AUC: ↑98% Cmax: ↑79% Cmin: ↑163%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Emtricitabine/Rilpivirine/Tenofovir disoproxil (200 mg/25 mg/245 mg q.d.)	Ledipasvir: AUC: — Cmax: — Cmin: — Sofosbuvir: AUC: — Cmax: — GS-3310072: AUC: — Cmax: — Cmin: — Emtricitabine: AUC: — Cmax: — Cmin: — Rilpivirine: AUC: — Cmax: — Cmin: — Tenofovir: AUC: ↑40% Cmax: — Cmin: ↑91%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Dolutegravir (50 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: — Cmax: — GS-3310072 AUC: — Cmax: — Cmin: — Ledipasvir: AUC: — Cmax: — Cmin: — Dolutegravir AUC: — Cmax: — Cmin: — Emtricitabine: AUC: — Cmax: — Cmin: — Tenofovir: AUC: ↑65% Cmax: ↑61% Cmin: ↑115%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Atazanavir/Ritonavir (300 mg q.d./100 mg q.d.)+ Emtricitabine/ Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: — Cmax: — GS-3310072: AUC: — Cmax: — Cmin: ↑42% Velpatasvir: AUC: ↑142% Cmax: ↑55% Cmin: ↑301% Atazanavir: AUC: — Cmax: — Cmin: ↑39% Ritonavir: AUC: — Cmax: — Cmin: ↑29% Emtricitabine: AUC: — Cmax: — Cmin: — Tenofovir: AUC: — Cmax: ↑55% Cmin: ↑39%	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, sofosbuvir/velpatasvir and atazanavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil 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 q.d.) + Darunavir/Ritonavir (800 mg q.d./100 mg q.d.)+ Emtricitabine/ Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↓28% Cmax: ↓38% GS-3310072: AUC: — Cmax: — Cmin: — Velpatasvir: AUC: — Cmax: ↓24% Cmin: — Darunavir: AUC: — Cmax: — Cmin: — Ritonavir: AUC: — Cmax: — Cmin: — Emtricitabine: AUC: — Cmax: — Cmin: — Tenofovir: AUC: ↑39% Cmax: ↑55% Cmin: ↑52%	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, sofosbuvir/velpatasvir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil 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 q.d.) + Darunavir/Ritonavir (800 mg q.d./100 mg q.d.)+ Emtricitabine/ Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↓29% Cmax: ↓41% GS-3310072: AUC: — Cmax: — Cmin: — Velpatasvir: AUC: — Cmax: ↓30% Cmin: ↑63% Lopinavir: AUC: — Cmax: — Cmin: — Ritonavir: AUC: — Cmax: — Cmin: — Emtricitabine: AUC: — Cmax: — Cmin: — Tenofovir: AUC: — Cmax: ↑42% Cmin: —	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, sofosbuvir/velpatasvir and lopinavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil 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 q.d.) + Raltegravir (400 mg b.i.d) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: — Cmax: — GS-3310072: AUC: — Cmax: — Cmin: — Velpatasvir: AUC: — Cmax: — Cmin: — Raltegravir: AUC: — Cmax: — Cmin: ↓21% Emtricitabine: AUC: — Cmax: — Cmin: — Tenofovir: AUC: ↑40% Cmax: ↑46% Cmin: ↑70%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.)+ Efavirenz/ Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Sofosbuvir: AUC: — Cmax: ↑38% GS-3310072: AUC: — Cmax: — Cmin: — Velpatasvir: AUC: ↓53% Cmax: ↓47% Cmin: ↓57% Efavirenz: AUC: — Cmax: — Cmin: — Emtricitabine: AUC: — Cmax: — Cmin: — Tenofovir: AUC: ↑81% Cmax: ↑77% Cmin: ↑121%	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.
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.)+ Emtricitabine/ Rilpivirine/Tenofovir disoproxil (200 mg/25 mg/245 mg q.d.)	Sofosbuvir: AUC: — Cmax: — GS-3310072: AUC: — Cmax: — Cmin: — Velpatasvir: AUC: — Cmax: — Cmin: — Emtricitabine: AUC: — Cmax: — Cmin: — Rilpivirine: AUC: — Cmax: — Cmin: — Tenofovir: AUC: ↑40% Cmax: ↑44% min: ↑84%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, 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.)3 + Darunavir (800 mg q.d.) + Ritonavir (100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: — Cmax: ↓30% Cmin: N/A GS-3310072: AUC: — Cmax:— Cmin: N/A Velpatasvir: AUC: — Cmax: — Cmin: — Voxilaprevir: AUC: ↑143% Cmax: ↑72% Cmin: ↑300% Darunavir: AUC: — Cmax: — Cmin: ↓34% Ritonavir: AUC: ↑45% Cmax: ↑60% Cmin: — Emtricitabine: AUC: — Cmax: — Cmin: — Tenofovir: AUC: ↑39% Cmax: ↑48% Cmin: ↑47%	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 (see section 4.4).
Sofosbuvir (400 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Sofosbuvir: AUC: — Cmax: ↓19% GS-3310072: AUC: — Cmax: ↓23% Efavirenz: AUC: — Cmax: — Cmin: — Emtricitabine: AUC: — Cmax: — Cmin: — Tenofovir: AUC: — Cmax: ↑25% Cmin: —	No dose adjustment is required.

[1] Data generated from simultaneous dosing with ledipasvir/sofosbuvir. Staggered administration (12 hours apart) provided similar results.
[2] The predominant circulating metabolite of sofosbuvir.
[3] Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.
Studies conducted with other medicinal products
There were no clinically significant pharmacokinetic interactions 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.
Studies conducted with other medicinal products
There were no clinically significant pharmacokinetic interactions 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.
Tenofovir disoproxil must be taken with food, as food enhances the bioavailability of tenofovir (see section 5.2).

4.6 Fertility, pregnancy and lactation
Dolutegravir:
Pregnancy
There are limited amount of data from the use of dolutegravir in pregnant women. The effect of dolutegravir on human pregnancy is unknown. In reproductive toxicity studies in animals, dolutegravir was shown to cross the placenta. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Dolutegravir should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus.

Breast-feeding
It is unknown whether dolutegravir is excreted in human milk. Available toxicological data in animals has shown excretion of dolutegravir in milk. In lactating rats that received a single oral dose of 50 mg/kg at 10 days postpartum, dolutegravir was detected in milk at concentrations typically higher than blood. It is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

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

Lamivudine:
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.
Animal studies with lamivudine showed an increase in early embryonic deaths in rabbits but not in rats (see section 5.3). Placental transfer of lamivudine has been shown to occur in humans.
More than 1000 outcomes from first trimester and more than 1000 outcomes from second and third trimester exposure in pregnant women indicate no malformative and foeto/neonatal effect. Lamivudine can be used during pregnancy if clinically needed. The malformative risk is unlikely in humans based on those data.
For patients co-infected with hepatitis who are being treated with lamivudine and subsequently become pregnant, consideration should be given to the possibility of a recurrence of hepatitis on discontinuation of lamivudine.

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

Breast-feeding
Following oral administration lamivudine was excreted in breast milk at similar concentrations to those found in serum. Based on more than 200 mother/child pairs treated for HIV, serum concentrations of lamivudine in breastfed infants of mothers treated for HIV are very low (< 4% of maternal serum concentrations) and progressively decrease to undetectable levels when breastfed infants reach 24 weeks of age. There are no data available on the safety of lamivudine when administered to babies less than three months old. It is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

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

Tenofovir
Pregnancy
A large amount of data on pregnant women (more than 1,000 pregnancy outcomes) indicate no malformations or foetal/neonatal toxicity associated with tenofovir disoproxil. Animal studies do not indicate reproductive toxicity (see section 5.3). The use of tenofovir disoproxil may be considered during pregnancy, if necessary.

Breast-feeding
Tenofovir has been shown to be excreted in human milk. There is insufficient information on the effects of tenofovir in newborns/infants. Therefore Tenofovir disoproxil fumarate should not be used during breast-feeding.
As a general rule, it is recommended that HIV and HBV infected women do not breast-feed their infants in order to avoid transmission of HIV and HBV to the infant.

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

4.7 Effects on ability to drive and use machines
Dolutegravir and tenofovir disoproxil, may have a minor influence on the ability to drive and use machines. Dizziness may occur following administration of dolutegravir and tenofovir disoproxil (see section 4.8).

4.8 Undesirable effects
Dolutegravir:
Summary of the safety profile
The most severe adverse reaction, seen 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%).

Tabulated list of adverse reactions
The adverse reactions considered at least possibly related to dolutegravir are listed by body system, organ class and absolute frequency. Frequencies 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 3 Adverse Reactions

Immune system disorders	Uncommon	Hypersensitivity (see section 4.4)
	Uncommon	Immune Reconstitution Syndrome (see section 4.4)**
Psychiatric disorders	Common	Insomnia
	Common	Abnormal dreams
	Common	Depression
	Common	Anxiety
	Uncommon	Suicidal ideation*, suicide attempt* *particularly in patients with a pre-existing history of depression or psychiatric illness.
Nervous system disorders	Very common	Headache
	Common	Dizziness
Gastrointestinal disorders	Very common	Nausea
	Very common	Diarrhoea
	Common	Vomiting
	Common	Flatulence
	Common	Upper abdominal pain
	Common	Abdominal pain
	Common	Abdominal discomfort
Hepatobiliary disorders	Uncommon	Hepatitis
	Rare	Acute hepatic failure
Skin and subcutaneous tissue disorders	Common	Rash
	Common	Pruritus
Musculoskeletal and connective tissue disorders	Uncommon	Arthralgia
	Uncommon	Myalgia
General disorders and administration site conditions	Common	Fatigue
Investigations	Common	Alanine aminotransferase (ALT) and/or Aspartate aminotransferase (AST) elevations
	Common	Creatine phosphokinase (CPK) elevations

**see below under Description of selected adverse reactions.
Description of selected adverse reactions
Changes in laboratory biochemistries
Increases in serum creatinine occurred 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 observed 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
In Phase III studies patients with hepatitis B and/or C co-infection were permitted to enrol provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal (ULN). Overall, the safety profile in patients co-infected with hepatitis B and/or C was similar to that observed 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 observed 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.

Immune reactivation 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; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Paediatric population
Based on limited available data in children and adolescents (6 to less than 18 years of age and weighing at least 15 kg), there were no additional types of adverse reactions beyond those observed in the adult population.

Lamivudine**:**
The following adverse reactions have been reported during therapy for HIV disease with lamivudine.
The adverse reactions considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency. Frequencies 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). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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

Metabolism and nutrition disorders
Very rare: Lactic acidosis

Nervous system disorders
Common: Headache, insomnia
Very rare: Peripheral neuropathy (or paraesthesia)

Respiratory, Thoracic and mediastinal disorders
Common: Cough, nasal symptoms
Gastrointestinal disorders
Common: Nausea, vomiting, abdominal pain or cramps, diarrhoea
Rare: Pancreatitis, elevations in serum amylase

Hepatobiliary disorders
Uncommon: Transient elevations in liver enzymes (AST, ALT)
Rare: Hepatitis

Skin and subcutaneous tissue disorders
Common: Rash, alopecia
Rare: Angioedema

Musculoskeletal and connective tissue disorders
Common: Arthralgia, muscle disorders
Rare: Rhabdomyolysis

General disorders and administration site conditions
Common: Fatigue, malaise, fever
Weight and levels of blood lipids and glucose may increase during antiretroviral therapy.
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.
Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term combined antiretroviral exposure (CART). The frequency of which is unknown.

Paediatric population
1206 HIV-infected paediatric patients aged 3 months to 17 years were enrolled in the ARROW Trial (COL105677), 669 of whom received abacavir and lamivudine either once or twice daily (see section 5.1). No additional safety issues have been identified in paediatric subjects receiving either once or twice daily dosing compared to adults.

Tenofovir Disoproxil Fumarate**:**
Summary of the safety profile
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 fumarate (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 fumarate and didanosine is not recommended as this may result in an increased risk of adverse reactions (see section 4.5). Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported (see section 4.4).

Hepatitis B: Approximately one quarter of patients can be expected to experience adverse reactions following treatment with tenofovir disoproxil, most of which are mild. In clinical trials of HBV infected patients, the most frequently occurring adverse reaction to tenofovir disoproxil was nausea (5.4%).
Acute exacerbation of hepatitis has been reported in patients on treatment as well as in patients who have discontinued hepatitis B therapy (see section 4.4).

Tabulated summary of adverse reactions
Assessment of adverse reactions for tenofovir disoproxil is based on safety data from clinical studies and post-marketing experience. All adverse reactions are presented in Table 4.

HIV-1 clinical studies: Assessment of adverse reactions from HIV-1 clinical study data is based on experience in two studies in 653 treatment-experienced patients receiving treatment with tenofovir disoproxil (n = 443) or placebo (n = 210) in combination with other antiretroviral medicinal products for 24 weeks and also in a double-blind comparative controlled study in which 600 treatment-naive patients received treatment with tenofovir disoproxil 245 mg (n = 299) or stavudine (n = 301) in combination with lamivudine and efavirenz for 144 weeks.

Hepatitis B clinical studies: Assessment of adverse reactions from HBV clinical study data is primarily based on experience in two double-blind comparative controlled studies in which 641 adult patients with chronic hepatitis B and compensated liver disease received treatment with tenofovir disoproxil 245 mg daily (n = 426) or adefovir dipivoxil 10 mg daily (n = 215) for 48 weeks. The adverse reactions observed with continued treatment for 384 weeks were consistent with the safety profile of tenofovir disoproxil. After an initial decline of approximately -4.9 ml/min (using Cockcroft-Gault equation) or -3.9 ml/min/1.73 m^2 (using modification of diet in renal disease [MDRD] equation) after the first 4 weeks of treatment, the rate of annual decline post baseline of renal function reported in tenofovir disoproxil treated patients was -1.41 ml/min per year (using Cockcroft-Gault equation) and -0.74 ml/min/1.73 m^2 per year (using MDRD equation).

