1. NAME OF THE MEDICINAL PRODUCT

Dolutegravir 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg dolutegravir equivalent to 52.6 mg dolutegravir sodium, 300 mg lamivudine and 300 mg tenofovir disoproxil fumarate (TDF) equivalent to 245 mg of tenofovir disoproxil or 136 mg of tenofovir.

Excipient with known effect: Each film-coated tablet contains about 15.4 mg (0.67mmol) of sodium and 120 mg of mannitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to off-white, capsule shaped, film coated tablet debossed with 'F67' on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

sis indicated for the treatment of human immunodeficiency virus (HIV) infection in adults and adolescents weighing at least 30 kg.

Treatment regimens should follow most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

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 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsshould be prescribed by a health care provider experienced in the management of HIV infection.

Posology

Adults and adolescents weighing at least 30 kg

The dose in adults and adolescents weighing at least 30 kg with HIV-1 infection not resistant tointegrase inhibitors is one tablet of Dolutegravir 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsonce daily.

Dose adjustments in adults and adolescents

Where discontinuation of therapy with one of the components of Dolutegravir 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsis 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 may be given in adults. Please refer to the product information of dolutegravir for further information or consult current WHO treatment guidelines. There is insufficient information on the use of dolutegravir in adolescents with HIV-1 infection resistant to integrase inhibitors.

[†] Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

Children

Dolutegravir 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsshould 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 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsshould 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 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsis 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 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsshould be used with caution in these patients.

Discontinuation of therapy

If Dolutegravir 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsis 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 and vomiting after a dose

It is important that the patient takes the medicine regularly as prescribed. Missing doses can increase therisk of resistance and reduce its effectiveness.

The patient should take a missed dose if it was due fewer than 12 hours ago. If more than 12 hours have passed since the dose was due, the patient should omit the missed dose and take the next scheduled dose at the usual time. The patient should not take a double dose.

If the patient vomits within 1 hour of taking [HA713 trade name], the patient should take an extra dose. If vomiting occurs more than an hour after taking the dose, the patient does not need to take an extra dose and can take the next dose as usual when it is due.

Method of administration

The recommended dose should be administered orally and the Dolutegravir 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletstablets should be swallowed whole with water.

Dolutegravir 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletscan usually be taken with food or between meals.

4.3 Contraindications

Hypersensitivity to dolutegravir, lamivudine and tenofovir disoproxil fumarate or to any of theexcipients listed in section 6.1.

Dolutegravir 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsmust not be

administered concurrently with medicines with narrow therapeutic windows that are substrates of organic cation transporter 2 (OCT2), including dofetilide and fampridine (also known as dalfampridine; see section 4.5).

4.4 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).

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 integraseinhibitors.

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 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsshould be stopped immediately if clinical signs, symptoms orlaboratory 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 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsis not recommended for patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min). Patients with moderate orsevere 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 [HA713 trade name]. 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 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsis 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 Dolutegravir 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsand 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 biomarkerschanged 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 thetenofovir 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 bonemetabolism, Dolutegravir 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsshould 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 difficultyin movement.

Liver function

The safety and efficacy of Dolutegravir 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletshas not been established in patients with significant underlying liver disorders. Patients with pre-existing liver dysfunction, including chronic activehepatitis 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 managementof 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 anincreased risk of severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapyfor 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 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsin 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 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsshould be closely monitored with both clinical and laboratory follow-up for at least 6 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 increasesin 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 orcirrhosis, 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.

Use with 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 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsshould not be administered concomitantly with othermedicinal products containing any of the same active components, dolutegravir, lamivudine or tenofovir disoproxil.
Due to similarities with lamivudine, Dolutegravir 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsshould not be administered concomitantly with other cytidine analogues, such as emtricitabine. Dolutegravir 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsshould not be administered concomitantly with medicinal products containing adefovir dipivoxil or tenofovir alafenamide.

Factors that decrease dolutegravir exposure should be avoided in the presence of integrase classresistance. 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, garlic andcertain antiepileptic medicinal products) (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 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 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsor 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 following exposure in utero

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.

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per tablet that is to say essentially 'sodium free'. It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been performed using [HA713 trade name]. 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, rifapentine, 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).

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 and/or MATE-1 (e.g. fampridine [also known as dalfampridine], metformin), see table below.

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

Established and theoretical interactions with selected antiretrovirals and non-antiretroviral medicinal products are listed in 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, patients should be monitored clinically. Co-administration of lamivudine with high doses of co-trimoxazole for the treatment of *Pneumocystis jirovecii* pneumonia (PCP) and toxoplasmosis should be avoided.

The possibility of interactions with other medicinal products administered concurrently should be considered, particularly when the main route of elimination is active renal secretion via the organic cationic transport system e.g. trimethoprim. Other medicinal products (e.g. ranitidine, cimetidine) are eliminated only

in part by this mechanism and were shown not to interact with lamivudine. The nucleoside analogueslike zidovudine, are not eliminated by this mechanism and are unlikely to interact with lamivudine.

