WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[HA722 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg dolutegravir (as sodium), 300 mg lamivudine and 300 mg tenofovir disoproxil fumarate (equivalent to tenofovir disoproxil 245 mg or tenofovir 136 mg).

Excipients with potential clinical effect

Each film-coated tablet contains about 184.4 mg of mannitol and 153 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

White, capsule-shaped, film-coated tablets. They are biconvex (rounded on top and bottom) with a bevelled edge. The tablets have 'HP533' debossed (stamped into) on one side and are plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HA722 trade name] is 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.

[HA722 trade name] may also be used in these patients for post-exposure prophylaxis to HIV. 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

[HA722 trade name] should be prescribed by a health care provider experienced in the management of HIV infection.

Posology

Treatment of HIV infection

The dose in adults and adolescents weighing at least 30 kg with *HIV-1 infection not resistant to integrase inhibitors* is one tablet of [HA722 trade name] once daily.

When the patient's HIV-1 infection is known or suspected to be *resistant to integrase inhibitors*, **adults** should be given an additional daily dose of dolutegravir 50 mg. There is insufficient information on the use of dolutegravir in adolescents with HIV-1 infection resistant to integrase inhibitors.

A similar additional daily dose of dolutegravir 50 mg should also be considered if co-administration of [HA722 trade name] with *medicines that reduce dolutegravir exposure* (see section 4.5) cannot be avoided.

For further information on use in potentially resistant infection or with medicines reducing dolutegravir exposure, please refer to the product information of dolutegravir or consult current WHO and other authoritative treatment guidelines.

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

Dose adjustments

Where discontinuation of therapy with one of the components of [HA722 trade name] is indicated or where dose modification is necessary, separate preparations of dolutegravir, lamivudine and tenofovir disoproxil should be used. Please refer to the individual product information for these medicinal products.

Post-exposure prophylaxis (PEP)

The recommended dose of [HA722 trade name] when given for PEP in adults and adolescents weighing at least 30 kg is one tablet of [HA722 trade name] once daily.

PEP should start as early as possible after exposure and ideally within 72 hours of exposure, and is given for a total of 28 days.

Dosing in special populations

Children

[HA722 trade name] should not be used in children weighing less than 30 kg since appropriate dose adjustments cannot be achieved with this product. Separate formulations containing lower amounts of dolutegravir, lamivudine or tenofovir disoproxil are required.

Elderly

[HA722 trade name] should be administered with caution to elderly patients (see section 4.4).

Renal impairment

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

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

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

[HA722 trade name] is not recommended for use in patients with creatinine clearance <50 mL/minute (see sections 4.4. and 5.2), as appropriate dose adjustments are not possible. For these patients, separate formulations of dolutegravir, lamivudine and tenofovir disoproxil should be used.

Hepatic impairment

No dose adjustment is needed for patients with mild or moderate hepatic impairment (Child-Pugh grade A or B). No data are available for dolutegravir in patients with severe hepatic impairment (Child-Pugh grade C); therefore, [HA722 trade name] should be used with caution in these patients.

Discontinuation of therapy

If [HA722 trade name] is discontinued in patients co-infected with HIV and hepatitis B virus (HBV), these patients should be closely monitored for evidence of exacerbation of hepatitis (see section 4.4).

Missed dose and vomiting after a dose

It is important that the patient takes the medicine regularly as prescribed. Missing doses can increase the risk 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 [HA722 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 [HA722 trade name] tablets should be swallowed whole with water.

[HA722 trade name] can usually be taken with food or between meals. In patients with HIV infection that has known or suspected resistance to integrase inhibitors, both [HA722 trade name] and any additional dose of dolutegravir should be taken with a meal.

4.3 Contraindications

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

[HA722 trade name] must 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 'Patients with HIV and hepatitis B (HBV) or C virus (HCV) co-infections', below).

HIV-1 resistant to integrase inhibitors

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

Hypersensitivity reactions

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 [HA722 trade name] should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur (see section 4.8).

