Summary of Product Characteristics SmPC

KOCITAF
Dolutegravir/ Emtricitabine/ Tenofovir Alafenamide Tablets 50 mg/ 200 mg/ 25 mg

1. NAME OF THE MEDICINAL PRODUCT

Dolutegravir, Emtricitabine and Tenofovir Alafenamide Tablets 50 mg/ 200 mg/ 25 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Dolutegravir Sodium equivalent to Dolutegravir 50

mg Emtricitabine 200 mg

Tenofovir Alafenamide Fumarate equivalent to Tenofovir Alafenamide 25 mg

Excipient with known effect

Each tablet contains 120 mg lactose (as

monohydrate). For the full list of excipients, see

section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet.

A white to off white, film coated, oval shaped, biconvex beveled edge tablet debossed with M on one side of the tablet and TD1 on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Dolutegravir, Emtricitabine and Tenofovir alafenamide 50 mg/ 200 mg/ 25 mg is indicated in combination with other antiretroviral agents for the treatment of adults and adolescents (aged 12 years and older with body weight at least 40 kg) infected with human immunodeficiency virus type 1 (HIV-1) (see sections 4.2 and 5.1).

Combination of Dolutegravir, Emtricitabine and Tenofovir alafenamide has not been studied so far.

4.2. Posology and method of administration

Therapy should be initiated by a physician experienced in the management of HIV infection.

Posology

Adults and adolescents aged 12 years and older, weighing at least 40 kg

1. Patients infected with HIV-1 without documented or clinically supected resistance to the integrase class

    a. Fixed dose combination of Dolutegravir, Emtricitabine and Tenofovir alafenamide 50 mg/ 200 mg/ 25 mg should be administered orally once daily.
2. Patients infected with HIV-1 with documented or clinically supected resistance to the integrase class
    a. The recommended dose of dolutegravir is 50 mg (one tablet) twice daily.
    b. Separate preparations of Dolutegravir, Emtricitabine and Tenofovir alafenamide are available in cases where discontinuation or dose adjustment of one of the active substances is indicated.
    c. In these cases the physician should refer to the individual product information for these medicinal products

Missed doses
If the patient misses a dose of Dolutegravir, Emtricitabine and Tenofovir alafenamide within 18 hours of the time it is usually taken, the patient should take Dolutegravir, Emtricitabine and Tenofovir alafenamide as soon as possible and resume the normal dosing schedule. If a patient misses a dose of Dolutegravir, Emtricitabine and Tenofovir alafenamide by more than 18 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.

If the patient vomits within 1 hour of taking Dolutegravir, Emtricitabine and Tenofovir alafenamide another tablet should be taken.

Elderly

There are limited data available on the use of Dolutegravir, Emtricitabine and Tenofovir alafenamide in patients aged 65 years and over. There is no evidence that elderly patients require a different dose than younger adult patients (see section 5.2).

Renal impairment

No dose adjustment of Dolutegravir, Emtricitabine and Tenofovir alafenamide is required in adults or adolescents (aged at least 12 years and of at least 40 kg body weight) with estimated creatinine clearance (CrCl) ≥ 30 mL/min.

Dolutegravir, Emtricitabine and Tenofovir alafenamide should not be initiated in patients with estimated CrCl < 30 mL/min as there are no data available regarding the use of Dolutegravir, Emtricitabine and Tenofovir alafenamide in this population, although difference in pharmacokinetics are not expected in this population. (see sections 5.1 and 5.2).

Dolutegravir, Emtricitabine and Tenofovir alafenamide should be discontinued in patients with estimated CrCl that declines below 30 mL/min during treatment (see sections 5.1 and 5.2).

Hepatic impairment

No dose adjustment of Dolutegravir, Emtricitabine and Tenofovir alafenamide is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Dolutegravir, Emtricitabine and Tenofovir alafenamide has not been studied in patients with severe hepatic impairment (Child-Pugh Class C); therefore, Dolutegravir, Emtricitabine and Tenofovir alafenamide is not recommended for use in patients with severe hepatic impairment (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of Dolutegravir, Emtricitabine and Tenofovir alafenamide in children younger than 12 years of age, or weighing < 40 kg, has not yet been established. No data are available. In the presence of integrase inhibitor resistance, there are insufficient data to recommend a dose for dolutegravir in children and adolescents. (See section 4.8, 5.1 and 5.2).

Method of administration

Oral Use
Dolutegravir, Emtricitabine and Tenofovir alafenamide can be taken with or without food (see section 5.2). In the presence of integrase class resistance, Dolutegravir, Emtricitabine and Tenofovir alafenamide should preferabley be taken with food to enhance exposure (particulary in patients with Q148 mutations) (see section 5.2)
The film-coated tablet should not be chewed, crushed, or split.

4.3.Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1. Co-administration with dofetilide. (see section 4.5)

4.4.Special warnings and precautions for use

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Integrase class resistance of particular concern
The decision to use dolutegravir in the presence of integrase class resistance should take into account that the activity of dolutegravir is considerably compromised for viral strains harbouring Q148+≥2 secondary mutations from G140A/C/S, E138A/K/T, L74I (see section 5.1). To what extent dolutegravir provides added efficacy in the presence of such integrase class resistance is uncertain (see section 5.2).

Hypersensitivity reactions
Hypersensitivity reactions have been reported with dolutegravir, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including severe liver reactions. Dolutegravir and other suspect agents should be discontinued immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by raised liver enzymes, fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, eosinophilia, angioedema). Clinical status including liver aminotransferases and bilirubin should be monitored. Delay in stopping treatment with dolutegravir or other suspect active substances after the onset of hypersensitivity may result in a life-threatening allergic reaction.

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

The safety and efficacy of Dolutegravir, Emtricitabine and Tenofovir alafenamide in patients co-infected with HIV-1 and hepatitis C virus (HCV) have not been established. Tenofovir alafenamide is active against

hepatitis B virus (HBV), but its clinical efficacy against this virus is under investigation and is not yet fully established.

Discontinuation of Dolutegravir, Emtricitabine and Tenofovir alafenamide therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis. Patients co-infected with HIV and HBV who discontinue Dolutegravir, Emtricitabine and Tenofovir alafenamide should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment.

Dolutegravir, Emtricitabine and Tenofovir alafenamide should not be administered concomitantly with medicinal products containing tenofovir disoproxil (as fumarate), lamivudine or adefovir dipivoxil used for the treatment of HBV infection.

Liver disease

The safety and efficacy of Dolutegravir, Emtricitabine and Tenofovir alafenamide in patients with significant underlying liver disorders have not been established (see sections 4.2 and 5.2).

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Mitochondrial dysfunction

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

Immune Reactivation Syndrome

In HIV infected patients treated with CART, immune reactivation syndrome has been reported. In HIV infected patients with severe immune deficiency at the time of institution of CART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few

weeks or months of initiation of CART. Relevant examples include cytomegalovirus retinitis, generalized and/or focal mycobacterial infections, and Pneumocystis jirovecii pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable, and these events can occur many months after initiation of treatment.

Liver biochemistry elevations consistent with immune reconstitution syndrome were observed in some hepatitis B and/or C co-infected patients at the start of dolutegravir therapy. Monitoring of liver biochemistries is recommended in patients with hepatitis B and/or C co-infection. Particular diligence should be applied in initiating or maintaining effective hepatitis B therapy (referring to treatment guidelines) when starting dolutegravir-based therapy in hepatitis B co-infected patients (see section 4.8).

Patients with HIV-1 harbouring mutations

Dolutegravir, Emtricitabine and Tenofovir alafenamide should be avoided in antiretroviral-experienced patients with HIV-1 harbouring the K65R mutation (see section 5.1).

Triple nucleoside therapy

There have been reports of a high rate of virological failure and of emergence of resistance at an early stage when tenofovir disoproxil fumarate was combined with lamivudine and abacavir as well as with lamivudine and didanosine as a once daily regimen. Therefore, the same problems may be seen if Dolutegravir, Emtricitabine and Tenofovir alafenamide is administered with a third nucleoside analogue.

Opportunistic infections

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

Drug interactions

Factors that decrease dolutegravir exposure should be avoided in the presence of integrase class resistance. This includes co-administration with medicinal products that reduce dolutegravir exposure (e.g. magnesium/ aluminium-containing antacid, iron and calcium supplements, multivitamins and inducing agents, etravirine (without boosted protease inhibitors), tipranavir/ ritonavir, rifampicin, St. John's wort and certain antiepileptic drugs) (see section 4.5).

Dolutegravir increased metformin concentrations. A dose adjustment of metformin should be considered when starting and stopping coadministration of dolutegravir with metformin, to maintain glycaemic control (see section 4.5). Metformin is eliminated renally and therefore it is of importance to monitor renal function when co-treated with dolutegravir. This combination may increase the risk for lactic acidosis in patients with moderate renal impairment (stage 3a creatinine clearance [CrCl] 45– 59 mL/min) and a cautious approach is recommended. Reduction of the metformin dose should be highly considered.

Osteonecrosis

Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV disease and/or long-term exposure to CART. Patients

should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Nephrotoxicity
A potential risk of nephrotoxicity resulting from chronic exposure to low levels of tenofovir due to dosing with tenofovir alafenamide cannot be excluded (see section 5.3).

Co-administration of other medicinal products
The co-administration of Dolutegravir, Emtricitabine and Tenofovir alafenamide is not recommended with certain anticonvulsants (e.g., carbamazepine, oxcarbazepine, phenobarbital and phenytoin), antimycobacterials (e.g., rifampicin, rifabutin, rifapentine), boceprevir, telaprevir, St. John's wort and HIV protease inhibitors (PIs) other than atazanavir, lopinavir and darunavir (see section 4.5).

Dolutegravir, Emtricitabine and Tenofovir alafenamide should not be administered concomitantly with medicinal products containing tenofovir disoproxil (as fumarate), emtricitabine, lamivudine or adefovir dipivoxil.

4.5.Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Dolutegravir, Emtricitabine and Tenofovir alafenamide should not be administered concomitantly with medicinal products containing tenofovir disoproxil (as fumarate), emtricitabine, lamivudine or adefovir dipivoxil.

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

Dolutegravir is eliminated mainly through metabolism by UGT1A1. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP; therefore medicinal products that induce those enzymes may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir (see Table 2). Co-administration of dolutegravir and other medicinal products that inhibit these enzymes may increase dolutegravir plasma concentration (see Table 2).

The absorption of dolutegravir is reduced by certain anti-acid agents (see

Table 2). Effect of dolutegravir on the pharmacokinetics of other agents

In vivo, dolutegravir did not have an effect on midazolam, a CYP3A4 probe. Based on *in vivo* and/or *in vitro* data, dolutegravir is not expected to affect the pharmacokinetics of medicinal products that are substrates of any major enzyme or transporter such as CYP3A4, CYP2C9 and P-gp (for more information see section 5.2).

In vitro, dolutegravir inhibited the renal organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter (MATE) 1. *In vivo*, a 10-14% decrease of creatinine clearance (secretory fraction is dependent on OCT2 and MATE-1 transport) was observed in patients. *In vivo*, dolutegravir may increase plasma concentrations of medicinal products in which excretion is dependent upon OCT2 or MATE-1 (e.g. dofetilide, metformin) (see Table 2 and section 4.3).

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

Emtricitabine

In vitro and clinical pharmacokinetic drug-drug interaction studies have shown that the potential for CYP- mediated interactions involving emtricitabine with other medicinal products is low. Co-administration of emtricitabine with medicinal products that are eliminated by active tubular secretion may increase concentrations of emtricitabine, and/or the co-administered medicinal product. Medicinal products that decrease renal function may increase concentrations of emtricitabine.