Patients with decompensated liver disease: The safety profile of tenofovir disoproxil in patients with decompensated liver disease was assessed in a double-blind active controlled study (GS-US-174-0108) in which adult patients received treatment with tenofovir disoproxil (n = 45) or emtricitabine plus tenofovir disoproxil (n = 45) or entecavir (n = 22) for 48 weeks.
In the tenofovir disoproxil treatment arm, 7% of patients discontinued treatment due to an adverse event; 9% of patients experienced a confirmed increase in serum creatinine of ≥ 0.5 mg/dl or confirmed serum phosphate of < 2 mg/dl through week 48; there were no statistically significant differences between the combined tenofovir-containing arms and the entecavir arm. After 168 weeks, 16% (7/45) of the tenofovir disoproxil group, 4% (2/45) of the emtricitabine plus tenofovir disoproxil group, and 14% (3/22) of the entecavir group experienced tolerability failure. Thirteen percent (6/45) of the tenofovir disoproxil group, 13% (6/45) of the emtricitabine plus tenofovir disoproxil group, and 9% (2/22) of the entecavir group had a confirmed increase in serum creatinine ≥ 0.5 mg/dl or confirmed serum phosphate of < 2 mg/dl.
At week 168, in this population of patients with decompensated liver disease, the rate of death was of 13% (6/45) in the tenofovir disoproxil group, 11% (5/45) in the emtricitabine plus tenofovir disoproxil group and 14% (3/22) in the entecavir group. The rate of hepatocellular carcinoma was 18% (8/45) in the tenofovir disoproxil group, 7% (3/45) in the emtricitabine plus tenofovir disoproxil group and 9% (2/22) in the entecavir group.
Subjects with a high baseline CPT score were at higher risk of developing serious adverse events (see section 4.4).

Patients with lamivudine-resistant chronic hepatitis B: No new adverse reactions to tenofovir disoproxil were identified from a randomised, double-blind study (GS-US-174-0121) in which 280 lamivudine-resistant patients received treatment with tenofovir disoproxil (n = 141) or emtricitabine/tenofovir disoproxil (n = 139) for 240 weeks.
The adverse reactions with suspected (at least possible) relationship to treatment are listed below by body system organ class and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) or rare (≥ 1/10,000 to < 1/1,000).

Table 4: Tabulated summary of adverse reactions associated with tenofovir disoproxil based on clinical study and post-marketing experience

Frequency	**Tenofovir disoproxil**
Metabolism and nutrition disorders:	
Very common:	hypophosphataemia[1]
Uncommon:	hypokalaemia[1]
Rare:	lactic acidosis
Nervous system disorders:	
Very common:	dizziness
Common:	headache
Gastrointestinal disorders:	
Very common:	diarrhoea, vomiting, nausea
Common:	abdominal pain, abdominal distension, flatulence
Uncommon:	pancreatitis
Hepatobiliary disorders:	
Common:	increased transaminases
Rare:	hepatic steatosis, hepatitis
Skin and subcutaneous tissue disorders:	
Very common:	rash
Rare:	angioedema
Musculoskeletal and connective tissue disorders:	
Uncommon:	rhabdomyolysis1, muscular weakness[1]
Rare:	osteomalacia (manifested as bone pain and infrequently contributing to fractures)[1, 2] myopathy[1]
Renal and urinary disorders:	
Uncommon:	increased creatinine, proximal renal tubulopathy (including Fanconi syndrome)

XXXXXX

Pharmacode Direction

34 mm

Market/Customer :	Malawi	**Location :**	Nagpur
Prepared On :	01/06/2021	**Tracking No. :**	05
Product Name :	Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets Leaflet		
Material Code :	267781	**Supersedes Material code :**	NA
Open Size :	634 x 450 mm (L x W)	**Barcode :**	NA
Folded Size :	34 x 34 mm (L x W)	**Barcode Type (Ex. NDC, PZN, EAN-13)**	NA
Substrate :	GSM : 40 gsm	**Component :**	Pack Insert
	Paper : Bible Paper	**Font Size :**	5 pt
Font Name :	Helvetica condensed	**Gluing :**	YES
Perforation :	NA	**Pharma Code :**	7579
Cover Page Substrate :	NA		
Pantone Colours :	Black / Dieline (does not print)		
Reason for Change :	New Artwork		
Unicorn Creation D/Lupin/Export/Malawi/Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets/			

634mm

450mm

Rare:	acute renal failure, renal failure, acute tubular necrosis, nephritis (including acute interstitial nephritis)2, nephrogenic diabetes insipidus
General disorders and administration site conditions:	
Very common:	asthenia
Common:	fatigue

[1] This 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.
[2] This adverse reaction was identified through post-marketing surveillance but not observed in randomised controlled clinical trials or the tenofovir disoproxil expanded access program. The frequency category was estimated from a statistical calculation based on the total number of patients exposed to tenofovir disoproxil in randomised controlled clinical trials and the expanded access program (n = 7,319).

Description of selected adverse reactions
HIV-1 and hepatitis B:
Renal impairment
As tenofovir disoproxil fumarate may cause renal damage monitoring of renal function is recommended. Proximal renal tubulopathy generally resolved or improved after tenofovir disoproxil discontinuation. However, in some patients, 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.

HIV-1:
Interaction with didanosine
Co-administration of tenofovir disoproxil and didanosine is not recommended as it results 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.

Metabolic parameters
Weight and levels of blood lipids and glucose may increase during antiretroviral therapy.

Immune reactivation syndrome
In HIV infected patients with severe immune deficiency at the time of initiation of 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; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

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.

Hepatitis B:
Exacerbations of hepatitis during treatment
In 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 have occurred after discontinuation of HBV therapy.

Paediatric population
HIV-1
Assessment of adverse reactions is based on two randomised trials (studies GS-US-104-0321 and GS-US-104-0352) in 184 HIV-1 infected paediatric patients (aged 2 to < 18 years) who received treatment with tenofovir disoproxil (n = 93) or placebo/active comparator (n = 91) in combination with other antiretroviral agents for 48 weeks. The adverse reactions observed in paediatric patients who received treatment with tenofovir disoproxil were consistent with those observed in clinical studies of tenofovir disoproxil in adults.
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 observed in subjects who received placebo. In HIV-1 infected children, the BMD Z-scores observed in subjects who switched to tenofovir disoproxil were lower than those observed in subjects who remained on their stavudine- or zidovudine-containing regimen.
In study GS-US-104-0352, 4 out of 89 paediatric patients exposed to tenofovir disoproxil (median tenofovir disoproxil exposure 312 weeks) discontinued due to adverse reactions consistent with proximal renal tubulopathy. Seven patients had estimated glomerular filtration rate (GFR) values between 70 and 90 mL/min/1.73 m². Among them, two patients experienced a clinically meaningful decline in estimated GFR which improved after discontinuation of tenofovir disoproxil.

Chronic hepatitis B
Assessment of adverse reactions is based on one randomised study (study GS-US-174-0115) in 106 adolescent patients (12 to < 18 years of age) with chronic hepatitis B receiving treatment with tenofovir disoproxil 245 mg (n = 52) or placebo (n = 54) for 72 weeks. The adverse reactions observed in adolescent patients who received treatment with tenofovir disoproxil were consistent with those observed in clinical studies of tenofovir disoproxil in adults.
Reductions in BMD have been observed in HBV infected adolescents. The BMD Z-scores observed in subjects who received tenofovir disoproxil were lower than those observed in subjects who received placebo.

Other special population(s)
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.

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 fumarate. The use of tenofovir disoproxil is not recommended in paediatric patients with renal impairment.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 **Overdose**
Dolutegravir:
There is currently limited experience with overdosage in dolutegravir.
Limited experience of single higher doses (up to 250 mg in healthy subjects) revealed 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 acute animal studies did not result in any organ toxicity. Limited data are available on the consequences of ingestion of acute overdoses in humans. No fatalities occurred, and the patients recovered. No specific signs or symptoms have been identified following such overdose.
If overdose 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 overdose, although this has not been studied.

Tenofovir Disoproxil Fumarate:
Symptoms
If overdose occurs the patient must be monitored for evidence of toxicity (see sections 4.8 and 5.3), and standard supportive treatment applied as necessary.

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

5. **PHARMACOLOGICAL PROPERTIES**
5.1 **Pharmacodynamic properties**
ATC codes: J05AX12 (**Dolutegravir**), J05AF05 (**Lamivudine**) and J05AF07 (**Tenofovir Disoproxil Fumarate**)

Dolutegravir:
Mechanism of action
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.

Pharmacodynamic effects
Antiviral activity in cell culture
The IC$_{50}$ for dolutegravir in various labstrains using PBMC was 0.5 nM, and when using MT-4 cells it ranged from 0.7-2 nM. Similar IC$_{50}$s were seen for clinical isolates without any major difference between subtypes; in a panel of 24 HIV-1 isolates of clades A, B, C, D, E, F and G and group O the mean IC$_{50}$ value was 0.2 nM (range 0.02-2.14). The mean IC$_{50}$ for 3 HIV-2 isolates was 0.18 nM (range 0.09-0.61).

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

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

Resistance
Resistance in vitro
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 appeared 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 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 using clinical isolates of subtype B, mutation R263K was seen in all five isolates (after 20 weeks and onwards). In subtype C (n=2) and A/G (n=2) isolates the integrase substitution R263K was selected in one isolate, and G118R in two isolates. R263K was reported from two ART experienced, INI naive individual patients with subtypes B and C in the clinical program, but without effects on dolutegravir susceptibility in vitro. G118R lowers the susceptibility to dolutegravir in site directed mutants (FC 10) but was not detected in patients receiving dolutegravir in the Phase III program.
Primary mutations for raltegravir/elvitegravir (Q148H/R/K, N155H, Y143R/H/C, E92Q and T66I) do not affect the in vitro susceptibility of dolutegravir as single mutations. When mutations listed as secondary integrase inhibitor associated mutations (for raltegravir/elvitegravir) are added to these primary mutations in experiments with site directed mutants, dolutegravir susceptibility is still unchanged (FC <2 vs wild type virus), except in the case of Q148-mutations, where a FC 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 vs wild type virus) has not been determined; genotypic resistance was a better predictor for outcome.
Seven hundred and five raltegravir resistant isolates from raltegravir experienced patients were analyzed for susceptibility to dolutegravir. Dolutegravir has a less than or equal to 10 FC against 94% of the 705 clinical isolates.

Resistance in vivo
In previously untreated patients receiving dolutegravir + 2 NRTIs in Phase IIb and Phase III, no development of resistance to the integrase class, or to the NRTI class was seen (n=1118 follow-up of 48-96 weeks). In previously untreated patients receiving dolutegravir + lamivudine in the 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 (SAILING study), integrase inhibitor substitutions were observed in 4/354 patients (follow-up 48 weeks) treated with dolutegravir, which was given in combination with an investigator selected background regimen (BR). Of these four, two subjects had a unique R263K integrase substitution, with a maximum FC of 1.93, one subject had a polymorphic V151V/I integrase substitution, with maximum FC of 0.92, and one subject had pre-existing integrase mutations and is assumed to have been integrase experienced or infected with integrase resistant virus by transmission. The R263K mutation was also selected in vitro (see above).
In the presence of integrase class-resistance (VIKING-3 study) the following mutations were selected in 32 patients with protocol defined virological failure (PDVF) through Week 24 and with paired genotypes (all treated with dolutegravir 50 mg twice daily + optimized background agents): L74L/M (n=1), E92Q (n=2), T97A (n=9), E138K/A/T (n=8), G140S (n=2), Y143H (n=1), S147G (n=1), Q148H/K/R (n=4), and N155H (n=1) and E157E/Q (n=1). Treatment emergent integrase resistance typically appeared in patients with a history of the Q148-mutation (baseline or historic). Five further subjects experienced PDVF between weeks 24 and 48, and 2 of these 5 had treatment emergent mutations. Treatment-emergent mutations or mixtures of mutations observed were L74I (n=1), N155H (n=2).
The VIKING-4 study examined dolutegravir (plus optimized background therapy) in subjects with primary genotypic resistance to INIs at Screening in 30 subjects. Treatment-emergent mutations observed were consistent with those observed in the VIKING-3 study.

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

Clinical efficacy and safety
Previously untreated patients
The efficacy of dolutegravir in HIV-infected, therapy naïve subjects is based on the analyses of 96-week data from two randomized, international, double-blind, active-controlled trials, SPRING-2 (ING113086) and SINGLE (ING114467). This is supported by 96-week data from an open-label, randomized and active-controlled study FLAMINGO (ING114915) and additional data from the open-label phase of SINGLE to 144 weeks. The efficacy of dolutegravir in combination with lamivudine in adults is supported by 48-week primary endpoint data from two identical 148-week, randomised, multicentre, double-blind, non-inferiority studies GEMINI-1 (204861) and GEMINI-2 (205543).
In SPRING-2, 822 adults were randomized and received at least one dose of either dolutegravir 50 mg once daily or raltegravir (RAL) 400 mg twice daily, both administered with either ABC/3TC or TDF/FTC. At baseline, median patient age was 36 years, 14% were female, 15% non-white, 11% had hepatitis B and/or C co-infection and 2% were CDC Class C, these characteristics were similar between treatment groups.
In SINGLE, 833 subjects were randomized and received at least one dose of either dolutegravir 50 mg once daily with fixed-dose abacavir-lamivudine (DTG + ABC/3TC) or fixed-dose efavirenz-tenofovir-emtricitabine (EFV/TDF/FTC). At baseline, median patient age was 35 years, 16% were female, 32% non-white, 7% had hepatitis C co-infection and 4% were CDC Class C, these characteristics were similar between treatment groups.
The primary endpoint and other week 48 outcomes (including outcomes by key baseline covariates) for SPRING-2 and SINGLE are shown in Table 5.