Renal function

Lamivudine and tenofovir disoproxil are primarily excreted by the kidneys, through a combination of glomerular filtration and active tubular secretion. [HA722 trade name] is not recommended for patients with

moderate or severe renal impairment (creatinine clearance < 50 mL/min). Patients with moderate or severe renal impairment require a dose adjustment of lamivudine and tenofovir disoproxil that cannot be achieved with the combination tablet (see sections 4.2 and 5.2).

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

It is recommended that creatinine clearance /estimated glomerular function is calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with [HA722 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 [HA722 trade name] is a combination product and the dosing interval of the individual components cannot be altered, treatment with this medicine must be interrupted in patients with confirmed creatinine clearance <50 ml/min or decreases in serum phosphate to <1.0 mg/dL (0.32 mmol/L).

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

This medicine should be avoided with concurrent or recent use of a nephrotoxic medicinal product (e.g. high-dose or multiple non-steroidal anti-inflammatory drugs, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir, interleukin-2). If concomitant use of [HA722 trade name] and nephrotoxic agents is unavoidable, renal function must be monitored weekly (see section 4.5).

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

Elderly patients

Elderly patients are more likely to have decreased renal function; therefore, caution should be exercised when treating elderly patients with medicines such as [HA722 trade name] that contain tenofovir disoproxil.

Bone effects

Reductions of bone mineral density (BMD) have been observed with tenofovir disoproxil in randomized controlled clinical trials of duration up to 144 weeks in HIV or HBV-infected patients (see also section 4.8). These BMD decreases generally improved after treatment discontinuation. However, over 144 weeks, the risk of fractures was not increased and there was no evidence of clinically relevant bone abnormalities. Nonetheless, in view of the bone abnormalities associated with tenofovir disoproxil and the limitations of

long-term data on the impact of tenofovir disoproxil on bone health and fracture risk, benefit-risk should be considered carefully for patients with osteoporosis or with a history of bone fractures.

In HIV-1 infected adolescents 12 years of age and older, the mean rate of bone gain was less in the tenofovir disoproxil-treated group compared to the placebo group. Skeletal growth (height) appeared to be unaffected. Markers of bone turnover in tenofovir disoproxil-treated adolescents suggest increased bone turnover, consistent with the effects observed in adults. Due to the possible effects of tenofovir on bone metabolism, [HA722 trade name] should only be used in adolescents under the age of 18 if the benefits are considered to exceed the risk (see also section 4.8).

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

Osteonecrosis

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

Liver function

The safety and efficacy of [HA722 trade name] has not been established in patients with significant underlying liver disorders. Patients with pre-existing liver dysfunction, including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy, and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

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

Health care providers should refer to current relevant treatment guidelines for the optimal management of HIV infection in patients co-infected with HBV or HCV. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Lamivudine and tenofovir disoproxil are also active against HBV and a regimen based on tenofovir disoproxil in combination with lamivudine or emtricitabine is recommended for the treatment of co-infected patients. However, patients with chronic hepatitis B or C and treated with combination antiretroviral therapy may be at an increased risk of severe and potentially fatal hepatic adverse reactions, so appropriate monitoring is needed.

After initiating antiviral therapy, serum ALT may increase in some patients (see section 4.8). In patients with compensated liver disease, these increases in serum ALT are generally not accompanied by an increase in serum bilirubin concentrations or hepatic decompensation. Patients with cirrhosis may be at a higher risk for hepatic decompensation following hepatitis exacerbation, and therefore should be monitored closely during therapy.

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. In patients with advanced liver disease or cirrhosis, post-treatment exacerbation of hepatitis may lead to hepatic decompensation. If [HA722 trade name] needs to be discontinued due to HIV drug resistance or adverse effects, it is therefore recommended that treatment with tenofovir and lamivudine be continued as part of the new regimen. Patients co-infected with HIV and HBV who discontinue [HA722 trade name] should be closely monitored with both clinical and laboratory follow-up for at least 6 months after stopping treatment.