Tenofovir alafenamide

Tenofovir alafenamide is transported by P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Medicinal products that strongly affect P-gp activity and BCRP may lead to changes in tenofovir alafenamide absorption. Medicinal products that induce P-gp activity (e.g., rifampicin, rifabutin, carbamazepine, phenobarbital) are expected to decrease the absorption of tenofovir alafenamide, resulting in decreased plasma concentration of tenofovir alafenamide, which may lead to loss of therapeutic effect of Dolutegravir, Emtricitabine and Tenofovir alafenamide and development of resistance. Co-administration of Dolutegravir, Emtricitabine and Tenofovir alafenamide with other medicinal products that inhibit P-gp (e.g., cobicistat, ritonavir, ciclosporin) are expected to increase the absorption and plasma concentration of tenofovir alafenamide. It is not known whether the co- administration of Dolutegravir, Emtricitabine and Tenofovir alafenamide and xanthine oxidase inhibitors (e.g., febuxostat) would increase systemic exposure to tenofovir.

Tenofovir alafenamide is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 *in vitro*. It is not an inhibitor of CYP3A4 *in vivo*. Tenofovir alafenamide is a substrate of OATP1B1 and OATP1B3 *in vitro*. The distribution of tenofovir alafenamide in the body may be affected by the activity of OATP1B1 and OATP1B3.

Other interactions

Interactions between potential co-administered medicinal products and the components of Dolutegravir are listed in Table 1 and for Emtricitabine and Tenofovir alafenamide are listed in Table 2 (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 "Cτ").

The interactions described are based on studies conducted with the components of Dolutegravir, Emtricitabine and Tenofovir alafenamide as individual agents and/or in combination, or are potential drug-drug interactions that may occur with Dolutegravir, Emtricitabine and Tenofovir alafenamide.

Table 1: Interactions between Dolutegravir and other medicinal products

Medicinal products by therapeutic areas	Interaction Geometric mean change (%)	Recommendations concerning co-administration
HIV-1 Antiviral Agents		

Non-nucleoside Reverse Transcriptase Inhibitors

Etravirine without boosted protease inhibitors	Dolutegravir ↓ AUC ↓71% C_{max} ↓52% C_T ↓88% Etravirine ↔ (induction of UGT1A1 and CYP3A enzymes)	Etravirine without boosted protease inhibitors decreased plasma dolutegravir concentration. The recommended dose of dolutegravir is 50 mg twice daily when co-administered with etravirine without boosted protease inhibitors. Dolutegravir should not be used with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir in INI-resistant patients (see further below in table).
Lopinavir/ritonavir + etravirine	Dolutegravir ↔ AUC ↑11% C_{max} ↑7% C_T ↑28% LPV ↔ RTV ↔	No dose adjustment is necessary.
Darunavir/ritonavir + etravirine	Dolutegravir ↓ AUC ↓25% C_{max} ↓12% C_T ↓36% DRV ↔ RTV ↔	No dose adjustment is necessary.
Efavirenz	Dolutegravir ↓ AUC ↓57% C_{max} ↓39% C_T ↓75% Efavirenz ↔ (historical controls) (induction of UGT1A1 and CYP3A enzymes)	The recommended dose of dolutegravir is 50 mg twice daily when co-administered with efavirenz. In the presence of integrase class resistance alternative combinations that do not include efavirenz should be considered (see section 4.4).
Nevirapine	Dolutegravir ↓ (Not studied, a similar reduction in exposure as observed with efavirenz is expected, due to induction)	The recommended dose of dolutegravir is 50 mg twice daily when co-administered with nevirapine. In the presence of integrase class resistance alternative combinations that do not include nevirapine should be considered (see section 4.4).

Rilpivirine	Dolutegravir ↔ AUC↑12% C_{max}↑13% C_T ↑22% Rilpivirine ↔	No dose adjustment is necessary.
Nucleoside Reverse Transcriptase Inhibitors		
Tenofovir	Dolutegravir ↔	No dose adjustment is necessary.

	AUC↑1% C_{max}↓3% C_T ↓8% Tenofovir ↔	
Protease Inhibitors		
Atazanavir	Dolutegravir ↑ AUC↑91% C_{max}↑50% C_T↑180% Atazanavir ↔ (historical controls) (inhibition of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary. Dolutegravir should not be dosed higher than 50 mg twice daily in combination with atazanavir (see section 5.2) due to lack of data.
Atazanavir/ ritonavir	Dolutegravir ↑ AUC↑62% C_{max}↑34% C_T ↑121% Atazanavir ↔ Ritonavir ↔ (inhibition of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary. Dolutegravir should not be dosed higher than 50 mg twice daily in combination with atazanavir (see section 5.2) due to lack of data.
Tipranavir/ ritonavir (TPV+RTV)	Dolutegravir ↓ AUC↓59% C_{max}↓47% C_T ↓ 76% (induction of UGT1A1 and CYP3A enzymes)	The recommended dose of dolutegravir is 50 mg twice daily when co-administered with tipranavir/ritonavir the absence of integrase class resistance. In the presence of integrase class resistance this combination should be avoided (see section 4.4).
Fosamprenavir/ ritonavir (FPV+RTV)	Dolutegravir ↓ AUC↓35% C_{max}↓24% C_T ↓ 49% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary in the absence of integrase class resistance. In the presence of integrase class resistance alternative combinations that do not include fosamprenavir/ritonavir should be considered.
Nelfinavir	Dolutegravir ↔ (Not studied)	No dose adjustment is necessary.

Darunavir/ritonavir	Dolutegravir ↓ AUC ↓ 22% C_{max} ↓ 11% C24 ↓ 38% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.

Lopinavir/ritonavir	Dolutegravir ↔ AUC ↓4% C_{max} ↔ 0% C24 ↓6%	No dose adjustment is necessary.
Other Antiviral agents		
Telaprevir	Dolutegravir ↑ AUC↑25% C_{max}↑19% Cτ ↑37% Telaprevir ↔ (historical controls) (inhibition of CYP3A enzyme)	No dose adjustment is necessary.
Boceprevir	Dolutegravir ↔ AUC↑7% C_{max}↑5% Cτ ↑8% Boceprevir ↔ (historical controls)	No dose adjustment is necessary.
Daclatasvir	Dolutegravir ↔ AUC↑33% C_{max}↑29% Cτ ↑45% Daclatasvir ↔	Daclatasvir did not change dolutegravir plasma concentration to a clinically relevant extent. Dolutegravir did not change daclatasvir plasma concentration. No dose adjustment is necessary.
Other agents		
Antiarrhythmics		
Dofetilide	Dofetilide ↑ (Not studied, potential increase via inhibition of OCT2 transporter)	Dolutegravir and dofetilide co-administration is contraindicated due to potential life-threatening toxicity caused by high dofetilide concentration (see section 4.3).
Anticonvulsants		
Carbamazepine	Dolutegravir ↓ AUC↓49% C_{max}↓33% Cτ ↓ 73%	The recommended dose of dolutegravir is 50 mg twice daily when co-administered with carbamazepine. Alternatives to carbamazepine should be used where possible for INI resistant patients.

Oxcarbazepine Phenytoin Phenobarbital	Dolutegravir ↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a similar reduction in exposure as observed with carbamazepine is expected)	The recommended dose of dolutegravir is 50 mg twice daily when co-administered with these metabolic inducers. Alternative combinations that do not include these metabolic inducers should be used where possible in INI-resistant patients.
Azole anti-fungal agents		

Ketoconazole Fluconazole Itraconazole Posaconazole Voriconazole	Dolutegravir ↔ (Not studied)	No dose adjustment is necessary. Based on data from other CYP3A4 inhibitors, a marked increase is not expected.
Herbal products		
St. John's wort	Dolutegravir ↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a similar reduction in exposure as observed with carbamazepine is expected)	The recommended dose of dolutegravir is 50 mg twice daily when co-administered with St. John's wort. Alternative combinations that do not include St. John's wort should be used where possible in INI-resistant patients.
Antacids and supplements		
Magnesium/ aluminium-containing antacid	Dolutegravir ↓ AUC↓74% C_{max}↓72% (Complex binding to polyvalent ions)	Magnesium/ aluminium-containing antacid should be taken well separated in time from the administration of dolutegravir (minimum 2 hours after or 6 hours before).
Calcium supplements	Dolutegravir ↓ AUC↓39% C_{max}↓37% C24↓39% (Complex binding to polyvalent ions)	Calcium supplements, iron supplements or multivitamins should be taken well separated in time from the administration of dolutegravir (minimum 2 hours after or 6 hours before).
Iron supplements	Dolutegravir ↓ AUC↓54% C_{max}↓57% C24↓56% (Complex binding to polyvalent ions)	
Multivitamin	Dolutegravir ↓ AUC↓33% C_{max}↓35% C24↓32% (Complex binding to polyvalent ions)	
Corticosteroids		

Prednisone	Dolutegravir ↔ AUC ↑11% C_{max} ↑6% C_T ↑17%	No dose adjustment is necessary.
Antidiabetics		
Metformin	Metformin ↑ When co-administered with dolutegravir 50mg once daily:	A dose adjustment of metformin should be considered when starting and stopping coadministration of

	Metformin AUC↑79% C_{max}↑66% When co-administered with dolutegravir 50mg twice daily: Metformin AUC ↑145 % C_{max} ↑111%	dolutegravir with metformin, to maintain glycaemic control. In patients with moderate renal impairment a dose adjustment of metformin should be considered when coadministered with dolutegravir, because of the increased risk for lactic acidosis in patients with moderate renal impairment due to increased metformin concentration (section 4.4).
Antimycobacterials		
Rifampicin	Dolutegravir ↓ AUC ↓54% C_{max} ↓ 43% C_T ↓72% (induction of UGT1A1 and CYP3A enzymes)	The recommended dose of dolutegravir is 50 mg twice daily when co-administered with rifampicin in the absence of integrase class resistance. In the presence of integrase class resistance this combination should be avoided (see section 4.4).
Rifabutin	Dolutegravir ↔ AUC ↓5% C_{max} ↑16% C_T ↓ 30% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Oral contraceptives		
Ethinyl estradiol (EE) and Norelgestromin (NGMN)	Dolutegravir ↔ EE ↔ AUC ↑ 3% C_{max} ↓ 1 % NGMN ↔ AUC ↓2% C_{max}↓11%	Dolutegravir had no pharmacodynamic effect on Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH) and progesterone. No dose adjustment of oral contraceptives is necessary when co-administered with dolutegravir.
Analgesics		
Methadone	Dolutegravir ↔ Methadone ↔ AUC ↓2% C_{max} ↔ 0% C_T ↓1%	No dose adjustment is necessary of either agent.

Paediatric population
Interaction studies have only been performed in adults.

Tenofovir alafenamide is not an inhibitor of human uridine diphosphate glucuronosyltransferase (UGT) 1A1 *in vitro*. It is not known whether tenofovir alafenamide is an inhibitor of other UGT enzymes. Emtricitabine did not inhibit the glucuronidation reaction of a non-specific UGT substrate *in vitro*.