Table 5 Response in **SPRING-2 and SINGLE at 48 Weeks (Snapshot algorithm, <50 copies/mL)**

	SPRING-2		SINGLE	
	Dolutegravir 50 mg Once Daily + 2 NRTI N=411	**RAL 400 mg Twice Daily + 2 NRTI N=411**	**Dolutegravir 50 mg + ABC/3TC Once Daily N=414**	**EFV/TDF/FTC Once Daily N=419**
HIV-1 RNA <50 copies/mL	88%	85%	88%	81%
Treatment Difference*	2.5% (95% CI: -2.2%, 7.1%)		7.4% (95% CI: 2.5%, 12.3%)	
Virologic non-response†	5%	8%	5%	6%
HIV-1 RNA <50 copies/mL by baseline covariates				
Baseline Viral Load (cps/mL)				
≤100,000	267 / 297 (90%)	264 / 295 (89%)	253 / 280 (90%)	238 / 288 (83%)
>100,000	94 / 114 (82%)	87 / 116 (75%)	111 / 134 (83%)	100 / 131 (76%)
Baseline CD4+ (cells/ mm³)				
<200	43 / 55 (78%)	34 / 50 (68%)	45 / 57 (79%)	48 / 62 (77%)
200 to <350	128 / 144 (89%)	118 / 139 (85%)	143 / 163 (88%)	126 / 159 (79%)
≥350	190 / 212 (90%)	199 / 222 (90%)	176 / 194 (91%)	164 / 198 (83%)
NRTI backbone				
ABC/3TC	145 / 169 (86%)	142 / 164 (87%)	N/A	N/A
TDF/FTC	216 / 242 (89%)	209 / 247 (85%)	N/A	N/A
Gender				
Male	308 / 348 (89%)	305 / 355 (86%)	307 / 347 (88%)	291 / 356 (82%)
Female	53 / 63 (84%)	46 / 56 (82%)	57 / 67 (85%)	47 / 63 (75%)
Race				
White	306 / 346 (88%)	301 / 352 (86%)	255 / 284 (90%)	238 /285 (84%)
African-America/African Heritage/Other	55 / 65 (85%)	50 / 59 (85%)	109 / 130 (84%)	99 / 133 (74%)
Age (years)				
<50	324/370 (88%)	312/365 (85%)	319/361 (88%)	302/375 (81%)
≥50	37/41 (90%)	39/46 (85%)	45/53 (85%)	36/44 (82%)
Median CD4 change from baseline	230	230	246‡	187‡

* Adjusted for baseline stratification factors.
† Includes subjects who changed BR to new class or changed BR not permitted per protocol or due to lack of efficacy prior to Week 48 (for SPRING-2 only), subjects who discontinued prior to Week 48 for lack or loss of efficacy and subjects who are ≥50 copies in the 48 week window.
‡ Adjusted mean treatment difference was statistically significant (p<0.001)

At week 48, dolutegravir was non-inferior to raltegravir in the SPRING-2 study, and in the SINGLE study dolutegravir + ABC/3TC was superior to efavirenz/TDF/FTC (p=0.003), table 5 above. In SINGLE, the median time to viral suppression was shorter in the dolutegravir treated patients (28 vs 84 days, (p<0.0001, analysis pre-specified and adjusted for multiplicity).
At week 96, results were consistent with those seen at week 48. In SPRING-2, dolutegravir was still non-inferior to raltegravir (viral suppression in 81% vs 76% of patients), and with a median change in CD4 count of 276 vs 264 cells/mm³, respectively. In SINGLE, dolutegravir + ABC/3TC was still superior to EFV/TDF/FTC (viral suppression in 80% vs 72%, treatment difference 8.0% (2.3, 13.8), p=0.006, and with an adjusted mean change in CD4 count of 325 vs 281 cells/ mm³, respectively. At 144 weeks in the open-label phase of SINGLE, virologic suppression was maintained, the dolutegravir + ABC/3TC arm (71%) was superior to the EFV/TDF/FTC arm (63%), treatment difference was 8.3% (2.0, 14.6).
n FLAMINGO (ING114915), an open-label, randomised and active-controlled study, 484 HIV-1 infected antiretroviral naïve adults received one dose of either dolutegravir 50 mg once daily (n=242) or darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily (n=242), both administered with either ABC/3TC or TDF/FTC. At baseline, median patient age was 34 years, 15% were female, 28% non-white, 10% had hepatitis B and/or C co-infection, and 3% were CDC Class C; these characteristics were similar between treatment groups. Virologic suppression (HIV-1 RNA <50 copies/mL) in the dolutegravir group (90%) was superior to the DRV/r group (83%) at 48 weeks. The adjusted difference in proportion and 95% CI were 7.1% (0.9, 13.2), p=0.025. At 96 weeks, virologic suppression in the dolutegravir group (80%) was superior to the DRV/r group (68%), (adjusted treatment difference [DTG-(DRV+RTV)]: 12.4%; 95% CI: [4.7, 20.2].
In GEMINI-1 (204861) and GEMINI-2 (205543), identical 148-week, randomised, double-blind studies, 1433 adult HIV-1 infected antiretroviral naïve subjects were randomised to either a two-drug regimen of dolutegravir 50 mg plus lamivudine 300 mg once daily, or to a three-drug regimen of dolutegravir 50 mg once daily with fixed dose TDF/FTC. Subjects were enrolled with a screening plasma HIV-1 RNA of 1000 c/mL to ≤500,000 c/mL. At baseline, in the pooled analysis, median patient age was 33 years, 15% were female, 32% non-white, 6% had hepatitis C co-infection and 9% were CDC Stage 3. Approximately one third of the patients were infected with an HIV non-B subtype; these characteristics were similar between treatment groups. Virologic suppression (HIV-1 RNA <50 copies/mL) in the dolutegravir plus lamivudine group was non-inferior to the dolutegravir plus TDF/FTC group at 48 weeks, as shown in Table 6. The results of the pooled analysis were in line with those of the individual studies, for which the primary endpoint (difference in proportion <50 copies/mL plasma HIV-1 RNA at week 48 based on the Snapshot algorithm) was met. The adjusted difference was -2.6% (95% CI: -6.7; 1.5) for GEMINI-1 and -0.7% (95% CI: -4.3; 2.9) for GEMINI-2 with a prespecified non-inferiority margin of 10%.

Table 6 Response (<50 cps/ml, snapshot) in GEMINI 1 + 2, pooled data.

	DTG + 3TC (N=716) n/N (%)	DTG + TDF/FTC (N=717) n/N (%)
All patients	655/716 (91)	669/717 (93)
	adjusted diff -1.7% (CI95-4.4, 1.1) [a]	
By BL HIV-1 RNA		
≤100,000 cps/mL	526/576 (91)	531/564 (94)
>100,000 cps/mL	129/140 (92)	138/150 (92)
By CD4+		
≤200 c/ mm3	50/63 (79)	51/55 (93)
>200 c/ mm3	605/653 (93)	618/662 (93)
By HIV-1 subtype		
B	424/467 (91)	452/488 (93)
Non-B	231/249 (93)	217/229 (95)
Rebound up to week 48 [b]	6 (<1)	4 (<1)
Mean change in CD4 count from baseline at Week 48, c/ mm3	224	217

[a] adjusted for BL stratification factors: Plasma HIV-1 RNA (≤100,000 c/mL vs. >100,000 c/mL) and CD4+ cell count (≤200 cells/mm3 vs. >200 cells/mm3).
[b] Confirmed plasma HIV-1 RNA levels to ≥200 cps/mL after prior confirmed suppression to <200 cps/mL.

Treatment emergent resistance in previously untreated patients failing therapy
Through 96 weeks in SPRING-2 and FLAMINGO and 144 weeks in SINGLE, no cases of treatment emergent primary resistance to the integrase- or NRTI-class were seen in the dolutegravir-containing arms. For the comparator arms, the same lack of treatment emergent resistance was also the case for patients treated with darunavir/r in FLAMINGO. In SPRING-2, four patients in the RAL-arm failed with major NRTI mutations and one with raltegravir resistance; in SINGLE, six patients in the EFV/TDF/FTC-arm failed with mutations associated with NNRTI resistance, and one developed a major NRTI mutation. Through 48 weeks in the GEMINI-1 and GEMINI-2 studies, no cases of emergent resistance to the integrase- or NRTI-class were seen in either the DTG+3TC or comparator DTG+ TDF/FTC arms.

Patients with prior treatment failure, but not exposed to the integrase class
In the international multicentre, double-blind SAILING study (ING111762), 719 HIV-1 infected, antiretroviral therapy (ART)-experienced adults were randomized and received either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily with investigator selected background regimen consisting of up to 2 agents (including at least one fully active agent). At baseline, median patient age was 43 years, 32% were female, 50% non-white, 16% had hepatitis B and/or C co-infection, and 46% were CDC Class C. All patients had at least two class ART resistance, and 49% of subjects had at least 3-class ART resistance at baseline.
Week 48 outcomes (including outcomes by key baseline covariates) for SAILING are shown in Table 6.

Table 6 Response in SAILING at 48 Weeks (Snapshot algorithm, <50 copies/mL)

	Dolutegravir 50 mg Once Daily + BR N=354§	RAL 400 mg Twice Daily + BR N=361§
HIV-1 RNA <50 copies/mL	71%	64%
Adjusted treatment difference‡	7.4% (95% CI: 0.7%, 14.2%)	
Virologic non-response	20%	28%
HIV-1 RNA <50 copies/mL by baseline covariates		
Baseline Viral Load (copies/mL)		
≤50,000 copies/mL	186 / 249 (75%)	180 / 254 (71%)
>50,000 copies/mL	65 / 105 (62%)	50 / 107 (47%)
Baseline CD4+ (cells/ mm³)		
<50	33 / 62 (53%)	30 / 59 (51%)
50 to <200	77 / 111 (69%)	76 / 125 (61%)
200 to <350	64 / 82 (78%)	53 / 79 (67%)
≥350	77 / 99 (78%)	71 / 98 (72%)
Background Regimen		
Genotypic Susceptibility Score* <2	155 / 216 (72%)	129 / 192 (67%)
Genotypic Susceptibility Score* =2	96 / 138 (70%)	101 / 169 (60%)
Use of DRV in background regimen		
No DRV use	143 / 214 (67%)	126 / 209 (60%)
DRV use with primary PI mutations	58 / 68 (85%)	50 / 75 (67%)
DRV use without primary PI mutations	50 / 72 (69%)	54 / 77 (70%)
Gender		
Male	172 / 247 (70%)	156 / 238 (66%)
Female	79 / 107 (74%)	74 / 123 (60%)
Race		
White	133 / 178 (75%)	125 / 175 (71%)
African-America/African Heritage/Other	118 / 175 (67%)	105 / 185 (57%)
Age (years)		
<50	196 / 269 (73%)	172 / 277 (62%)
≥50	55 / 85 (65%)	58 / 84 (69%)
HIV sub type		
Clade B	173 / 241 (72%)	159 / 246 (65%)
Clade C	34 / 55 (62%)	29 / 48 (60%)
Other†	43 / 57 (75%)	42 / 67 (63%)
Mean increase in CD4+ T cell (cells/mm³)	162	153

‡ Adjusted for baseline stratification factors.
§ 4 subjects were excluded from the efficacy analysis due to data integrity at one study site
* The Genotypic Susceptibility Score (GSS) was defined as the total number of ARTs in BR to which a subject's viral isolate showed susceptibility at baseline based upon genotypic resistance tests.
†Other clades included: Complex (43), F1 (32), A1 (18), BF (14), all others <10.

In the SAILING study, virologic suppression (HIV-1 RNA <50 copies/mL) in the Dolutegravir arm (71%) was statistically superior to the raltegravir arm (64%), at Week 48 (p=0.03).
Statistically fewer subjects failed therapy with treatment-emergent integrase resistance on Dolutegravir (4/354, 1%) than on raltegravir (17/361, 5%) (p=0.003) (refer to section 'Resistance in vivo' above for details).

Patients with prior treatment failure that included an integrase inhibitor (and integrase class resistance)
In the multicentre, open-label, single arm VIKING-3 study (ING112574), HIV-1 infected, ART-experienced adults with virological failure and current or historical evidence of raltegravir and/or elvitegravir resistance received Dolutegravir 50 mg twice daily with the current failing background regimen for 7 days but with optimised background ART from Day 8. The study enrolled 183 patients, 133 with INI-resistance at Screening and 50 with only historical evidence of resistance (and not at Screening). Raltegravir/elvitegravir was part of the current failing regimen in 98/183 patients (part of prior failing therapies in the others). At baseline, median patient age was 48 years, 23% were female, 29% non-white, and 20% had hepatitis B and/or C co-infection. Median baseline CD4+ was 140 cells/mm³, median duration of prior ART was 14 years, and 56% were CDC Class C. Subjects showed multiple class ART resistance at baseline: 79% had ≥2 NRTI, 75% ≥1 NNRTI, and 71% ≥2 PI major mutations; 62% had non-R5 virus.
Mean change from baseline in HIV RNA at day 8 (primary endpoint) was -1.4log$_{10}$ copies/mL (95% CI -1.3 – -1.5log$_{10}$, p<0.001). Response was associated with baseline INI mutation pathway, as shown in Table 7.

Table 7 Virologic response (day 8) after 7 days of functional monotherapy, in patients with RAL/EVG as part of current failing regimen, VIKING 3

Baseline parameters	**DTG 50 mg BID N=88***		
	n	Mean (SD) Plasma HIV-1 RNA log10 c/mL	Median
Derived IN mutation group at Baseline with ongoing RAL/EVG			
Primary mutation other than Q148H/K/Ra	48	-1.59 (0.47)	-1.64
Q148+1 secondary mutation[b]	26	-1.14 (0.61)	-1.08
Q148+≥2 secondary mutations[b]	14	-0.75 (0.84)	-0.45

*Of 98 on RAL/EVG as part of current failing regimen, 88 had detectable primary INI mutations at Baseline and a Day 8 Plasma HIV-1 RNA outcome for evaluation
[a] Included primary IN resistance mutations N155H, Y143C/H/R, T66A, E92Q
[b] Secondary mutations from G140A/C/S, E138A/K/T, L74I.

In patients without a primary mutation detected at baseline (N=60) (i.e. RAL/EVG not part of current failing therapy) there was a 1.63 log$_{10}$ reduction in viral load at day 8.
After the functional monotherapy phase, subjects had the opportunity to re-optimize their background regimen when possible. The overall response rate through 24 weeks of therapy, 69% (126/183), was generally sustained through 48 weeks with 116/183 (63%) of patients with HIV-1 RNA <50c/mL (ITT-E, Snapshot algorithm). When excluding patients who stopped therapy for non-efficacy reasons, and those with major protocol deviations (incorrect dolutegravir dosing, intake of prohibited co-medication), namely, "the Virological Outcome (VO)-population)", the corresponding response rates were 75% (120/161, week 24) and 69% (111/160, week 48).
The response was lower when the Q148-mutation was present at baseline, and in particular in the presence of ≥2 secondary mutations, Table 8. The overall susceptibility score (OSS) of the optimised background regimen (OBR) was not associated with Week 24 response, nor with the week 48 response.

