SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50mg dolutegravir (as sodium), 300mg lamivudine and 300mg tenofovir disoproxil fumarate.

Each film-coated tablet contains about 131.38 mg of mannitol and 150.40 mg of lactose monohydrate For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets

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

No score-line.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg is indicated for the treatment of human immunodeficiency virus (HIV) infection in adults and adolescents weighing at least 30 kg.

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

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

4.2 Posology and method of administration

Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg should be prescribed by a health care provider experienced in the management of HIV infection.

Posology

Adults

The dose of Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg. is one tablet once daily.

Dose adjustments

Where discontinuation of therapy with one of the components of Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg is indicated or where dose modification is necessary, separate preparations of dolutegravir, lamivudine and tenofovir disoproxil should be used.

Please refer to the individual product information for these medicinal products.

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

Adolescents weighing at least 30 kg

The dose in adolescents weighing at least 30 kg with HIV-1 infection not resistant to integrase inhibitors is one tablet of Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg once daily. There is insufficient information on the use of dolutegravir in adolescents with HIV-1 infection resistant to integrase inhibitors.

Children

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

Elderly

Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg should be administered with caution to elderly patients (see section 4.4).

Renal impairment

Mild renal impairment (creatinine clearance 50-80 mL/minute):
No dose adjustment is required in patients with mild renal impairment.

Moderate or severe renal impairment (creatinine clearance >50 mL/minute):

Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg is not recommended for use in patients with creatinine clearance < 50 ml/minute (see sections 4.4. and 5.2), as appropriate dose adjustments are not possible. For these patients, separate formulations of dolutegravir, lamivudine and tenofovir disoproxil should be used.

Hepatic impairment

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

Discontinuation of therapy

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

Missed dose

If the patient misses a dose of Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg , the patient should take it as soon as possible, provided the next dose is not due within 12 hours. If the next dose is due within 12 hours, the patient should not take the missed dose and take the next dose at the usual time.

Method of administration

Oral use.

It is recommended that Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg be swallowed whole with water. Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg can usually be taken with food or between meals.

If the HIV-1 is resistant to integrase inhibitors, Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg should preferably be taken with food to increase

4.3 Contraindications

- Hypersensitivity to active substances or to any of the excipients listed in section 6.1.
- Co-administration with dofetilide.

Special warnings and precautions for use

General

HBV antibody testing should be offered to all individuals before initiating lamivudine and tenofovir disoproxil-containing therapies (see below *Patients with HIV and hepatitis B (HBV) or C virus (HCV) co-infections*).

Transmission of HIV

Effective antiviral therapy can substantially reduce the risk of sexual transmission. However, the risk may not be eliminated entirely. Therefore, to prevent transmission, it is essential to take precautions according to national and other authoritative guidelines.

HIV-1 resistant to integrase inhibitors

The decision to use dolutegravir in the presence of HIV-1 resistance to integrase inhibitors should take into account that it is considerably less active against viral strains with Q148 with two or more secondary mutations from G140A/C/S, E138A/K/T, L74I. Dolutegravir's contribution to efficacy is uncertain when it is used to treat HIV-1 with this type of resistance to integrase inhibitors.

Hypersensitivity reactions

Hypersensitivity reactions reported with dolutegravir are characterised by rash, constitutional findings, and sometimes, organ dysfunction, including severe liver reactions. Dolutegravir and other suspect substances should be discontinued immediately if hypersensitivity reactions develop (including severe rash or rash accompanied by raised liver enzymes, fever, general malaise, fatigue, muscle or

joint aches, blisters, oral lesions, conjunctivitis, facial oedema, eosinophilia, and angioedema). Clinical status including liver aminotransferases and bilirubin should be monitored. Delay in stopping treatment with dolutegravir or other suspect substances after the onset of hypersensitivity may result in a life-threatening allergic reaction.

Immune reactivation syndrome

In HIV-infected patients with severe immune deficiency, when starting combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions or aggravate symptoms. Typically, such reactions occur within the first few weeks or months of CART. Examples of such conditions are cytomegalovirus retinitis, generalised or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treated when necessary.

Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported in the setting of immune reconstitution, but the reported time to onset is more variable and these events can occur many months after starting treatment.

Raised liver enzymes, consistent with immune reconstitution syndrome, occurred in some patients who also had hepatitis B or C infection at the start of dolutegravir therapy. Monitoring of liver function is recommended in patients with hepatitis B or C infection. Particular care should be taken in initiating or maintaining effective hepatitis B therapy (referring to treatment guidelines) when starting dolutegravir-based therapy in patients with hepatitis B.

Pancreatitis

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

Renal function

Lamivudine and tenofovir disoproxil are primarily excreted by the kidneys, through a combination of glomerular filtration and active tubular secretion. Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg is not recommended for patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min). Patients with moderate or severe renal impairment require a dose adjustment of lamivudine and tenofovir disoproxil that 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 in clinical practice (see section 4.8).

It is recommended that creatinine clearance /estimated glomerular function is calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg. If the creatinine test is routinely available, the estimated glomerular filtration rate at baseline should be used before initiating tenofovir disoproxil containing regimens. If the creatinine test is not routinely available urine dipsticks may be used to detect glycosuria or severe tenofovir

disoproxil nephrotoxicity in individuals without risk factors. Creatinine testing is particularly advisable for high-risk patients (those who are older or have underlying renal disease, long-term diabetes or uncontrolled hypertension concomitant with boosted PIs or nephrotoxic drugs) to detect and limit further progression of renal impairment. Benefit and risks should be carefully weighed. If available, also serum phosphate should be measured in these patients. If serum phosphate is < 1.5 mg/dl (0.48 mmol/l) or creatinine clearance is decreased to < 50 ml/min in any patient receiving this medicine renal function must be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). Since Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg is a combination product and the dosing interval of the individual components cannot be altered, treatment with this medicine must be interrupted in patients with confirmed creatinine clearance < 50 ml/min or decreases in serum phosphate to < 1.0 mg/dl (0.32 mmol/l).

Interrupting treatment should also be considered in case of progressive decline of renal function when no other cause has been identified. Where discontinuation of therapy with one of the components is indicated or where dose modification is necessary, separate preparations of dolutegravir, lamivudine and tenofovir disoproxil are available.