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

Due to similarities, lamivudine should not be administered concomitantly with other cytidine analogues,such as emtricitabine. Moreover, Dolutegravir 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsshould 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 supporta possible interaction between lamivudine and cladribine. Therefore, the concomitant use of lamivudine with cladribine is not recommended.

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

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

Interactions relevant to tenofovir

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, thepotential for CYP450 mediated interactions involving tenofovir with other medicinal products islow.

Dolutegravir 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsshould not be administered with any other medicines containing:

- tenofovir disoproxil
- tenofovir alafenamide
- adefovir dipivoxil
- didanosine

Interaction table

Interactions between Dolutegravir 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsand 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%; C_{max} ↓ 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 the table).
Lopinavir/ritonavir + etravirine/dolutegravir	Dolutegravir ↔ AUC ↑ 11%; C_{max} ↑ 7%; C_{τ} ↑28% LPV ↔ RTV ↔	No dose adjustment is necessary.
Darunavir/ritonavir + etravirine/dolutegravir	Dolutegravir ↓ AUC ↓ 25%; C_{max} ↓ 12%; C_{τ} ↓ 36% DRV ↔ RTV ↔	No dose adjustment is necessary.
Efavirenz/dolutegravir	Dolutegravir ↓ AUC ↓ 57%; C_{max} ↓ 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.
Rilpivirine/dolutegravir	Dolutegravir ↔ AUC ↑ 12%; C_{max} ↑ 13%; C_{τ} ↑ 22% Rilpivirine ↔	No dose adjustment is necessary.
Nucleoside reverse transcriptase inhibitors (NRTI)		
Emtricitabine / lamivudine		Dolutegravir 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsshould not be co-administered, due to the similarity between emtricitabine and lamivudine, and consequently expected additive toxicity and no benefit in efficacy.

Medicines by therapeutic area	Interaction Changes shown as geometric mean	Recommendations on co-administration
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 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsand didanosine is not recommended.
Adefovir dipivoxil/ tenofovir disoproxil	AUC: ↔ C_{max}: ↔	Tenofovir disoproxil should not be administered concurrently with adefovir dipivoxil.
Entecavir/ tenofovir disoproxil	AUC: ↔ C_{max}: ↔	No clinically significant pharmacokinetic interactions when tenofovir disoproxil was co-administered with entecavir.
Protease inhibitors (PIs)		
Atazanavir/dolutegravir	Dolutegravir ↑ AUC ↑ 91%; C_{max} ↑ 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+ritonavir/ Dolutegravir	Dolutegravir ↑ AUC ↑ 62%; C_{max} ↑ 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%; C_{max}: ↑ 34%; C_{min}: ↑ 29% Atazanavir: AUC: ↓ 25%; C_{max}: ↓ 28%; C_{min}: ↓ 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%; C_{max} ↓ 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. In the presence of integrase class resistance this combination should be avoided.
Fosamprenavir + ritonavir/dolutegravir	Dolutegravir ↓ AUC ↓ 35%; C_{max} ↓ 24%; Cτ ↓ 49% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary in the absence of integrase class resistance. For infection resistant to integrase inhibitors, alternative combinations that do not include fosamprenavir/ritonavir should be considered.

Medicines by therapeutic area	**Interaction** **Changes shown as geometric mean**	**Recommendations on co-administration**
Darunavir+ritonavir/ Dolutegravir	Dolutegravir ↓ AUC ↓ 22%; C_{max} ↓ 11%; $C_{24hours}$ ↓ 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%; C_{min}: ↑ 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.
Antivirals against hepatitis C		
Daclatasvir/ dolutegravir	Daclatasvir ↔ Dolutegravir ↔ AUC ↑ 33%; C_{max} ↑ 29%; Cτ ↑ 45%	No dose adjustment is necessary.
Daclatasvir/tenofovir disoproxil	Daclatasvir ↔ AUC: 1.10 (1.01, 1.21) C_{max}: 1.06 (0.98, 1.15) Cmin: 1.15 (1.02, 1.30) Tenofovir ↔ AUC: 1.10 (1.05, 1.15) C_{max}: 0.95 (0.89, 1.02) C_{min}: 1.17 (1.10, 1.24)	