Table 8 Response by baseline Resistance, VIKING-3. VO Population (HIV-1 RNA <50 c/mL, Snapshot algorithm)

	Week 24 (N=161)					Week 48 (N=160)
Derived IN Mutation Group	**OSS=0**	**OSS=1**	**OSS=2**	**OSS>2**	**Total**	**Total**
No primary IN mutation[1]	2/2 (100%)	15/20 (75%)	19/21 (90%)	9/12 (75%)	45/55 (82%)	38/55 (69%)
Primary mutation other than Q148H/K/R[2]	2/2 (100%)	20/20 (100%)	21/27 (78%)	8/10 (80%)	51/59 (86%)	50/58 (86%)
Q148 + 1 secondary mutation[3]	2/2 (100%)	8/12 (67%)	10/17 (59%)	-	20/31 (65%)	19/31 (61%)
Q148 +≥2 secondary mutations [3]	1/2 (50%)	2/11 (18%)	1/3 (33%)	-	4/16 (25%)	4/16 (25%)

[1] Historical or phenotypic evidence of INI resistance only.
[2] N155H, Y143C/H/R, T66A, E92Q
[3] G140A/C/S, E138A/K/T, L74I
OSS: combined genotypic and phenotypic resistance (Monogram Biosciences Net Assessment)

The median change in CD4+ T cell count from baseline for VIKING-3 based on observed data was 61 cells/mm³ at Week 24 and 110 cells/mm³ at Week 48.
In the double blind, placebo-controlled VIKING-4 study (ING116529), 30 HIV-1 infected, ART-experienced adults with primary genotypic resistance to INIs at Screening, were randomised to receive either dolutegravir 50 mg twice daily or placebo with the current failing regimen for 7 days followed by an open label phase with all subjects receiving dolutegravir. At baseline, median patient age was 49 years, 20% were female, 58% non-white, and 23% had hepatitis B and/or C co-infection. Median baseline CD4+ was 160 cells/mm³, median duration of prior ART was 13 years, and 63% were CDC Class C. Subjects showed multiple class ART resistance at baseline: 80% had ≥2 NRTI, 73% ≥1 NNRTI, and 67% ≥2 PI major mutations; 83% had non-R5 virus. Sixteen of 30 subjects (53%) harboured Q148 virus at baseline. The primary endpoint at Day 8 showed that dolutegravir 50 mg twice daily was superior to placebo, with an adjusted mean treatment difference for the change from Baseline in Plasma HIV-1 RNA of -1.2 log$_{10}$ copies/mL (95% CI -1.5 - -0.8log$_{10}$ copies/mL, p<0.001). The day 8 responses in this placebo-controlled study were fully in line with those seen in VIKING-3 (not placebo controlled), including by baseline integrase resistance categories. At week 48, 12/30 (40%) subjects had HIV-1 RNA <50 copies/mL (ITT-E, Snapshot algorithm).
In a combined analysis of VIKING-3 and VIKING-4 (n=186, VO population), the proportion of subjects with HIV RNA <50 copies/mL at Week 48 was 123/186 (66%). The proportion of subjects with HIV RNA <50 copies/mL was 96/126 (76%) for No Q148 mutations, 22/41 (54%) for Q148+1 and 5/19 (26%) for Q148+≥2 secondary mutations.

Paediatric population
In a Phase I/II 48 week multicentre, open-label study (P1093/ING112578), the pharmacokinetic parameters, safety, tolerability and efficacy of Dolutegravir has been evaluated in combination regimens in HIV-1 infected, treatment-experienced, INI naive children and adolescents (6 to less than 18 years of age). Subjects were stratified by age, receiving Dolutegravir (70 mg, as 35 mg twice daily, n=1; 50 mg once daily, n=5; 35 mg once daily, n=6; 25 mg once daily, n=8; and 20 mg once daily, n=3) plus OBR.

Table 9 Virologic (Snapshot algorithm) and Immunologic Activity of Treatment for Subjects 6 Years and Older in P1093

	DOLUTEGRAVIR ~1 mg/kg Once Daily + OBR	
	Cohort I 12 to <18 years) (n=23)	Cohort IIA (6 to <12 years) (n=23)
HIV-1 RNA <50 copies/mL at 24 weeks, n (%)	16 (70%)	14 (61%)
HIV-1 RNA <50 copies/mL at 48 weeks, n (%)	14 (61%)	-
HIV-1 RNA <400 copies/mL at 24 weeks, n (%)	19 (83%)	18 (78%)
HIV-1 RNA <400 copies/mL at 48 weeks, n (%)	17 (74%)	-
Virologic non response	6	3
Cd4+ Cell Count		
Median Change from Baseline, cells/mm³	84[a]	209[b]
Median Percent Change from Baseline	5%[a]	8%[b]

[a] 22 subjects contributed Week 48 CD4+ cell count data
[b] 21 subjects contributed Week 24 CD4+ cell count data

The European Medicines Agency has deferred the obligation to submit the results of studies with Dolutegravir in paediatric patients aged 4 weeks to below 6 years with HIV infection (see section 4.2 for information on paediatric use).
There are no data available on the use of dolutegravir plus lamivudine as a two-drug regimen in paediatric patients.

Lamivudine:
Mechanism of action
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. 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 were seen with lamivudine and other anti retrovirals (tested agents: abacavir, didanosine, nevirapine and zidovudine).

Resistance
HIV-1 resistance to lamivudine involves the development of a M184V amino acid change close to the active site of the viral reverse transcriptase (RT). This variant arises both in vitro and in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy. M184V mutants display greatly reduced susceptibility to lamivudine and show diminished viral replicative capacity in vitro. In vitro studies indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. The clinical relevance of such findings remains, however, not well defined.
In vitro data tend to suggest that the continuation of lamivudine in anti-retroviral regimen despite the development of M184V might provide residual anti-retroviral activity (likely through impaired viral fitness). The clinical relevance of these findings is not established. Indeed, the available clinical data are very limited and preclude any reliable conclusion in the field. In any case, initiation of susceptible NRTI's should always be preferred to maintenance of lamivudine therapy. Therefore, maintaining lamivudine therapy despite emergence of M184V mutation should only be considered in cases where no other active NRTI's are available.
Cross-resistance conferred by the M184V RT is limited within the nucleoside inhibitor class of antiretroviral agents. Zidovudine and stavudine maintain their antiretroviral activities against lamivudine-resistant HIV-1. Abacavir maintains its antiretroviral activities against 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 demonstrates low cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines, and to a variety of bone marrow progenitor cells in vitro.

Clinical efficacy and safety
In clinical trials, lamivudine in combination with zidovudine has been shown to reduce HIV-1 viral load and increase CD4 cell count. Clinical end-point data indicate that lamivudine in combination with zidovudine, results in a significant reduction in the risk of disease progression and mortality.
Evidence from clinical studies shows that lamivudine plus zidovudine delays the emergence of zidovudine resistant isolates in individuals with no prior antiretroviral therapy.
Lamivudine has been widely used as a component of antiretroviral combination therapy with other antiretroviral agents of the same class (NRTIs) or different classes (PIs, non-nucleoside reverse transcriptase inhibitors).
Clinical trial evidence from paediatric patients receiving lamivudine with other antiretroviral drugs (abacavir, nevirapine/efavirenz or zidovudine) has shown that the resistance profile observed in paediatric patients is similar to that observed in adults, in terms of the genotypic substitutions detected and their relative frequency.
Children receiving lamivudine oral solution concomitantly with other antiretroviral oral solutions in clinical trials developed viral resistance more frequently than children receiving tablets (see the description of the clinical experience in paediatric population (ARROW study) and section 5.2).
Multiple drug antiretroviral therapy containing lamivudine has been shown to be effective in antiretrovirally-naïve patients as well as in patients presenting with viruses containing the M184V mutations.
The relationship between in vitro susceptibility of HIV to lamivudine and clinical response to lamivudine-containing therapy remains under investigation.
Lamivudine at a dose of 100 mg once daily has also been shown to be effective for the treatment of adult patients with chronic HBV infection (for details of clinical studies, see the prescribing information for Zeffix). However, for the treatment of HIV infection only a 300 mg daily dose of lamivudine (in combination with other antiretroviral agents) has been shown to be efficacious.

Lamivudine has not been specifically investigated in HIV patients co-infected with HBV.
Once daily dosing (300 mg once a day): a clinical study has demonstrated the non inferiority between Lamivudine once a day and Lamivudine twice a day containing regimens. These results were obtained in an antiretroviral naïve-population, primarily consisting of asymptomatic HIV infected patients (CDC stage A).

Paediatric population: a randomised comparison of a regimen including once daily vs twice daily dosing of abacavir and lamivudine was undertaken within a randomised, multicentre, controlled study of HIV-infected, paediatric patients. 1206 paediatric patients aged 3 months to 17 years enrolled in the ARROW Trial (COL105677) and were dosed according to the weight - band dosing recommendations in the World Health Organisation treatment guidelines (Antiretroviral therapy of HIV infection in infants and children, 2006). After 36 weeks on a regimen including twice daily abacavir and lamivudine, 669 eligible subjects were randomised to either continue twice daily dosing or switch to once daily abacavir and lamivudine for at least 96 weeks. Of note, from this study clinical data were not available for children under one year old. The results are summarised in the table below:

Table 10 Virological Response Based on Plasma HIV-1 RNA less than 80 copies/ml at Week 48 and Week 96 in the Once Daily versus Twice Daily abacavir + lamivudine randomisation of ARROW (Observed Analysis)

	Twice Daily N (%)	Once Daily N (%)
Week 0 (After ≥36 Weeks on Treatment)		
Plasma HIV-1 RNA <80 c/ml	250/331 (76)	237/335 (71)
Risk difference (once daily-twice daily)	-4.8% (95% CI -11.5% to +1.9%), p=0.16	531/564 (94)
Week 48		
Plasma HIV-1 RNA <80 c/ml	242/331 (73)	236/330 (72)
Risk difference (once daily-twice daily)	-1.6% (95% CI -8.4% to +5.2%), p=0.65	
Week 96		
Plasma HIV-1 RNA <80 c/ml	234/326 (72)	230/331 (69)
Risk difference (once daily-twice daily)	-2.3% (95% CI -9.3% to +4.7%), p=0.52	

In a pharmacokinetic study (PENTA 15), four virologically controlled subjects less than 12 months of age switched from abacavir plus lamivudine oral solution twice daily to a once daily regimen. Three subjects had undetectable viral load and one had plasmatic HIV-RNA of 900 copies/ml at Week 48. No safety concerns were observed in these subjects.

The abacavir + lamivudine once daily dosing group was demonstrated to be non-inferior to the twice daily group according to the pre-specified non-inferiority margin of -12%, for the primary endpoint of <80 c/ml at Week 48 as well as at Week 96 (secondary endpoint) and all other thresholds tested (<200c/ml, <400c/ml, <1000c/ml), which all fell well within this non-inferiority margin. Subgroup analyses testing for heterogeneity of once vs twice daily demonstrated no significant effect of sex, age, or viral load at randomisation. Conclusions supported non-inferiority regardless of analysis method.
At the time of randomization to once daily vs twice daily dosing (Week 0), those patients who had received tablet formulations had a higher rate of viral load suppression than those who had received any solution formulations at any time. These differences were observed in each different age group studied. This difference in suppression rates between tablets and solutions remained through Week 96 with once daily dosing.

Table 11 Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <80 copies/ml: Subgroup Analysis by Formulation

	Twice Daily Plasma HIV-1 RNA <80 c/ml: n/N (%)	Once Daily Plasma HIV-1 RNA <80 c/ml: n/N (%)
Week 0 (after 36 weeks on Treatment)		
Any solution regimen at any time	14/26 (54)	15/30 (50)
All tablet based regimen throughouts	236/305 (77)	222/305 (73)
Week 96		
Any solution regimen at any time	13/26 (50)	17/30 (57)
All tablet based regimen throughouts	221/300 (74)	213/301 (71)

Genotypic resistance analyses were conducted on samples with plasma HIV-1 RNA >1000 copies/ml. More cases of resistance were detected among patients who had received lamivudine solution, in combination with other antiretroviral solutions, compared with those who received similar doses of tablet formulation. This is consistent with the lower rates of antiviral suppression observed in these patients.
Tenofovir:
Mechanism of action and pharmacodynamic effects
Tenofovir disoproxil fumarate is the fumarate 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 hours in activated and 50 hours 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 shown no effect on the synthesis of mitochondrial DNA or the production of lactic acid in in vitro assays.

Data pertaining to HIV
HIV antiviral activity in vitro: The concentration of tenofovir required for 50% inhibition (EC50) 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 EC50 of 4.9 µmol/l in MT-4 cells.
Resistance: Strains of HIV-1 with reduced susceptibility to tenofovir and a K65R mutation in reverse transcriptase have been selected in vitro and in some patients (see Clinical efficacy and safety). 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.
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. The 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.