This medicine should be avoided with concurrent or recent use of a nephrotoxic medicinal product (e.g. high-dose or multiple non-steroidal anti-inflammatory drugs, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir, interleukin-2). If concomitant use of is a combination product and the dosing interval of the individual components cannot be altered, treatment with this medicine must be interrupted in patients with confirmed creatinine clearance < 50 ml/min or decreases in serum phosphate to < 1.0 mg/dl (0.32 mmol/l) and nephrotoxic agents is unavoidable, renal function must be monitored weekly (see section 4.5).

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

Elderly patients

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

Bone effects

In a controlled clinical study in adults comparing tenofovir disoproxil and stavudine (each in combination with lamivudine and efavirenz), bone mineral density of the spine decreased and bone biomarkers changed from baseline in both treatment groups, but the changes were significantly greater in the tenofovir disoproxil group at 144 weeks. Decreases in bone mineral density of the hip were significantly greater in this group until 96 weeks. However, over 144 weeks, the risk of fractures was not increased and there was no evidence of clinically relevant bone abnormalities.

In HIV-1 infected adolescents 12 years of age and older, the mean rate of bone gain was less in the tenofovir disoproxil -treated group compared to the placebo group. Skeletal growth (height) appeared to be unaffected. Markers of bone turnover in tenofovir disoproxil-treated adolescents 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 Tablets 50 mg/300 mg/300 mg 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.

Osteonecrosis

Osteonecrosis has been reported particularly in patients with advanced HIV disease or following long-term combination antiretroviral therapy. Their aetiology can be multifactorial and include corticosteroid use, excessive alcohol consumption, severe immunosuppression, and being overweight. Patients should be advised to speak to their health care provider if they have joint aches and pain, joint stiffness or difficulty in movement.

Liver function

The safety and efficacy of Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg has not been established in patients with significant underlying liver disorders. 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.

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

Health care providers should refer to current relevant treatment guidelines for the optimal management of HIV infection in patients co-infected with HBV or HCV.

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 reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Lamivudine and tenofovir disoproxil are also active against HBV. Therefore, discontinuation of Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg 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 Tablets 50 mg/300 mg/300 mg should be closely monitored with both clinical and laboratory follow-up for at least six months after stopping treatment. 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.

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.

Antivirals against HCV

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 (e.g. ritonavir). Patients receiving ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir concomitantly with tenofovir disoproxil should be monitored for adverse reactions related to tenofovir disoproxil.

Co-administration of other medicinal products

As a fixed combination, Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg should not be administered concomitantly with other medicinal products containing any of the same active components, dolutegravir, lamivudine or tenofovir disoproxil.

Due to similarities with lamivudine, Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg should not be administered concomitantly with other cytidine analogues, such as emtricitabine. Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg should not be administered concomitantly with medicinal products containing adefovir dipivoxil or tenofovir alafenamide.

Co-administration of tenofovir disoproxil and didanosine is not recommended since exposure to didanosine is significantly increased following co-administration with tenofovir disoproxil (see section 4.5). Rare cases of pancreatitis and lactic acidosis, sometimes fatal, have been reported.

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

No data are available on the safety and efficacy of combined dolutegravir, lamivudine and tenofovir disoproxil in combination with other antiretroviral agents.

Opportunistic infections

Patients receiving Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by health care providers experienced in the treatment of HIV infection.

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 lifestyle. 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. Established HIV treatment guidelines should be consulted on monitoring blood lipids and glucose. Lipid disorders should be managed as clinically appropriate.

Mitochondrial dysfunction

Nucleoside and nucleotide analogues can cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* or postnatally to nucleoside analogues; these have predominantly concerned treatment with regimens containing zidovudine.
The main adverse events are haematological (anaemia, neutropenia) and metabolic (hyperlactataemia, hyperlipasaemia). These events are often transitory. Some late-onset neurological disorders have been reported rarely (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

national recommendations on antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been performed using Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg. As this medicine contains dolutegravir, lamivudine and tenofovir disoproxil, any interactions that have been identified with these agents individually may occur with this combination tablet. Interaction studies with these agents have only been performed in adults.

Interactions relevant to dolutegravir

Factors that lower plasma concentration of dolutegravir should be avoided in the presence of HIV-1 resistant to integrase inhibitors. This includes concomitant use of medicines that reduce blood concentration of dolutegravir (e.g. magnesium- or 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 medicines) (see table, below).

Dolutegravir is eliminated mainly through metabolism by UGT1A1. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4, P-gp, and BCRP; therefore, medicines that induce these enzymes may decrease dolutegravir plasma concentration and reduce its therapeutic effect (see table, below). Co-administration of dolutegravir and other medicinal products that inhibit these enzymes may increase dolutegravir plasma concentration (see table below).

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

Established and theoretical interactions with selected antiretrovirals and non-antiretroviral medicinal products are listed in the following table; the pharmacokinetic data reflect studies in adults.

Interactions relevant to lamivudine

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, Pp a g ti e en 9 t 7 s o s f h o u l d be monitored clinically. Co-administration of

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 Cmax (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, Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg should not be administered concomitantly with other cytidine analogues, such as emtricitabine. Moreover, Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg should not be taken with any other medicinal products containing lamivudine.
In vitro lamivudine inhibits the intracellular phosphorylation of cladribine leading to a potential risk of cladribine loss of efficacy in case of combination in the clinical setting. Some clinical findings also support a possible interaction between lamivudine and cladribine. Therefore, the concomitant use of lamivudine with cladribine is not recommended (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 Cmax of lamivudine in adults. When possible, avoid chronic coadministration of Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg with medicinal products containing sorbitol or other osmotic acting polyalcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol). Consider more frequent monitoring of HIV-1 viral load when chronic coadministration cannot be avoided.

Interactions relevant to tenofovir

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

Use of tenofovir disoproxil should be avoided with concurrent use of a nephrotoxic medicinal product. Examples include, but are not limited to high-dose or multiple non-steroidal anti-inflammatory drugs, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir and 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.

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.

Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg should not be administered with any other medicines containing:
- tenofovir disoproxil
- tenofovir alafenamide
- adefovir dipivoxil
- didanosine
-

Interaction table

Interactions between Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg and co-administered medicinal products are listed in the following table (increase is indicated as ↑, decrease as ↓, no change as ↔, area under the concentration versus time curve as AUC, maximum observed concentration as C_{max}, concentration at end of dosing interval as C_τ).

Medicines by therapeutic area	**Interaction Changes shown as geometric mean**	**Recommendations on co-administration**
ANTI-INFECTIVES		
Antiretrovirals		
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Etravirine without boosted protease inhibitors/ dolutegravir	Dolutegravir ↓ AUC ↓ 71%; Cmax ↓ 52%; C_τ ↓ 88% Etravirine ↔ (induction of UGT1A1 and CYP3A enzymes)	Etravirine decreased plasma dolutegravir concentration. The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with etravirine without boosted protease inhibitors. In paediatric patients the weight-based once-daily dose should be given twice daily. When used with etravirine for infection resistant to integrase inhibitors, dolutegravir should be co-administered with atazanavir/ritonavir, or darunavir/ritonavir, or lopinavir/ritonavir (see below in table).
Lopinavir/ritonavir + etravirine/dolutegravir	Dolutegravir ↔ AUC ↑ 11%; Cmax ↑ 7%; C_τ ↑ 28%	No dose adjustment is necessary.

Lopinavir/ritonavir + tenofovir disoproxil	LPV ↔ RTV ↔ No significant effect on lopinavir/ritonavir PK parameters. Tenofovir: AUC: ↑ 32% Cmax: ↔ Cmin: ↑ 51%	
Darunavir/ritonavir + etravirine/dolutegravir	Dolutegravir ↓ AUC ↓ 25%; Cmax ↓ 12%; C_τ ↓ 36% DRV ↔ RTV ↔	No dose adjustment is necessary.
Efavirenz/dolutegravir	Dolutegravir ↓ AUC ↓ 57%; Cmax ↓ 39%; C_τ ↓ 75% Efavirenz ↔ (historical controls) (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with efavirenz. In paediatric patients the weight-based once-daily dose should be given twice daily. For infection resistant to integrase inhibitors, alternative combinations that do not include efavirenz should be considered.
Nevirapine/dolutegravir	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 given with nevirapine. In paediatric patients the weight-based once-daily dose should be given twice daily. For infection resistant to integrase inhibitors, alternative combinations that do not include nevirapine should be considered.

Medicines by therapeutic area	**Interaction Changes shown as geometric mean**	**Recommendations on co-administration**
Rilpivirine/dolutegravir	Dolutegravir ↔ AUC ↑ 12%; Cmax ↑ 13%; C_τ ↑ 22% Rilpivirine ↔	No dose adjustment is necessary.
Nucleoside reverse transcriptase inhibitors (NRTI)		
Emtricitabine / lamivudine		Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg should not be coadministered, due to the similarity between emtricitabine and lamivudine, and consequently expected additive toxicity and no benefit in efficacy.
Didanosine / tenofovir disoproxil	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 co-administration. Also didanosine at 250 mg co-administered with tenofovir disoproxil within several different antiretroviral combination regimens has been associated with a high rate of virological failure. Co-administration of Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg and didanosine is not recommended (see section 4.4).
Adefovir dipivoxil/ tenofovir disoproxil	AUC: ↔ Cmax: ↔	Tenofovir disoproxil should not be administered concurrently with adefovir dipivoxil (see section 4.4).
Entecavir/ tenofovir disoproxil	AUC: ↔ Cmax: ↔	No clinically significant pharmacokinetic interactions when tenofovir disoproxil was co-administered with entecavir.
Protease inhibitors (PIs)		

Atazanavir/dolutegravir	Dolutegravir ↑ AUC ↑ 91%; Cmax ↑ 50%; C_τ ↑ 180% Atazanavir ↔ (historical controls) (inhibition of UGT1A1 and CYP3A enzymes)	The dose of dolutegravir should not exceed 50 mg twice daily in combination with atazanavir because data are not available.
Atazanavir/tenofovir disoproxil	Atazanavir: AUC: ↓ 25%; Cmax: ↓ 21% ; Cmin: ↓ 40% Tenofovir: AUC: ↑ 24%; Cmax: ↑ 14%; Cmin: ↑ 22%	If atazanavir and Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg are co-administered, the dose of atazanavir should be 300 mg once daily together with ritonavir 100 mg once daily ("ritonavir-boosting", see below)

Medicines by therapeutic area	**Interaction Changes shown as geometric mean**	**Recommendations on co-administration**
Atazanavir+ritonavir/ Dolutegravir	Dolutegravir ↑ AUC ↑ 62%; Cmax ↑ 34%; C_τ ↑ 121% Atazanavir ↔ Ritonavir ↔ (inhibition of UGT1A1 and CYP3A enzymes	No dose adjustment is necessary. The dose of dolutegravir should not exceed 50 mg twice daily in combination with atazanavir because data are not available.
Atazanavir+ritonavir/ Tenofovir disoproxil	Tenofovir: AUC: ↑ 37%; Cmax: ↑ 34%; Cmin: ↑ 29% Atazanavir: AUC: ↓ 25%; Cmax: ↓ 28%; Cmin: ↓ 26%	The increased exposure of tenofovir could potentiate tenofovir-associated adverse events, including renal disorders. Renal function should be closely monitored
Tipranavir + ritonavir/ dolutegravir	Dolutegravir ↓ AUC ↓ 59%; Cmax ↓ 47%; C_τ ↓ 76% (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with tipranavir/ritonavir. In paediatric patients the weight-based once daily dose should be given twice daily. For infection resistant to integrase inhibitors, alternative combinations that do not include nevirapine should be considered.
Fosamprenavir + ritonavir/dolutegravir	Dolutegravir ↓ AUC ↓ 35%; Cmax ↓ 24%; C_τ ↓ 49% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary in the absence of integrase class resistance. For infection resistant to integrase inhibitors, alternative combinations that do not include fosamprenavir/ritonavir should be considered.