In general, clinical stabilisation of HIV disease with antiretrovirals such as [HA722 trade name]is advisable before starting treatment for HCV, especially for people with CD4 count below 200 cells/mm^3. Direct-acting antiviral therapy is generally considered safe and effective for people with HIV and HCV but it is important to consider the relevant interactions (see section 4.5).

Opportunistic infections

Patients receiving [HA722 trade name] or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by health care providers experienced in the treatment of HIV infection.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and lifestyle. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. Monitoring of blood lipids and glucose should be carried out as clinically appropriate and in line with operative HIV treatment guidelines. 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

[HA722 trade name] contains mannitol, which may have a mild laxative effect.

[HA722 trade name] contains a small amount of lactose. Patients with congenital lactase deficiency, galactosaemia or glucose-galactose intolerance must not be given this medicine unless strictly necessary.

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 [HA722 trade name]. As this medicine contains dolutegravir, lamivudine and tenofovir disoproxil, 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

Medicines that lower plasma concentration of dolutegravir should be avoided in the presence of HIV-1 resistant to integrase inhibitors. These medicines include magnesium- or aluminium-containing antacid, iron and calcium supplements, multivitamins and inducing agents such as etravirine (without boosted protease inhibitors), tipranavir/ritonavir, rifampicin, St. John’s wort and certain antiepileptic medicines (see table, below).

Dolutegravir is eliminated mainly through metabolism by UGT1A1. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4 and the transporters P-gp, and BCRP; therefore, medicines that induce the function of these proteins may decrease dolutegravir plasma concentration and reduce its therapeutic effect (see table, below). Conversely, giving dolutegravir with 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

Metabolic interactions with lamivudine are less likely because of its limited metabolism and plasma protein binding and almost complete renal clearance.

Lamivudine metabolism does not involve CYP3A and interactions with medicines metabolised by this system (e.g. protease inhibitors) are unlikely.

Lamivudine is predominantly eliminated renally by active organic cationic secretion. Other medicines which are mainly eliminated by renal secretion via the organic cationic transport system, e.g. trimethoprim, may interact with lamivudine. Sulfamethoxazole/trimethoprim increases plasma concentrations of lamivudine, but a clinically significant effect is not expected; the patient should be monitored for lamivudine toxicity in case of marked renal impairment or if high doses of sulfamethoxazole/trimethoprim are used (e.g. for treating *Pneumocystis jirovecii* pneumonitis).

Medicines (e.g. ranitidine, cimetidine), which are eliminated only in part by this mechanism, were shown not to interact with lamivudine.

Due to their similarities with lamivudine, other cytidine analogues, such as emtricitabine should not be administered concomitantly with [HA722 trade name]. Moreover, [HA722 trade name] should not be taken with any other medicinal products containing lamivudine.

In vitro, lamivudine inhibits the intracellular phosphorylation of cladribine, raising the possibility of a loss of cladribine's efficacy if the two are used concomitantly. Some clinical findings also support a possible interaction between lamivudine and cladribine. Therefore, the concomitant use of [HA722 trade name] with cladribine is not recommended.

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 [HA722 trade name] with medicinal products containing sorbitol or other osmotic acting polyalcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol). Consider more frequent monitoring of HIV-1 viral load when chronic co-administration cannot be avoided.

The co-administration of sulfadiazine and cisplatin with lamivudine has a potential for renal toxicity and would require monitoring of renal function.

The co-administration of flucytosine with lamivudine has potential for haematological toxicity which requires monitoring of haematological parameters and dose reduction should be considered.

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 (see section 4.4). 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.

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

Based on the results of in vitro experiments and the known elimination pathway of tenofovir, the potential for CYP450 mediated interactions involving tenofovir with other medicinal products is low.

[HA722 trade name] should not be administered with any other medicines containing:

- tenofovir disoproxil
- tenofovir alafenamide
- adefovir dipivoxil
- didanosine

Interaction table

Some key interactions between the components of [HA722 trade name] and co-administered medicinal products are listed in the following table (increase is indicated as ↑, decrease as ↓, no change as ↔, area under the concentration versus time curve as AUC, maximum observed concentration as C_{max}, concentration at end of dosing interval as C_{τ}).