Medicines by therapeutic area	**Interaction** **Changes shown as geometric mean**	**Recommendations on co-administration**
Sofosbuvir/tenofovir disoproxil	Tenofovir ↑ C_{max} 1.25 (1.08, 1.45) ↔ AUC 0.98 (0.91, 1.05) ↔ C_{min} 0.99 (0.91, 1.07) Sofosbuvir ↓ C_{max} 0.81 (0.60, 1.10) ↔ AUC 0.94 (0.76, 1.16) C_{min} (NA) GS-331007 (predominant inactive metabolite of sofosbuvir) ↓ C_{max} 0.77 (0.70, 0.84) ↔ AUC 0.84 (0.76, 0.92) C_{min} (NA)	No dose adjustment of sofosbuvir or Dolutegravir 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsis required when sofosbuvir and Dolutegravir 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsare used concomitantly.
Ledipasvir/Sofosbuvir +Dolutegravir + Tenofovir disoproxil (+Emtricitabine)	Sofosbuvir: AUC: ↔; C_{max}: ↔ GS-331007: AUC: ↔; C_{max}: ↔; C_{min}: ↔ Ledipasvir: AUC: ↔; C_{max}: ↔ $C_{min:}$ ↔ Dolutegravir: AUC: ↔; C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔; C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 65; C_{max}: ↑ 61% C_{min}: ↑ 115%	No dose adjustment is recommended. Monitor for tenofovir-associated adverse reactions in patients receiving ledipasvir/sofosbuvir concomitantly with [HA713 trade name]. Renal function should be closely monitored.

Medicines by therapeutic area	Interaction Changes shown as geometric mean	Recommendations on co-administration
Ledipasvir/Sofosbuvir+ Atazanavir/Ritonavir + Emtricitabine/Tenofovir disoproxil	Ledipasvir: AUC: ↑ 96%; C_{max}: ↑ 68%; C_{min}: ↑ 118% Sofosbuvir: AUC: ↔; C_{max}: ↔ GS-331007 (metabolite sofosbuvir): AUC: ↔; C_{max}: ↔; C_{min}: ↑ 42% Atazanavir: AUC: ↔; C_{max}: ↔ C_{min}: ↑ 63% Ritonavir: AUC: ↔; C_{max}: ↔ C_{min}: ↑ 45% Emtricitabine: AUC: ↔ ; C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔; C_{max}: ↑ 47% Cmin: ↑ 47%	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, ledipasvir/sofosbuvir and atazanavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with ledipasvir/sofosbuvir and a pharmacokinetic enhancer (e.g. ritonavir) has not been established. The combination should be used with caution with frequent renal monitoring, if other alternatives are not available.
Ledipasvir/Sofosbuvir + Darunavir/Ritonavir + Emtricitabine/Tenofovir disoproxil	Ledipasvir: AUC: ↔; C_{max}: ↔ C_{min}: ↔ Sofosbuvir: AUC↓ 27%; C_{max}: ↓37% GS-331007 : AUC: ↔ C_{max}: ↔ C_{min}: ↔ Darunavir: AUC ↔ ;C_{max}: ↔; C_{min}: ↔ Ritonavir: AUC: ↔; C_{max}: ↔; C_{min}: ↑ 48% Emtricitabine: AUC: ↔; C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 50%; C_{max}: ↑ 64% ; C_{min}: ↑ 59%	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, ledipasvir/sofosbuvir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with ledipasvir/sofosbuvir and a pharmacokinetic enhancer (e.g. ritonavir) has not been established. The combination should be used with caution with frequent renal monitoring, if other alternatives are not available.
Ledipasvir/Sofosbuvir + Efavirenz/Emtricitabine/ Tenofovir disoproxil	Ledipasvir: AUC: ↓ 34%; C_{max}:↓34%; C_{min}: ↓ 34% Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007 : AUC: ↔; C_{max}: ↔ C_{min}: ↔ Efavirenz: AUC: ↔; C_{max}: ↔; C_{min}: ↔ Emtricitabine: AUC: ↔; C_{max}: ↔; C_{min}: ↔ Tenofovir: AUC: ↑ 98% C_{max}: ↑ 79% C_{min}: ↑ 163%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored.

Medicines by therapeutic area	Interaction Changes shown as geometric mean	Recommendations on co-administration
Ledipasvir/Sofosbuvir + Emtricitabine/Rilpivirine /Tenofovir disoproxil	Sofosbuvir: AUC: ↔; C_{max}: ↔ GS-331007 : AUC: ↔; C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔; C_{max}: ↔ C_{min}: ↔ Rilpivirine: AUC: ↔; C_{max}: ↔ ; C_{min}: ↔ Tenofovir: AUC: ↑ 40% C_{max}: ↔ C_{min}: ↑ 91%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored.
Sofosbuvir/Velpatasvir + Tenofovir disoproxil (+ Emtricitabine + atazanavir/ritonavir)	Sofosbuvir: AUC: ↔; C_{max}: ↔ GS-331007: AUC: ↔; C_{max}: ↔ C_{min}: ↑ 42% Velpatasvir: AUC: ↑ 142%; C_{max} ↑ 55%; C_{min}: ↑ 301% Tenofovir: AUC: ↔; C_{max}: ↑ 55% C_{min}: ↑ 39%	Sofosbuvir/velpatasvir has been shown to increase tenofovir exposure (P-gp-inhibition). The increase in tenofovir exposure (AUC and C_{max}) 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.
Sofosbuvir/Velpatasvir/ Voxilaprevir + Tenofovir disoproxil (+ Emtricitabine + Darunavir/ritonavir)	Sofosbuvir: AUC: ↔; C_{max}: ↓ 30% $C_{min:}$ N/A GS-3310072: AUC: ↔; C_{max}:↔ C_{min}: N/A Velpatasvir: AUC: ↔; C_{max}: ↔ C_{min}: ↔ Voxilaprevir: AUC:↑ 143%; C_{max}:↑ 72%; C_{min}: ↑ 300% Tenofovir: AUC: ↑ 39% C_{max}: ↑ 48%; C_{min}: ↑ 47%	Sofosbuvir/velpatasvir/voxilaprevir has been shown to increase tenofovir exposure (P-gp inhibition). The increase in tenofovir exposure (AUC and C_{max}) 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 monitored for adverse reactions associated with tenofovir disoproxil.