Darunavir+ritonavir/ Dolutegravir	<u>Dolutegravir ↓</u> AUC ↓ 22%; Cmax ↓ 11%; C24hours ↓ 38% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Darunavir+ritonavir/ Tenofovir disoproxil	Darunavir: No significant effect on darunavir/ritonavir PK parameters. Tenofovir: AUC: ↑ 22%; Cmin: ↑ 37%	The increased exposure of tenofovir could potentiate tenofovir-associated adverse events, including renal disorders. Renal function should be closely monitored.
Lopinavir+ritonavir/ Dolutegravir	Dolutegravir ↔ AUC ↓ 4%; Cmax ↔ 0%; C24hours ↓ 6%	No dose adjustment is necessary.
Lopinavir+ritonavir/ Tenofovir disoproxil	Lopinavir/ritonavir: No significant effect on lopinavir/ritonavir PK parameters. Tenofovir: AUC: ↑ 32%; Cmax: ↔; Cmin: ↑ 51%	The increased exposure of tenofovir could potentiate tenofovir-associated adverse events, including renal disorders. Renal function should be closely monitored.

Medicines by therapeutic area	**Interaction Changes shown as geometric mean**	**Recommendations on co-administration**
Antivirals against hepatitis C		
Daclatasvir/ dolutegravir	Dolutegravir ↔ AUC ↑ 33%; Cmax ↑ 29%; Cτ ↑ 45% Tenofovir ↔ AUC ↑ 10%, Cmax ↓5%, Cmin ↑17% .Daclatasvir ↔	No dose adjustment is necessary.
Daclatasvir/tenofovir disoproxil	— Daclatasvir AUC: 1.10 (1.01, 1.21) Cmax: 1.06 (0.98, 1.15) Cmin: 1.15 (1.02, 1.30) — Tenofovir AUC: 1.10 (1.05, 1.15) Cmax: 0.95 (0.89, 1.02) Cmin: 1.17 (1.10, 1.24)	

Sofosbuvir/tenofovir disoproxil	Tenofovir ↑ Cmax 1.25 (1.08, 1.45) — AUC 0.98 (0.91, 1.05) — Cmin 0.99 (0.91, 1.07) Sofosbuvir ↓ Cmax 0.81 (0.60, 1.10) — AUC 0.94 (0.76, 1.16) Cmin (NA) GS-331007 (predominant inactive metabolite of sofosbuvir) ↓ Cmax 0.77 (0.70, 0.84) — AUC 0.84 (0.76, 0.92) Cmin (NA)	No dose adjustment of sofosbuvir or Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg is required when sofosbuvir and Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg are used concomitantly.

Medicines by therapeutic area	**Interaction Changes shown as geometric mean**	**Recommendations on co-administration**
Ledipasvir/Sofosbuvir +Dolutegravir + Tenofovir disoproxil (+Emtricitabine)	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%	Monitor for tenofovir-associated adverse reactions in patients receiving ledipasvir/sofosbuvir concomitantly with Dolutegravir/ Lamivudine/ Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg. Renal function should be closely monitored (see section 4.4).

Sofosbuvir/Velpatasvir + Tenofovir disoproxil	Sofosbuvir: AUC: ↔ Cmax: ↔ GS-331007**2**: AUC: ↔ Cmax: ↔ Cmin: ↑ 42% Velpatasvir: AUC: ↑ 142% Cmax: ↑ 55% Cmin: ↑ 301% Tenofovir: AUC: ↔ Cmax: ↑ 55% Cmin: ↑ 39%	Sofosbuvir/velpatasvir has been shown to increase tenofovir exposure (P-gp-inhibition). The increase in tenofovir exposure (AUC and Cmax) was around 40-80% during cotreatment with sofosbuvir/velpatasvir and tenofovir disoproxil as part of various HIV regimens. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. Patients receiving tenofovir disoproxil and sofosbuvir/velpatasvir concomitantly should be monitored for adverse reactions associated with tenofovir disoproxil (see section 4.4).

Medicines by therapeutic area	**Interaction Changes shown as geometric mean**	**Recommendations on co-administration**
Sofosbuvir/Velpatasvir/ Voxilaprevir + Tenofovir disoproxil (+ Emtricitabine + Darunavir/ritonavir)	Sofosbuvir: AUC: ↔ Cmax: ↓ 30% Cmin: N/A GS-3310072: AUC: ↔ Cmax:↔ Cmin: N/A Velpatasvir: AUC: ↔ Cmax: ↔ Cmin: ↔ Voxilaprevir:	Sofosbuvir/velpatasvir/voxilaprevir has been shown to increase tenofovir exposure (P-gp inhibition). The increase in tenofovir exposure (AUC and Cmax) was around 40% during co-treatment with sofosbuvir/velpatasvir/voxilaprevir and darunavir + ritonavir + tenofovir disoproxil /emtricitabine. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir /voxilaprevir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. Patients receiving tenofovir disoproxil and sofosbuvir/velpatasvir/voxilaprevir concomitantly should be

	AUC: ↑ 143% Cmax:↑ 72% Cmin: ↑ 300% Tenofovir: AUC: ↑ 39% Cmax: ↑ 48% Cmin: ↑ 47%	monitored for adverse reactions associated with tenofovir disoproxil (see section 4.4).
Antibiotics		
Rifampicin/dolutegravir	Dolutegravir ↓ AUC ↓ 54%; Cmax ↓ 43%; C_τ ↓72% (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with rifampicin. In paediatric patients the weight-based once daily dose should be given twice daily. For infection resistant to integrase inhibitors, co-administration of dolutegravir and rifampicin should be avoided.
Rifabutin/dolutegravir	Dolutegravir ↔ AUC ↓ 5%; Cmax ↑ 16%; C_τ ↓ 30% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Antifungals		
Fluconazole Itraconazole Ketoconazole Posaconazole Voriconazole		Based on theoretical considerations, no interaction with dolutegravir, tenofovir disoproxil or lamivudine is expected.

