ACRIPTEGA
Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate Tablets 50mg/300mg/300mg

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:
Dolutegravir (as Dolutegravir Sodium) 50 mg
Lamivudine USP 300 mg
Tenofovir Disoproxil Fumarate (equivalent to 245 mg of Tenofovir Disoproxil)…300 mg

Excipient(s) with known effect

Each film coated tablet contains 136.0 mg of Lactose Monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated Tablets

A white to off-white, film coated, capsule shaped, biconvex beveled edge tablet debossed with **M** on one side and **LTD** on the other side of the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets is a fixed dose combination of Lamivudine, Tenofovir Disoproxil Fumarate and Dolutegravir.

It is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents (from 12 years of age and weighing $\geq$ 40 kg) with virologic suppression to HIV-1 RNA levels of < 50 copies/ml on their current combination antiretroviral therapy for more than three months. Patients must not have experienced virological failure on any prior antiretroviral therapy.

The choice of Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets to treat antiretroviral experienced patients with HIV-1 infection should be based on individual viral resistance testing and/or the treatment history of the patient. Consideration should be given to official treatment guidelines for HIV-1 infection (e.g. by WHO).

No data are available to support the combination of Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets and other antiretroviral agents.

4.2 Posology and method of administration

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

Posology

Adults and adolescents (from 12 years of age and weighing ≥ 40 kg)
The recommended dose of Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets in adults and adolescents is one tablet once daily.

Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets should not be administered to adults or adolescents who weigh less than 40 kg because it is a fixed-dose tablet that cannot be dose reduced.

Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets is a fixed-dose tablet and should not be prescribed for patients requiring dose adjustments. Separate preparations of Lamivudine, Tenofovir Disoproxil Fumarate and Dolutegravir are available in cases where discontinuation or dose adjustment of one of the active substances is indicated. In these cases the physician should refer to the individual product information for these medicinal products

Method of administration

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

Children

Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets is not recommended for use in children below 12 years of age due to a lack of data on safety and efficacy.

Elderly

There are limited data available on the use of Dolutegravir in patients aged 65 years and over. There is no evidence that elderly patients require a different dose than younger adult patients (see section 5.2). Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets should be administered with caution to elderly patients (see section 4.4).

Dose adjustments

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

Renal impairment

Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets is not recommended for patients with moderate or severe renal impairment (creatinine clearance (CrCl) < 50

ml/min). Patients with moderate or severe renal impairment require dose interval adjustment of lamivudine and tenofovir disoproxil fumarate that cannot be achieved with the combination tablet (see sections 4.4 and 5.2).

Hepatic impairment

The pharmacokinetics of Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets have not been studied in patients with hepatic impairment. Patients should be monitored carefully for adverse reactions.

If Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets is discontinued in patients co-infected with HIV and HBV, these patients should be closely monitored for evidence of exacerbation of hepatitis (see section 4.4).

4.3 Contraindications

Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets is contraindicated in patients with clinically significant hypersensitivity to tenofovir, lamivudine, Dolutegravir or to any of the excipients contained in the formulation.

Co-administration with dofetilide (see section 4.5).

4.4 Special warnings and precautions for use

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.

General

As a fixed combination, Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets should not be administered concomitantly with other medicinal products containing any of the same active components, Dolutegravir, lamivudine or tenofovir disoproxil fumarate. Dolutegravir Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets should not be administered concomitantly with other cytidine analogues such as emtricitabine. (see section 4.5). Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets should not be administered concomitantly with adefovir dipivoxil.

Transmission of HIV

Treatment with Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets has not been shown to eliminate the risk of transmission of HIV infection by sexual contact or by blood transfer, although the risk may be reduced. Patients should continue to use appropriate precautions to prevent transmission of HIV.

Liver disease

The safety and pharmacokinetics of Dolutegravir has not been investigated in patients with severe liver disease. Therefore Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets should only be used in this group of patients if the benefits are considered to outweigh the risks, and with close safety monitoring.

Patients with HIV and hepatitis B (HBV) or C virus (HCV) co-infection

Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

Physicians should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with HBV.

Lamivudine and tenofovir disoproxil fumarate are also active against HBV. Therefore, discontinuation of Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis. Patients co-infected with HIV and HBV who discontinue Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets must be closely monitored with both clinical and laboratory follow-up for at least four months after stopping treatment with Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets. If appropriate, resumption of specific anti-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.