Table 2: Interactions between the individual components of Emtricitabine, Tenofovir alafenamide and other medicinal products

Medicinal product by therapeutic areas	Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with Emtricitabine and Tenofovir alafenamide
ANTI-INFECTIVES		
Antifungals		
Ketoconazole Itraconazole	Interaction not studied with either of the components of Emtricitabine and Tenofovir alafenamide. Co-administration of ketoconazole or itraconazole, which are potent P-gp inhibitors, is expected to increase plasma concentrations of tenofovir alafenamide.	The recommended dose of Emtricitabine and Tenofovir alafenamide is 200/25 mg once daily.
Fluconazole Isavuconazole	Interaction not studied with either of the components of Emtricitabine and Tenofovir alafenamide. Co-administration of fluconazole or isavuconazole may increase plasma concentrations of tenofovir alafenamide.	Dose Emtricitabine and Tenofovir alafenamide according to the concomitant antiretroviral (see section 4.2).
Antimycobacterials		
Rifabutin Rifampicin Rifapentine	Interaction not studied with either of the components of Emtricitabine and Tenofovir alafenamide. Co-administration of rifampicin, rifabutin, and rifapentine, all of which are P-gp inducers, may decrease tenofovir alafenamide plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	Co-administration of Emtricitabine and Tenofovir alafenamide and rifabutin rifampicin, or rifapentine is not recommended.
Anti-hepatitis C virus medicinal products		

Boceprevir	Interaction not studied with either of the components of Emtricitabine and Tenofovir alafenamide.	Co-administration with boceprevir has the potential to adversely affect the intracellular activation and clinical antiviral efficacy of tenofovir alafenamide, therefore co- administration of Emtricitabine, Tenofovir alafenamide and boceprevir is not recommended.
Telaprevir	Interaction not studied with either of the components of Emtricitabine and Tenofovir alafenamide.	Co-administration with Telaprevir has the potential to adversely affect the intracellular activation and clinical antiviral efficacy of tenofovir alafenamide, therefore co-

		administration of Emtricitabine, Tenofovir alafenamide and Telaprevir is not recommended
Ledipasvir (90 mg once daily)/ sofosbuvir (400 mg once daily), emtricitabine (200 mg once daily)/ tenofovir alafenamide (10 mg once daily) [2]	Ledipasvir: AUC: ↑79% C_{max}: ↑65% C_{min}: ↑ 93% Sofosbuvir: AUC: ↑47% C_{max}: ↑29% Sofosbuvir metabolite GS-331007: AUC: ↑48% C_{max}: ↔ C_{min}: ↑ 66% Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir alafenamide: AUC: ↔ C_{max}: ↔	No dose adjustment of ledipasvir or sofosbuvir is required. Dose Emtricitabine and Tenofovir alafenamide according to the concomitant antiretroviral (see section 4.2).
Ledipasvir (90 mg once daily)/ sofosbuvir (400 mg once daily), emtricitabine (200 mg once daily)/ tenofovir alafenamide (25 mg once daily))[3]	Ledipasvir: AUC: ↔ Cmax: ↔ C_{min}: ↔ Sofosbuvir: AUC: ↔ C_{max}: ↔ Sofosbuvir metabolite GS-331007: AUC: ↔ Cmax: ↔ Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ C_{min}: ↔ Tenofovir alafenamide: AUC: ↑32% C_{max}: ↔	No dose adjustment of ledipasvir or sofosbuvir is required. Dose Emtricitabine and Tenofovir alafenamide according to the concomitant antiretroviral (see section 4.2).
ANTIRETROVIRALS		

HIV protease inhibitors		
Atazanavir/cobicistat (300 mg/150 mg once daily)	Tenofovir alafenamide: AUC: ↑75% C_{max}: ↑ 80% Atazanavir: AUC: ↔ C_{max}: ↔	The recommended dose of Emtricitabine and Tenofovir alafenamide is 200/10 mg once daily.

	C_{min}: ↔	
Atazanavir/ritonavir (300/100 mg once daily), tenofovir alafenamide (10 mg)	Tenofovir alafenamide: AUC: ↑91% C_{max}: ↑ 77% Atazanavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔	The recommended dose of Emtricitabine and Tenofovir alafenamide is 200/10 mg once daily.
Darunavir/cobicistat (800/150 mg once daily), tenofovir alafenamide (25 mg once daily)[4]	Tenofovir alafenamide: AUC: ↔ C_{max}: ↔ Tenofovir: AUC: ↑224% C_{max}: ↑216% C_{min}: ↑221% Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔	The recommended dose of Emtricitabine and Tenofovir alafenamide is 200/10 mg once daily.
Darunavir/ritonavir (800/100 mg once daily), tenofovir alafenamide (10 mg once daily)	Tenofovir alafenamide: AUC: ↔ C_{max}: ↔ Tenofovir: AUC: ↑105% C_{max}: ↑142% Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔	The recommended dose of Emtricitabine and Tenofovir alafenamide is 200/10 mg once daily.
Lopinavir/ritonavir (800/200 mg once daily), tenofovir alafenamide (10 mg once daily)	Tenofovir alafenamide: AUC: ↑47% C_{max}: ↑119% Lopinavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔	The recommended dose of Emtricitabine and Tenofovir alafenamide is 200/10 mg once daily.

Tipranavir/ritonavir	Interaction not studied with either of the components of with Emtricitabine and Tenofovir alafenamide. Tipranavir/ritonavir results in P-gp induction. Tenofovir alafenamide exposure is expected to decrease when tipranavir/ritonavir is used in	Co-administration with Emtricitabine and Tenofovir alafenamide is not recommended.

	combination with with Emtricitabine and Tenofovir alafenamide.	
Other protease inhibitors	Effect is unknown.	There are no data available to make dosing recommendations for co-administration with other protease inhibitors.
Other HIV antiretrovirals		
Dolutegravir (50 mg once daily), tenofovir alafenamide (10 mg once daily)[2]	Tenofovir alafenamide: AUC: ↔ Cmax: ↔ Dolutegravir: AUC: ↔ Cmax: ↔ C_{min}: ↔	The recommended dose of with Emtricitabine and Tenofovir alafenamide is 200/25 mg once daily.
Rilpivirine (25 mg once daily), tenofovir alafenamide (25 mg once daily)	Tenofovir alafenamide: AUC: ↔ Cmax: ↔ Rilpivirine: AUC: ↔ Cmax: ↔ C_{min}: ↔	The recommended dose of with Emtricitabine and Tenofovir alafenamide is 200/25 mg once daily.
Efavirenz (600 mg once daily), tenofovir alafenamide (40 mg once daily)[4]	Tenofovir alafenamide: AUC: ↓14% C_{max}: ↓22%	The recommended dose of with Emtricitabine and Tenofovir alafenamide is 200/25 mg once daily.
Maraviroc Nevirapine Raltegravir	Interaction not studied with either of the components of Dolutegravir, Emtricitabine and Tenofovir alafenamide. Tenofovir alafenamide exposure is not expected to be affected by maraviroc, nevirapine or raltegravir, nor is it expected to affect the metabolic and excretion pathways relevant to maraviroc, nevirapine or raltegravir.	The recommended dose of with Emtricitabine and Tenofovir alafenamide is 200/25 mg once daily.
ANTICONVULSANTS		

Oxcarbazepine Phenobarbital Phenytoin	Interaction not studied with either of the components of with Emtricitabine and Tenofovir alafenamide. Co-administration of oxcarbazepine, phenobarbital, or phenytoin, all of which are P-gp inducers, may decrease tenofovir alafenamide plasma concentrations, which may	Co-administration of with Emtricitabine and Tenofovir alafenamide and oxcarbazepine, phenobarbital or phenytoin is not recommended.

	result in loss of therapeutic effect and development of resistance.	
Carbamazepine (titrated from 100 mg to 300 mg twice a day), emtricitabine/ tenofovir alafenamide (200 mg/25 mg once daily)[4,5]	Tenofovir alafenamide: AUC: ↓55% C_{max}: ↓ 57% Co-administration of carbamazepine, a P-gp inducer, decreases tenofovir alafenamide plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	Co-administration of with Emtricitabine, Tenofovir alafenamide and carbamazepine is not recommended.
ANTIDEPRESSANTS		
Sertraline (50 mg once daily), tenofovir alafenamide (10 mg once daily)[2]	Tenofovir alafenamide: AUC: ↔ Cmax: ↔ Sertraline: AUC: ↑9% C_{max}: ↑14%	No dose adjustment of sertraline is required. Dose with Emtricitabine and Tenofovir alafenamide according to the concomitant antiretroviral (see section 4.2).
HERBAL PRODUCTS		
St. John's wort (*Hypericum perforatum*)	Interaction not studied with either of the components of with Emtricitabine and Tenofovir alafenamide. Co-administration of St. John's wort, a P-gp inducer, may decrease tenofovir alafenamide plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	Co-administration of with Emtricitabine and Tenofovir alafenamide with St. John's wort is not recommended.
IMMUNOSUPPRESSANTS		
Ciclosporin	Interaction not studied with either of the components of with Emtricitabine and Tenofovir alafenamide. Co-administration of ciclosporin, a potent P-gp inhibitor, is expected to increase plasma concentrations of tenofovir alafenamide.	The recommended dose of with Emtricitabine and Tenofovir alafenamide is 200/10 mg once daily.
SEDATIVES/HYPNOTICS		

Orally administered midazolam (2.5 mg once daily), tenofovir alafenamide (25 mg once daily)	Midazolam: AUC: ↔ Cmax: ↔	No dose adjustment of midazolam is required. Dose with Emtricitabine and Tenofovir alafenamide according to the concomitant antiretroviral (see section 4.2).
Intravenously administered midazolam (once daily),	Midazolam: AUC: ↔ C_{max}: ↔	

tenofovir alafenamide (25 mg once daily)		

1. When data are available from drug-drug interaction studies.
2. Study conducted with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fixed-dose combination tablet.
3. Study conducted with emtricitabine/rilpivirine/tenofovir alafenamide fixed-dose combination tablet.
4. Study conducted with with Emtricitabine and Tenofovir alafenamide.
5. Emtricitabine/tenofovir alafenamide was taken with food in this study.

4.6.Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies of Dolutegravir, Emtricitabine and Tenofovir alafenamide or its components in pregnant women. There are no or limited data (less than 300 pregnancy outcomes) from the use of tenofovir alafenamide in pregnant women. However, a large amount of data on pregnant women (more than 1,000 exposed outcomes) indicate no malformative nor foetal/neonatal toxicity associated with emtricitabine.

In reproductive toxicity studies in animals, dolutegravir was shown to cross the placenta. Animal studies do not indicate direct or indirect harmful effects of emtricitabine or dolutegravir with respect to fertility parameters, pregnancy, foetal development, parturition or postnatal development. Studies of tenofovir alafenamide in animals have shown no evidence of harmful effects on fertility parameters, pregnancy, or foetal development. (see section 5.3).

Dolutegravir, Emtricitabine and Tenofovir alafenamide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Breast-feeding

It is not known whether tenofovir alafenamide and dolutegravir is excreted in human milk. Emtricitabine is excreted in human milk. In animal studies it has been shown that tenofovir alafenamide and dolutegravir is excreted in milk. In lactating rats that received a single oral dose of 50 mg/kg at 10 days postpartum, dolutegravir was detected in milk at concentration typically higher than blood.

There is insufficient information on the effects of dolutegravir, emtricitabine and tenofovir alafenamide in newborns/infants. Therefore, Dolutegravir, Emtricitabine and Tenofovir alafenamide should not be used during breast-feeding.

In order to avoid transmission of HIV to the infant it is recommended that HIV infected women do not breast-feed their infants under any circumstances.

Fertility

There are no data on fertility from the use of Dolutegravir, Emtricitabine and Tenofovir alafenamide in humans. In animal studies there were no effects of emtricitabine and tenofovir alafenamide on mating or fertility parameters (see section 5.3).

4.7.Effects on ability to drive and use machines

Patients should be informed that dizziness has been reported during treatment with Dolutegravir, Emtricitabine and Tenofovir alafenamide. The clinical status of the patient and the adverse reaction profile should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8.Undesirable effects

Summary of the safety profile

Dolutegravir

The safety profile is based on pooled data from Phase IIb and Phase III clinical studies in 1222 previously untreated patients, 357 previously treated patients unexposed to integrase inhibitors and 264 patients with prior treatment failure that included an integrase inhibitor (including integrase class resistance). The most severe adverse reaction, seen in an individual patient, was a hypersensitivity reaction that included rash and severe liver effects (see section 4.4). The most commonly seen treatment emergent adverse reactions were nausea (13%), diarrhoea (18%) and headache (13%).

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

Emtricitabine and Tenofovir Alafenamide

Assessment of adverse reactions is based on safety data from across all Phase 2 and 3 studies in which 2,832 HIV-1 infected patients received medicinal products containing emtricitabine and tenofovir alafenamide. In clinical studies of 866 treatment-naïve adult patients receiving emtricitabine and tenofovir alafenamide with elvitegravir and cobicistat as the fixed-dose combination tablet elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide (as fumarate) 10 mg (E/C/F/TAF), the most frequently reported adverse reactions were diarrhoea (7%), nausea (10%), and headache (6%).