Medicines by therapeutic area	**Interaction Changes shown as geometric mean**	**Recommendations on co-administration**
ANTI-INFECTIVES		
Antiretrovirals		
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Etravirine without boosted protease inhibitors/ dolutegravir	Dolutegravir ↓ AUC ↓ 71%; 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.

Medicines by therapeutic area	**Interaction Changes shown as geometric mean**	**Recommendations on co-administration**
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		[HA722 trade name] should not be co-administered, due to the similarity between emtricitabine and lamivudine, and consequently expected additive toxicity and no benefit in efficacy.
Didanosine / tenofovir disoproxil	Didanosine AUC ↑ 40-60%	The risk of didanosine-related adverse effects (e.g., pancreatitis, lactic acidosis) appears to be increased, and CD4-cells may decrease significantly on co-administration. Also, didanosine at 250 mg co-administered with tenofovir disoproxil within several different antiretroviral combination regimens has been associated with a high rate of virological failure. Co-administration of [HA722 trade name] and 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.

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

Medicines by therapeutic area	**Interaction Changes shown as geometric mean**	**Recommendations on co-administration**
Daclatasvir/ dolutegravir Daclatasvir/tenofovir disoproxil	Daclatasvir ↔ Dolutegravir ↔ AUC ↑ 33%; C_{max} ↑ 29%; Cτ ↑ 45% 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)	No dose adjustment is necessary.
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 [HA722 trade name] is required when sofosbuvir and [HA722 trade name] are 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 [HA722 trade name]. Renal function should be closely monitored.
Antimycobacterials		

Medicines by therapeutic area	**Interaction Changes shown as geometric mean**	**Recommendations on co-administration**
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.
OTHER MEDICINES		
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.
Antacids and supplements		
Magnesium- or aluminium-containing antacid or supplement/dolutegravir	Dolutegravir ↓ AUC ↓ 74%; C_{max} ↓ 72% (Complex binding to polyvalent ions)	Magnesium- or aluminium-containing antacids or supplements should be taken well separated in time from dolutegravir (minimum 2 hours after or 6 hours before).

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

Medicines by therapeutic area	**Interaction Changes shown as geometric mean**	**Recommendations on co-administration**
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. Concomitant use of [HA722 trade name] with corticosteroids may increase the risk of osteonecrosis.
Drug abuse		
Methadone/dolutegravir	Dolutegravir ↔ Methadone ↔ AUC ↓ 2%; C_{max} ↔ 0%; C_{τ} ↓ 1%	No dose adjustment is necessary.
Herbal products		

Medicines by therapeutic area	Interaction Changes shown as geometric mean	Recommendations on co-administration
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 medicines		
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.

4.6 Fertility, pregnancy and breastfeeding

Women of childbearing potential

There has been concern about the potential risk of neural tube defects with *dolutegravir* (see below).

Dolutegravir-based regimens can be recommended for HIV treatment in women of childbearing potential, as the overall benefits are considered likely to outweigh the risks. Use of effective contraceptive measures, and pregnancy testing before beginning treatment, may be considered. Health care providers should discuss any concerns, and the benefits and risks of available treatment options, with women who are planning to become pregnant.

Pregnancy

[HA722 trade name] may be used for the treatment of HIV in pregnancy.

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.

There has been concern about the possibility of a small increased risk of neural tube defects with *dolutegravir* taken in the periconceptional period (see 'Human and animal data on pregnancy', below). However, it is unclear that the risks with dolutegravir-based regimens are genuinely greater than for alternative options, and the benefits of effective HIV treatment with dolutegravir are considered likely to outweigh the risks.

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.

Human and animal data on pregnancy

A birth outcome surveillance study in Botswana found a small increase of neural tube defects: 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.