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+$\geq$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 agents 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.

Renal function

Tenofovir is primarily excreted by the kidneys through a combination of glomerular filtration and active tubular secretion. Thus, clearance is decreased in patients with impaired renal function. There are limited data on the safety and efficacy of tenofovir disoproxil fumarate in patients with impaired renal function (< 80 ml/min). In such patients, Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets should only be used if the potential benefits of treatment are considered to outweigh the potential risks.

In patients with moderate to severe renal impairment, the plasma half-life of lamivudine is increased due to decreased clearance. Decreased doses are recommended for patients with creatinine clearance <50 ml/min.

The use of Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets is not recommended in patients with creatinine clearance < 50 ml/min, since appropriate dose reductions cannot be achieved with the combination tablet (see sections 4.2 and 5.2).

Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil fumarate in clinical practice (see section 4.8). It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets. Routine monitoring of calculated creatinine clearance and serum phosphate should be performed in patients at risk for renal impairment.

In patients receiving tenofovir disoproxil fumarate renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations, if serum phosphate is < 1.5 mg/dl (0.48 mmol/l) or creatinine clearance decreases below 50 ml/min (see section 4.8, proximal tubulopathy).

Consideration should also be given to interrupting treatment with Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets in patients whose creatinine clearance falls below 50 ml/min or whose serum phosphate decreases below 1.0 mg/dl (0.32 mmol/l).

Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets should be avoided with concurrent 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 fumarate and nephrotoxic agents is unavoidable, renal function should be monitored weekly.

Bone effects

In a controlled clinical study decreases in bone mineral density of spine and changes in bone biomarkers from baseline were observed in both treatment groups, but were significantly greater in the tenofovir disoproxil fumarate treatment group than in the comparator group treated with stavudine (each in combination with lamivudine and efavirenz) at 144 weeks. Decreases in bone mineral density 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.

Tenofovir was studied in HIV-1 infected paediatric subjects 12 years of age and older. Under normal circumstances, bone mineral density increases rapidly in this age group. In this study, the mean rate of bone gain was less in the tenofovir-treated group compared to the placebo group. Skeletal growth (height) appeared to be unaffected. Markers of bone turnover in tenofovir-treated paediatric subjects 12 years of age and older suggest increased bone turnover, consistent with the effects observed in adults. Due to the possible effects of tenofovir on bone metabolism, Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets should only be used in adolescents under the age of 18 if the benefits are considered to exceed the risk (see also section 4.8).

Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy (see section 4.8). If bone abnormalities are suspected then appropriate consultation should be obtained.

Lactic acidosis

Lactic acidosis is a rare but severe, potentially life-threatening complication associated with use of nucleoside reverse transcriptase inhibitors (NRTI). Several other agents of this class are known to cause lactic acidosis. Preclinical and clinical data suggest that the risk of occurrence of lactic acidosis, considered a putative class effect of nucleoside analogues, is very low for tenofovir disoproxil fumarate and lamivudine. However, this risk cannot be excluded. Lactic acidosis may occur after a few to several months of NRTI treatment. Patients with hyperlactataemia may be asymptomatic, critically ill, or may have non-specific symptoms such as dyspnoea, fatigue, nausea, vomiting, diarrhoea and abdominal pain. Risk factors for NRTI-related lactic acidosis include female gender and obesity. Patients at increased risk should be closely monitored clinically. Screening for hyperlactataemia in asymptomatic patients treated with NRTIs, however, is not recommended. Symptomatic patients usually have levels > 5 mmol/l and require discontinuation of all NRTIs. Lactic acid levels > 10 mmol/l usually are a medical emergency.

Lipodystrophy and metabolic disorders

Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV-infected patients. Whereas for some other antiretrovirals there is considerable evidence for this adverse reaction, the evidence for tenofovir and lamivudine as causative agents is weak; indeed switching from a thymidine analogue (e.g. stavudine) to tenofovir has been shown to increase limb fat in patients with lipoatrophy. A higher risk of lipodystrophy has been associated e.g. with older age of the patient, longer duration of antiretroviral therapy and related metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Measurement of fasting serum lipids and blood glucose as well as appropriate management of lipid disorders should be considered (see section 4.8).