Tabulated summary of adverse reactions for combination of Dolutegravir, Emtricitabine and Tenofovir Alafenamide.

The adverse reactions in Table 3 are listed by system organ class and frequency. Frequencies are defined as follows: *very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).*

Table 3: Tabulated list of adverse reactions[1]

Frequency	Adverse reaction
Blood and lymphatic system disorders	
Uncommon:	anaemia[2]
Immune system disorder	
Uncommon:	Hypersensitivity (see section 4.4), Immune Reconstitution Syndrome (see section 4.4)
Psychiatric disorders	
Common:	abnormal dreams, Insomnia, Depression
Uncommon:	Suicidal ideation or suicide attempt (particulary in patients with a pre-existing history of depression or psychiatric illness)

Nervous system disorders	
Common:	headache, dizziness
Gastrointestinal disorders	

Very common:	nausea
Common:	diarrhoea, vomiting, abdominal pain and discomfort, flatulence
Uncommon:	dyspepsia
Hepatobiliary disorders	
Uncommon:	Hepatitis
Skin and subcutaneous tissue disorders	
Common:	rash
Uncommon:	angioedema[2,3], pruritus
Musculoskeletal and connective tissue disorders	
Uncommon:	arthralgia
General disorders and administration site conditions	
Common:	fatigue
Investigations	
Common:	Alanine aminotransferase (ALT) and/or Aspartate aminotransferase (AST) elevations, Creatine phosphokinase (CPK) elevations

1. With the exception of angioedema and anaemia (see footnotes 2 and 3), all adverse reactions were identified from clinical studies of F/TAF containing products. The frequencies were derived from Phase 3 E/C/F/TAF clinical studies in 866 treatment-naïve adult patients through 48 weeks of treatment (GS-US- 292-0104 and GS-US-292-0111).
2. This adverse reaction was not observed in the clinical studies of F/TAF containing products but identified from clinical studies or post-marketing experience for emtricitabine when used with other antiretrovirals.
3. This adverse reaction was identified through post-marketing surveillance for emtricitabine but was not observed in randomized controlled clinical studies in adults or paediatric HIV clinical studies of emtricitabine. The frequency category of uncommon was estimated from a statistical calculation based on the total number of patients exposed to emtricitabine in these clinical studies (n = 1,563).

Description of selected adverse reactions

Changes in laboratory biochemistries

Increases in serum creatinine occurred within the first week of treatment with dolutegravir and remained stable through 48 weeks. A mean change from baseline of 9.96 µmol/L was observed after 48 weeks of treatment. Creatinine increases were comparable by various background regimens. These changes are not considered to be clinically relevant since they do not reflect a change in glomerular filtration rate.

Co-infection with Hepatitis B or C

In Phase III studies patients with hepatitis B and/or C co-infection were permitted to enrol provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal (ULN). Overall, the safety profile in patients co-infected with hepatitis B and/or C was similar to that observed in patients without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were higher in

the subgroup with hepatitis B and/or C co-infection for all treatment groups. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C co-infection at the start of dolutegravir therapy, particularly in those whose anti-hepatitis B therapy was withdrawn (see section 4.4).

Immune Reactivation Syndrome

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

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).

Changes in lipid laboratory tests

Increases from baseline were observed in both the Tenofovir alafenamide and tenofovir disoproxil fumarate containing treatment groups for the fasting lipid parameters total cholesterol, direct low-density lipoprotein (LDL)- and high-density lipoprotein (HDL)-cholesterol, and triglycerides at Week 48. The median increase from baseline for those parameters was greater in the E/C/F/TAF group compared with the elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil (as fumarate) 245 mg (E/C/F/TDF) group at Week 48 ($p < 0.001$ for the difference between treatment groups for fasting total cholesterol, direct LDL- and HDL-cholesterol, and triglycerides). The median (Q1, Q3) change from baseline in total cholesterol to HDL-cholesterol ratio at Week 48 was 0.1 (-0.3, 0.5) in the E/C/F/TAF group and 0.0 (-0.5, 0.4) in the E/C/F/TDF group ($p < 0.001$ for the difference between treatment groups).

Metabolic parameters

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

Paediatric population

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

The safety of emtricitabine and tenofovir alafenamide was evaluated through 48 weeks in an open-label clinical study (GS-US-292-0106) in which HIV-1 infected, treatment-naïve paediatric patients aged 12 to < 18 years received emtricitabine and tenofovir alafenamide as a fixed-dose combination tablet. The safety profile of emtricitabine, tenofovir alafenamide in 50 adolescent patients was similar to that in adults (see section 5.1).

Other special populations

Patients with renal impairment

The safety of emtricitabine and tenofovir alafenamide was evaluated through 48 weeks in an open-label clinical study (GS-US-292-0112) in which 248 HIV-1 infected patients who were either treatment-naïve (n
= 6) or virologically suppressed (n = 242) with mild to moderate renal impairment (estimated glomerular filtration rate by Cockcroft-Gault method [$eGFR_{CG}$]: 30-69 mL/min) received emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet. The safety profile in patients with mild to moderate renal impairment was similar to that in patients with normal renal function (see section 5.1).

Patients co-infected with HIV and HBV

The safety of emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet was evaluated in approximately 70 HIV/HBV co-infected patients currently receiving treatment for HIV in an open-label clinical study (GS-US-292-1249). Based on this limited experience, the safety profile of Dolutegravir, Emtricitabine and Tenofovir alafenamide in patients with HIV/HBV co-infection appears to be similar to that in patients with HIV-1 monoinfection (see section 4.4).

Reporting of suspected adverse reactions

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

4.9.Overdose

If overdose occurs, the patient must be monitored for evidence of toxicity (see section 4.8). Treatment of overdose with Dolutegravir, Emtricitabine and Tenofovir alafenamide consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient.

There is currently limited experience with overdosage in dolutegravir.
Limited experience of single doses (up to 250 mg in healthy subjects) revealed no specific symptoms or signs, apart from those listed as adverse reactions.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available. There is no specific treatment for an overdose of dolutegravir. If overdose occurs, the patient should be treated supportively with appropriate monitoring, as necessary. As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

Emtricitabine can be removed by haemodialysis, which removes approximately 30% of the emtricitabine dose over a 3 hour dialysis period starting within 1.5 hours of emtricitabine dosing. Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54%. It is not known whether emtricitabine or tenofovir can be removed by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1.Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral for systemic use; antivirals for treatment of HIV infections, combinations. ATC code: Not yet assigned.

Namibia Pharmacological Classification: 20.2.8 Antiviral agents

Mechanism of action

Combination of Dolutegravir, Emtricitabine and Tenofovir alafenamide has not been studied so far.

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.

Emtricitabine is a nucleoside reverse transcriptase inhibitor (NRTI) and nucleoside analogue of 2'-deoxycytidine. Emtricitabine is phosphorylated by cellular enzymes to form emtricitabine triphosphate. Emtricitabine triphosphate inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase (RT), which results in DNA chain-termination. Emtricitabine has activity against HIV-1, HIV- 2, and HBV.

Tenofovir alafenamide is a nucleotide reverse transcriptase inhibitor (NtRTI) and phosphonoamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). Tenofovir alafenamide is permeable into cells and due to increased plasma stability and intracellular activation through hydrolysis by cathepsin A, tenofovir alafenamide is more efficient than tenofovir disoproxil fumarate in concentrating tenofovir in peripheral blood mononuclear cells (PBMCs) or HIV target cells including lymphocytes and macrophages. Intracellular tenofovir is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV replication through incorporation into viral DNA by the HIV RT, which results in DNA chain-termination.
Tenofovir has activity against HIV-1, HIV-2, and HBV.

Pharmacodynamic

effects Antiviral activity

in vitro

The IC_{50} for dolutegravir in various labstrains using PBMC was 0.5 nM, and when using MT-4 cells it ranged from 0.7-2 nM. Similar IC_{50}s were seen for clinical isolates without any major difference between subtypes; in a panel of 24 HIV-1 isolates of clades A, B, C, D, E, F and G and group O the mean IC_{50} value was 0.2 nM (range 0.02-2.14). The mean IC_{50} for 3 HIV-2 isolates was 0.18 nM (range 0.09-0.61).
In 100% *human serum*, the mean protein fold shift was 75 fold, resulting in protein adjusted IC_{90} of 0.064 ug/mL.

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

Emtricitabine and tenofovir alafenamide demonstrated synergistic antiviral activity in cell culture. No antagonism was observed with emtricitabine or tenofovir alafenamide when combined with other antiretroviral agents.

The antiviral activity of emtricitabine against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, the MAGI CCR5 cell line, and PBMCs. The 50% effective concentration (EC_{50}) values for emtricitabine were in the range of 0.0013 to 0.64 μM. Emtricitabine displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007 to 0.075 μM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.007 to 1.5 μM).

The antiviral activity of tenofovir alafenamide against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells and CD4+ T- lymphocytes. The EC_{50} values for tenofovir alafenamide were in the range of 2.0 to 14.7 nM. Tenofovir alafenamide displayed antiviral activity in cell culture against all HIV-1 groups (M, N, and O), including subtypes A, B, C, D, E, F, and G (EC_{50} values ranged from 0.10 to

12.0 nM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.91 to 2.63 nM).

Resistance

In vitro

Dolutegravir

Serial passage is used to study resistance evolution *in vitro*. When using the lab-strain HIV-1 IIIB during passage over 112 days, mutations selected appeared slowly, with substitutions at positions S153Y and F, resulting in a maximal fold change in susceptibility of 4 (range 2-4). These mutations were not selected in patients treated with dolutegravir in the clinical studies. Using strain NL432, mutations E92Q (FC 3) and G193E (also FC 3) were selected. The E92Q mutation has been selected in patients with pre-existing raltegravir resistance who were then treated with dolutegravir (listed as a secondary mutation for dolutegravir).

In further selection experiments using clinical isolates of subtype B, mutation R263K was seen in all five isolates (after 20 weeks and onwards). In subtype C (n=2) and A/G (n=2) isolates the integrase substitution R263K was selected in one isolate, and G118R in two isolates. R263K was reported from two ART experienced, INI naive individual patients with subtypes B and C in the clinical program, but without effects on dolutegravir susceptibility *in vitro*. G118R lowers the susceptibility to dolutegravir in site directed mutants (FC 10), but was not detected in patients receiving dolutegravir in the Phase III program.

Primary mutations for raltegravir/elvitegravir (Q148H/R/K, N155H, Y143R/H/C, E92Q and T66I) do not affect the *in vitro* susceptibility of dolutegravir as single mutations. When mutations listed as secondary integrase inhibitor associated mutations (for raltegravir/elvitegravir) are added to these primary mutations in experiments with site directed mutants, dolutegravir susceptibility is still unchanged (FC <2 vs wild type virus), except in the case of Q148-mutations, where a FC of 5-10 or higher is seen with combinations of certain secondary mutations. The effect by the Q148-mutations (H/R/K) was also verified in passage experiments with site directed mutants. In serial passage with strain NL432, starting with site directed mutants harbouring N155H or E92Q, no further selection of resistance was seen (FC unchanged around 1).
In contrast, starting with mutants harbouring mutation Q148H (FC 1), a variety of secondary mutations were seen with a consequent increase of FC to values >10.

A clinically relevant phenotypic cut-off value (FC vs wild type virus) has not been determined; genotypic resistance was a better predictor for outcome.
Seven hundred and five raltegravir resistant isolates from raltegravir experienced patients were analyzed for susceptibility to dolutegravir. Dolutegravir has a less than or equal to 10 FC against 94% of the 705 clinical isolates.