Medicines by therapeutic area	**Interaction Changes shown as geometric mean**	**Recommendations on co-administration**
Antiepileptics		

Carbamazepine/ dolutegravir	Dolutegravir ↓ AUC ↓ 49%; Cmax ↓ 33%; C_τ ↓ 73%	The recommended adult dose of dolutegravir is 50 mg twice daily when given with carbamazepine. In paediatric patients the weight-based once-daily dose should be given twice daily. Alternatives to carbamazepine should be used in patients with infection resistant to integrase inhibitors.
Oxcarbazepine/ dolutegravir Phenytoin/dolutegravir Phenobarbital/ dolutegravir	Dolutegravir ↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a reduction in exposure similar to carbamazepine is expected)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with these enzyme inducers. In paediatric patients the weight-based once-daily dose should be given twice daily. Alternatives to these medicines that are not enzyme inducers should be used in patients with infection resistant to integrase inhibitors.
Antiarrhythmics		
Dofetilide/dolutegravir	Dofetilide ↑ (Not studied, potential increase via inhibition of OCT2 transporter)	Dolutegravir and dofetilide co-administration is contraindicated due to potential life-threatening toxicity caused by high dofetilide concentration.
Antacids and supplements		
Magnesium- or aluminium-containing antacid/dolutegravir	Dolutegravir ↓ AUC ↓ 74%; Cmax ↓ 72% (Complex binding to polyvalent ions)	Magnesium- or aluminium-containing antacid should be taken well separated in time from dolutegravir (minimum 2 hours after or 6 hours before).
Calcium supplements/ dolutegravir	Dolutegravir ↓ AUC ↓ 39%; Cmax ↓ 37%; C24hours ↓ 39% (Complex binding to polyvalent ions)	Calcium supplements, iron supplements or multivitamins should be taken well separated in time from the administration of dolutegravir (minimum 2 hours after or 6 hours before).
Iron supplements/ dolutegravir	Dolutegravir ↓ AUC ↓ 54%; Cmax ↓ 57%; C24hours ↓ 56% (Complex binding to polyvalent ions)	

Multivitamins/ dolutegravir	Dolutegravir ↓ AUC ↓ 33%; Cmax ↓ 35% C24hours ↓ 32% (Complex binding to polyvalent ions)	
Antidiabetics		
Metformin/dolutegravir	Co-administered with dolutegravir 50 mg once daily: Metformin ↑ AUC ↑ 79%; Cmax ↑ 66% Co-administered with dolutegravir 50 mg twice daily: Metformin ↑ AUC ↑ 145%; Cmax ↑ 111%	A dose adjustment of metformin should be considered when starting and stopping co-administration of dolutegravir with metformin, to maintain glycaemic control. In patients with moderate renal impairment a dose adjustment of metformin should be considered when given with dolutegravir, because the risk of lactic acidosis is increased in patients with moderate renal impairment due to increased metformin concentration.

Medicines by therapeutic area	**Interaction Changes shown as geometric mean**	**Recommendations on co-administration**
Contraceptives		
Ethinylestradiol and norelgestromin /dolutegravir	Dolutegravir ↔ Ethinylestradiol ↔ AUC ↑ 3%; Cmax ↓ 1% Norelgestromin ↔ AUC ↓ 2%; Cmax ↓ 11%	Dolutegravir had no pharmacodynamic effect on luteinizing hormone, follicle stimulating hormone and progesterone. No dose adjustment of oral contraceptives is necessary when given with dolutegravir.
Corticosteroids		
Prednisone/dolutegravir	Dolutegravir ↔ AUC ↑ 11%; Cmax ↑ 6%; C_τ ↑ 17%	No dose adjustment is necessary.
Drug abuse		
Methadone/dolutegravir	Dolutegravir ↔ Methadone ↔ AUC ↓ 2%; Cmax ↔ 0%; C_τ ↓ 1%	No dose adjustment is necessary.
Herbal products		

St. John's wort/ dolutegravir	Dolutegravir ↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a reduction in exposure similar to carbamazepine is expected)	The recommended adult dose of dolutegravir is 50 mg twice daily when given with St. John's wort. In paediatric patients the weight-based once-daily dose should be given twice daily. Alternatives to St. John's wort should be used in patients with infection resistant to integrase inhibitors.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

Dolutegravir

Preliminary data from a surveillance study in Botswana suggested an increased incidence of neural tube defects (NTD) (0.67%) in mothers exposed to dolutegravir at the time of conception compared with mothers exposed to non-dolutegravir containing regimens (0.1%). However, review of more mature data from the study, along with data from other countries, and modelling of population-level risks and benefits of dolutegravir use in women of childbearing potential, has indicated that the risk of NTD is smaller than initially reported, with a weighted estimated risk of 0.36% (95% CI 0.01 – 0.62). Although the risk of NTD remains statistically higher than the rate with other antiretrovirals and the background rate, the absolute risk is still very low. Continued surveillance is needed to more definitively confirm or refute the neural tube defect signal, and several studies are ongoing to address this. It should be noted that Botswana has no national food folate fortification programme and that most reports on NTDs come from countries where such programmes are in place, which significantly lowers the prevalence of NTDs in the general population.

Neural tube defects occur within the first 4 weeks of foetal development (after which the neural tubes close). The data therefore suggest that any increased risk would be associated with exposure to dolutegravir in the periconception period rather than later in the pregnancy.

The same observational study shows that the dolutegravir- and the efavirenz-containing (comparator) antiretroviral regimen when started later in pregnancy, have comparable pregnancy outcomes.

Dolutegravir has been shown to cross the placenta in animals. In animal reproductive toxicology studies, no adverse development outcomes, including neural tube defects, were identified (see section 5.3).

To better understand what risk there may be, active research and surveillance are ongoing in further pregnant women exposed to dolutegravir at the time of conception.

More than 1000 outcomes from second and third trimester exposure in pregnant women indicate no evidence of increased risk of malformations.

Women in the first trimester of pregnancy should be informed about the potential risk of an increased incidence of neural tube defects with use of dolutegravir. Preferred antiretroviral options may vary depending on the individual benefit/risk evaluation and local circumstances.

More than 1000 outcomes from second and third trimester exposure in pregnant women indicate no evidence of increased risk of malformations.

Dolutegravir was shown to cross the placenta in animals. In animal reproductive toxicology studies, no adverse development outcomes, including neural tube defects, were identified (see section 5.3).

Lamivudine and tenofovir disoproxil

Animal studies do not indicate direct or indirect harmful effects of tenofovir disoproxil or lamivudine with respect to reproductive toxicity (see section 5.3). The safety of tenofovir in human pregnancy has not been fully established. However, sufficient numbers of first trimester exposures have been monitored to detect at least a twofold increase in the risk of overall birth defects. No increase in birth defects was seen for tenofovir disoproxil or lamivudine (www.apregistry.com).