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) 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).

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 HIV-negative infants exposed *in utero* and/or postnatally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactataemia, hyperlipasaemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV-negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Pancreatitis

Treatment with Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur (see section 4.8).

Opportunistic infections

*P*atients receiving antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection. Therefore patients should remain under close clinical observation by physicians or health care providers experienced in the treatment of HIV infection.

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 antiepileptic drugs) (see section 4.5).

Dolutegravir increased metformin concentrations. A dose adjustment of metformin should be considered when starting and stopping coadministration 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.

Co-administration of Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets and didanosine is not recommended since exposure to didanosine is significantly increased following co-administration with tenofovir disoproxil fumarate (see section 4.5).

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.

Elderly patients

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

Excipients

Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets contain 136.00 mg of lactose per maximum recommended daily dose. Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions relevant to lamivudine

Co-administration with trimethoprim / sulfamethoxazole results in a 40% increase in lamivudine area under the concentration curve. No dose adjustment of Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate 50mg/300mg/300mg Tablets is necessary. Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole.

Interactions relevant to tenofovir

Didanosine
Co-administration of tenofovir disoproxil fumarate and didanosine is not recommended (see section 4.4 and the table below).

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

Tenofovir disoproxil fumarate should be avoided with concurrent use of a nephrotoxic medicinal product, such as 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 fumarate.

Interactions between tenofovir disoproxil fumarate and other medicinal products

Interactions between Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg and HIV protease inhibitors, as well as antiviral agents other than protease inhibitors, are listed in Table below (increased exposure is indicated as "↑", decreased exposure as "↓", no change as "↔", twice daily as "b.i.d.", and once daily as "q.d.").

Medicinal products by therapeutic areas (dose in mg)	Effects on drug levels Mean % change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with tenofovir disoproxil fumarate 300 mg
ANTI-INFECTIVES		
antiretrovirals		
Protease inhibitors		
Atazanavir (400 mg q.d.)	Atazanavir: AUC ↓ 25% C_{max} ↓ 21% C_{min} ↓ 40% Tenofovir: AUC ↑ 24% C_{max} ↑ 14% C_{min} ↑ 22%	If atazanavir and Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets are coadministered, atazanavir should be given at the dose 300 mg q.d. together with ritonavir 100 mg q.d. ("ritonavir-boosting", see below).
Atazanavir/Ritonavir (300 mg/100 mg q.d.)	Atazanavir: AUC ↓ 25% C_{max} ↓ 28% C_{min} ↓ 26% Tenofovir: AUC ↑ 37% C_{max} ↑ 34% C_{min} ↑ 29%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).

Lopinavir/Ritonavir (400 mg/100 mg b.i.d.)	Lopinavir/ritonavir: No significant effect on lopinavir/ritonavir PK parameters. Tenofovir: AUC ↑ 32% C_{max} ↔ C_{min} ↑ 51%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
Darunavir/Ritonavir (300 mg/100 mg b.i.d.)	Darunavir: No significant effect on darunavir/ritonavir PK parameters. Tenofovir: AUC ↑ 22% C_{min} ↑ 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 (400 mg q.d.)	Didanosine AUC ↑ 40-60%	The risk of didanosine-related adverse effects (e.g., pancreatitis, lactic acidosis appears to be increased, and CD4 cells may decrease significantly on coadministration. Also didanosine at 250 mg co-administered with tenofovir within several different antiretroviral combination regimens has been associated with a high rate of virological failure. Co-administration of Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets and didanosine is not recommended (see section 4.4).
Adefovir dipivoxil	AUC ↔ C_{max} ↔	Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets should not be administered concurrently with adefovir dipivoxil (see section 4.4).

Entecavir (1 mg q.d.)	AUC ↔ C_{max} ↔	No clinically significant pharmacokinetic interactions when Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets is co-administered with entecavir.

Studies conducted with other medicinal products
There were no clinically significant pharmacokinetic interactions when Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets is coadministered with indinavir, efavirenz, nelfinavir, saquinavir (ritonavir boosted), methadone, ribavirin, rifampicin, tacrolimus, or the hormonal contraceptive norgestimate/ethinyl oestradiol.