Emtricitabine

Reduced susceptibility to emtricitabine is associated with M184V/I mutations in HIV-1 RT.

Tenofovir Alafenamide

HIV-1 isolates with reduced susceptibility to tenofovir alafenamide express a K65R mutation in HIV-1 RT; in addition, a K70E mutation in HIV-1 RT has been transiently observed.

In vivo

Dolutegravir

In previously untreated patients receiving dolutegravir + 2 NRTIs in Phase-IIb and Phase-III, no development of resistance to the integrase class, or to the NRTI class was seen (n=1118 follow-up of 48- 96 weeks).

In patients with prior failed therapies, but naïve to the integrase class (SAILING study), integrase inhibitor substitutions were observed in 4/354 patients (follow-up 48 weeks) treated with dolutegravir, which was given in combination with an investigator selected background regimen (BR). Of these four, two subjects had a unique R263K integrase substitution, with a maximum FC of 1.93, one subject had a polymorphic V151V/I integrase substitution, with maximum FC of 0.92, and one subject had pre-existing integrase mutations and is assumed to have been integrase experienced or infected with integrase resistant virus by transmission. The R263K mutation was also selected *in vitro* (see above).

In the presence of integrase class-resistance (VIKING-3 study) the following mutations were selected in 32 patients with protocol defined virological failure (PDVF) through Week 24 and with paired genotypes (all treated with dolutegravir 50 mg twice daily + optimized background agents): L74L/M (n=1), E92Q (n=2), T97A (n=9), E138K/A/T (n=8), G140S (n=2), Y143H (n=1), S147G (n=1), Q148H/K/R (n=4), and N155H (n=1)
and E157E/Q (n=1). Treatment emergent integrase resistance typically appeared in patients with a history of the Q148-mutation (baseline or historic). Five further subjects experienced PDVF between weeks 24 and 48, and 2 of these 5 had treatment emergent mutations. Treatment-emergent mutations or mixtures of mutations observed were L74I (n=1), N155H (n=2).

The VIKING-4 study examined dolutegravir (plus optimized background therapy) in subjects with primary genotypic resistance to INIs at Screening in 30 subjects. Treatment-emergent mutations observed were consistent with those observed in the VIKING-3 study.

Effects on electrocardiogram

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

Clinical efficacy and safety

Previously untreated patients

The efficacy of dolutegravir in HIV-infected, therapy naïve subjects is based on the analyses of 96-week data from two randomized, international, double-blind, active-controlled trials, SPRING-2 (ING113086) and SINGLE (ING114467). This is supported by 96 week data from an open-label, randomized and active- controlled study FLAMINGO (ING114915) and additional data from the open-label phase of SINGLE to 144 weeks.

In SPRING-2, 822 adults were randomized and received at least one dose of either dolutegravir 50 mg once daily or raltegravir (RAL) 400 mg twice daily, both administered with either ABC/3TC or TDF/FTC. At baseline, median patient age was 36 years, 14% were female, 15% non-white, 11% had hepatitis B and/or C co-infection and 2% were CDC Class C, these characteristics were similar between treatment groups.

In SINGLE, 833 subjects were randomized and received at least one dose of either dolutegravir 50 mg once daily with fixed-dose abacavir-lamivudine (DTG + ABC/3TC) or fixed-dose efavirenz-tenofoviremtricitabine (EFV/TDF/FTC). At baseline, median patient age was 35 years, 16% were female, 32% nonwhite, 7% had hepatitis C co-infection and 4% were CDC Class C, these characteristics were similar between treatment groups.

The primary endpoint and other week 48 outcomes (including outcomes by key baseline covariates) for SPRING-2 and SINGLE are shown in Table 4.

Table 4: Response in SPRING-2 and SINGLE at 48 Weeks (Snapshot algorithm, <50 copies/mL)

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

Age (years)				
<50 ≥50	324/370 (88%) 37/41 (90%)	312/365 (85%) 39/46 (85%)	319/361 (88%) 45/53 (85%)	302/375 (81%) 36/44 (82%)
Median CD4 change from baseline	230	230	246‡	187‡

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

At week 48, dolutegravir was non-inferior to raltegravir in the SPRING-2 study, and in the SINGLE study dolutegravir + ABC/3TC was superior to efavirenz/TDF/FTC (p=0.003), table 7 above. In SINGLE, the median time to viral suppression was shorter in the dolutegravir treated patients (28 vs 84 days, (p<0.0001, analysis pre-specified and adjusted for multiplicity).

At week 96, results were consistent with those seen at week 48. In SPRING-2, dolutegravir was still non- inferior to raltegravir (viral suppression in 81% vs 76% of patients), and with a median change in CD4 count of 276 vs 264 cells/mm^3, respectively. In SINGLE, dolutegravir + ABC/3TC was still superior to EFV/TDF/FTC (viral suppression in 80% vs 72%, treatment difference 8.0% (2.3, 13.8), p=0.006, and with an adjusted mean change in CD4 count of 325 vs 281 cells/ mm^3, respectively. At 144 weeks in the open-label phase of SINGLE, virologic suppression was maintained, the dolutegravir + ABC/3TC arm (71%) was superior to the EFV/TDF/FTC arm (63%), treatment difference was 8.3% (2.0, 14.6).

In FLAMINGO (ING114915), an open-label, randomised and active-controlled study, 484 HIV-1 infected antiretroviral naïve adults received one dose of either dolutegravir 50 mg once daily (n=242) or darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily (n=242), both administered with either ABC/3TC or TDF/FTC. At baseline, median patient age was 34 years, 15% were female, 28% non-white, 10% had hepatitis B and/or C co-infection, and 3% were CDC Class C; these characteristics were similar between
treatment groups. Virologic suppression (HIV-1 RNA <50 copies/mL) in the dolutegravir group (90%) was superior to the DRV/r group (83%) at 48 weeks. The adjusted difference in proportion and 95% CI were 7.1% (0.9, 13.2), p=0.025. At 96 weeks, virologic suppression in the dolutegravir group (80%) was superior
to the DRV/r group (68%), (adjusted treatment difference [DTG-(DRV+RTV)]: 12.4%; 95% CI: [4.7, 20.2].

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

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

Week 48 outcomes (including outcomes by key baseline covariates) for SAILING are shown in Table 5.

Table 5: Response in SAILING at 48 Weeks (Snapshot algorithm, <50 copies/mL)

	Dolutegravir 50 mg Once Daily + BR: N=354§	RAL 400 mg Twice Daily + BR: N=361§
HIV-1 RNA <50 copies/mL	71%	64%
Adjusted treatment difference‡	7.4% (95% CI: 0.7%, 14.2%)	
Virologic non-response	20%	28%
HIV-1 RNA <50 copies/mL by baseline covariates		

Baseline Viral Load (copies/mL)		
≤50,000 copies/mL	186 / 249 (75%)	180 / 254 (71%)

>50,000 copies/mL	65 / 105 (62%)	50 / 107 (47%)
Baseline CD4+ (cells/ mm^3)		
<50 50 to <200 200 to <350 ≥350	33 / 62 (53%) 77 / 111 (69%) 64 / 82 (78%) 77 / 99 (78%)	30 / 59 (51%) 76 / 125 (61%) 53 / 79 (67%) 71 / 98 (72%)
Background Regimen		
Genotypic Susceptibility Score* <2 Genotypic Susceptibility Score* =2 Use of DRV in background regimen No DRV use DRV use with primary PI mutations DRV use without primary PI mutations	155 / 216 (72%) 96 / 138 (70%) 143 / 214 (67%) 58 / 68 (85%) 50 / 72 (69%)	129 / 192 (67%) 101 / 169 (60%) 126 / 209 (60%) 50 / 75 (67%) 54 / 77 (70%)
Gender		
Male	172 / 247 (70%)	156 / 238 (66%)
Female	79 / 107 (74%)	74 / 123 (60%)
Race		
White African-America/African Heritage/ Other	133 / 178 (75%) 118 / 175 (67%)	125 / 175 (71%) 105 / 185 (57%)
Age (years)		
<50 ≥50	196 / 269 (73%) 55 / 85 (65%)	172 / 277 (62%) 58 / 84 (69%)
HIV sub type		
Clade B	173 / 241 (72%)	159 / 246 (65%)
Clade C	34 / 55 (62%)	29 / 48 (60%)
Other†	43 / 57 (75%)	42 / 67 (63%)
Mean increase in CD4+ T cell (cells/mm^3)	162	153

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

In the SAILING study, virologic suppression (HIV-1 RNA <50 copies/mL) in the Dolutegravir arm (71%) was statistically superior to the raltegravir arm (64%), at Week 48 (p=0.03).

Statistically fewer subjects failed therapy with treatment-emergent integrase resistance on Dolutegravir (4/354, 1%) than on raltegravir (17/361, 5%) (p=0.003) (refer to section 'Resistance *in vivo*' above for details).

Patients with prior treatment failure that included an integrase inhibitor (and integrase class resistance) In the multicentre, open-label, single arm VIKING-3 study (ING112574), HIV-1 infected,

ART experienced adults with virological failure and current or historical evidence of raltegravir and/or elvitegravir resistance received Dolutegravir 50 mg twice daily with the current failing background regimen for 7 days but with optimised background ART from Day 8. The study enrolled 183 patients, 133 with INI-resistance at Screening and 50 with only historical evidence of resistance (and not at Screening). Raltegravir/ elvitegravir was part of the current failing regimen in 98/183 patients (part of prior failing therapies in the others). At baseline, median patient age was 48 years, 23% were female, 29% non-white, and 20% had

hepatitis B and/or C co-infection. Median baseline CD4+ was 140 cells/mm^3, median duration of prior ART was 14 years, and 56% were CDC Class C. Subjects showed multiple class ART resistance at baseline: 79% had ≥2 NRTI, 75% ≥1 NNRTI, and 71% ≥2 PI major mutations; 62% had non-R5 virus.

Mean change from baseline in HIV RNA at day 8 (primary endpoint) was -1.4log$_{10}$ copies/mL (95% CI -1.3 – -1.5log$_{10}$, p<0.001). Response was associated with baseline INI mutation pathway, as shown in Table 6.

Table 6: Virologic response (day 8) after 7 days of functional monotherapy, in patients with RAL/EVG as part of current failing regimen, VIKING 3

Baseline parameters	DTG 50 mg BID N=88*		
	n	Mean (SD) Plasma HIV-1 RNA log$_{10}$ c/mL	Median
Derived IN mutation group at			
Primary mutation other than Q148H/K/R[a]	48	-1.59 (0.47)	-1.64
Q148+1 secondary mutation[b]	26	-1.14 (0.61)	-1.08
Q148+≥2 secondary mutations[b]	14	-0.75 (0.84)	-0.45

*Of 98 on RAL/EVG as part of current failing regimen, 88 had detectable primary INI mutations at Baseline and a Day 8 Plasma HIV-1 RNA outcome for evaluation

a. Included primary IN resistance mutations N155H, Y143C/H/R, T66A, E92Q
b. Secondary mutations from G140A/C/S, E138A/K/T, L74I.

In patients without a primary mutation detected at baseline (N=60) (i.e. RAL/EVG not part of current failing therapy) there was a 1.63 log$_{10}$ reduction in viral load at day 8.

After the functional monotherapy phase, subjects had the opportunity to re-optimize their background regimen when possible. The overall response rate through 24 weeks of therapy, 69% (126/183), was generally sustained through 48 weeks with 116/183 (63%) of patients with HIV-1 RNA <50c/mL (ITT-E, Snapshot algorithm). When excluding patients who stopped therapy for non-efficacy reasons, and those with major protocol deviations (incorrect dolutegravir dosing, intake of prohibited co-medication), namely, "the Virological Outcome (VO)-population)", the corresponding response rates were 75% (120/161, week 24) and 69% (111/160, week 48).

The response was lower when the Q148-mutation was present at baseline, and in particular in the presence of ≥2 secondary mutations, Table 7. The overall susceptibility score (OSS) of the optimised background regimen (OBR) was not associated with Week 24 response, nor with the week 48 response.