Clinical efficacy and safety
The effects of tenofovir disoproxil in treatment-experienced and treatment-naïve HIV-1 infected adults have been demonstrated in trials of 48 weeks and 144 weeks duration, respectively.
In study GS-99-907, 550 treatment-experienced adult patients were treated with placebo or tenofovir disoproxil 245 mg for 24 weeks. The mean baseline CD4 cell count was 427 cells/mm3, the mean baseline plasma HIV-1 RNA was 3.4 log10 copies/ml (78% of patients had a viral load of < 5,000 copies/ml) and the mean duration of prior HIV treatment was 5.4 years. Baseline genotypic analysis of HIV isolates from 253 patients revealed that 94% of patients had HIV-1 resistance mutations associated with nucleoside reverse transcriptase inhibitors, 58% had mutations associated with protease inhibitors and 48% had mutations associated with non-nucleoside reverse transcriptase inhibitors.
At week 24 the time-weighted average change from baseline in log10 plasma HIV-1 RNA levels (DAVG24) was -0.03 log10 copies/ml and -0.61 log10 copies/ml for the placebo and tenofovir disoproxil 245 mg recipients (p < 0.0001). A statistically significant difference in favour of tenofovir disoproxil 245 mg was seen in the time-weighted average change from baseline at week 24 (DAVG24) for CD4 count (+13 cells/mm3 for tenofovir disoproxil 245 mg versus -11 cells/mm3 for placebo, p-value = 0.0008). The antiviral response to tenofovir disoproxil was durable through 48 weeks (DAVG48 was -0.57 log10 copies/ml, proportion of patients with HIV-1 RNA below 400 or 50 copies/ml was 41% and 18% respectively). Eight (2%) tenofovir disoproxil 245 mg treated patients developed the K65R mutation within the first 48 weeks.
The 144-week, double-blind, active controlled phase of study GS-99-903 evaluated the efficacy and safety of tenofovir disoproxil 245 mg versus stavudine when used in combination with lamivudine and efavirenz in HIV-1 infected adult patients naïve to antiretroviral therapy. The mean baseline CD4 cell count was 279 cells/mm3, the mean baseline plasma HIV-1 RNA was 4.91 log10 copies/ml, 19% of patients had symptomatic HIV-1 infection and 18% had AIDS. Patients were stratified by baseline HIV-1 RNA and CD4 count. Forty-three percent of patients had baseline viral loads > 100,000 copies/ml and 39% had CD4 cell counts < 200 cells/ml.
By intent to treat analysis (missing data and switch in antiretroviral therapy (ART) considered as failure), the proportion of patients with HIV-1 RNA below 400 copies/ml and 50 copies/ml at 48 weeks of treatment was 80% and 76% respectively in the tenofovir disoproxil 245 mg arm, compared to 84% and 80% in the stavudine arm. At 144 weeks, the proportion of patients with HIV-1 RNA below 400 copies/ml and 50 copies/ml was 71% and 68% respectively in the tenofovir disoproxil 245 mg arm, compared to 64% and 63% in the stavudine arm.
The average change from baseline for HIV-1 RNA and CD4 count at 48 weeks of treatment was similar in both treatment groups (-3.09 and -3.09 log10 copies/ml; +169 and 167 cells/mm3 in the tenofovir disoproxil 245 mg and stavudine groups, respectively). At 144 weeks of treatment, the average change from baseline remained similar in both treatment groups (-3.07 and -3.03 log10 copies/ml; +263 and +283 cells/mm3 in the tenofovir disoproxil 245 mg and stavudine groups, respectively). A consistent response to treatment with tenofovir disoproxil 245 mg was seen regardless of baseline HIV-1 RNA and CD4 count.
The K65R mutation occurred in a slightly higher percentage of patients in the tenofovir disoproxil group than the active control group (2.7% versus 0.7%). Efavirenz or lamivudine resistance either preceded or was coincident with the development of K65R in all cases. Eight patients had HIV that expressed K65R in the tenofovir disoproxil 245 mg arm, 7 of these occurred during the first 48 weeks of treatment and the last one at week 96. No further K65R development was observed up to week 144. One patient in the tenofovir disoproxil arm developed the K70E substitution in the virus. From both the genotypic and phenotypic analyses there was no evidence for other pathways of resistance to tenofovir.

Data pertaining to HBV
HBV antiviral activity in vitro: The in vitro antiviral activity of tenofovir against HBV was assessed in the HepG2 2.2.15 cell line. The EC50 values for tenofovir were in the range of 0.14 to 1.5 µmol/l, with CC50 (50% cytotoxicity concentration) values > 100 µmol/l.
Resistance: No HBV mutations associated with tenofovir disoproxil resistance have been identified (see Clinical efficacy and safety). In cell based assays, HBV strains expressing the rtV173L, rtL180M, and rtM204I/V mutations associated with resistance to lamivudine and telbivudine showed a susceptibility to tenofovir ranging from 0.7- to 3.4-fold that of wild-type virus. HBV strains expressing the rtL180M, rtT184G, rtS202G/I, rtM204V and rtM250V mutations associated with resistance to entecavir showed a susceptibility to tenofovir ranging from 0.6- to 6.9-fold that of wild-type virus. HBV strains expressing the adefovir-associated resistance mutations rtA181V and rtN236T showed a susceptibility to tenofovir ranging from 2.9- to 10-fold that of wild-type virus. Viruses containing the rtA181T mutation remained susceptible to tenofovir with EC50 values 1.5-fold that of wild-type virus.

Clinical efficacy and safety
The demonstration of benefit of tenofovir disoproxil in compensated and decompensated disease is based on virological, biochemical and serological responses in adults with HBeAg positive and HBeAg negative chronic hepatitis B. Treated patients included those who were treatment-naïve, lamivudine-experienced, adefovir dipivoxil-experienced and patients with lamivudine and/or adefovir dipivoxil resistance mutations at baseline. Benefit has also been demonstrated based on histological responses in compensated patients.
Experience in patients with compensated liver disease at 48 weeks (studies GS-US-174-0102 and GS-US-174-0103)
Results through 48 weeks from two randomised, phase 3 double-blind studies comparing tenofovir disoproxil to adefovir dipivoxil in adult patients with compensated liver disease are presented in Table 12 below. Study GS-US-174-0103 was conducted in 266 (randomised and treated) HBeAg positive patients while study GS-US-174-0102 was conducted in 375 (randomised and treated) patients negative for HBeAg and positive for HBeAb.
In both of these studies tenofovir disoproxil was significantly superior to adefovir dipivoxil for the primary efficacy endpoint of complete response (defined as HBV DNA levels < 400 copies/ml and Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis). Treatment with tenofovir disoproxil 245 mg was also associated with significantly greater proportions of patients with HBV DNA < 400 copies/ml, when compared to adefovir dipivoxil 10 mg treatment. Both treatments produced similar results with regard to histological response (defined as Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis) at week 48 (see Table 12 below).
In study GS-US-174-0103 a significantly greater proportion of patients in the tenofovir disoproxil group than in the adefovir dipivoxil group had normalised ALT and achieved HBsAg loss at week 48 (see Table 12 below).

Table 12: Efficacy parameters in compensated HBeAg negative and HBeAg positive patients at week 48

Parameter	Study 174-0102 (HBeAg negative)		Study 174-0103 (HBeAg positive)	
	Tenofovir disoproxil 245 mg n = 250	Adefovir dipivoxil 10 mg n = 125	Tenofovir disoproxil 245 mg n = 176	Adefovir dipivoxil 10 mg n = 90
Complete response (%)a	71*	49	67*	12
Histology				
Histological response (%)b	72	69	74	68
Median HBV DNA reduction from baselinec (log10 copies/ml)	-4.7*	-4.0	-6.4*	-3.7
HBV DNA (%) < 400 copies/ml (< 69 IU/ml)	93*	63	76*	13
ALT (%) Normalised ALTd	76	77	68*	54
Serology (%) HBeAg loss/seroconversion	n/a	n/a	22/21	18/18
HBsAg loss/seroconversion	0/0	0/0	3*/1	0/0

* p-value versus adefovir dipivoxil < 0.05.
[a] Complete response defined as HBV DNA levels < 400 copies/ml and Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis.
[b] Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis.
[c] Median change from baseline HBV DNA merely reflects the difference between baseline HBV DNA and the limit of detection (LOD) of the assay.
[d] The population used for analysis of ALT normalisation included only patients with ALT above ULN at baseline.
[n/a] = not applicable.

Tenofovir disoproxil was associated with significantly greater proportions of patients with undetectable HBV DNA (< 169 copies/ml [< 29 IU/ml]; the limit of quantification of the Roche Cobas Taqman HBV assay), when compared to adefovir dipivoxil (study GS-US-174-0102; 91%, 56% and study GS-US-174-0103; 69%, 9%), respectively.
Response to treatment with tenofovir disoproxil was comparable in nucleoside-experienced (n = 51) and nucleoside-naïve (n = 375) patients and in patients with normal ALT (n = 21) and abnormal ALT (n = 405) at baseline when studies GS-US-174-0102 and GS-US-174-0103 were combined. Forty-nine of the 51 nucleoside-experienced patients were previously treated with lamivudine. Seventy-three percent of nucleoside-experienced and 69% of nucleoside-naïve patients achieved complete response to treatment; 90% of nucleoside-experienced and 88% of nucleoside-naïve patients achieved HBV DNA suppression < 400 copies/ml. All patients with normal ALT at baseline and 88% of patients with abnormal ALT at baseline achieved HBV DNA suppression < 400 copies/ml.

Experience beyond 48 weeks in studies GS-US-174-0102 and GS-US-174-0103
In studies GS-US-174-0102 and GS-US-174-0103, after receiving double-blind treatment for 48 weeks (either tenofovir disoproxil 245 mg or adefovir dipivoxil 10 mg), patients rolled over with no interruption in treatment to open-label tenofovir disoproxil. In studies GS-US-174-0102 and GS-US-174-0103, 77% and 61% of patients continued in the study through to 384 weeks, respectively. At weeks 96, 144, 192, 240, 288 and 384, viral suppression, biochemical and serological responses were maintained with continued tenofovir disoproxil treatment (see Tables 13 and 14 below).

Table 13: Efficacy parameters in compensated HBeAg negative patients at week 96, 144, 192, 240, 288 and 384 open-abel treatment

Parametera	Study 174-0102 (HBeAg negative)						Study 174-0103 (HBeAg positive)					
	Tenofovir disoproxil 245 mg n = 250						Adefovir dipivoxil 10 mg roll over to tenofovir disoproxil 245 mg n = 125					
Week	96b	144e	192g	240i	288l	384o	96c	144f	192h	240j	288m	384p
HBV DNA (%) < 400 copies/ml (< 69 IU/ml)	90	87	84	83	80	74	89	88	87	84	84	76
ALT (%) Normalised ALTd	72	73	67	70	68	64	68	70	77	76	74	69
Serology (%) HBeAg loss/seroconversion	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
HBsAg loss/seroconversion	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0

[a] Based upon Long Term Evaluation algorithm (LTE Analysis) - Patients who discontinued the study at any time prior to week 384 due to a protocol defined endpoint, as well as those completing week 384, are included in the denominator.
[b] 48 weeks of double-blind tenofovir disoproxil followed by 48 weeks open-label.
[c] 48 weeks of double-blind adefovir dipivoxil followed by 48 weeks open-label tenofovir disoproxil.
[d] The population used for analysis of ALT normalisation included only patients with ALT above ULN at baseline.
[e] 48 weeks of double-blind tenofovir disoproxil followed by 96 weeks open-label.
[f] 48 weeks of double-blind adefovir dipivoxil followed by 96 weeks open-label tenofovir disoproxil .
[g] 48 weeks of double-blind tenofovir disoproxil followed by 144 weeks open-label.
[h] 48 weeks of double-blind adefovir dipivoxil followed by 144 weeks open-label tenofovir disoproxil.
[i] 48 weeks of double-blind tenofovir disoproxil followed by 192 weeks open-label.
[j] 48 weeks of double-blind adefovir dipivoxil followed by 192 weeks open-label tenofovir disoproxil.
[k] One patient in this group became HBsAg negative for the first time at the 240 week visit and was ongoing in the study at the time of the data cut-off. However, the subject's HBsAg loss was ultimately confirmed at the subsequent visit.
[l] 48 weeks of double-blind tenofovir disoproxil followed by 240 weeks open-label.
[m] 48 weeks of double-blind adefovir dipivoxil followed by 240 weeks open-label tenofovir disoproxil.
[n] Figures presented are cumulative percentages based upon a Kaplan Meier analysis excluding data collected after the addition of emtricitabine to open-label tenofovir disoproxil (KM-tenofovir disoproxil).
[o] 48 weeks of double-blind tenofovir disoproxil followed by 336 weeks open-label.
[p] 48 weeks of double-blind adefovir dipivoxil followed by 336 weeks open-label tenofovir disoproxil .
n/a = not applicable.

Table 14: Efficacy parameters in compensated HBeAg positive patients at week 96, 144, 192, 240, 288 and 384 open-label treatment

Parametera	Study 174-0103 (HBeAg positive)											
	Tenofovir disoproxil 245 mg n = 176						Adefovir dipivoxil 10 mg roll over to tenofovir disoproxil 245 mg n = 90					
Week	96b	144e	192h	240j	288m	384o	96c	144f	192i	240k	288n	384p
HBV DNA (%) < 400 copies/ml (< 69 IU/ml)	76	72	68	64	61	56	74	71	72	66	65	61
ALT (%) Normalised ALTd	60	55	56	46	47	47	65	61	59	56	57	56
Serology (%) HBeAg loss/ seroconversion	26/ 23	29/ 23	34/ 25	38/ 30	37/ 25	30/ 20	24/ 20	33/ 26	36/ 30	38/ 31	40/ 31	35/ 24
HBsAg loss/seroconversion	5/ 4	8/ 6g	11/ 8g	11/ 8l	12/ 8l	15/ 12l	6/ 5	8/ 7g	8/ 7g	10/ 10l	11/ 10l	13/ 11l

[a] Based upon Long Term Evaluation algorithm (LTE Analysis) - Patients who discontinued the study at any time prior to week 384 due to a protocol defined endpoint, as well as those completing week 384, are included in the denominator.
[b] 48 weeks of double-blind tenofovir disoproxil followed by 48 weeks open-label.
[c] 48 weeks of double-blind adefovir dipivoxil followed by 48 weeks open-label tenofovir disoproxil.
[d] The population used for analysis of ALT normalisation included only patients with ALT above ULN at baseline.
[e] 48 weeks of double-blind tenofovir disoproxil followed by 96 weeks open-label.
[f] 48 weeks of double-blind adefovir dipivoxil followed by 96 weeks open-label tenofovir disoproxil.
[g] Figures presented are cumulative percentages based upon a Kaplan Meier analysis including data collected after the addition of emtricitabine to open-label tenofovir disoproxil (KM-ITT).
[h] 48 weeks of double-blind tenofovir disoproxil followed by 144 weeks open-label.
[i] 48 weeks of double-blind adefovir dipivoxil followed by 144 weeks open-label tenofovir disoproxil.
[j] 48 weeks of double-blind tenofovir disoproxil followed by 192 weeks open-label.
[k] 48 weeks of double-blind adefovir dipivoxil followed by 192 weeks open-label tenofovir disoproxil.
[l] Figures presented are cumulative percentages based upon a Kaplan Meier analysis excluding data collected after the addition of emtricitabine to open-label tenofovir disoproxil (KM-tenofovir disoproxil).
[m] 48 weeks of double-blind tenofovir disoproxil followed by 240 weeks open-label.
[n] 48 weeks of double-blind adefovir dipivoxil followed by 240 weeks open-label tenofovir disoproxil.
[o] 48 weeks of double-blind tenofovir disoproxil followed by 336 weeks open-label.
[p] 48 weeks of double-blind adefovir dipivoxil followed by 336 weeks open-label tenofovir disoproxil.