Food effect
Tenofovir disoproxil fumarate must be taken with food, as food enhances the bioavailability of tenofovir (see section 5.2).

Interactions relevant to dolutegravir

Effect of other agents on the pharmacokinetics of dolutegravir
All factors that decrease dolutegravir exposure should be avoided in the presence of integrase class resistance.

Dolutegravir is eliminated mainly through metabolism by UGT1A1. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP; therefore medicinal products that induce those enzymes may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir.

Co-administration of dolutegravir and other medicinal products that inhibit these enzymes may increase dolutegravir plasma concentration. The absorption of dolutegravir is reduced by certain anti-acid agents.

Effect of dolutegravir on the pharmacokinetics of other agents
In vivo, dolutegravir did not 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 Ta 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 medical products in which excretion is dependent upon OAT3.

Established and theoretical interactions with selected antiretrovirals and non-antiretroviral medicinal products are listed in Table.

Interaction table dolutegravir

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

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% C_τ ↓ 88% Etravirine ↔ (induction of UGT1A1 and CYP3A enzymes)	Etravirine without boosted protease inhibitors decreased plasma dolutegravir concentration. The recommended dose of dolutegravir is 50 mg twice daily when co-administered with etravirine without boosted protease inhibitors. Dolutegravir should not be used with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir in INI- resistant patients (see further below in table).
Lopinavir/ritonavir + etravirine	Dolutegravir ↔ AUC ↑ 11% C_{max} ↑ 7% C_τ ↑ 28% LPV ↔ RTV ↔	No dose adjustment is necessary.
Darunavir/ritonavir + etravirine	Dolutegravir ↓ AUC ↓ 25% C_{max} ↓ 12% C_τ ↓ 36% DRV ↔ RTV ↔	No dose adjustment is necessary.

Efavirenz	Dolutegravir ↓ AUC ↓ 57% C_{max} ↓ 39% C_{τ} ↓ 75% Efavirenz ↔ (historical controls) (induction of UGT1A1 and CYP3A enzymes)	The recommended dose of dolutegravir is 50 mg twice daily when co-administered with efavirenz. 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 dose of dolutegravir is 50 mg twice daily when co-administered with nevirapine. 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% C_{τ} ↑ 22% Rilpivirine ↔	No dose adjustment is necessary.
Nucleoside Reverse Transcriptase Inhibitors		
Tenofovir	Dolutegravir ↔ AUC ↑ 1% C_{max} ↓ 3% C_{τ} ↓ 8% Tenofovir ↔	No dose adjustment is necessary.
Protease Inhibitors		
Atazanavir	Dolutegravir ↑ AUC ↑ 91% C_{max} ↑ 50% C_{τ} ↑ 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% C_{τ} ↑ 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% C_{τ} ↓ 76% (induction of UGT1A1 and CYP3A enzymes)	The recommended dose of dolutegravir is 50 mg twice daily when co-administered with tipranavir/ritonavir the absence of integrase class resistance. 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% C_{τ} ↓ 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		

Telaprevir	Dolutegravir ↑ AUC ↑ 25% C_{max} ↑ 19% C_{τ} ↑ 37% Telaprevir ↔ (historical controls) (inhibition of CYP3A enzyme)	No dose adjustment is necessary.
Boceprevir	Dolutegravir ↔ AUC ↑ 7% C_{max} ↑ 5% C_{τ} ↑ 8% Boceprevir ↔ (historical controls)	No dose adjustment is necessary.
Daclatasvir	Dolutegravir ↔ AUC ↑ 33% C_{max} ↑ 29% C_{τ} ↑ 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% C_{τ} ↓ 73%	The recommended dose of dolutegravir is 50 mg twice daily when co-administered with carbamazepine. 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 dose of dolutegravir is 50 mg twice daily when co-administered with these metabolic inducers. 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 dose of dolutegravir is 50 mg twice daily when co-administered with St. John's wort. 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%	No dose adjustment is necessary.

	C_{max} ↑ 6% C_{τ} ↑ 17%	
Antidiabetics		
Metformin	Metformin ↑ When co-administered with dolutegravir 50 mg 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% C_{τ} ↓72% (induction of UGT1A1 and CYP3A enzymes)	The recommended dose of dolutegravir is 50 mg twice daily when co-administered with rifampicin in the absence of integrase class resistance. In the presence of integrase class resistance this combination should be avoided (see section 4.4).
Rifabutin	Dolutegravir ↔ AUC ↓ 5% C_{max} ↑ 16% C_{τ} ↓ 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%	No dose adjustment is necessary of either agent.