Medicines by therapeutic area	**Interaction Changes shown as geometric mean**	**Recommendations on co-administration**
Sofosbuvir/Velpatasvir + Lopinavir/Ritonavir + Emtricitabine/Tenofovir disoproxil	Sofosbuvir: AUC: ↓ 29% C_{max}: ↓ 41% GS-3310072 : AUC: ↔; C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔; C_{max}: ↓ 30% C_{min}: ↑ 63% Lopinavir: AUC: ↔ ; C_{max}: ↔ C_{min}: ↔ Ritonavir: AUC: ↔; C_{max}: ↔; C_{min}: ↔ Emtricitabine: AUC: ↔; C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔; C_{max}: ↑ 42% C_{min}: ↔	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, sofosbuvir/velpatasvir and lopinavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g. ritonavir) has not been established. The combination should be used with caution with frequent renal monitoring.
Sofosbuvir/Velpatasvir + Raltegravir + Emtricitabine/Tenofovir disoproxil	Sofosbuvir: AUC: ↔; C_{max}: ↔ GS-3310072 : AUC: ↔; C_{max}: ↔; C_{min}: ↔ Velpatasvir: AUC: ↔; C_{max}: ↔ C_{min}: ↔ Raltegravir: AUC: ↔; C_{max}: ↔ C_{min}: ↓ 21% Emtricitabine: AUC: ↔; C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 40%; C_{max}: ↑ 46%; C_{min}: ↑ 70%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored.

Medicines by therapeutic area	**Interaction Changes shown as geometric mean**	**Recommendations on co-administration**
Sofosbuvir/Velpatasvir + Emtricitabine/Rilpivirine /Tenofovir disoproxil	Sofosbuvir: AUC: ↔; C_{max}: ↔ GS-3310072 : AUC: ↔; C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↔ ; C_{min}: ↔ Emtricitabine: AUC: ↔; C_{max}: ↔ C_{min}: ↔ Rilpivirine: AUC: ↔ C_{max}: ↔; C_{min}: ↔ Tenofovir: AUC: ↑ 40%; C_{max}: ↑ 44%; C_{min}: ↑ 84%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored.
Antimycobacterials		
Rifampicin/dolutegravir	Dolutegravir ↓ AUC ↓ 54%; C_{max} ↓ 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%; C_{max} ↑ 16%; C_{τ} ↓ 30% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Rifapentine/dolutegravir	Dolutegravir: ↓	Co-administration decreased dolutegravir concentrations, but trough concentrations remained above the target value. No dose adjustment of dolutegravir 50 mg once daily is needed when co-administered with once weekly isoniazid/rifapentine. However, dolutegravir 50 mg twice daily should be considered in individuals with suspicion of failure.
Antifungals		
Fluconazole Itraconazole Ketoconazole Posaconazole Voriconazole	Tenofovir Disoproxil: ↑	Itraconazole or ketoconazole co-administration may increase tenofovir exposure. Monitoring of tenofovir-associated adverse reactions, including frequent renal monitoring, is recommended. Based on theoretical considerations, no interaction with dolutegravir or lamivudine is expected.
Flucytosine/ Lamivudine/ Tenofovir Disoproxil		Potential haematological toxicity. Monitor haematological parameters and consider dose reduction if required.

Medicines by therapeutic area	Interaction Changes shown as geometric mean	Recommendations on co-administration
Antiepileptics		
Carbamazepine/ dolutegravir	Dolutegravir ↓ AUC ↓ 49%; C_{max} ↓ 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.
Amiodarone/Tenofovir Disoproxil Quinidine/Tenofovir Disoproxil		Co-administration may increase tenofovir exposure. Monitoring of tenofovir-associated adverse reactions, including frequent renal monitoring, is recommended.
Antacids and supplements		
Magnesium- or aluminium-containing antacid/dolutegravir	Dolutegravir ↓ AUC ↓ 74%; C_{max} ↓ 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%; C_{max} ↓ 37%; $C_{24hours}$ ↓ 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%; C_{max} ↓ 57%; $C_{24hours}$ ↓ 56% (Complex binding to polyvalent ions)	
Multivitamins/ dolutegravir	Dolutegravir ↓ AUC ↓ 33%; C_{max} ↓ 35% $C_{24hours}$ ↓ 32% (Complex binding to polyvalent ions)	