Women of childbearing potential

Although the absolute risk is low, there remains the possibility of an approximately 3-fold increased risk of neural tube defects in women receiving dolutegravir in the periconception period compared with other HIV drugs, including efavirenz. Women should be provided with information about benefits and risks, to make an informed choice regarding the use of dolutegravir or other antiretroviral therapy. Preferred alternative options may vary depending on the individual benefit/risk evaluation and local circumstances.

If feasible, women of childbearing potential should undergo pregnancy testing before initiation of dolutegravir.

Breast-feeding

Dolutegravir, lamivudine and tenofovir disoproxil are found in breast milk of lactating mothers.

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

Fertility

There are no data on dolutegravir's effects on human male or female fertility. Animal studies indicate no effects of dolutegravir on male or female fertility. Animal studies indicate no harmful effects of dolutegravir, lamivudine and tenofovir disoproxil on fertility.

4.7 Effects on ability to drive and use machines

Patients should be informed that Dolutegravir/Lamivudine/Tenofovir Disoproxil

fumarate Tablets 50 mg/300 mg/300 mg. Renal function should be closely monitored (see section 4.4). can cause dizziness. The patient's clinical status and side effects of Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg. should be considered for evaluating the patient's ability to drive or operate machinery.

4.8 Undesirable effects

Data from clinical trials were used to estimate the frequency of adverse events linked to dolutegravir treatment. The most severe adverse reactions are hypersensitivity reactions that include rash and severe liver effects. The most common adverse reactions of dolutegravir are nausea (13%), diarrhoea (18%) and headache (13%).

In patients receiving tenofovir disoproxil, rare events of renal impairment, renal failure and 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 Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg. (see section 4.4).

The adverse reactions considered related to dolutegravir, tenofovir disoproxil and lamivudine 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 (1/1000 to 1/100), rare (1/10 000 to 1/1000), and very rare (< 1/10 000).

Blood and lymphatic systems disorders:

Uncommon	neutropenia, anaemia (occasionally severe),
Very rare	thrombocytopenia pure red cell aplasia

Metabolism and nutrition disorders: Very common hypophosphataemia

Rare	lactic acidosis
Not known	hypokalaemia

Respiratory, thoracic and mediastinal disorders:

Common	Cough, nasal symptoms
Very rare	Dyspnoea

Immune system disorders

Uncommon	hypersensitivity (see section 4.4) immune reactivation syndrome (see section 4.4 and also described below)

Psychiatric disorders

Common	insomnia, abnormal dreams, depression, anxiety
Uncommon	suicidal ideation or suicide attempt (particularly in patients with history of depression or psychiatric illness)

Nervous system disorders

Very common	headache
Common	Dizziness
Very rare	Peripheral neuropathy (paraesthesia)

Gastrointestinal disorders

Very common	nausea, diarrhoea
Comm on	vomiting, flatulence, upper abdominal pain, abdominal pain, abdominal discomfort pancreatitis, elevated serum amylases
Rare	

Hepatobiliary disorders

Uncommon	Hepatitis
Not known	Hepatic steatosis

Skin and subcutaneous tissue disorders

Common	rash, pruritus, hair loss

Musculoskeletal and connective tissue disorders

Uncom mon Not known	arthralgia, myalgia rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), muscular weakness, osteonecrosis

Renal and urinary disorders

Rare	Rare acute renal failure, renal failure, proximal renal tubulopathy (including Fanconi syndrome), increased serum creatinine
Very rare	acute tubular necrosis
Not known	nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus

General disorders

Commo n Very rare Not known	Fatigue, malaise, fever Asthenia Immune reconstitution syndrome

Investigations	
Common	raised alanine aminotransferase (ALT) and aspartate aminotransferase (AST) raised creatine kinase

Description of selected adverse reactions

Changes in serum creatinine

Serum creatinine can increase in the first week of treatment with dolutegravir and then remain stable. A mean change from baseline of 10 µmol/litre occurred after 48 weeks of treatment. Creatinine increases were comparable between various background regimens. These changes are not considered clinically relevant since they do not reflect a change in glomerular filtration rate.

Immune reactivation syndrome

In HIV patients with severe immune deficiency at the start 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 time to onset is more variable and these events can occur many months after starting treatment (see section 4.4).

Renal impairment

As lamivudine and tenofovir disoproxil may cause renal damage, monitoring of renal function is recommended (see section 4.4). 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 (see section 4.4).

Renal tubulopathy

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 likely to be causally associated with tenofovir disoproxil therapy in the absence of proximal renal tubulopathy.

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. (see section 4.5). 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 (see section 4.4).

Osteonecrosis

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

Co-infection with hepatitis B or C

In clinical studies with dolutegravir, the side effects profile in patients also infected with hepatitis B or C or both was similar to that in patients without hepatitis, provided that the baseline liver function tests did not exceed 5 times the upper limit of normal. However, the rates of AST and ALT abnormalities were higher in patients with hepatitis B or C co-infection. Liver enzymes elevations consistent with immune reactivation syndrome occurred in some subjects with hepatitis B or C co-infection at the start of dolutegravir therapy, particularly in those whose hepatitis B therapy was stopped.

Limited data on patients co-infected with HIV/HBV or HIV/HCV indicate that the adverse reaction profile of emtricitabine† and tenofovir disoproxil in patients co-infected with HIV/HBV or HIV/HCV was similar to that observed in patients infected with HIV without co-infection. However, as would be expected, elevations in AST and ALT occurred more frequently than in the general HIV infected population.

Exacerbations of hepatitis after discontinuation of treatment

In HIV infected patients co-infected with HBV, clinical and laboratory evidence of hepatitis may occur after discontinuation of treatment (see section 4.4).

Special populations

Paediatric population

The limited data available for children and adolescents (aged 6 to 18 years and weighing at least 15 kg) using dolutegravir suggest no additional adverse reactions beyond those that occur in adults.

The adverse reactions observed in paediatric patients who received treatment with tenofovir disoproxil or lamivudine as single entities were consistent with those observed in clinical studies in adults.