	$C_{max} \leftrightarrow 0\%$ $C_{\tau} \downarrow 1\%$	

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Lamivudine/Tenofovir Disoproxil Fumarate
Animal studies do not indicate direct or indirect harmful effects of tenofovir disoproxil fumarate with respect to pregnancy, foetal development, parturition or postnatal development (see section 5.3). In humans, the safety of tenofovir in pregnancy has not been fully established. Sufficient numbers of first trimester exposures have been monitored, however, to detect at least a twofold increase in the risk of overall birth defects. No increase in birth defects was seen (www.apregistry.com).

No increased risk of birth defects has been reported for lamivudine (www.apregistry.com). However, risks to the fetus cannot be ruled out.

Dolutegravir
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

Lamivudine/Tenofovir Disoproxil Fumarate
In animal studies it has been shown that tenofovir is excreted into milk. It is not known whether tenofovir is excreted in human milk. Lamivudine is excreted into the breast milk of lactating mothers.

Current recommendations on HIV and breastfeeding (e.g. those from the WHO) should be consulted before advising patients on this matter. Preferred options may vary depending on the local circumstances.

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

Fertility

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

4.7 Effects on ability to drive and use machines

There have been no studies to investigate the effect of dolutegravir on driving performance or the ability to operate machines. However, patients should be informed that dizziness has been reported during treatment with dolutegravir. The clinical status of the patient and the adverse reaction profile of dolutegravir should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

Lamivudine/Tenofovir Disoproxil Fumarate

Adverse events considered at least possibly related to treatment with lamivudine are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000), very rare (<1/10,000), unknown (frequency cannot be estimated from the available data).

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

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

Nervous system disorders
Very common: dizziness
Common: headache and insomnia
Very rare: peripheral neuropathy (paraesthesia)

Respiratory, thoracic and mediastinal disorders
Common: cough, nasal symptoms
Very rare: dyspnoea

Gastrointestinal disorders
Very common: diarrhoea, nausea, vomiting
Common: abdominal pain/cramps, flatulence
Rare: pancreatitis, elevated serum amylases

Hepatobiliary disorders
Uncommon: transient elevation in liver enzymes

Rare: hepatitis
Unknown: hepatic steatosis

Skin and subcutaneous tissue disorders
Common: Rash, hair loss

Musculoskeletal and connective tissue disorders
Common: arthralgia, muscle disorder
Unknown: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), muscular weakness, myopathy, osteonecrosis

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

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

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), hypokalaemia, muscular weakness, myopathy and hypophosphataemia. These events are not considered to be causally associated with tenofovir disoproxil fumarate therapy in the absence of proximal renal tubulopathy.

In HBV infected patients, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of HBV therapy (see section 4.4).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Dolutegravir

Summary of the safety profile
The safety profile is based on pooled data from Phase IIb and Phase III clinical studies in 1222 previously untreated patients, 357 previously treated patients unexposed to integrase inhibitors and 264 patients with prior treatment failure that included an integrase inhibitor (including integrase class resistance). 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%).

The safety profile was similar across the different treatment populations mentioned above.

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).

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
	Uncommon	Suicidal ideation or 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
Skin and subcutaneous tissue disorders	Common	Rash
	Common	Pruritus
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 (see section 4.4).

Immune response syndrome
In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Paediatric population
Based on limited available data in adolescents (12 to less than 18 years of age and weighing at least 40 kg), there were no additional types of adverse reactions beyond those observed in the adult population.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

Lamivudine/Tenofovir Disoproxil Fumarate

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.

Tenofovir can be removed by haemodialysis; the median haemodialysis clearance of tenofovir is 134 ml/min. The elimination of tenofovir by peritoneal dialysis has not been studied.

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

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Not yet assigned, ATC code: Not yet assigned
Namibia Pharmacological Classification: 20.2.8 - Antiviral agents

Lamivudine/Tenofovir Disoproxil Fumarate

Mechanism of action and pharmacodynamic effects
Lamivudine, the negative enantiomer of 2'-deoxy-3'-thiacytidine, is a dideoxynucleoside analogue. Tenofovir disoproxil fumarate is converted *in vivo* to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate.