Paired baseline and week 240 liver biopsy data were available for 331/489 patients who remained in studies GS-US-174-0102 and GS-US-174-0103 at week 240 (see Table 15 below). Ninety-five percent (225/237) of patients without cirrhosis at baseline and 99% (93/94) of patients with cirrhosis at baseline had either no change or an improvement in fibrosis (Ishak fibrosis score). Of the 94 patients with cirrhosis at baseline (Ishak fibrosis score: 5 - 6), 26% (24) experienced no change in Ishak fibrosis score and 72% (68) experienced regression of cirrhosis by week 240 with a reduction in Ishak fibrosis score of at least 2 points.

Table 15: Histological response (%) in compensated HBeAg negative and HBeAg positive subjects at week 240 compared to baseline

Parameter	Study 174-0102 (HBeAg negative)		Study 174-0103 (HBeAg positive)	
	Tenofovir disoproxil 245 mg n = 250c	Adefovir dipivoxil 10 mg roll over to tenofovir disoproxil 245 mg n = 125d	Tenofovir disoproxil 245 mg n = 176c	Adefovir dipivoxil 10 mg roll over to tenofovir disoproxil 245 mg n = 90d
Histological responsea,b (%)	88 [130/148]	85 [63/74]	90 [63/70]	92 [36/39]

[a] The population used for analysis of histology included only patients with available liver biopsy data (Missing = Excluded) by week 240. Response after addition of emtricitabine is excluded (total of 17 subjects across both studies).
[b] Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis score.
[c] 48 weeks double-blind tenofovir disoproxil followed by up to 192 weeks open-label.
[d] 48 weeks double-blind adefovir dipivoxil followed by up to 192 weeks open-label tenofovir disoproxil.

Experience in patients with HIV co-infection and prior lamivudine experience
In a randomised, 48-week double-blind, controlled study of tenofovir disoproxil 245 mg in adult patients co-infected with HIV-1 and chronic hepatitis B with prior lamivudine experience (study ACTG 5127), the mean serum HBV DNA levels at baseline in patients randomised to the tenofovir arm were 9.45 log10 copies/ml (n = 27). Treatment with tenofovir disoproxil 245 mg was associated with a mean change in serum HBV DNA from baseline, in the patients for whom there was 48-week data, of -5.74 log10 copies/ml (n = 18). In addition, 61% of patients had normal ALT at week 48.

Experience in patients with persistent viral replication (study GS-US-174-0106)
The efficacy and safety of tenofovir disoproxil 245 mg or tenofovir disoproxil 245 mg plus 200 mg emtricitabine has been evaluated in a randomised, double-blind study (study GS-US-174-0106), in HBeAg positive and HBeAg negative adult patients who had persistent viraemia (HBV DNA ≥ 1,000 copies/ml) while receiving adefovir dipivoxil 10 mg for more than 24 weeks. At baseline, 57% of patients randomised to tenofovir disoproxil versus 60% of patients randomised to emtricitabine plus tenofovir disoproxil treatment group had previously been treated with lamivudine. Overall at week 24, treatment with tenofovir disoproxil resulted in 66% (35/53) of patients with HBV DNA < 400 copies/ml (< 69 IU/ml) versus 69% (36/52) of patients treated with emtricitabine plus tenofovir disoproxil (p = 0.672). In addition 55% (29/53) of patients treated with tenofovir disoproxil had undetectable HBV DNA (< 169 copies/ml [< 29 IU/ml]; the limit of quantification of the Roche Cobas TaqMan HBV assay) versus 60% (31/52) of patients treated with emtricitabine plus tenofovir disoproxil (p = 0.504). Comparisons between treatment groups beyond week 24 are difficult to interpret since investigators had the option to intensify treatment to open-label emtricitabine plus tenofovir disoproxil. Long-term studies to evaluate the benefit/risk of bitherapy with emtricitabine plus tenofovir disoproxil in HBV monoinfected patients are ongoing.

Experience in patients with decompensated liver disease at 48 weeks (study GS-US-174-0108)
Study GS-US-174-0108 is a randomised, double-blind, active controlled study evaluating the safety and efficacy of tenofovir disoproxil (n = 45), emtricitabine plus tenofovir disoproxil (n = 45), and entecavir (n = 22), in patients with decompensated liver disease. In the tenofovir disoproxil treatment arm, patients had a mean CPT score of 7.2, mean HBV DNA of 5.8 log10 copies/ml and mean serum ALT of 61 U/l at baseline. Forty-two percent (19/45) of patients had at least 6 months of prior lamivudine experience, 20% (9/45) of patients had prior adefovir dipivoxil experience and 9 of 45 patients (20%) had lamivudine and/or adefovir dipivoxil resistance mutations at baseline. The co-primary safety endpoints were discontinuation due to an adverse event and confirmed increase in serum creatinine ≥ 0.5 mg/dl or confirmed serum phosphate of < 2 mg/dl.
In patients with CPT scores ≤ 9, 74% (29/39) of tenofovir disoproxil, and 94% (33/35) of emtricitabine plus tenofovir disoproxil treatment groups achieved HBV DNA < 400 copies/ml after 48 weeks of treatment.
Overall, the data derived from this study are too limited to draw any definitive conclusions on the comparison of emtricitabine plus tenofovir disoproxil versus tenofovir disoproxil, (see Table 16 below).

Table 16: Safety and efficacy parameters in decompensated patients at week 48

Parameter	Study 174-0108		
	Tenofovir disoproxil 245 mg (n = 45)	Emtricitabine 200 mg/ tenofovir disoproxil 245 mg (n = 45)	Entecavir (0.5 mg or 1 mg) n = 22
Tolerability failure (permanent discontinuation of study drug due to a treatment emergent AE) n (%)a	3 (7%)	2 (4%)	2 (9%)
Confirmed increase in serum creatinine ≥ 0.5 mg/dl from baseline or confirmed serum phosphate of < 2 mg/dl n (%)b	4 (9%)	3 (7%)	1 (5%)
Confirmed increase in serum creatinine ≥ 0.5 mg/dl from baseline or confirmed serum phosphate of < 2 mg/dl n (%)b	4 (9%)	3 (7%)	1 (5%)
HBV DNA n (%) < 400 copies/ml n (%)	31/44 (70%)	36/41 (88%)	16/22 (73%)
ALT n (%) Normal ALT	25/44 (57%)	31/41 (76%)	12/22 (55%)
2 point decrease in CPT from baseline n (%)	7/27 (26%)	12/25 (48%)	5/12 (42%)
Mean change from baseline in CPT score	-0.8	-0.9	-1.3
Mean change from baseline in MELD score	-1.8	-2.3	-2.6

[a] p-value comparing the combined tenofovir-containing arms versus the entecavir arm = 0.622,
[b] p-value comparing the combined tenofovir-containing arms versus the entecavir arm = 1.000.

Experience beyond 48 weeks in study GS-US-174-0108

Using a noncompleter/switch = failure analysis, 50% (21/42) of subjects receiving tenofovir disoproxil, 76% (28/37) of subjects receiving emtricitabine plus tenofovir disoproxil and 52% (11/21) of subjects receiving entecavir achieved HBV DNA < 400 copies/ml at week 168.
Experience in patients with lamivudine-resistant HBV at 240 weeks (study GS-US-174-0121)
The efficacy and safety of 245 mg tenofovir disoproxil was evaluated in a randomised, double-blind study (GS-US-174-0121) in HBeAg positive and HBeAg negative patients (n = 280) with compensated liver disease, viraemia (HBV DNA ≥ 1,000 IU/ml), and genotypic evidence of lamivudine resistance (rtM204I/V +/- rtL180M). Only five had adefovir-associated resistance mutations at baseline. One hundred forty-one and 139 adult subjects were randomised to a tenofovir disoproxil and emtricitabine plus tenofovir disoproxil treatment arm, respectively. Baseline demographics were similar between the two treatment arms: At baseline, 52.5% of subjects were HBeAg negative, 47.5% were HBeAg positive, mean HBV DNA level was 6.5 log10 copies/ml, and mean ALT was 79 U/l, respectively.
After 240 weeks of treatment, 117 of 141 subjects (83%) randomised to tenofovir disoproxil had HBV DNA < 400 copies/ml, and 51 of 79 subjects (65%) had ALT normalisation. After 240 weeks of treatment with emtricitabine plus tenofovir disoproxil, 115 of 139 subjects (83%) had HBV DNA < 400 copies/ml, and 59 of 83 subjects (71%) had ALT normalisation. Among the HBeAg positive subjects randomised to tenofovir disoproxil, 16 of 65 subjects (25%) experienced HBeAg loss, and 8 of 65 subjects (12%) experienced anti-HBe seroconversion through week 240. In the HBeAg positive subjects randomised to emtricitabine plus tenofovir disoproxil, 13 of 68 subjects (19%) experienced HBeAg loss, and 7 of 68 subjects (10%) experienced anti-HBe seroconversion through week 240. Two subjects randomised to tenofovir disoproxil experienced HBsAg loss by Week 240, but not seroconversion to anti-HBs. Five subjects randomised to emtricitabine plus tenofovir disoproxil experienced HBsAg loss, with 2 of these 5 subjects experiencing seroconversion to anti-HBs.

Clinical resistance
Four hundred and twenty-six HBeAg negative (GS-US-174-0102, n = 250) and HBeAg positive (GS-US-174-0103, n = 176) patients initially randomised to double-blind tenofovir disoproxil treatment and then switched to open-label tenofovir disoproxil treatment were evaluated for genotypic changes in HBV polymerase from baseline. Genotypic evaluations performed on all patients with HBV DNA > 400 copies/ml at week 48 (n = 39), 96 (n = 24), 144 (n = 6), 192 (n = 5), 240 (n = 4), 288 (n = 6) and 384 (n = 2) of tenofovir disoproxil monotherapy showed that no mutations associated with tenofovir disoproxil resistance have developed.
Two hundred and fifteen HBeAg negative (GS-US-174-0102, n = 125) and HBeAg positive (GS-US-174-0103, n = 90) patients initially randomised to double-blind adefovir dipivoxil treatment and then switched to open-label tenofovir disoproxil treatment were evaluated for genotypic changes in HBV polymerase from baseline. Genotypic evaluations performed on all patients with HBV DNA > 400 copies/ml at week 48 (n = 16), 96 (n = 5), 144 (n = 1), 192 (n = 2), 240 (n = 1), 288 (n = 1) and 384 (n = 2) of tenofovir disoproxil monotherapy showed that no mutations associated with tenofovir disoproxil resistance have developed.
In study GS-US-174-0108, 45 patients (including 9 patients with lamivudine and/or adefovir dipivoxil resistance mutations at baseline) received tenofovir disoproxil for up to 168 weeks. Genotypic data from paired baseline and on treatment HBV isolates were available for 6/8 patients with HBV DNA > 400 copies/ml at week 48. No amino acid substitutions associated with resistance to tenofovir disoproxil were identified in these isolates. Genotypic analysis was conducted for 5 subjects in the tenofovir disoproxil arm post week 48. No amino acid substitutions associated with tenofovir disoproxil resistance were detected in any subject.
In study GS-US-174-0121, 141 patients with lamivudine resistance substitutions at baseline received tenofovir disoproxil for up to 240 weeks. Cumulatively, there were 4 patients who experienced a viremic episode (HBV DNA>400 copies/ml) at their last timepoint on tenofovir disoproxil. Among them, sequence data from paired baseline and on treatment HBV isolates were available for 2 of 4 patients. No amino acid substitutions associated with resistance to tenofovir disoproxil were identified in these isolates.
In a paediatric study (GS-US-174-0115), 52 patients (including 6 patients with lamivudine resistance mutations at baseline) initially received blinded tenofovir disoproxil for up to 72 weeks and then 51/52 patients switched to open-label tenofovir disoproxil (tenofovir disoproxil-tenofovir disoproxil group). Genotypic evaluations were performed on all patients within this group with HBV DNA > 400 copies/ml at week 48 (n = 6), week 72 (n = 5), week 96 (n = 4), week 144 (n = 2), and week 192 (n = 3). Fifty-four patients (including 2 patients with lamivudine resistance mutations at baseline) initially received blinded placebo treatment for 72 weeks, and 52/54 patients followed with tenofovir disoproxil (PLB-tenofovir disoproxil group). Genotypic evaluations were performed on all patients within this group with HBV DNA > 400 copies/ml at week 96 (n = 17), week 144 (n = 7), and week 192 (n = 8). No amino acid substitutions associated with resistance to tenofovir disoproxil were identified in these isolates.