Reductions in bone mineral density (BMD) have been reported with tenofovir disoproxil in paediatric patients. In HIV-infected adolescents, the BMD Z-scores in subjects who received tenofovir disoproxil were lower than those in subjects who received placebo. In HIV-infected children, the BMD Z-scores in subjects who switched to tenofovir disoproxil were lower than those in subjects who remained on regimens containing stavudine or zidovudine.

Elderly

Caution should be exercised since elderly patients are more likely to have decreased

renal function.

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. Health care professionals are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

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† Based on a systematic review it is suggested that emtricitabine and lamivudine are pharmacologically equivalent, and hence clinically interchangeable for therapy of HIV infection. Therefore, herein reference is made also to data obtained with emtricitabine.

4.9 Overdose

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

Treatment

There is no specific treatment for an overdose of Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg. If overdose occurs, the patient should be treated supportively with appropriate monitoring, as necessary. 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 be clinically beneficial in a lamivudine overdose. Tenofovir disoproxil can be removed by haemodialysis; the median haemodialysis clearance of tenofovir disoproxil is 134 ml/minute. The elimination of tenofovir disoproxil by peritoneal dialysis has not been studied. 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

Dolutegravir:
Direct acting antivirals, other antivirals, ATC code: J05AX12

Lamivudine and tenofovir disoproxil:
Direct acting antivirals, Antivirals for treatment of HIV infections, combinations, ATC code: J05AR12

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.

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

Tenofovir disoproxil is converted *in vivo* to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate.

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

Pharmacodynamic effects

Antiviral activity in cell

culture Dolutegravir
The IC50 for dolutegravir in various HIV-1 lab-strains using peripheral blood mononuclear cells (PBMC) was

0.5 nM, and when using MT-4 cells it ranged from 0.7 to 2 nM. The IC50 was similar for clinical isolates without any major difference between subtypes (A, B, C, D, E, F and G). The mean IC50 for three HIV-2 isolates was 0.18 nM (range 0.09–0.61 nM).

Lamivudine
The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines including monocytes and (PBMCs) using standard susceptibility assays. EC50 values were in the range of 0.003 to 15microM. against HIV-1 clades A-G and group O viruses.

Tenofovir disoproxil
The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in T lymphoblastoid cell lines, primary monocyte/macrophage cells and PBMCs. The EC50 values for tenofovir were in the range of 0.04-8.5microM. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC50 values ranged from 0.5-2.2microM).

Antiviral activity in combination with other antiviral agents

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

No antagonistic effects *in vitro* were seen with lamivudine and other antiretrovirals (tested agents: abacavir, didanosine, nevirapine and zidovudine).

Resistance in vitro (dolutegravir)

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

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

Primary mutations for raltegravir/elvitegravir (Q148H/R/K, N155H, Y143R/H/C, E92Q and T66I) do not affect the *in vitro* susceptibility of dolutegravir as single mutations. When mutations listed as secondary integrase-inhibitor-associated mutations (for raltegravir/elvitegravir) are added to these primary mutations in experiments with site-directed mutants, dolutegravir susceptibility is still unchanged (FC < 2 vs wild type virus), except in the case of Q148-mutations, where a FC is 5–10 or higher with combinations of certain secondary mutations. The effect by the Q148-mutations (H/R/K) was also verified in passage experiments with site-directed mutants. In serial passage with strain NL432, starting with site-directed mutants harbouring N155H or E92Q, further selection of resistance did not occur (FC unchanged around 1). In contrast, starting with mutants harbouring mutation Q148H (FC 1), a variety of secondary mutations were seen with a consequent increase of FC to values > 10.

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

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

Resistance in vivo (dolutegravir)

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

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

In the presence of integrase-inhibitor class-resistance the following mutations were selected after 24 weeks in 32 patients with protocol-defined virological failure (PDVF) and with paired genotypes (all treated with dolutegravir 50 mg twice daily + optimised background agents): L74L/M (n=1), E92Q (n=2), T97A (n=9),

E138K/A/T (n=8), G140S (n=2), Y143H (n=1), S147G (n=1), Q148H/K/R (n=4), and N155H (n=1) and
E157E/Q (n=1). Treatment-emergent integrase-inhibitor-resistance typically appeared in patients with a history of the Q148-mutation (baseline or historic). Five further subjects had PDVF between weeks 24 and 48, and 2 of these 5 had treatment-emergent mutations. Treatment-emergent mutations or mixtures of mutations observed were L74I (n=1), N155H (n=2).

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

Resistance in vitro and in vivo (lamivudine and tenofovir)

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. HIV strains which expressed 3 or more TAMs that included either the M41L or L210W mutation showed reduced response to tenofovir.

In many cases when a lamivudine-containing treatment regimen fails (though less often when the treatment regimen contains a ritonavir-boosted protease inhibitor), 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. In vitro data suggest that continuation of lamivudine in an antiretroviral regimen despite the development of M184V might provide residual antiretroviral activity (likely through impaired viral fitness). The clinical relevance of these findings is not established. Therefore, maintaining lamivudine therapy despite emergence of M184V mutation should be considered only when the activity of the best available NRTI backbone is significantly compromised.
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 activity against lamivudine-resistant HIV-1. Abacavir maintains its antiretroviral activity 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.

Effects on electrocardiogram

No relevant effects were seen on the QTc interval, with doses 3-fold higher than the clinical dose.

Clinical efficacy and safety

Several clinical studies have confirmed the efficacy of the individual components of this fixed dose combination product. Dolutegravir, lamivudine and tenofovir disoproxil were used as single entities in different combination regimens. No

clinical studies have been conducted with the combination dolutegravir, lamivudine and tenofovir disoproxil.

When emtricitabine§ and tenofovir disoproxil were combined with dolutegravir in treatment-naïve patients with HIV-1 infection in two clinical studies, the proportions of patients (ITT) with HIV-RNA <
50 copies/mL were 93% and 94% at 48 weeks.

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‡ Based on a systematic review it is suggested that emtricitabine and lamivudine are pharmacologically equivalent, and hence clinically interchangeable for therapy of HIV infection. Therefore, herein reference is made also to data obtained with emtricitabine.