Table 7: Response by baseline Resistance, VIKING-3. VO Population (HIV-1 RNA<50 c/mL, Snapshot algorithm)

	Week 24 (N=161)					Week 48 (N=160)
Derived IN Mutation Group	OSS=0	OSS=1	OSS=2	OSS>2	Total	Total
No primary IN mutation[1]	2/2 (100%)	15/20 (75%)	19/21 (90%)	9/12 (75%)	45/55 (82%)	38/55 (69%)

Primary mutation other than Q148H/ K/R[2]	2/2 (100%)	20/20 (100%)	21/27 (78%)	8/10 (80%)	51/59 (86%)	50/58 (86%)

Q148 + 1 secondary mutation[3]	2/2 (100%)	8/12 (67%)	10/17 (59%)	-	20/31 (65%)	19/31 (61%)
Q148 +≥2 secondary mutations[3]	1/2 (50%)	2/11 (18%)	1/3 (33%)	-	4/16 (25%)	4/16 (25%)

1. Historical or phenotypic evidence of INI resistance only. 2. N155H, Y143C/H/R, T66A, E92Q
3. G140A/C/S, E138A/K/T, L74I

OSS: combined genotypic and phenotypic resistance (Monogram Biosciences Net Assessment)

The median change in CD4+ T cell count from baseline for VIKING-3 based on observed data was 61 cells/mm^3 at Week 24 and 110 cells/mm^3 at Week 48.

In the double blind, placebo controlled VIKING-4 study (ING116529), 30 HIV-1 infected, ART-experienced adults with primary genotypic resistance to INIs at Screening, were randomised to receive either dolutegravir 50 mg twice daily or placebo with the current failing regimen for 7 days followed by an open label phase with all subjects receiving dolutegravir. At baseline, median patient age was 49 years, 20% were female, 58% non-white, and 23% had hepatitis B and/or C co-infection. Median baseline CD4+ was 160 cells/mm^3, median duration of prior ART was 13 years, and 63% were CDC Class C. Subjects showed multiple class ART resistance at baseline: 80% had ≥2 NRTI, 73% ≥1 NNRTI, and 67% ≥2 PI major mutations; 83% had non-R5 virus. Sixteen of 30 subjects (53%) harboured Q148 virus at baseline. The primary endpoint at Day 8 showed that dolutegravir 50 mg twice daily was superior to placebo, with an adjusted mean treatment difference for the change from Baseline in Plasma HIV-1 RNA of -1.2 $\log_{10}$ copies/mL (95% CI -1.5 - - 0.8$\log_{10}$ copies/mL, p<0.001). The day 8 responses in this placebo controlled study were fully in line with those seen in VIKING-3 (not placebo controlled), including by baseline integrase resistance categories. At week 48, 12/30 (40%) subjects had HIV-1 RNA <50 copies/mL (ITT-E, Snapshot algorithm).

In a combined analysis of VIKING-3 and VIKING-4 (n=186, VO population), the proportion of subjects with HIV RNA <50 copies/mL at Week 48 was 126/186 (68%). The proportion of subjects with HIV RNA <50 copies/mL was 96/126 (76%) for No Q148 mutations, 22/41 (54%) for Q148+1 and 5/19 (26%) for Q148+≥2 secondary mutations.

Paediatric population

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

At 24 weeks, 16 of 23 (70%) adolescents (12 to less than 18 years of age) treated with Dolutegravir once daily (35 mg n=4, 50 mg n=19) plus OBR achieved viral load <50 copies/mL.

Four subjects had virologic failure none of which had INI resistance at the time of virologic failure.

The European Medicines Agency has deferred the obligation to submit the results of studies with combination of Dolutegravir in one or more subsets of the paediatric population (aged 4 weeks to below 12 years) in the treatment of HIV-1 infection (see section 4.2 for information on paediatric use).

Emtricitabine and Tenofovir alafenamide

In treatment-naïve patients

In a pooled analysis of antiretroviral-naïve patients receiving emtricitabine and tenofovir alafenamide (10 mg) given with elvitegravir and cobicistat as a fixed-dose combination tablet in GS-US-292-0104, GS-US- 292-0111, and GS-US-292-0102, genotyping was performed on plasma HIV-1 isolates from all patients with HIV-1 RNA > 400 copies/mL at confirmed virological failure, at

Week 48, or at the time of early study

drug discontinuation. Through Week 48, the development of one or more primary emtricitabine, tenofovir alafenamide, or elvitegravir resistance-associated mutations was observed in HIV-1 isolates from 7 of 14 patients with evaluable genotypic data from paired baseline and E/C/F/TAF treatment-failure isolates (7 of 978 patients [0.7%]) compared with 7 of 15 treatment-failure isolates from patients in the E/C/F/TDF
group (7 of 925 patients [0.8%]). In the E/C/F/TAF group, the mutations that emerged were M184V/I (n = 7) and K65R (n = 1) in RT and T66T/A/I/V (n = 2), E92Q (n = 2), Q148Q/R (n = 1), and N155H (n = 1) in
integrase. In the E/C/F/TDF group, the mutations that emerged were M184V/I (n = 7) and K65R (n = 2) in RT and E92E/Q (n = 3) and Q148R (n = 2) in integrase. All HIV-1 isolates from patients in both treatment groups who developed resistance mutations to elvitegravir in integrase also developed resistance mutations to emtricitabine in RT.

Cross-resistance in HIV-1 infected, treatment-naïve or virologically suppressed patients
Emtricitabine-resistant viruses with the M184V/I substitution were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir, and zidovudine.

The K65R and K70E mutations result in reduced susceptibility to abacavir, didanosine, lamivudine, emtricitabine, and tenofovir, but retain sensitivity to zidovudine.

Multinucleoside-resistant HIV-1 with a T69S double insertion mutation or with a Q151M mutation complex including K65R showed reduced susceptibility to tenofovir alafenamide.

Clinical data
Clinical efficacy of with Emtricitabine and Tenofovir alafenamide was established from studies conducted with emtricitabine and tenofovir alafenamide when given with elvitegravir and cobicistat as the fixed- dose combination tablet E/C/F/TAF.

HIV-1 infected, treatment-naïve patients
In studies GS-US-292-0104 and GS-US-292-0111, patients were randomized in a 1:1 ratio to receive either emtricitabine 200 mg and tenofovir alafenamide 10 mg (n = 866) once daily or emtricitabine 200 mg + tenofovir disoproxil (as fumarate) 245 mg (n = 867) once daily, both given with elvitegravir 150 mg + cobicistat 150 mg as a fixed-dose combination tablet. The mean age was 36 years (range: 18-76), 85% were male, 57% were White, 25% were Black, and 10% were Asian. Nineteen percent of patients were identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.5 $\log_{10}$ copies/mL (range: 1.3- 7.0) and 23% had baseline viral loads > 100,000 copies/mL. The mean baseline CD4+ cell count was 427 cells/mm^3 (range: 0-1,360) and 13% had a CD4+ cell count < 200 cells/mm^3.

E/C/F/TAF met the non-inferiority criteria in achieving HIV-1 RNA < 50 copies/mL when compared to E/C/F/TDF. Pooled treatment outcomes at 48 weeks are shown in Table 8.

Table 8: Pooled virological outcomes of studies GS-US-292-0104 and GS-US-292-0111 at Week 48[a,b]

	E/C/F/ TAF (n = 866)	**E/C/F/ TDF[e] (n = 867)**
HIV-1 RNA < 50 copies/mL	92%	90%
Treatment difference	2.0% (95% CI: -0.7% to 4.7%)	
HIV-1 RNA ≥ 50 copies/mL[c]	4%	4%
No virologic data at Week 48 window	4%	6%
Discontinued study drug due to AE or death[d]	1%	2%

Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[e]	2%	4%
Missing data during window but on study drug	1%	< 1%
Proportion (%) of patients with HIV-1 RNA < 50 copies/mL by subgroup		
Age < 50 years ≥ 50 years	 716/777 (92%) 84/89 (94%)	 680/753 (90%) 104/114 (91%)
Sex Male Female	 674/733 (92%) 126/133 (95%)	 673/740 (91%) 111/127 (87%)
Race Black Non-black	 197/223 (88%) 603/643 (94%)	 177/213 (83%) 607/654 (93%)
Baseline viral load ≤ 100,000 copies/mL > 100,000 copies/mL	 629/670 (94%) 171/196 (87%)	 610/672 (91%) 174/195 (89%)
Baseline CD4+ cell count < 200 cells/mm^3 ≥ 200 cells/mm^3	 96/112 (86%) 703/753 (93%)	 104/117 (89%) 680/750 (91%)
HIV-1 RNA < 20 copies/mL	84.4%	84.0 %
Treatment difference	0.4% (95% CI: -3.0% to 3.8%)	

E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide E/C/F/TDF = elvitegravir/cobicistat/emtricitabine/ tenofovir disoproxil fumarate

a. Week 48 window was between Day 294 and 377 (inclusive).
b. In both studies, patients were stratified by baseline HIV-1 RNA (≤ 100,000 copies/mL, > 100,000 copies/mL to ≤ 400,000 copies/mL, or > 400,000 copies/mL), by CD4+ cell count (< 50 cells/μL, 50-199 cells/μL, or ≥ 200 cells/μL), and by region (US or ex-US).
c. Included patients who had ≥ 50 copies/mL in the Week 48 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.
d. Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
e. Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy; e.g., withdrew consent, loss to follow-up, etc.

The mean increase from baseline in CD4+ cell count at Week 48 was 230 cells/mm^3 in patients receiving emtricitabine and tenofovir alafenamide and 211 cells/mm^3 in patients receiving emtricitabine and tenofovir disoproxil fumarate (p = 0.024).

Clinical efficacy of with Emtricitabine and Tenofovir alafenamide in treatment-naïve patients was also established from a study conducted with emtricitabine and tenofovir alafenamide (10 mg) when given with darunavir (800 mg) and cobicistat as a fixed-dose combination tablet (D/C/F/TAF). In study GS-US- 299-0102, patients were randomized in a 2:1 ratio to receive either fixed-dose combination D/C/F/TAF once daily (n = 103) or darunavir and cobicistat and emtricitabine/tenofovir disoproxil fumarate once daily (n = 50). The proportions of patients with plasma HIV-1 RNA < 50 copies/mL and < 20 copies/mL are shown in Table 5.

Table 5: Virological outcomes of study GS-US-299-0102 at Week 24 and 48[a]

	Week 24		Week 48	
	D/C/F/ TAF (n = 103)	Darunavir, cobicistat and emtricitabine/ tenofovir disoproxil fumarate (n = 50)	D/C/F/ TAF (n = 103)	Darunavir, cobicistat and emtricitabine/ tenofovir disoproxil fumarate (n = 50)
HIV-1 RNA < 50 copies/mL	75%	74%	77 %	84%
Treatment difference	3.3% (95% CI: -11.4% to 18.1%)		-6.2% (95% CI: -19.9% to 7.4%)	
HIV-1 RNA ≥ 50 copies/mL[b]	20%	24%	16 %	12%
No virologic data at Week 48 window	5%	2%	8%	4%
Discontinued study drug due to AE or death[c]	1%	0	1%	2%
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[d]	4%	2%	7%	2%
Missing data during window but on study drug	0	0	0	0
HIV-1 RNA < 20 copies/mL	55%	62%	63 %	76%
Treatment difference	-3.5% (95% CI: -19.8% to 12.7%)		-10.7% (95% CI: -26.3% to 4.8%)	

D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide

a. Week 48 window was between Day 294 and 377 (inclusive).
b. Included patients who had ≥ 50 copies/mL in the Week 48 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.
c. Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
d. Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy; e.g., withdrew consent, loss to follow-up, etc.