Paediatric population
HIV-1: In study GS-US-104-0321, 87 HIV-1 infected treatment-experienced patients 12 to < 18 years of age were treated with tenofovir disoproxil (n = 45) or placebo (n = 42) in combination with an optimised background regimen (OBR) for 48 weeks. Due to limitations of the study, a benefit of tenofovir disoproxil over placebo was not demonstrated based on plasma HIV-1 RNA levels at week 24. However, a benefit is expected for the adolescent population based on extrapolation of adult data and comparative pharmacokinetic data (see section 5.2).
In patients who received treatment with tenofovir disoproxil or placebo, mean lumbar spine BMD Z-score was -1.004 and -0.809, and mean total body BMD Z-score was -0.866 and -0.584, respectively, at baseline. Mean changes at week 48 (end of double-blind phase) were -0.215 and -0.165 in lumbar spine BMD Z-score, and -0.254 and -0.179 in total body BMD Z-score for the tenofovir disoproxil and placebo groups, respectively. The mean rate of BMD gain was less in the tenofovir disoproxil group compared to the placebo group. At week 48, six adolescents in the tenofovir disoproxil group and one adolescent in the placebo group had significant lumbar spine BMD loss (defined as > 4% loss). Among 28 patients receiving 96 weeks of treatment with tenofovir disoproxil, BMD Z-scores declined by -0.341 for lumbar spine and -0.458 for total body.
In study GS-US-104-0352, 97 treatment-experienced patients 2 to < 12 years of age with stable, virologic suppression on stavudine- or zidovudine-containing regimens were randomised to either replace stavudine or zidovudine with tenofovir disoproxil (n = 48) or continue on their original regimen (n = 49) for 48 weeks. At week 48, 83% of patients in the tenofovir disoproxil treatment group and 92% of patients in the stavudine or zidovudine treatment group had HIV-1 RNA concentrations < 400 copies/ml. The difference in the proportion of patients who maintained < 400 copies/ml at week 48 was mainly influenced by the higher number of discontinuations in the tenofovir disoproxil treatment group. When missing data were excluded, 91% of patients in the tenofovir disoproxil treatment group and 94% of patients in the stavudine or zidovudine treatment group had HIV-1 RNA concentrations < 400 copies/ml at week 48.
Reductions in BMD have been reported in paediatric patients. In patients who received treatment with tenofovir disoproxil, or stavudine or zidovudine, mean lumbar spine BMD Z-score was -1.034 and -0.498, and mean total body BMD Z-score was -0.471 and -0.386, respectively, at baseline. Mean changes at week 48 (end of randomised phase) were 0.032 and 0.087 in lumbar spine BMD Z-score, and -0.184 and -0.027 in total body BMD Z-score for the tenofovir disoproxil and stavudine or zidovudine groups, respectively. The mean rate of lumbar spine bone gain at week 48 was similar between the tenofovir disoproxil treatment group and the stavudine or zidovudine treatment group. Total body bone gain was less in the tenofovir disoproxil treatment group compared to the stavudine or zidovudine treatment group. One tenofovir disoproxil treated subject and no stavudine or zidovudine treated subjects experienced significant (> 4%) lumbar spine BMD loss at week 48. BMD Z-scores declined by -0.012 for lumbar spine and by -0.338 for total body in the 64 subjects who were treated with tenofovir disoproxil for 96 weeks. BMD Z-scores were not adjusted for height and weight.
In study GS-US-104-0352, 4 out of 89 paediatric patients exposed to tenofovir disoproxil discontinued due to adverse reactions consistent with proximal renal tubulopathy (median tenofovir disoproxil exposure 104 weeks).
Chronic hepatitis B: In study GS-US-174-0115, 106 HBeAg negative and HBeAg positive patients aged 12 to < 18 years with chronic HBV infection [HBV DNA ≥ 105 copies/ml, elevated serum ALT (≥ 2 x ULN) or a history of elevated serum ALT levels in the past 24 months] were treated with tenofovir disoproxil 245 mg (n = 52) or placebo (n = 54) for 72 weeks. Subjects must have been naïve to tenofovir disoproxil, but could have received interferon based regimens (> 6 months prior to screening) or any other non-tenofovir disoproxil containing oral anti-HBV nucleoside/nucleotide therapy (> 16 weeks prior to screening). At week 72, overall 88% (46/52) of patients in the tenofovir disoproxil treatment group and 0% (0/54) of patients in the placebo group had HBV DNA < 400 copies/ml. Seventy-four percent (26/35) of patients in the tenofovir disoproxil group had normalised ALT at week 72 compared to 31% (13/42) in the placebo group. Response to treatment with tenofovir disoproxil was comparable in nucleos(t)ide-naïve (n = 20) and nucleos(t)ide-experienced (n = 32) patients, including lamivudine-resistant patients (n = 6). Ninety-five percent of nucleos(t)ide-naïve patients, 84% of nucleos(t)ide-experienced patients, and 83% of lamivudine-resistant patients achieved HBV DNA < 400 copies/ml at week 72. Thirty-one of the 32 nucleos(t)ide-experienced patients had prior lamivudine experience. At week 72, 96% (27/28) of immune-active patients (HBV DNA ≥ 105 copies/ml, serum ALT > 1.5 x ULN) in the tenofovir disoproxil treatment group and 0% (0/32) of patients in the placebo group had HBV DNA < 400 copies/ml. Seventy-five percent (21/28) of immune-active patients in the tenofovir disoproxil group had normal ALT at week 72 compared to 34% (11/32) in the placebo group.
After 72 weeks of blinded randomized treatment, each subject could switch to open-label tenofovir disoproxil treatment up to week 192. After week 72, virologic suppression was maintained for those receiving double-blind tenofovir disoproxil followed by open-label tenofovir disoproxil (tenofovir disoproxil tenofovir disoproxil group): 86.5% (45/52) of subjects in the tenofovir disoproxil tenofovir disoproxil group had HBV DNA < 400 copies/ml at week 192. Among the subjects who received placebo during the double-blind period, the proportion of subjects with HBV DNA < 400 copies/ml rose sharply after they began treatment with open-label tenofovir disoproxil (PLB- tenofovir disoproxil group): 74.1% (40/54) of subjects in the PLB-tenofovir disoproxil group had HBV DNA < 400 copies/ml at week 192. The proportion of subjects with ALT normalization at week 192 in the tenofovir disoproxil tenofovir disoproxil group was 75.8% (25/33) among those who were HBeAg positive at baseline and 100.0% (2 of 2 subjects) among those who were HBeAg negative at baseline. Similar percentages of subjects in the tenofovir disoproxil tenofovir disoproxil and PLB-tenofovir disoproxil groups (37.5% and 41.7%, respectively) experienced seroconversion to anti-HBe through week 192.

Bone Mineral Density (BMD) data from Study GS-US-174-0115 are summarized in Table 17:
Table 17: Bone Mineral Density Evaluation at Baseline, Week 72 and 192

	Baseline		Week 72		Week 192	
	Tenofovir disoproxil-tenofovir disoproxil	PLB-tenofovir disoproxil	Tenofovir disoproxil-tenofovir disoproxil	PLB-tenofovir disoproxil	Tenofovir disoproxil-tenofovir disoproxil	PLB-tenofovir disoproxil
Lumbar spine mean (SD) BMD Z-scorea	−0.42 (0.762)	-0.26 (0.806)	-0.49 (0.852)	-0.23 (0.893)	-0.37 (0.946)	-0.44 (0.920)
Lumbar spine mean (SD) change from baseline BMD Z-scorea	NA	NA	-0.06 (0.320)	0.10 (0.378)	0.02 (0.548)	-0.10 (0.543)
Whole body mean (SD) BMD Z-scorea	−0.19 (1.110)	49	−0.36 (1.077)	−0.12 (0.916)	−0.38 (0.934)	−0.42 (0.942)
Whole body mean (SD) change from baseline BMD Z-scorea	NA	−0.23 (0.859)	−0.16 (0.355)	0.09 (0.349)	-0.16 (0.521)	-0.19 (0.504)
Lumbar spine BMD at least 6% decreaseb	NA	NA	1.9% (1 subject)	0%	3.8% (2 subjects)	3.7% (2 subjects)
Whole body BMD at least 6% decreaseb	NA	NA	0%	0%	0%	1.9% (1 subject)
Lumbar spine BMD mean % increase	NA	NA	5.14%	8.08%	10.05%	11.21%
Whole body BMD mean % increase	NA	NA	3.07%	5.39%	6.09%	7.22%

NA = Not Applicable
[a] BMD Z-scores not adjusted for height and weight
[b] Primary safety endpoint through week 72

The European Medicines Agency has deferred the obligation to submit the results of studies with Tenofovir disoproxil fumarate in one or more subsets of the paediatric population in HIV and chronic hepatitis B (see section 4.2 for information on paediatric use).
5.2 **Pharmacokinetic properties**
Dolutegravir, lamivudine and tenofovir disoproxil fumarate from the combination tablets (50 mg/300 mg/300 mg) were comparable to that from TIVICAY® (containing dolutegravir 50 mg) and EPIVIR® of ViiV U.S.A. (containing lamivudine 300 mg) and Gilead Sciences, Inc. U.S.A. VIREAD® (containing tenofovir disoproxil fumarate 300 mg), when single doses were administered to healthy subjects under fasted and fed conditions.

Dolutegravir:
Dolutegravir pharmacokinetics are similar between healthy and HIV-infected subjects. The PK variability of dolutegravir is low to moderate. In Phase I studies in healthy subjects, between-subject CVb% for AUC and C$_{max}$ ranged from ~20 to 40% and Cτ from 30 to 65% across studies. The between-subject PK variability of dolutegravir was higher in HIV-infected subjects than healthy subjects. Within-subject variability (Cvw%) is lower than between-subject variability.
Bioequivalence has not been unequivocally shown for 1x50 mg tablet compared to 5x10 mg tablets. Therefore, the 50 mg once daily dose should not be given as five 10 mg tablets.

Absorption
Dolutegravir is rapidly absorbed following oral administration, with median T$_{max}$ at 2 to 3 hours post dose for tablet formulation.
Food increased the extent and slowed the rate of absorption of dolutegravir. Bioavailability of dolutegravir depends on meal content: low, moderate, and high fat meals increased dolutegravir AUC$_{(0-∞)}$ by 33%, 41%, and 66%, increased C$_{max}$ by 46%, 52%, and 67%, prolonged T$_{max}$ to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively. These increases may be clinically relevant in the presence of certain integrase class resistance. Therefore, Dolutegravir is recommended to be taken with food by patients infected with HIV with integrase class resistance (see section 4.2).
The absolute bioavailability of dolutegravir has not been established.

Distribution
Dolutegravir is highly bound (>99%) to human plasma proteins based on in vitro data. The apparent volume of distribution is 17 L to 20 L in HIV-infected patients, based on a population pharmacokinetic analysis. Binding of dolutegravir to plasma proteins is independent of dolutegravir concentration. Total blood and plasma drug-related radioactivity concentration ratios averaged between 0.441 to 0.535, indicating minimal association of radioactivity with blood cellular components. The unbound fraction of dolutegravir in plasma is increased at low levels of serum albumin (<35 g/L) as seen in subjects with moderate hepatic impairment.
Dolutegravir is present in cerebrospinal fluid (CSF). In 13 treatment-naïve subjects on a stable dolutegravir plus abacavir/lamivudine regimen, dolutegravir concentration in CSF averaged 18 ng/mL (comparable to unbound plasma concentration, and above the Ic50).
Dolutegravir is present in the female and male genital tract. AUC in cervicovaginal fluid, cervical tissue and vaginal tissue were 6-10% of those in corresponding plasma at steady state. AUC in semen was 7% and 17% in rectal tissue of those in corresponding plasma at steady state.

Biotransformation
Dolutegravir is primarily metabolized through glucuronidation via UGT1A1 with a minor CYP3A component. Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged active substance is low (< 1% of the dose). Fifty-three percent of total oral dose is excreted unchanged in the faeces. It is unknown if all or part of this is due to unabsorbed active substance or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. Thirty-two percent of the total oral dose is 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 demonstrated no direct, or weak inhibition (IC50>50 M) of the enzymes cytochrome P$_{450}$ (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 did not induce CYP1A2, CYP2B6 or CYP3A4. Based on this 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 a substrate of human OATP 1B1, OATP 1B3 or OCT 1.

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

Linearity/non-linearity
The linearity of dolutegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of tablet formulations, in general, dolutegravir exhibited nonlinear 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 hours was approximately doubled compared to 50 mg once daily.

Pharmacokinetic/pharmacodynamic relationship(s)
In a randomized, dose-ranging trial, HIV-1–infected subjects treated with dolutegravir monotherapy (ING111521) demonstrated rapid and dose-dependent antiviral activity, 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.
PK/PD modelling using pooled data from clinical studies in integrase resistant patients suggest that increasing the dose from 50 mg twice daily to 100 mg twice daily may increase the effectiveness of dolutegravir in patients with integrase 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 clinical trials, 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 clinical data on the safety or efficacy of the 100 mg twice daily dose. Co-treatment with atazanavir increases the exposure of dolutegravir markedly, and should not be used in combination with this high dose, since safety with the resulting dolutegravir exposure has not been established.

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

Elderly
Population pharmacokinetic analysis of dolutegravir using data in HIV-1 infected adults showed that there was no clinically relevant effect of age on dolutegravir exposure.
Pharmacokinetic data for dolutegravir in subjects >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 performed in subjects with severe renal impairment (CLcr <30 mL/min) and matched healthy controls. The exposure to dolutegravir was decreased by approximately 40% in subjects with severe renal impairment. The mechanism for the decrease is unknown. No dosage adjustment is considered necessary for patients with renal impairment. Dolutegravir has not been studied in patients on dialysis.

Hepatic impairment
Dolutegravir is primarily metabolized and eliminated by the liver. A single dose of 50 mg of dolutegravir was administered to 8 subjects with moderate hepatic impairment (Child-Pugh class B) and to 8 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 observed 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 studied.

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 meta-analysis using pharmacogenomics samples collected in clinical studies in healthy subjects, subjects with UGT1A1 (n=7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n=41).

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

Race
Population PK analyses using pooled pharmacokinetic data from Phase IIb and Phase III adult trials 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 observed parameters in Western (US) subjects.

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

Lamivudine:
Absorption
Lamivudine is well absorbed from the gastrointestinal tract, and the bioavailability of oral lamivudine in adults is normally between 80 and 85%. Following oral administration, the mean time (t$_{max}$) to maximal serum concentrations (C$_{max}$) is about an hour. Based on data derived from a 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 hours 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 24h AUC are 2.0 µg/ml (26%), 0.04 µg/ml (34%) and 8.9 µg.h/ml (21%), respectively.
The 150 mg tablet is bioequivalent and dose proportional to the 300 mg tablet with respect to AUC , C$_{max}$, and t$_{max}$. Administration of Lamivudine tablets is bioequivalent to Lamivudine oral solution with respect to AUC and C$_{max}$ in adults. Absorption differences have been observed between adult and paediatric populations (see Special populations).
Co-administration of lamivudine with food results in a delay of t$_{max}$ and a lower C$_{max}$ (decreased by 47%). However, the extent (based on the AUC) of lamivudine absorbed is not influenced.
Administration of crushed tablets with a small amount of semi-solid food or liquid would not be expected to have an impact on the pharmaceutical quality, and would therefore not be expected to alter the clinical effect. This conclusion is based on the physiochemical and pharmacokinetic data assuming that the patient crushes and transfers 100% of the tablet and ingests immediately.
Co-administration of zidovudine results 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 intravenous studies, the mean volume of distribution is 1.3 l/kg. The observed half-life of elimination is 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0.32 l/h/kg, with predominantly renal clearance (> 70%) via the organic cationic transport system.
Lamivudine exhibits 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).
Limited data show that lamivudine penetrates the central nervous system and reaches the cerebro-spinal fluid (CSF). The mean ratio CSF/serum lamivudine concentration 2-4 hours after oral administration was approximately 0.12. The true extent of penetration or relationship with any clinical efficacy is unknown.