Medicines by therapeutic area	Interaction Changes shown as geometric mean	Recommendations on co-administration
Antidiabetics		
Metformin/dolutegravir	Co-administered with dolutegravir 50 mg once daily: Metformin ↑ AUC ↑ 79%; C_{max} ↑ 66% Co-administered with dolutegravir 50 mg twice daily: Metformin ↑ AUC ↑ 145%; C_{max} ↑ 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.
Cancer Therapies		
Cisplatin		Tenofovir disoproxil and lamivudine: Potential renal toxicity. Monitor renal function.
Oxaliplatin	Co-administration of dolutegravir decrease oxaliplatin efficacy. Tenofovir Disoproxil: ↑	Dolutegravir: Co-administration may decrease the efficacy of oxaliplatin. When possible, use raltegravir. Tenofovir disoproxil: Potential renal toxicity. Monitor renal function. Lamivudine: weak interaction, no dose adjustment required.
Dacarbazine	Co-administration may increase tenofovir and dacarbazine exposure.	No a priori dosage adjustment is recommended but renal function and haematological parameters should be monitored.
Paclitaxel	Co-administered with dolutegravir: dolutegravir ↓	Co-administration may decrease exposure of dolutegravir. Monitor response to antiretroviral therapy.
Vinblastine	Co-administered with dolutegravir: dolutegravir ↓	Co-administration may decrease exposure of dolutegravir. Monitor response to antiretroviral therapy.
Contraceptives		
Ethinylestradiol and norelgestromin /dolutegravir	Dolutegravir ↔ Ethinylestradiol ↔ AUC ↑ 3%; C_{max} ↓ 1% Norelgestromin ↔ AUC ↓ 2%; C_{max} ↓ 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%; C_{max} ↑ 6%; C_{τ} ↑ 17%	No dose adjustment is necessary.
Drug abuse		
Methadone/dolutegravir	Dolutegravir ↔ Methadone ↔ AUC ↓ 2%; C_{max} ↔ 0%; C_{τ} ↓ 1%	No dose adjustment is necessary.

Medicines by therapeutic area	Interaction Changes shown as geometric mean	Recommendations on co-administration
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.
Garlic/Dolutegravir		Co-administration is not recommended as it may decrease exposure of dolutegravir.
Multiple sclerosis		
Fampridine (also known as dalfampridine) / dolutegravir	Fampridine ↑	Co-administration of dolutegravir has the potential to cause seizures due to increased fampridine plasma concentration via inhibition of OCT2 transporter; co-administration has not been studied. Fampridine co-administration with dolutegravir is contraindicated.
Analgesics		
Aspirin (Analgesic) /Ibuprofen + Tenofovir disoproxil		No pharmacokinetic interaction expected. However, co-administration could potentially result in increased risk of nephrotoxicity. Alternatives to NSAIDs should be considered in patients at risk for renal dysfunction. If tenofovir disoproxil is co-administered with an NSAID, renal function should be monitored adequately.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

Dolutegravir

Women of childbearing potential

Women of childbearing potential should be counselled about the potential risk of neural tube defects with dolutegravir (see below) and about effective contraceptive measures.

If a woman plans pregnancy, she should be given information about the benefits and the risks of continuing treatment with dolutegravir, to help her make an informed choice between the different antiretroviral regimens. Options for antiretroviral therapy will depend on the woman's treatment history and preference as well as local policies and treatment availability.

If feasible, women of childbearing potential should have pregnancy testing before starting dolutegravir.

Pregnancy

Women in the first trimester of pregnancy should be informed about the possibility of a small increased risk of neural tube defects with dolutegravir (see *Human and animal data on pregnancy*, below).

More than 1000 outcomes in women who took dolutegravir in the second and third trimester of pregnancy do not indicate increased risk of fetal or neonatal toxicity.

Dolutegravir may be used during the second and third trimester of pregnancy when the expected benefit justifies the potential risk to the fetus.

Human and animal data on pregnancy

A birth outcome surveillance study in Botswana found a small increase of neural tube defects with dolutegravir: an incident of 0.19% (7 cases in 3591 deliveries) to mothers taking dolutegravir-containing regimens at the time of conception compared to 0.11% (21 cases in 19 361) to women not taking dolutegravir.

However, Botswana does not have a national food folate fortification programme, which can significantly lower the prevalence of neural tube defects. Reports from countries which have national food folate fortification programmes show an incidence of neural tube defects in the general population ranging from 0.05 to 0.1%.

The Botswana study found that dolutegravir-containing and efavirenz-containing antiretroviral regimens, when started later in pregnancy, have comparable pregnancy outcomes. Most neural tube defects occur in the first 4 weeks of fetal development. Therefore, any increased risk is likely to be associated with exposure to dolutegravir in the periconception period rather than later in the pregnancy.