HIV-1 infected virologically suppressed patients

In study GS-US-311-1089, the efficacy and safety of switching from emtricitabine/tenofovir disoproxil fumarate to with Emtricitabine and Tenofovir alafenamide while maintaining the third antiretroviral agent were evaluated in a randomized, double-blind study of virologically suppressed

HIV-1 infected adults (n = 663). Patients must have been stably suppressed (HIV-1 RNA < 50 copies/mL) on their baseline regimen for at least 6 months and had HIV-1 with no resistance mutations to emtricitabine or tenofovir alafenamide prior to study entry. Patients were randomized in a 1:1 ratio to either switch to with Emtricitabine and Tenofovir alafenamide (n = 333), or stay on their baseline emtricitabine/tenofovir disoproxil fumarate containing regimen (n = 330). Patients were stratified by the class of the third agent in their prior treatment regimen. At baseline, 46% of patients were receiving emtricitabine/tenofovir disoproxil fumarate in combination with a boosted PI and 54% of patients were receiving emtricitabine/tenofovir disoproxil fumarate in combination with an unboosted third agent.

Treatment outcomes of study GS-US-311-1089 through 48 weeks are presented in Table 10.

Table 10: Virological outcomes of study GS-US-311-1089 at Week 48[a]

	Emtricitabine + tenofovir alafenamide containing regimen (n = 333)	Baseline regimen (n = 330)
HIV-1 RNA < 50 copies/mL	94%	93%
Treatment difference	1.3% (95% CI: -2.5% to 5.1%)	
HIV-1 RNA ≥ 50 copies/mL[b]	< 1%	2%
No virologic data at Week 48 window	5%	5%
Discontinued study drug due to AE or death[c]	2%	1%
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[d]	3%	5%
Missing data during window but on study drug	< 1%	0
Proportion (%) of patients with HIV-1 RNA < 50 copies/mL by prior treatment regimen		
Boosted PIs	142/155 (91.6%)	140/151 (92.7%)
Other third agents	172/178 (96.6%)	167/179 (93.3%)

PI = protease inhibitor

a. Week 48 window was between Day 294 and 377 (inclusive).
b. Included patients who had ≥ 50 copies/mL in the Week 48 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.
c. Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
d. Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy; e.g., withdrew consent, loss to follow-up, etc.

HIV-1 infected patients with mild to moderate renal impairment

In study GS-US-292-0112, the efficacy and safety of emtricitabine and tenofovir alafenamide were evaluated in an open-label clinical study in which 242 HIV-1 infected patients with mild to moderate renal impairment ($eGFR_{CG}$: 30-69 mL/min) were switched to emtricitabine and tenofovir alafenamide (10 mg) given with elvitegravir and cobicistat as a fixed-dose combination tablet. Patients were virologically suppressed (HIV-1 RNA < 50 copies/mL) for at least 6 months before switching.

The mean age was 58 years (range: 24-82), with 63 patients (26%) who were ≥ 65 years of age. Seventy- nine percent were male, 63% were White, 18% were Black, and 14% were Asian. Thirteen percent of patients were identified as Hispanic/Latino. At baseline, median eGFR was 56 mL/min, and 33% of patients had an eGFR from 30 to 49 mL/min. The mean baseline CD4+ cell count was

664 cells/mm^3 (range: 126- 1,813). At Week 48, 92% (222/242 patients) maintained HIV-1 RNA < 50 copies/mL after switching to emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat as a fixed-dose combination tablet. Three patients had virological failure at Week 48.

Changes in measures of bone mineral density

In studies in treatment-naïve patients, emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat or darunavir and cobicistat as a fixed-dose combination tablet was associated with smaller reductions in bone mineral density (BMD; as measured by hip and lumbar spine dual energy X ray absorptiometry [DXA] analysis) compared to E/C/F/TDF or darunavir, cobicistat, emtricitabine and

tenofovir disoproxil fumarate after 48 weeks of treatment. Small improvements in BMD were noted at 48 weeks after switching to emtricitabine and tenofovir alafenamide containing regimen from a TDF containing regimen compared to maintaining the TDF containing regimen.

Changes in measures of renal function

In studies in treatment-naïve patients, emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat or darunavir and cobicistat as a fixed-dose combination tablet was associated with lower impact of renal safety parameters (as measured by $eGFR_{CG}$, urine protein to creatinine ratio, and urine albumin to creatinine ratio) compared to E/C/F/TDF or darunavir and cobicistat and emtricitabine/tenofovir disoproxil fumarate after 48 weeks of treatment (see also section 4.4).

Paediatric population

In study GS-US-292-0106, the efficacy, safety, and pharmacokinetics of emtricitabine and tenofovir alafenamide were evaluated in an open-label study in which 50 HIV-1 infected, treatment-naïve adolescents received emtricitabine and tenofovir alafenamide (10 mg) given with elvitegravir and cobicistat as a fixed-dose combination tablet. Patients had a mean age of 15 years (range: 12-17), and 56% were female, 12% were Asian, and 88% were Black. At baseline, median plasma HIV-1 RNA was 4.7 log_{10} copies/mL, median CD4+ cell count was 456 cells/mm^3 (range: 95-1,110), and median CD4+% was 23% (range: 7-45%). Overall, 22% had baseline plasma HIV-1 RNA > 100,000 copies/mL. At 48 weeks, 92% (46/50) achieved HIV-1 RNA < 50 copies/mL, similar to response rates in studies of treatment-naïve HIV- 1 infected adults. The mean increase from baseline in CD4+ cell count at Week 48 was 224 cells/mm^3. No emergent resistance to E/C/F/TAF was detected through Week 48.

5.2.Pharmacokinetic properties

Dolutegravir pharmacokinetics are similar between healthy and HIV-infected subjects. The PK variability of dolutegravir is low to moderate. In Phase I studies in healthy subjects, between-subject CVb% for AUC and C_{max} ranged from ~20 to 40% and C_T from 30 to 65% across studies. The between-subject PK variability of dolutegravir was higher in HIV-infected subjects than healthy subjects. Within-subject variability (CVw%) is lower than between-subject variability.

Absorption

Dolutegravir is rapidly absorbed following oral administration, with median T_{max} at 2 to 3 hours post dose for tablet formulation.

Food increased the extent and slowed the rate of absorption of dolutegravir. Bioavailability of dolutegravir depends on meal content: low, moderate, and high fat meals increased dolutegravir $AUC_{(0-\infty)}$ by 33%, 41%, and 66%, increased C_{max} by 46%, 52%, and 67%, prolonged T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively. These increases may be clinically relevant in the presence of certain integrase class resistance. Therefore, Dolutegravir is recommended to be taken with food by patients infected with HIV with integrase class resistance (see section 4.2).

The absolute bioavailability of dolutegravir has not been established.

Emtricitabine is rapidly and extensively absorbed following oral administration with peak plasma concentrations occurring at 1 to 2 hours post-dose. Following multiple dose oral administration of emtricitabine to 20 HIV-1 infected subjects, the (mean ± SD) steady state plasma emtricitabine peak concentrations (C_{max}) were 1.8 ± 0.7 µg/mL and the area-under the plasma concentration-time curve over

a 24-hour dosing interval (AUC) was 10.0 ± 3.1 µg•h/mL. The mean steady state plasma trough concentration at 24 hours post-dose was equal to or greater than the mean *in vitro* IC_{90} value for anti-HIV-1 activity.
Emtricitabine systemic exposure was unaffected when emtricitabine was administered with food.

Following administration of food in healthy subjects, peak plasma concentrations were observed approximately 1 hour post-dose for tenofovir alafenamide administered as F/TAF (25 mg) or E/C/F/TAF (10 mg). The mean C_{max} and AUC_{last}, (mean ± SD) under fed conditions following a single 25 mg dose of tenofovir alafenamide administered in Dolutegravir, Emtricitabine and Tenofovir alafenamide were 0.21
± 0.13 µg/mL and 0.25 ± 0.11 µg•h/mL, respectively. The mean C_{max} and AUC_{last} following a single 10 mg dose of tenofovir alafenamide administered in E/C/F/TAF were 0.21 ± 0.10 µg/mL and 0.25 ± 0.08 µg•h/mL, respectively.
Relative to fasting conditions, the administration of tenofovir alafenamide with a high fat meal (~800 kcal, 50% fat) resulted in a decrease in tenofovir alafenamide C_{max} (15-37%) and an increase in AUC_{last} (17-77%).

Distribution

Dolutegravir is highly bound (>99%) to human plasma proteins based on *in vitro* data. The apparent volume of distribution is 17 L to 20 L in HIV-infected patients, based on a population pharmacokinetic analysis. Binding of dolutegravir to plasma proteins is independent of dolutegravir concentration. Total blood and plasma drug-related radioactivity concentration ratios averaged between 0.441 to 0.535, indicating minimal association of radioactivity with blood cellular components. The unbound fraction of dolutegravir in plasma is increased at low levels of serum albumin (<35 g/L) as seen in subjects with moderate hepatic impairment.
Dolutegravir is present in cerebrospinal fluid (CSF). In 13 treatment-naïve subjects on a stable dolutegravir plus abacavir/lamivudine regimen, dolutegravir concentration in CSF averaged 18 ng/mL (comparable to unbound plasma concentration, and above the IC_{50}).
Dolutegravir is present in the female and male genital tract. AUC in cervicovaginal fluid, cervical tissue and vaginal tissue were 6-10% of those in corresponding plasma at steady state. AUC in semen was 7% and 17% in rectal tissue of those in corresponding plasma at steady state.

In vitro binding of emtricitabine to human plasma proteins was < 4% and independent of concentration over the range of 0.02-200 µg/mL. At peak plasma concentration, the mean plasma to blood drug concentration ratio was ~1.0 and the mean semen to plasma drug concentration ratio was ~4.0.

In vitro binding of tenofovir to human plasma proteins is < 0.7% and is independent of concentration over the range of 0.01-25 µg/mL. *Ex vivo* binding of tenofovir alafenamide to human plasma proteins in samples collected during clinical studies was approximately 80%.

Biotransformation

Dolutegravir is primarily metabolized through glucuronidation via UGT1A1 with a minor CYP3A component. Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged active substance is low (< 1% of the dose). Fifty-three percent of total oral dose is excreted unchanged in the faeces. It is unknown if all or part of this is due to unabsorbed active substance or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. Thirty-two percent of the total oral dose is excreted in the urine, represented by ether

glucuronide of dolutegravir (18.9% of total dose), N-dealkylation metabolite (3.6% of total dose), and a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose).

In vitro studies indicate that emtricitabine is not an inhibitor of human CYP enzymes. Following administration of [^{14}C]-emtricitabine, complete recovery of the emtricitabine dose was achieved in urine (~86%) and faeces (~14%). Thirteen percent of the dose was recovered in the urine as three putative metabolites. The biotransformation of emtricitabine includes oxidation of the thiol moiety to form the 3'- sulfoxide diastereomers (~9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (~4% of dose). No other metabolites were identifiable.

Metabolism is a major elimination pathway for tenofovir alafenamide in humans, accounting for > 80% of an oral dose. *In vitro* studies have shown that tenofovir alafenamide is metabolised to tenofovir (major metabolite) by cathepsin A in PBMCs (including lymphocytes and other HIV target cells) and macrophages; and by carboxylesterase-1 in hepatocytes. *In vivo*, tenofovir alafenamide is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite tenofovir diphosphate. In human clinical studies, a 10 mg oral dose of tenofovir alafenamide (given with emtricitabine and elvitegravir and cobicistat) resulted in tenofovir diphosphate concentrations > 4-fold higher in PBMCs and
> 90% lower concentrations of tenofovir in plasma as compared to a 245 mg oral dose of tenofovir disoproxil (as fumarate) (given with emtricitabine and elvitegravir and cobicistat).
In vitro, tenofovir alafenamide is not metabolised by CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Tenofovir alafenamide is minimally metabolised by CYP3A4. Upon co-administration with the moderate CYP3A inducer probe efavirenz, tenofovir alafenamide exposure was not significantly affected. Following administration of tenofovir alafenamide, plasma [^{14}C]-radioactivity showed a time-dependent profile with tenofovir alafenamide as the most abundant species in the initial few hours and uric acid in the remaining period.