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

Resistance
In many cases when a lamivudine-containing treatment regimen fails, the M184V mutation will be selected for at an early stage. M184V causes high-level resistance to lamivudine (>300-fold reduced susceptibility). Virus with M184V replicates less well than does wild type virus. M184V causes high-level resistance to lamivudine (>300-fold reduced susceptibility).

In vitro data tend to suggest that the continuation of lamivudine in an antiretroviral 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.

Cross-resistance conferred by the M184V mutation is limited within the nucleoside/nucleotide inhibitor class of antiretroviral agents. M184V confers full cross-resistance against emtricitabine. 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 mutant shows a <4-fold decrease in susceptibility to didanosine; the clinical significance of this is unknown.

The K65R mutation is selected *in vitro* when HIV-1 is cultured in the presence of increasing tenofovir concentrations. It may also emerge *in vivo* upon virological failure of a treatment regimen including tenofovir. K65R reduces tenofovir susceptibility *in vitro* approximately 2-fold, and has been associated with a lack of response to tenofovir-containing regimens.

Clinical studies in treatment-experienced patients have assessed the anti-HIV activity of tenofovir against strains of HIV-1 with thymidine analogue mutations (TAMs), which are not selected for by tenofovir. Patients whose HIV expressed 3 or more TAMs that included either the M41L or L210W mutation showed reduced response to tenofovir.

Clinical efficacy
When tenofovir disoproxil fumarate and lamivudine were combined with efavirenz in treatment-naïve patients with HIV-1, the proportion of patients (ITT) with HIV-RNA <50 copies/ml were 76.3% and 67.8% at 48 and 144 weeks, respectively

No specific studies with the combination tenofovir disoproxil fumarate, Lamivudine and dolutegravir have been conducted in adolescents.

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 ug/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 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 activecontrolled study FLAMINGO (ING114915) and additional data from the open-label phase of SINGLE to 144 weeks.

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% nonwhite, 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.

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 >100,000	267 / 297 (90%) 94 / 114 (82%)	264 / 295 (89%) 87 / 116 (75%)	253 / 280 (90%) 111 / 134 (83%)	238 / 288 (83%) 100 / 131 (76%)
Baseline CD4+ (cells/ mm^3)				
<200 200 to <350 ≥350	43 / 55 (78%)	34 / 50 (68%)	45 / 57 (79%)	48 / 62 (77%)

	128 / 144 (89%) 190 / 212 (90%)	118 / 139 (85%) 199 / 222 (90%)	143 / 163 (88%) 176 / 194 (91%)	126 / 159 (79%) 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 Female	308 / 348 (89%) 53 / 63 (84%)	305 / 355 (86%) 46 / 56 (82%)	307 / 347 (88%) 57 / 67 (85%)	291 / 356 (82%) 47 / 63 (75%)
Race				
White African-America/African Heritage/Other	306 / 346 (88%) 55 / 65 (85%)	301 / 352 (86%) 50 / 59 (85%)	255 / 284 (90%) 109 / 130 (84%)	238 /285 (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 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 noninferior to raltegravir (viral suppression in 81% vs 76% of patients), and with a median change in CD4 count of 276 vs 264 cells/mm^3, 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/ mm^3, respectively. At 144 weeks in the openlabel 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).

In 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].

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.

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.

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/ mm^3)		
<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*	155 / 216 (72%)	129 / 192 (67%)
<2 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/mm^3)	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).

Paediatric population
In a Phase I/II 48 week multicentre, open-label study (P1093/ING112578), the pharmacokinetic parameters, safety, tolerability and efficacy of Tivicay will be evaluated in combination regimens in HIV-1 infected adolescents.

At 24 weeks, 16 of 23 (70%) adolescents (12 to less than 18 years of age) treated with Tivicay once daily (35 mg n=4, 50 mg n=19) plus OBR achieved viral load <50 copies/mL. Four subjects had virologic failure none of which had INI resistance at the time of virologic failure.