Biotransformation
The active moiety, intracellular lamivudine triphosphate, has a prolonged terminal half-life in the cell (16 to 19 hours) compared to the plasma lamivudine half-life (5 to 7 hours). In 60 healthy adult volunteers, Lamivudine 300 mg once daily has been demonstrated to be pharmacokinetically equivalent at steady-state to Lamivudine 150 mg twice daily with respect to intracellular triphosphate AUC$_{24}$ and C$_{max}$.
Lamivudine is 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
Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction. A recommended dosage regimen for patients with creatinine clearance below 50 ml/min is shown in the dosage section (see section 4.2).
An interaction with trimethoprim, a constituent of co-trimoxazole, causes a 40% increase in lamivudine exposure at therapeutic doses. This does not require dose adjustment unless the patient also has renal impairment (see sections 4.5 and 4.2). Administration of co-trimoxazole with lamivudine in patients with renal impairment should be carefully assessed.

Special populations
Children: The absolute bioavailability of lamivudine (approximately 58-66%) was reduced in paediatric patients below 12 years of age. In children, administration of tablets given concomitantly with other antiretroviral tablets delivered higher plasma lamivudine AUC and C$_{max}$ than oral solution given concomitantly with other antiretroviral oral solutions. Children receiving lamivudine oral solution according to the recommended dosage regimen achieve plasma lamivudine exposure within the range of values observed in adults. Children receiving lamivudine oral tablets according to the recommended dosage regimen achieve higher plasma lamivudine exposure than children receiving oral solution because higher mg/kg doses are administered with the tablet formulation and the tablet formulation has higher bioavailability (see section 4.2). Paediatric pharmacokinetic studies with both oral solution and tablet formulations have demonstrated that once daily dosing provides equivalent AUC$_{0-24}$ to twice daily dosing of the same total daily dose.
There are limited pharmacokinetic data for patients less than three months of age. In neonates one week of age, lamivudine oral clearance was reduced when compared to paediatric patients and is likely to be due to immature renal function and variable absorption. Therefore to achieve similar adult and paediatric exposure, an appropriate dose for neonates is 4 mg/kg/day. Glomerular filtration estimates suggests that to achieve similar adult and paediatric exposure, an appropriate dose for children aged six weeks and older could be 8 mg/kg/day.
Pharmacokinetic data were derived from 3 pharmacokinetic studies (PENTA 13, PENTA 15 and ARROW PK substudy) enrolling children under 12 years of age. The data are displayed in the table below:

Summary of Stead-State Plasma Lamivudine AUC (0-24) (µg.h/ml) and Statistical Comparisons for Once and Twice-Daily Oral Administration Across Studies

Study	Age Group	Lamivudine 8mg/kg Once-Daily Dosing Geometric Mean (95% CI)	Lamivudine 4 mg/kg Twice-Daily Dosing Geometric Mean (95% CI)	Once-Versus Twice-Daily Comparison GLS Mean Ratio (90% CI)
ARROW PK Substudy Part 1	3 to 12 years (N=35)	13.0 (11.4,14.9)	12.0 (10.7, 13.4)	1.09 (0.979, 1.20)
PENTA 13	2 to 12 years (N=19)	9.80 (8.64, 11.1)	8.88 (7.67, 10.3)	1.12 (1.03, 1.21)
PENTA 15	3 to 36 months (N=17)	8.66 (7.46, 10.1)	9.48 (7.89, 11.40)	0.91 (0.79, 1.06)

In PENTA 15 study, the geometric mean plasma lamivudine AUC(0-24) (95% CI) of the four subjects under 12 months of age who switch from a twice daily to a once daily regimen (see section 5.1) are 10.31 (6.26, 17.0) µg.h/ml in the once-daily dosing and 9.24 (4.66, 18.3) µg.h/ml in the twice-daily dosing.
Pregnancy: Following oral administration, lamivudine pharmacokinetics in late-pregnancy were 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 rapidly absorbed and converted to tenofovir. Administration of multiple doses of tenofovir disoproxil with a meal to HIV infected patients resulted in mean (%CV) tenofovir C$_{max}$, AUC, and C$_{min}$ values of 326 (36.6%) ng/ml, 3,324 (41.2%) µg/mL and 64.4 (39.4%) ng/ml, respectively. Maximum tenofovir concentrations are observed in serum within one hour of dosing in the fasted state and within two hours when taken with food. The oral bioavailability of tenofovir from tenofovir disoproxil in fasted patients was approximately 25%. Administration of tenofovir disoproxil with a high fat meal enhanced the oral bioavailability, with an increase in tenofovir AUC by approximately 40% and C$_{max}$ by approximately 14%. Following the first dose of tenofovir disoproxil in fed patients, the median C$_{max}$ in serum ranged from 213 to 375 ng/ml. However, administration of tenofovir disoproxil with a light meal did not have a significant effect on the pharmacokinetics of tenofovir.

Distribution
Following intravenous administration the steady-state volume of distribution of tenofovir was estimated to be approximately 800 ml/kg. After oral administration of tenofovir disoproxil, tenofovir is distributed to most tissues with the highest concentrations occurring in the kidney, liver and the intestinal contents (preclinical studies). In vitro protein binding of tenofovir to plasma or serum protein was less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 µg/ml.

Biotransformation
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 observed 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 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 observed. Based on these 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 estimated to be approximately 230 ml/h/kg (approximately 300 ml/min). Renal clearance has been estimated to be approximately 160 ml/h/kg (approximately 210 ml/min), which is in excess of the glomerular filtration rate. This indicates that active tubular secretion is an important part of the elimination of tenofovir. Following oral administration the terminal half-life of tenofovir is approximately 12 to 18 hours.
Studies have established the pathway of active tubular secretion of tenofovir to be influx into proximal tubule cell by the human organic anion transporters (hOAT) 1 and 3 and efflux into the urine by the multidrug resistant protein 4 (MRP 4).

Linearity/non-linearity
The pharmacokinetics of tenofovir were independent of tenofovir disoproxil dose over the dose range 75 to 600 mg and were not affected by repeated dosing at any dose level.

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

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

Ethnicity
Pharmacokinetics have not been specifically studied in different ethnic groups.

Paediatric population
HIV-1: Steady-state pharmacokinetics of tenofovir were evaluated in 8 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 g/ml and 3.39 ± 1.22 g.h/ml, respectively. Tenofovir exposure achieved in adolescent patients receiving oral daily doses of tenofovir disoproxil 245 mg was similar to exposures achieved in adults receiving once-daily doses of tenofovir disoproxil 245 mg.
Chronic hepatitis B: Steady-state tenofovir exposure in HBV infected adolescent patients (12 to < 18 years of age) receiving an oral daily dose of tenofovir disoproxil 245 mg was similar to exposures achieved in adults receiving once-daily doses of tenofovir disoproxil 245 mg.
Pharmacokinetic studies have not been performed with tenofovir disoproxil 245 mg tablets in children under 12 years or with renal impairment.

Renal impairment
Pharmacokinetic parameters of tenofovir were determined following administration of a single dose of tenofovir disoproxil 245 mg to 40 non-HIV, non-HBV infected 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%) µg/mL in subjects with CrCl > 80 ml/min to respectively 3,064 (30%) µg/mL, 6,009 (42%) µg/mL and 15,985 (45%) µg/mL in patients with mild, moderate and severe renal impairment. The dosing recommendations in patients with renal impairment, with increased dosing interval, are expected to result in higher peak plasma concentrations and lower C$_{min}$ levels in patients with renal impairment compared with patients with normal renal function. The clinical implications of this are unknown.
In patients with end-stage renal disease (ESRD) (CrCl < 10 ml/min) requiring haemodialysis, between dialysis tenofovir concentrations substantially increased over 48 hours achieving a mean C$_{max}$ of 1,032 ng/ml and a mean AUC$_{0-48h}$ of 42,857 µg/mL.
It is recommended that the dosing interval for tenofovir disoproxil 245 mg is modified in adult patients with creatinine clearance < 50 ml/min or in patients who already have ESRD and require dialysis (see section 4.2).
The pharmacokinetics of tenofovir in non-haemodialysis patients with creatinine clearance < 10 ml/min and in patients with ESRD managed by peritoneal or other forms of dialysis have not been studied.
The pharmacokinetics of tenofovir in paediatric patients with renal impairment have not been studied. No data are available to make dose recommendations (see sections 4.2 and 4.4).

Hepatic impairment
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. Tenofovir pharmacokinetics were 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$_{0-∞}$ values were 223 (34.8%) ng/ml and 2,050 (50.8%) µg/mL, respectively, in normal subjects compared with 289 (46.0%) ng/ml and 2,310 (43.5%) µg/mL in subjects with moderate hepatic impairment, and 305 (24.8%) ng/ml and 2,740 (44.0%) µg/mL in subjects with severe hepatic impairment.

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

5.3 **Preclinical safety data**
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
Dolutegravir:
Dolutegravir was not 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 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 observed at 1000 mg/kg (0.40 times the 50 mg twice daily human clinical exposure based on AUC).
In a juvenile toxicity study in rats, dolutegravir administration resulted in two 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 study, decreased body weight of the developing offspring was observed 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 evaluated 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/m2 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/m2 equivalent dose for a clinical dose of 50 mg twice daily. .

Lamivudine:
Administration of lamivudine in animal toxicity studies at high doses was not associated with any major organ toxicity. At the highest dosage levels, minor effects on indicators of liver and kidney function were seen together with occasional reductions in liver weight. The clinically relevant effects noted were a reduction in red blood cell count and neutropenia.
Lamivudine was not mutagenic in bacterial tests but, like many nucleoside analogues, showed activity in an in vitro cytogenetic assay and the mouse lymphoma assay. Lamivudine was not 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 genotoxicity study conducted in monkeys compared zidovudine alone with the combination of zidovudine and lamivudine at human-equivalent exposures. The study demonstrated that foetuses exposed in utero to the combination sustained a higher level of nucleoside analogue-DNA incorporation into multiple foetal organs, and showed evidence of more telomere shortening than in those exposed to zidovudine alone. The clinical significance of these findings is unknown.
The results of long-term carcinogenicity studies in rats and mice did not show any carcinogenic potential relevant for humans.
A fertility study in rats has shown that lamivudine had no effect on male or female fertility.

Tenofovir Disoproxil Fumarate:
Non-clinical safety pharmacology studies reveal no special hazard for humans. Findings in 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). 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.
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.
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.
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**

Mannitol (Pearlitol 50C) USP
Microcrystalline Cellulose (Avicel PH101) NF
Sodium Starch Glycolate (Primojel Type A) NF
Povidone (Kollidon 30) USP
Lactose monohydrate[#] (Pharmatose 200M)
Croscarmellose Sodium (Ac-di-sol)
Hypromellose (Methocel E5 L V Premium)
Colloidal Silicon Dioxide (Aerosil 200)
Talc
Magnesium Stearate (Vegetable Grade)
Colloidal Silicon Dioxide (Aerosil 200)

6.2 Incompatibilities: Not applicable
6.3 **Shelf life:** 24 months (proposed)
6.4 **Special precautions for storage**
Do not store above 30°C. protect from light.
6.5 Nature and contents of container
30 Tablets in HDPE Bottle: Tablets are packed in 120 cc Round Opaque White HDPE bottle with 38 mm Child Resistant Closure of polypropylene with HS 123-35 Printed Liner with One Molecular Sieve Sachet of 5g.
60 Tablets in HDPE Bottle: Tablets are packed in 200 cc Round Opaque White HDPE bottle with 38 mm Child Resistant Closure of polypropylene with HS 123-35 Printed Liner with Two Molecular Sieve Sachet of 5g
90 Tablets in HDPE bottle: Tablets packed in 300 cc Round Opaque White HDPE bottle with 53 mm Child Resistant Closure (White round polypropylene 38 mm,) with HS 123-35 Printed Liner with Three Molecular Sieve Sachet
180 Tablets in HDPE bottle: Tablets packed in 400 cc Round Opaque White HDPE bottle with 53 mm Child Resistant Closure (White round polypropylene 38 mm,) with HS 123-35 Printed Liner with three Molecular Sieve Sachet
6.6 Special precautions for disposal
No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.
7. SUPPLIER: -Lupin Ltd
Kalpataru Inspire
3rd Floor, Off Western Express Highway
Santacruz (East)
Mumbai 400055
India
8. Marketing authorisation holder: Lupin Limited
Plot No. 6A1, 6A2, Sector-17, Special Economic Zone, MIHAN Notified Area, Nagpur, Maharashtra-4411 08, India.
9. Marketing authorisation number(s): ND/59

To report suspected adverse reactions, contact Lupin Limited on drugsafety@lupin.com

Manufactured by:
LUPIN LTD.
Plot No. 6A1, 6A2, Sector 17, Special Economic Zone, Mihan, Nagpur - 441108, Tal: Nagpur Rural, Dist: Nagpur, INDIA.

267781

34 mm

Market/Customer :	Malawi	**Location :**	Nagpur
Prepared On :	01/06/2021	**Tracking No. :**	05
Product Name :	Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets Leaflet		
Material Code :	267781	**Supersedes Material code :**	NA
Open Size :	634 x 450 mm (L x W)	**Barcode :**	NA
Folded Size :	34 x 34 mm (L x W)	**Barcode Type (Ex. NDC, PZN, EAN-13)**	NA
Substrate :	GSM : 40 gsm	**Component :**	Pack Insert
	Paper : Bible Paper	**Font Size :**	5 pt
Font Name :	Helvetica condensed	**Gluing :**	YES
Perforation :	NA	**Pharma Code :**	7579
Cover Page Substrate :	NA		
Pantone Colours :	Black; Dieline (does not print)		
Reason for Change :	New Artwork		
Unicorn Creation D/Lupin/Export/Malawi/Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets/			