Subsequent update of the Botswana study up to March 2022 reported 10 cases among 9 460 deliveries to mothers taking dolutegravir-containing regimens at conception compared to 25 cases among 23 664 deliveries to women using regimens not containing dolutegravir (both 0.11%).

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 [HA722 trade name] can cause dizziness. The patient's clinical status and side effects of [HA722 trade name] should be considered when 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 treatment with the components of [HA722 trade name].

The most severe adverse reactions to dolutegravir are hypersensitivity reactions that include rash and severe liver effects. The most common adverse reactions of dolutegravir are nausea (13%), diarrhoea (18%) and headache (13%).

The most common adverse reactions to lamivudine include malaise and fatigue, upper respiratory tract symptoms, headache, and gastrointestinal disturbances.

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

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 [HA722 trade name] (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
Common	weight gain
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 history of depression or psychiatric illness); deaths from suicide have occurred.

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, decreased bone mineral density
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 to dolutegravir, lamivudine or tenofovir disoproxil

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 increases were comparable between various background regimens. These changes are not considered clinically relevant since they do not reflect a change in glomerular filtration rate.

Immune reactivation syndrome

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

Renal impairment

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

Renal tubulopathy

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

Interaction with didanosine

Co-administration of tenofovir disoproxil and didanosine is not recommended as it results in a 40-60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions. (see section 4.5). Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported.

Metabolic parameters

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

Osteonecrosis

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

Co-infection with hepatitis B or C

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

syndrome occurred in some subjects with hepatitis B or C co-infection at the start of dolutegravir therapy, particularly in those whose hepatitis B therapy was stopped.

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

Exacerbations of hepatitis after discontinuation of treatment

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

Special populations

Paediatric population

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

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

Reductions in bone mineral density (BMD) have been reported with tenofovir disoproxil in paediatric patients. In HIV-infected adolescents, the BMD Z-scores in subjects who received tenofovir disoproxil were lower than those in subjects who received placebo. In HIV-infected children, the BMD Z-scores in subjects who switched to tenofovir disoproxil were lower than those in subjects who remained on regimens containing stavudine or zidovudine. If bone abnormalities are detected or suspected in paediatric patients, consultation with an endocrinologist and/or nephrologist should be obtained.

In one study, 8 out of 89 paediatric patients treated with tenofovir disoproxil (median tenofovir disoproxil treatment 331 weeks) discontinued due to adverse reactions consistent with proximal renal tubulopathy. Seven patients had estimated glomerular filtration rate (GFR) values between 70 and 90 mL/minute/1.73 m^2. Among them, 3 patients had a clinically meaningful decline in estimated GFR which improved after discontinuation of tenofovir disoproxil.

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 adverse reactions 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 [HA722 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 significantly removed 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 strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle.

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

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

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

Pharmacodynamic effects

Antiviral activity in cell culture

Dolutegravir

The 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

Dolutegravir (in vitro)

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. The E92Q mutation has been selected in patients with pre-existing raltegravir resistance who were then treated with dolutegravir (listed as a secondary mutation for dolutegravir).

Dolutegravir (in vivo)

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.

In paediatric patients with prior failed therapies, but naïve to the integrase class, the integrase inhibitor substitution G118R was observed in 5/159 patients treated with dolutegravir, given in combination with an investigator selected background regimen. Of these five, 4 also had additional integrase associated substitutions.

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.

Tenofovir

In many cases when a lamivudine-containing treatment regimen fails (though less often when the treatment regimen contains a ritonavir-boosted protease inhibitor), the M184V mutation will be selected for at an early stage. M184V causes high-level resistance to lamivudine (> 300-fold reduced susceptibility). Virus with M184V replicates less well than does wild-type virus. In vitro data suggest that continuation of lamivudine in an antiretroviral regimen despite the development of M184V might provide residual antiretroviral activity (likely through impaired viral fitness). The clinical relevance of these findings is not established. Therefore, maintaining lamivudine therapy despite emergence of M184V mutation should be considered only when the activity of the best available NRTI backbone is significantly compromised.