5.2 Pharmacokinetic properties

Lamivudine

Absorption and Bioavailability
Lamivudine is rapidly absorbed following oral administration. Bioavailability is between 80 and 85%. Following single dose administration of one tablet of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600 mg/300 mg/300 mg Tablets in healthy volunteers, the mean (±SD) lamivudine C_{max} value was 2483 (±706) ng/ml and the corresponding value for AUC was 13457 (±3717) ng.h/ml. The mean (±SD) lamivudine t_{max} value was 1.92 (±0.93) hours.

Co-administration of lamivudine with food results in a delay of t_{max} and a lower C_{max} (decreased by 47%). However, the extent (based on the AUC) of lamivudine absorbed is not influenced.

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

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

Elimination
The observed lamivudine half-life of elimination is 5 to 7 hours. The half-life of intracellular lamivudine triphosphate has been estimated to approximately 22 hours. The mean systemic clearance of lamivudine is approximately 0.32 l/h/kg, with predominantly renal clearance (> 70%), including tubular secretion through the organic cationic transport system.

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

Tenofovir disoproxil fumarate

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

Absorption
Following oral administration of tenofovir disoproxil fumarate to HIV infected patients, tenofovir disoproxil fumarate is rapidly absorbed and converted to tenofovir. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted patients was approximately 25%. Administration of tenofovir disoproxil fumarate 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 single dose administration of one tablet of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600 mg/300 mg/300 mg Tablets in healthy volunteers, the mean (±SD) tenofovir C_{max} value was 277 (±79) ng/ml and the corresponding value for AUC was 2358 (±627) ng.h/ml. The mean (±SD) tenofovir t_{max} value was 1.17 (±0.57) hours.

Distribution
Following intravenous administration the steady-state volume of distribution of tenofovir was estimated to be approximately 800 ml/kg. *In vitro* protein binding of tenofovir to plasma or serum protein was less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 µg/ml.

Elimination
Tenofovir is primarily excreted by the kidney, both by filtration and an active tubular transport system with approximately 70-80% of the dose excreted unchanged in urine following intravenous

administration. Total clearance has been estimated to be approximately 230 ml/h/kg (approximately 300 ml/min). Renal clearance has been estimated to be approximately 160 ml/h/kg (approximately 210 ml/min), which is in excess of the glomerular filtration rate. This indicates that active tubular secretion is an important part of the elimination of tenofovir. Following oral administration the terminal half-life of tenofovir is approximately 12 to 18 hours.

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

Age and gender
Limited data on the pharmacokinetics of tenofovir in women indicate no major gender effect. Tenofovir exposure achieved in adolescent patients receiving oral daily doses of tenofovir 300 mg was similar to exposures achieved in adults receiving once-daily doses of tenofovir 300 mg. Pharmacokinetic studies have not been performed in children or in the elderly (over 65 years). Pharmacokinetics have not been specifically studied in different ethnic groups.

Renal impairment
Pharmacokinetic parameters of tenofovir were determined following administration of a single dose of tenofovir disoproxil fumarate 300 mg to 40 non-HIV, non-HBV infected patients with varying degrees of renal impairment defined according to baseline creatinine clearance (CrCl) (normal renal function when CrCl > 80 ml/min; mild with CrCl = 50-79 ml/min; moderate with CrCl = 30-49 ml/min and severe with CrCl = 10-29 ml/min). Compared with patients with normal renal function, the mean (%CV) tenofovir exposure increased from 2,185 (12%) ng·h/ml in subjects with CrCl > 80 ml/min to respectively 3,064 (30%) ng·h/ml, 6,009 (42%) ng·h/ml and 15,985 (45%) ng·h/ml in patients with mild, moderate and severe renal impairment. The 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 ng·h/ml. It is recommended that the dosing interval for tenofovir disoproxil fumarate 300 mg is modified in patients with creatinine clearance < 50 ml/min or in patients who already have ESRD and require dialysis (see section 4.2).

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

Hepatic impairment
A single 300 mg dose of tenofovir disoproxil fumarate was administered to non-HIV, non-HBV infected patients with varying degrees of hepatic impairment defined according to Child-Pugh-Turcotte (CPT) classification. Tenofovir pharmacokinetic parameters were not substantially altered in subjects with hepatic impairment suggesting that no dose adjustment is required in these subjects. The mean (%CV) tenofovir C_{max} and $AUC_{0-\infty}$ values were 223 (34.8%) ng/ml and 2,050 (50.8%) ng·h/ml, respectively, in normal subjects compared with 289 (46.0%) ng/ml and 2,31 (43.5%) ng·h/ml in subjects with moderate

hepatic impairment, and 305 (24.8%) ng/ml and 2,740 (44.0%) ng·h/ml in subjects with severe hepatic impairment.