Data from the Antiretroviral Pregnancy Registry do not indicate an increased risk of major birth defects in over 600 women taking dolutegravir during pregnancy, but these data are insufficient to address the risk of neural tube defects. To better understand the risk, research and surveillance are ongoing in pregnant women taking dolutegravir at the time of conception.

In animal reproductive toxicity studies, no adverse developmental outcomes, including neural tube defects, were identified. Dolutegravir crosses the placenta in animals (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). Data on exposure in pregnant women indicate no malformative and fetal/neonatal effect associated with tenofovir disoproxil or lamivudine.

Tenofovir disoproxil and lamivudine may be considered during pregnancy if clinically needed.

Breast-feeding

Dolutegravir, lamivudine and tenofovir disoproxil are found in breast milk of breast-feeding 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

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 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletscan cause dizziness. The patient's clinical status and side effects of Dolutegravir 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsshould 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 severeliver 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 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tablets(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), thrombocytopenia
Very rare	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

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	panic attack, suicidal ideation or suicide attempt (particularly in patients with historyof depression or psychiatric illness)

Nervous system disorders

Very common	headache, dizziness
Very rare	peripheral neuropathy (paraesthesia)

Gastrointestinal disorders

Very common	nausea, diarrhoea, vomiting
Common	flatulence, abdominal pain, abdominal discomfort, abdominal distension
Rare	pancreatitis, elevated serum amylases

Hepatobiliary disorders

Common	raised alanine aminotransferase (ALT) and aspartate aminotransferase (AST)
Uncommon	hepatitis
Rare	hepatic steatosis, acute hepatic failure, increased bilirubin (in combination with increased transaminases)

Skin and subcutaneous tissue disorders

Very common	rash
Common	hair loss, pruritus
Rare	angioedema

Musculoskeletal and connective tissue disorders

Common	arthralgia, muscle disorders

Uncommon	myalgia, rhabdomyolysis, muscular weakness
Rare	osteomalacia (manifested as bone pain and infrequently contributing to fractures) myopathy
Unknown	osteonecrosis

Renal and urinary disorders

Uncommon	increased creatinine, proximal renal tubulopathy (including Fanconi syndrome)
Rare	rare acute renal failure, renal failure, acute tubular necrosis, nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus

General disorders

Very common	asthenia
Common	fatigue, malaise, fever

Investigations

Common	raised creatine phosphokinase (CPK)

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/L occurred after 48 weeks of treatment. Creatinine increaseswere 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 variableand 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 beenreported.

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 riskfactors, 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 didnot 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 immunereactivation 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 occurafter 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 inadults.

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 disoproxilwere 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 of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adversereactions to a medicine are important for the monitoring of the medicine's benefits and risks.

4.9 Overdose

There is no specific treatment for an overdose of [HA713 trade name]. 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.

Dolutegravir is highly bound to plasma proteins; it is therefore unlikely that it will be significantlyremoved by dialysis.

A negligible amount of lamivudine was removed via (4-hour) haemodialysis, continuous ambulatory peritoneal dialysis and automated peritoneal dialysis; it is thus 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strandtransfer 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 IC_{50} 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 IC_{50} was similar for clinical isolates without any major difference between subtypes (A, B, C, D, E, F and G). The mean IC_{50} 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. EC_{50} values were in the range of 0.003 to 15 microM. 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 EC_{50} values for tenofovir were in the range of 0.04-8.5 microM. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC50 values ranged from 0.5-2.2 microM).

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)

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.

Resistance in vitro and in vivo (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 anearly 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. 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 (dolutegravir)

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.

5.2 Pharmacokinetic properties

The absorption characteristics of Dolutegravir 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletshave been determined after administration of tablets of [HA173 trade name] in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	**Mean value ± standard deviation** (*)		
	Dolutegravir	**Lamivudine**	**Tenofovir**
Maximum concentration (C_{max}) ng/ml	2736 ± 901 (2605)	2499 ± 615 (2434)	304 ± 97 (287)
Area under the curve (AUC_{0-}	58058 ± 19461	13139 ± 3276	2594 ± 732

[‡] 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 dataobtained

with emtricitabine.