Cross-resistance conferred by the M184V mutation is limited within the nucleoside/nucleotide inhibitor class of antiretroviral agents. 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. (Based on a systematic review it is suggested that emtricitabine and *lamivudine* are pharmacologically equivalent, and hence clinically interchangeable for therapy of HIV infection.)

5.2 Pharmacokinetic properties

The absorption characteristics of [HA722 trade name] have been determined after administration of a single dose tablet of [HA722 trade name] in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	**Mean value ± standard deviation** arithmetic mean ± SD		
	Dolutegravir	**Lamivudine**	**Tenofovir**
Maximum concentration (C_{max}) ng/mL	2646 ± 784	2386 ± 623	369 ± 88
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption ng.h/mL	56817 ± 22961	12996 ± 2524	2874 ± 600
Time to attain maximum concentration (t_{max}) h	2.77 ± 1.39	2.05 ± 0.92	1.20 ± 0.66

Pharmacokinetics of dolutegravir, lamivudine and tenofovir disoproxil

<table>
<tr><th></th><th>Dolutegravir</th><th>Lamivudine</th><th>Tenofovir disoproxil</th></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="4">General</td></tr>
<tr><td></td><td>PK similar for healthy and HIV-infected subjects.
Low to moderate PK variability.</td><td></td><td>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.</td></tr>
<tr><td colspan="4">Absorption</td></tr>
<tr><td>Absolute bioavailability</td><td>Not known</td><td>NA</td><td>NA</td></tr>
<tr><td>Oral bioavailability</td><td>At least 32%</td><td>80-85%</td><td>25%</td></tr>
<tr><td>Food effect</td><td><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.</td><td>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.</td><td><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></td></tr>
<tr><td colspan="4">Distribution</td></tr>
<tr><td>Volume of distribution (mean)</td><td>17 to 20 L</td><td>1.3 L/kg</td><td>800 mL/kg</td></tr>
<tr><td>Plasma protein binding in vitro</td><td>>99%, increase in unbound fraction with low serum albumin (as in moderate hepatic impairment)</td><td><36% serum albumin in vitro</td><td><0.7% (serum protein binding <7.2%)</td></tr>
<tr><td>Tissue distribution</td><td>CSF: mean 18 ng/mL (comparable to unbound plasma concentration, and >IC50)
Vaginal, cervical tissue, cervicovaginal fluid: 6-10%
Semen: 7%
Rectal tissue: 17%
(each of corresponding plasma levels at steady state)</td><td></td><td>Well distributed, with highest concentrations in kidney and liver.</td></tr>
</table>

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 antiviral activity, with mean decline in HIV-1 RNA of 2.5 $\log_{10}$ at day 11 for 50-mg dose. This antiviral response was maintained for 3 to 4 days after the last dose in the 50 mg group.

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. There are 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 for dolutegravir. 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 with renal dysfunction due to decreased clearance. Based on the lamivudine data, [HA722 trade name] is 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/min and 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 severe hepatic impairment on the pharmacokinetics of dolutegravir has not been studied.

The pharmacokinetic parameters of lamivudine were not altered by reduced hepatic function in a study in adults. Safety and efficacy of lamivudine have not been established in the presence of decompensated liver disease

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. No substantial 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 no clinically 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 and rat.

Dolutegravir did not affect male or female fertility in rats at doses up to 1000 mg/kg daily (around 25 times the normal human clinical exposure based on AUC). Oral administration of dolutegravir to pregnant rats at similar doses 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 (decreased food 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 the active substance, comparison based on bodyweight or on body surface area is appropriate for this toxicity. Gastrointestinal intolerance in monkeys occurred at 15 times the human mg/kg equivalent dose (based on a 50-kg human), and 5 times the human mg/m^2 equivalent dose for a clinical dose of 50 mg twice daily.

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.