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

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 C_{τ} 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.

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 $AUC_{(0-\infty)}$ by 33%, 41%, and 66%, increased C_{max} by 46%, 52%, and 67%, prolonged T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively. These increases may be clinically relevant in the presence of certain integrase class resistance. Therefore, 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 IC_{50}).

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

Biotransformation
Dolutegravir is primarily metabolized through glucuronidation via UGT1A1 with a minor CYP3A component. Dolutegravir is the predominant circulating compound in plasma; renal elimination of

unchanged active substance is low (< 1% of the dose). 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 (IC_{50}>50 μM) of the enzymes cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7, or the transporters Pgp, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, MATE2-K, MRP2 or MRP4. *In vitro*, dolutegravir 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 + $\geq$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 + $\geq$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.

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.

5.3 Preclinical safety data

Lamivudine

Administration of lamivudine in animal toxicity studies at high doses was not associated with any major organ toxicity. Lamivudine was not mutagenic in bacterial tests, but showed activity in an *in vitro* cytogenetic assay and the mouse lymphoma assay. Lamivudine was not genotoxic *in vitro* at doses that gave plasma concentrations around 40-50 times higher than the anticipated clinical plasma levels. As the *in vitro* mutagenic activity of lamivudine could not be confirmed in *in vivo* tests, it is concluded that lamivudine should not represent a genotoxic hazard to patients undergoing treatment.

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

Tenofovir

Preclinical studies conducted in rats, dogs and monkeys revealed target organ effects in gastrointestinal tract, kidney, bone and a decrease in serum phosphate concentration. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (rats and dogs). Findings in the rat and monkey studies indicated that there was a substance-related decrease in intestinal absorption of phosphate with potential secondary reduction in bone mineral density. However, no conclusion could be drawn on the mechanism(s) underlying these toxicities.

Reproductive studies were conducted in rats and rabbits. There were no effects on mating or fertility parameters or on any pregnancy or foetal parameter. There were no gross foetal alterations of soft or skeletal tissues. Tenofovir disoproxil fumarate reduced the viability index and weight of pups in peri-post natal toxicity studies.

Genotoxicity studies have shown that tenofovir disoproxil fumarate was negative in the *in vivo* mouse bone marrow micronucleus assay but was positive for inducing forward mutations in the *in vitro* L5178Y mouse lymphoma cell assay in the presence or absence of S9 metabolic activation. Tenofovir disoproxil fumarate was positive in the Ames test (strain TA 1535) in two out of three studies, once in the presence of S9 mix (6.2- to 6.8-fold increase) and once without S9 mix. Tenofovir disoproxil fumarate was also weakly positive in an *in vivo/in vitro* unscheduled DNA synthesis test in primary rat hepatocytes.
Tenofovir disoproxil fumarate did not show any carcinogenic potential in a long-term oral carcinogenicity study in rats. A long-term oral carcinogenicity study in mice showed a low incidence of duodenal tumours, considered likely related to high local concentrations of tenofovir disoproxil fumarate in the gastrointestinal tract at a dose of 600 mg/kg/day. While the mechanism of tumour formation is uncertain, the findings are unlikely to be of relevance to humans.

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).

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet

Mannitol, Microcrystalline cellulose, Povidone, Sodium Starch Glycolate, Lactose Monohydrate, Croscarmellose Sodium, Magnesium Stearate

Film coat

Polyvinyl alcohol, Titanium dioxide, Macrogol, Talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container.

6.5 Nature and contents of container

HDPE Bottle Pack of 30's, 90's & 180's*

* Not all packs may be marketed

6.6 Instructions for use and handling and disposal

No special requirements.

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

7. MARKETING AUTHORISATION HOLDER

Mylan Laboratories Limited, India

Mfd. by:
Mylan Laboratories Limited,
Plot no: 11, 12 & 13, Indore SEZ, Pharma Zone,
Phase-II, Sector-III, Pithampur – 454775
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