$_{\infty}$), a measure of the extent of absorption ng.hour/ml	--	--	--
Time to attain maximum concentration (t_{max}) hour	2.88 ± 1.27	1.72 ± 0.75	1.31 ± 0.68

*geometric mean

Pharmacokinetics of dolutegravir, lamivudine and tenofovir disoproxil

	Dolutegravir	**Lamivudine**	**Tenofovir disoproxil**
General			
	PK similar for healthy and HIV-infected subjects. Low to moderate PK variability.		Tenofovir disoproxil is a water-soluble ester prodrug, which is rapidly converted in vivo to tenofovir. Tenofovir is converted intracellularly to tenofovir monophosphate and to the active component, tenofovir diphosphate.
Absorption			
Absolute bioavailability	Not known	NA	NA
Oral bioavailability	At least 32%	80-85%	25%
Food effect	<table><tr><th></th><th>AUC (0-∞)</th><th>C_{max}</th><th>T_{max}</th></tr><tr><td>Low fat</td><td>33%↑</td><td>46%↑</td><td>3 h</td></tr><tr><td>Moderate fat</td><td>41%↑</td><td>52%↑</td><td>4 h</td></tr><tr><td>High fat</td><td>66%↑</td><td>67%↑</td><td>5 h</td></tr></table>Increases may be clinically relevant in the presence of certain integrase class resistance. Therefore, it is recommended that patients infected with HIV resistant to integrase inhibitors take dolutegravir with food.	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.	<table><tr><th></th><th>AUC (0-∞)</th><th>C_{max}</th><th>T_{max}</th></tr><tr><td>Light meal</td><td>No significant effect</td><td>No significant effect</td><td>No significant effect</td></tr><tr><td>High fat meal</td><td>40%↑</td><td>14%↑</td><td>1h↑</td></tr></table>
Distribution			
Volume of distribution (mean)	17 to 20 L	1.3 L/kg	800 mL/kg
Plasma protein binding *in vitro*	>99%, increase in unbound fraction with low serum albumin (as in moderate hepatic impairment)	<36% serum albumin in vitro	<0.7% (serum protein binding <7.2%)
Tissue distribution	CSF: mean 18 ng/mL (comparable to unbound plasma concentration, and >IC50) Vaginal, cervical tissue,		Well distributed, with highest concentrations in kidney and liver.

	cervicovaginal fluid: 6-10% Semen: 7% Rectal tissue: 17% (each of corresponding plasma levels at steady state)		
Metabolism			
	Hepatic metabolism: glucuronidation via UGT1A1 minor pathway CYP3A	Only minor route (<10%)	In vitro studies have determined that neither tenofovir disoproxil nor tenofovir is a substrate for the CYP450 enzymes.
Active metabolite(s)	NA	NA	Tenofovir
Elimination			
Elimination half life	14 h	5-7 h 22 h for intracellular lamivudine triphosphate	Tenofovir: 12 to 18 h Tenofovir diphosphate: 10 h in intracellular activated resting peripheral blood mononuclear cells and 50 h in resting peripheral blood mononuclear cells.
Mean systemic clearance (Cl/F)	≈1 L/h	0.32 L/h/kg	0.23 L/h/kg
% of dose excreted in urine	32% in total; <1% unchanged, 19% as ether glucuronide Other metabolites; N-dealkylation metabolite and metabolite formed by oxidation at the benzylic carbon	>70% (Pre-dominantly cleared unchanged)	70-80% as unchanged drug
% of dose excreted in faeces	53% is excreted unchanged in the faeces		NA
Pharmacokinetic linearity	Depending on dose and formulation. For tablets: Dose-proportional increases from 25 to 50 mg	Linear pharmaco-kinetics	Linear pharmacokinetics (dose range 75 to 600 mg)
Drug interactions *(in vitro)*			
Transporters	No relevant inhibition of P-gp, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, MATE2-K, MRP2 or MRP4. No substrate of human OATP 1B1, OATP 1B3 or OCT 1.	OCT (organic cationic transporters)	Substrate of hOAT 1, hOAT3 and MRP 4.
Metabolizing enzymes	No relevant inhibition of (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7. No induction of CYP1A2, CYP2B6 or CYP3A4.		No significant inhibition of CYP3A4, CYP2D6, CYP2C9, CYP2E1, or CYP1A1/2

Pharmacokinetic/pharmacodynamic relationship

A dose-ranging trial involving dolutegravir monotherapy found rapid and dose-dependent antiviralactivity, 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.

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

Special populations

Children

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

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

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

Limited data are available in adolescents receiving a daily dose of 300 mg of lamivudine. Pharmacokinetic parameters are comparable to those reported in adults.

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, tenofovir and lamivudine in subjects aged over 65 years are limited.

Renal impairment

Pharmacokinetic data have been obtained for dolutegravir, tenofovir and lamivudine separately.

Renal clearance of unchanged active substance is a minor pathway of elimination fordolutegravir. Pharmacokinetics of 50-mg dolutegravir were studied in adults with severe renal impairment (creatinine clearance less than 30 ml/minute) and matched healthy controls. The exposure to dolutegravir was decreased by about 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.

Studies with lamivudine show that plasma concentrations (AUC) are increased in patients withrenal dysfunction due to decreased clearance. Based on the lamivudine data, Dolutegravir 50 mg Lamivudine 300 mg & Tenofovir disoproxil Fumarate 300 mg Tabletsis not recommended for patients with creatinine

clearance of < 50 ml/min.