Tenofovir

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

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

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

Tenofovir disoproxil did not show any carcinogenic potential in a long-term oral carcinogenicity study in rats. A long-term oral carcinogenicity study in mice showed a low incidence of duodenal tumours, considered likely related to high local concentration of tenofovir disoproxil in the gastrointestinal tract at a dose of 600 mg/kg/day. While the mechanism of tumour formation is uncertain, the findings are unlikely to be of relevance to humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet: microcrystalline cellulose
croscarmellose sodium
povidone
lactose monohydrate
pregelatinized starch
magnesium stearate
mannitol
sodium starch glycolate
sodium stearyl fumarate

Film coat: polyvinyl alcohol partially hydrolysed
titanium dioxide
macrogol/polyethylene glycol
talc

This medicine is essentially ‘sodium-free’. It contains less than 1 mmol sodium (23 mg) per tablet.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

In-use period (for pack size of 90’s)

Discard the product 90 days after initial opening.

In-use period (for pack size of 180’s)

Discard the product 30 days after initial opening.

6.4 Special precautions for storage

Do not store above 30ºC

6.5 Nature and contents of container

Opaque white plastic (HDPE) bottle containing 30 tablets. It also contains one canister of 3 g silica gel (a drying material). The bottle has an opaque white, polypropylene screw cap with heat seal liner.

Opaque white plastic (HDPE) bottle containing 90 tablets. It also contains one canister of 3 g silica gel (a drying material). The bottle has an opaque white, polypropylene screw cap with heat seal liner.

Opaque white plastic (HDPE) bottle containing 180 tablets. It also contains two canisters of 2 g silica gel (a drying material). The bottle has an opaque white, polypropylene screw cap with heat seal liner.

6.6 Special precautions for disposal and other handling

No special requirements

Any unused 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)

HA722

9. DATE OF PREQUALIFICATION

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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. Geneva: World Health Organization July 2021 (https://www.who.int/publications/i/item/9789240031593, accessed 12 March 2024).

Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV. Interim guidance. World Health Organization 2018, available at https://www.who.int/hiv/pub/guidelines/ARV2018update/en/

Update of recommendations on first-and second-line antiretroviral regimens. Policy brief. World Health Organization, July 2019, available at https://apps.who.int/iris/bitstream/handle/10665/325892/WHO-CDS-HIV-19.15-eng.pdf?ua=1

Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children: recommendations for a public health approach. Geneva: World Health Organization; 2014. (https://www.who.int/publications/i/item/9789241506830, accessed 12 March 2024).

Update on the transition to dolutegravir-based antiretroviral therapy: report of a WHO meeting, 29–30 March 2022. Geneva: World Health Organization; 2022 (https://iris.who.int/bitstream/handle/10665/360836/9789240053335-eng.pdf, accessed 12 March 2024).

Tivicay 5 mg dispersible tablets and 10, 25 and 50 mg film-coated tablets: summary of product characteristics. European Medicines Agency; 14 August 2023 (https://www.ema.europa.eu/en/documents/product-information/tivicay-epar-product-information_en.pdf, accessed 12 March 2024).

Epivir150 and 300 mg film-coated tablets: summary of product characteristics. European Medicines Agency; 29 August 2022 (https://www.ema.europa.eu/en/documents/product-information/epivir-epar-product-information_en.pdf, accessed 5 May 2024)

Zeffix 100 mg film-coated tablets: summary of product characteristics. European Medicines Agency; 20 March 2024 (https://www.ema.europa.eu/en/documents/product-information/zeffix-epar-product-information_en.pdf, accessed 5 May 2024)

Viread: summary of product characteristics. European Medicines Agency; 29 February 2024 (https://www.ema.europa.eu/en/documents/product-information/viread-epar-product-information_en.pdf, accessed 5 May 2024)

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/

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.

Zash R, et al. Update on neural tube defects with antiretroviral exposure in the Tsepamo Study, Botswana [conference report]; 2022. Available at: https://programme.aids2022.org/PAGMaterial/PPT/3726_4873/AIDS2022_TsepamoUpdate.pdf

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.

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products