Elimination

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

Emtricitabine is primarily excreted by the kidneys with complete recovery of the dose achieved in urine (approximately 86%) and faeces (approximately 14%). Thirteen percent of the emtricitabine dose was recovered in urine as three metabolites. The systemic clearance of emtricitabine averaged 307 mL/min. Following oral administration, the elimination half-life of emtricitabine is approximately 10 hours.

Renal excretion of intact tenofovir alafenamide is a minor pathway with < 1% of the dose eliminated in urine. Tenofovir alafenamide is mainly eliminated following metabolism to tenofovir. Tenofovir alafenamide and tenofovir have a median plasma half-life of 0.51 and 32.37 hours, respectively. Tenofovir is eliminated from the body by the kidneys by both glomerular filtration and active tubular secretion.

Drug interactions

In vitro, dolutegravir demonstrated no direct, or weak inhibition (IC_{50}>50 µM) of the enzymes cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 CYP3A, uridine diphosphate
glucuronosyl transferase (UGT)1A1 or UGT2B7, or the transporters Pgp, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, MATE2-K, MRP2 or MRP4. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. Based

on this data, dolutegravir is not expected to affect the pharmacokinetics of medicinal products that are substrates of major enzymes or transporters (see section 4.5).

In vitro, dolutegravir was not a substrate of human OATP 1B1, OATP 1B3 or OCT 1.

Age, gender, and ethnicity

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

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

The pharmacokinetics of dolutegravir following single dose oral administration to Japanese subjects appear similar to observed parameters in Western (US) subjects.

No clinically relevant pharmacokinetic differences due to age, gender or ethnicity have been identified for emtricitabine, or tenofovir alafenamide.

Elderly

Population pharmacokinetic analysis of dolutegravir using data in HIV-1 infected adults showed that there was no clinically relevant effect of age on dolutegravir exposure.
Pharmacokinetic data for dolutegravir in subjects >65 years of age are limited

Paediatric population

The pharmacokinetics of dolutegravir in 10 antiretroviral treatment-experienced HIV-1 infected adolescents (12 to <18 years of age) showed that Dolutegravir 50 mg once daily oral dosage resulted in dolutegravir exposure comparable to that observed in adults who received Dolutegravir 50 mg orally once daily.

Exposures of emtricitabine and tenofovir alafenamide (given with elvitegravir and cobicistat) achieved in 24 paediatric patients aged 12 to < 18 years who received emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat in study GS-US-292-0106 were similar to exposures achieved in treatment- naïve adults (Table 11).

Table 11: Pharmacokinetics of emtricitabine and tenofovir alafenamide in antiretroviral-naïve adolescents and adults

	Adolescents			Adults		
	FTC[a]	TAF[b]	TFV[b]	FTC[a]	TAF[c]	TFV[c]
AUC_{tau} (ng•h/mL)	14,424.4 (23.9)	242.8 (57.8)	275.8 (18.4)	11,714.1 (16.6)	206.4 (71.8)	292.6 (27.4)
C_{max} (ng/mL)	2,265.0 (22.5)	121.7 (46.2)	14.6 (20.0)	2,056.3 (20.2)	162.2 (51.1)	15.2 (26.1)
C_{tau} (ng/mL)	102.4 (38.9)[b]	N/A	10.0 (19.6)	95.2 (46.7)	N/A	10.6 (28.5)

E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/Tenofovir alafenamide FTC = emtricitabine; TAF = Tenofovir alafenamide; TFV = tenofovir
N/A = not applicable
Data are presented as mean (%CV).

a. n = 24 adolescents (GS-US-292-0106); n = 19 adults (GS-US-292-0102)
b. n = 23 adolescents, (GS-US-292-0106, population PK analysis)

c. n = 539 (TAF) or 841 (TFV) adults (GS-US-292-0111 and GS-US-292-0104, population PK analysis)

Linearity/non-linearity

The linearity of dolutegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of tablet formulations, in general, dolutegravir exhibited nonlinear pharmacokinetics with less than dose-proportional increases in plasma exposure from 2 to 100 mg; however increase in dolutegravir exposure appears dose proportional from 25 mg to 50 mg for the tablet formulation. With 50 mg twice daily, the exposure over 24 hours was approximately doubled compared to 50 mg once daily.

Pharmacokinetic/pharmacodynamic relationship(s)

In a randomized, dose-ranging trial, HIV-1–infected subjects treated with dolutegravir monotherapy (ING111521) demonstrated rapid and dose-dependent antiviral activity, with mean decline in HIV-1 RNA of 2.5 $\log_{10}$ at day 11 for 50 mg dose. This antiviral response was maintained for 3 to 4 days after the last dose in the 50 mg group.

PK/PD modelling using pooled data from clinical studies in integrase resistant patients suggest that increasing the dose from 50 mg twice daily to 100 mg twice daily may increase the effectiveness of dolutegravir in patients with integrase resistance and limited treatment options due to advanced multi class resistance. The proportion of responders (HIV-1 RNA<50 c/mL) at week 24 was predicted to increase around 4-18% in the subjects with Q148 + ≥2 secondary mutations from G140A/C/S, E138A/K/T, L74I. Although these simulated results have not been confirmed in clinical trials, this high dose may be considered in the presence of the Q148 + ≥2 secondary mutations from G140A/C/S, E138A/K/T, L74I in patients with overall limited treatment options due to advanced multi class resistance. There is no clinical data on the safety or efficacy of the 100 mg twice daily dose. Co-treatment with atazanavir increases the exposure of dolutegravir markedly, and should not be used in combination with this high dose, since safety with the resulting dolutegravir exposure has not been established.

Renal impairment

Renal clearance of unchanged active substance is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of dolutegravir was performed in subjects with severe renal impairment (CrCL
<30 mL/min) and matched healthy controls. The exposure to dolutegravir was decreased by approximately 40% in subjects with severe renal impairment. The mechanism for the decrease is unknown. No dosage adjustment is considered necessary for patients with renal impairment. Dolutegravir has not been studied in patients on dialysis.

No clinically relevant differences in tenofovir alafenamide, or tenofovir pharmacokinetics were observed between healthy subjects and patients with severe renal impairment (estimated CrCl > 15 but < 30 mL/min) in studies of tenofovir alafenamide. There are no pharmacokinetic data on tenofovir alafenamide in patients with estimated CrCl < 15 mL/min. Mean systemic emtricitabine exposure was higher in patients with severe renal impairment (CrCl < 30 mL/min) (33.7 µg•h/ml) than in subjects with normal renal function (11.8 µg•h/mL).

Hepatic impairment

Dolutegravir is primarily metabolized and eliminated by the liver. A single dose of 50 mg of dolutegravir was administered to 8 subjects with moderate hepatic impairment (Child-Pugh class B) and to 8 matched healthy adult controls. While the total dolutegravir concentration in plasma was similar, a 1.5- to 2-fold increase in unbound exposure to dolutegravir was observed in subjects with moderate hepatic impairment compared to healthy controls. No dosage adjustment is considered necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of Dolutegravir has not been studied.

The pharmacokinetics of emtricitabine have not been studied in subjects with hepatic impairment; however, emtricitabine is not significantly metabolised by liver enzymes, so the impact of liver impairment should be limited. Clinically relevant changes in tenofovir pharmacokinetics in patients with hepatic impairment were not observed in patients with mild to moderate hepatic impairment, and no tenofovir alafenamide dose adjustment is required in patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of tenofovir alafenamide has not been studied.

Hepatitis B and/or hepatitis C virus co-infection

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

The pharmacokinetics of emtricitabine and tenofovir alafenamide have not been fully evaluated in patients co-infected with HBV and/or HCV.

Polymorphisms in drug metabolising enzymes

There is no evidence that common polymorphisms in drug metabolising enzymes alter dolutegravir pharmacokinetics to a clinically meaningful extent. In a meta-analysis using pharmacogenomics samples collected in clinical studies in healthy subjects, subjects with UGT1A1 (n=7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n=41).

5.3.Preclinical safety

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

Dolutegravir did not affect male or female fertility in rats at doses up to 1000 mg/kg/day, the highest dose tested (24 times the 50 mg twice daily human clinical exposure based on AUC).

Oral administration of dolutegravir to pregnant rats at doses up to 1000 mg/kg daily from days 6 to 17 of gestation did not elicit maternal toxicity, developmental toxicity or teratogenicity (27 times the 50 mg twice daily human clinical exposure based on AUC).

Oral administration of dolutegravir to pregnant rabbits at doses up to 1000 mg/kg daily from days 6 to 18 of gestation did not elicit developmental toxicity or teratogenicity (0.40 times the 50 mg twice daily human clinical exposure based on AUC). In rabbits, maternal toxicity (decreased food consumption, scant/no

faeces/urine, suppressed body weight gain) was observed at 1000 mg/kg (0.40 times the 50 mg twice daily human clinical exposure based on AUC).

The effect of prolonged daily treatment with high doses of dolutegravir has been evaluated in repeat oral dose toxicity studies in rats (up to 26 weeks) and in monkeys (up to 38 weeks). The primary effect of dolutegravir was gastrointestinal intolerance or irritation in rats and monkeys at doses that produce systemic exposures approximately 21 and 0.82 times the 50 mg twice daily human clinical exposure based on AUC, respectively. Because gastrointestinal (GI) intolerance is considered to be due to local active substance administration, mg/kg or mg/m^2 metrics are appropriate determinates of safety cover for this toxicity. GI intolerance in monkeys occurred at 15 times the human mg/kg equivalent dose (based on a 50 kg human), and 5 times the human mg/m^2 equivalent dose for a clinical dose of 50 mg twice daily.

Emtricitabine and Tenofovir alafenamide
Non-clinical data on emtricitabine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. Emtricitabine has demonstrated low carcinogenic potential in mice and rats.

Non-clinical studies of tenofovir alafenamide in rats and dogs revealed bone and kidney as the primary target organs of toxicity. Bone toxicity was observed as reduced BMD in rats and dogs at tenofovir exposures at least four times greater than those expected after administration of with Emtricitabine and Tenofovir alafenamide. A minimal infiltration of histiocytes was present in the eye in dogs at tenofovir alafenamide and tenofovir exposures of approximately 4 and 17 times greater, respectively, than those expected after administration of Dolutegravir, Emtricitabine and Tenofovir alafenamide.

Tenofovir alafenamide was not mutagenic or clastogenic in conventional genotoxicity assays.

Because there is a lower tenofovir exposure in rats and mice after the administration of tenofovir alafenamide compared to tenofovir disoproxil fumarate, carcinogenicity studies and a rat peri-postnatal study were conducted only with tenofovir disoproxil fumarate. No special hazard for humans was revealed in conventional studies of carcinogenic potential and toxicity to reproduction and development. Reproductive toxicity studies in rats and rabbits showed no effects on mating, fertility, pregnancy or fetal parameters. However, tenofovir disoproxil fumarate reduced the viability index and weight of pups in a peri-postnatal toxicity study at maternally toxic doses.

6. PHARMACEUTICAL PARTICULARS

6.1.List of

excipients Core

Tablet

Mannitol, Microcrystalline Cellulose, Sodium Starch Glycolate, Povidone, Lactose monohydrate, Croscarmellose sodium, Magnesium stearate.

Film coat
Polyvinyl Alcohol, Titanium Dioxide, Macrogol, Talc.

6.2.Incompatibilities

Not applicable.

6.3.Shelf life

24 months.

6.4.Special precautions for storage
Do not store above 30°C, store in original container.

6.5.Nature and contents of container
HDPE bottle of 30's, 90's & 180's*
* Not all packs may be marketed

6.6.Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER
Mylan Laboratories Limited, India.

Manufactured By
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