5.2 Pharmacokinetic properties

The absorption characteristics of Dolutegravir/Lamivudine/Tenofovir Disoproxil fumarate Tablets 50 mg/300 mg/300 mg. have been determined after administration of a single dose tablet in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	Arithmetic mean value (± standard deviation)		
	Dolutegravir	Lamivudine	Tenofovir
Maximum concentration (Cmax)	2827 ± 575	2199 ± 607	409 ± 96
Area under the curve (AUC0–∞), a measure of the extent of absorption	56040 ± 18013	13597 ± 2920	3460 ± 769
Time to attain maximum concentration (tmax)	3.0 (0.5 – 5.5)	1.75 (0.83 – 4.0)	0.75 (0.5 – 2.67)

Pharmacotherapeutic group

Dolutegravir:
Direct acting antivirals, other antivirals, ATC code: J05AX12

Lamivudine and tenofovir disoproxil:
Direct acting antivirals, Antivirals for treatment of HIV infections, combinations, ATC code: J05AR12

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.

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

Tenofovir disoproxil is converted *in vivo* to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate.

Lamivudine and tenofovir are phosphorylated by cellular enzymes to form

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

Pharmacodynamic effects

Antiviral activity in cell

culture Dolutegravir
The IC50 for dolutegravir in various HIV-1 lab-strains using peripheral blood mononuclear cells (PBMC) was
0.5 nM, and when using MT-4 cells it ranged from 0.7 to 2 nM. The IC50 was similar for clinical isolates without any major difference between subtypes (A, B, C, D, E, F and G). The mean IC50 for three HIV-2 isolates was 0.18 nM (range 0.09–0.61 nM).

Lamivudine
The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines including monocytes and (PBMCs) using standard susceptibility assays. EC50 values were in the range of 0.003 to 15microM. against HIV-1 clades A-G and group O viruses

Tenofovir disoproxil
The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in T lymphoblastoid cell lines, primary monocyte/macrophage cells and PBMCs. The EC50 values for tenofovir were in the range of 0.04-8.5microM. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC50 values ranged from 0.5-2.2microM).

Antiviral activity in combination with other antiviral agents

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

No antagonistic effects *in vitro* were seen with lamivudine and other antiretrovirals (tested agents: abacavir, didanosine, nevirapine and zidovudine).

Resistance in vitro (dolutegravir)

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50 copies/mL were 93% and 94% at 48 weeks.

5.3 Preclinical safety data

Dolutegravir

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

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

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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. In rabbits, maternal toxicity (decreased food consumption, reduced urine or feaces, suppressed bodyweight gain) was observed at 1000 mg/kg.

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

The primary effect of high doses of dolutegravir and prolonged daily treatment (up to 26 weeks in rats and up to 38 weeks in monkeys) was gastrointestinal intolerance or irritation in rats and monkeys at doses that produce systemic exposures about 21 and 0.82 times the 50 mg twice daily human clinical exposure based on AUC, respectively. Because gastrointestinal intolerance is considered to be due to local effects of the active substance, comparison based on bodyweight or on body surface area is appropriate for this toxicity.
Gastrointestinal intolerance in monkeys occurred at 15 times the human mg/kg equivalent dose (based on a 50-kg human), and 5 times the human mg/m^2 equivalent dose for a clinical dose of 50 mg twice daily.

Tenofovir

Preclinical studies in rats, dogs and monkeys revealed target-organ effects on 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 fetal parameter. There were no gross fetal alterations of soft or skeletal tissues. Tenofovir disoproxil reduced the viability index and weight of pups in peri-post-natal toxicity studies.

Genotoxicity studies have shown that tenofovir disoproxil was negative in the *in vivo* mouse bone marrow micronucleus assay but was positive for inducing forward mutations in the *in vitro* L5178Y mouse lymphoma cell assay in the presence or absence of S9 metabolic activation. Tenofovir disoproxil was positive in the Ames test (strain TA 1535) in two out of three studies, once in the presence of S9 mix (6.2- to 6.8-fold increase) and once without S9 mix. Tenofovir disoproxil was also weakly positive in an *in vivo*/*in vitro* unscheduled DNA synthesis test in primary rat hepatocytes.

Tenofovir disoproxil did not show any carcinogenic potential in a long-term oral carcinogenicity study in rats. A long-term oral carcinogenicity study in mice showed a low incidence of duodenal tumours, considered likely related to high

local concentration of tenofovir disoproxil in the gastrointestinal tract at a dose of 600 mg/kg/day. While the mechanism of tumour formation is uncertain, the findings are unlikely to be of relevance to humans.

Lamivudine

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 expected clinical plasma levels. As the *in vitro* mutagenic activity of lamivudine could not be confirmed *in vivo*, 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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Core tablet:

Mannitol
Microcrystalline
cellulose Sodium
starch glycolate
Povidone
Lactose
monohydrate
Pregelatinized
starch
Croscarmellose
sodium Sodium
stearyl fumarate

Film coat:

Polyvinyl alcohol
Titanium dioxide
Macrogol/polyethylene
glycol Talc

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container**.** Keep the bottle tightly closed. Do not remove desiccant. Discard the product 90 days after first opening

6.5. Nature and contents of container

30’s Count:

White HDPE (100cc) bottle containing 1 g silica gel canister closed with CR closure (38mm) including induction sealing wad.

or

White HDPE (100cc) bottle containing 2 g silica gel canister closed with CT closure (38mm) including induction sealing wad.

Or

White HDPE (85cc) bottle containing 2 g CAN SORB-IT canister closed with CR closure (33mm) including induction sealing wad.

90's Count:

White HDPE (250cc) bottle containing 2 g silica gel canister closed with CR closure (53mm) including induction sealing wad.

or

White HDPE (250cc) bottle containing 2 g silica gel canister closed with CT closure (53mm) including induction sealing wad.

White HDPE (200cc) bottle containing 2 g silica gel canister closed with CR closure (38mm) including induction sealing wad.

7. SUPPLIER

Laurus Labs Limited
2nd Floor, serene Chambers, Road
No.7 Banjara hills, Hyderabad,
Telangana- 500034 India

8. MARKETTING AUTHORIZATION NUMBER

H2019/CTD7486/14555

9. DATE OF REGISTRATION

Date of renewal: 07/04/2026

10. DATE OF REVISION OF THE TEXT

April 2026