Compared with patients with normal renal function, the mean tenofovir exposure increased from 2,185 ng·hour/ml in subjects not infected by HIV or hepatitis B virus with creatinine clearance over 80 ml/minute to 3064 ng·hour/ml, 6009 ng·hour/ml and 15,985 ng·hour/ml in patients with mild, moderate and severe renal impairment respectively. 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) (creatinine clearance less than 10 ml/minute) requiring haemodialysis, between-dialysis tenofovir concentrations substantially increased over 48 hours achieving a mean C_{max} of 1032 ng/ml and a mean $AUC_{0\text{-}48hour}$ of 42,857 ng·hour/ml. It is recommended that the dosing interval for tenofovir disoproxil 245 mg is modified in patients with creatinine clearance < 50 ml/minute or in patients who already have ESRD and require dialysis.

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

Hepatic impairment

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

The pharmacokinetics of tenofovir following a 245 mg single dose of tenofovir disoproxil have been studied in non-HIV infected subjects with moderate to severe (ChildPugh B to C) hepatic impairment. Nosubstantial alterations in the pharmacokinetics of lamivudine and tenofovir disoproxil was observed in subjects with variable degrees of hepatic impairment.

Polymorphisms in drug metabolising enzymes

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

Gender

Analyses of pooled pharmacokinetic data from trials in adults revealed no clinically relevant effect of gender on the exposure of dolutegravir. There is no evidence that a dose adjustment of dolutegravir, tenofovir or lamivudine would be required based on the effects of gender on PK parameters.

Race/ethnicity

Population PK analyses using pooled pharmacokinetic data from trials in adults revealed noclinically relevant effect of race on the exposure of dolutegravir. There is no evidence that a dose adjustment of dolutegravir, tenofovir or lamivudine would be required based on the effects of race/ethnicity on PK parameters.

Co-infection with hepatitis B or C

Pharmacokinetic analysis indicated that hepatitis C 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

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 andrat.

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

Oral administration of dolutegravir to pregnant rabbits at doses up to 1000 mg/kg daily from days 6 to 18 of gestation did not elicit developmental toxicity or teratogenicity. In rabbits, maternal toxicity (decreasedfood consumption, reduced urine or faeces, 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 theactive 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 twicedaily.

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 orskeletal 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 ata dose of 600 mg/kg/day. While the mechanism of tumour formation is uncertain, the findings are unlikelyto 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: Microcrystalline cellulose
Pregelatinized starch
Croscarmellose sodium
Magnesium stearate
Mannitol
Ferric oxide yellow
Sodium starch glycolate
Povidone
Sodium stearyl fumarate

Film coat: Hypromellose
Titanium dioxide
Triacetin

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Pack size 30, 90 and 180 tablets: 36 months

In-Use Period

30's HDPE Container

Should be used within 30 days, once opened

180's HDPE Container

Should be used within 180 days, once opened

90's HDPE Container

Should be used within 90 days, once opened

6.4 Special precautions for storage

Do not store above 30°C, protect from light. Store in the original container. Avoid excursions above 30° C.

6.5 Nature and contents of container

White, round HDPE bottle with PP continuous thread closure with pulp and white printed heat seal liner. The bottle also contains 3 sachets of 3 gm silica gel desiccant. Pack size: 180 tablets.

White, round HDPE bottle with PP continuous thread closure with pulp and white printed heat seal liner. The bottle also contains 2 sachets of 3 gm silica gel desiccant. Pack sizes: 30, 90 tablets.

6.6 Special precautions for disposal and other handling

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

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

HA713

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10. DATE OF REVISION OF THE TEXT

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References

General reference sources for this SmPC include:

Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. World Health Organization 2021, available at https://www.who.int/hiv/pub/guidelines/ARV2018update/en/

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EU Summary of product characteristics for Tivicay, available at https://www.ema.europa.eu/documents/product-information/tivicay-epar-product-information_en.pdf

EU Summary of product characteristics for Epivir, available at https://www.ema.europa.eu/en/documents/product-information/epivir-epar-product-information_en.pdf

EU Summary of product characteristics Viread, available at https://www.ema.europa.eu/en/documents/product-information/viread-epar-product-information_en.pdf

Further references relevant to sections of the SmPC include:

Section 4.5

University of Liverpool, HIV Drug interactions, available at: http://www.hiv-druginteractions.org

Section 4.6

Drug and Lactation Database (LactMed) Available at: https://www.ncbi.nlm.nih.gov/books/NBK500631/

Kobbe R, Schalkwijk S, Dunay G, et al. Dolutegravir in breast milk and maternal and infant plasma during breastfeeding. AIDS. 2016;30 (17):2731-2733.

Reefhuis J. et al. Neural Tube Defects in Pregnancies Among Women with Diagnosed HIV Infection – 15 Jurisdictions, 2013-2017. MMWR 2020: Vol 69(1):1-5.

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Section 5.1

Cahn P, Madero JS, Arribas JR, et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. Lancet. 2019;393(10167):143-155.

Weblinks were last accessed on 27.11.2022

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/pqweb/medicines