1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

VULANTE 300 mg/300 mg/50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of VULANTE contains 300 mg of tenofovir disoproxil fumarate, 300 mg of lamivudine and dolutegravir sodium equivalent to 50 mg of dolutegravir.

Contains sugar: Lactose monohydrate 150,4 mg; mannitol 131,38 mg.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

VULANTE is an oval, white, film-coated, biconvex tablet marked II0 on one side and plain on the other side, free from cracking, peeling or chipping.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

VULANTE is indicated in adults aged 18 years and older for:

- The treatment of human immunodeficiency virus (HIV-1) infection.

4.2. Posology and method of administration

Posology

VULANTE therapy should be initiated by a medical practitioner experienced in the management of HIV infection.

Adults

The dose of VULANTE is one tablet taken orally, once daily, without regard to food.

For treatment-naïve and treatment experienced patients, the recommended dose of VULANTE is one tablet daily.

Rifampicin decreases the blood levels of dolutegravir. A supplementary dose of dolutegravir should be given to patients taking VULANTE.

There is evidence that the concentration of isoniazid is increased by dolutegravir, as in VULANTE.

Special populations

Elderly population

There are limited data available on the use of dolutegravir in patients aged 65 years and over. There is no evidence that elderly patients require a different dose than younger adult patients. Special care is advised in this age group due to age-associated changes such as the decrease in renal function and alteration of haematological parameters.

Renal impairment

VULANTE is contraindicated in patients with renal impairment with creatinine clearance less than 80 mL/min) (see section 4.3, 4.4 and 5.2).

Significantly increased exposure occurred when tenofovir, as in VULANTE, was

administered to patients with renal impairment (see section 4.3).

The pharmacokinetics of tenofovir, as in VULANTE, has not been evaluated in non-haemodialysis patients with creatinine clearance < 80 mL/min; therefore, no dosing recommendations are available for these patients.

Rifampicin decreases the blood levels of dolutegravir. A supplementary dose of dolutegravir should be given to patients taking VULANTE (see section 4.5).

Hepatic impairment

VULANTE is contraindicated in patients with moderate or severe hepatic impairment (see section 4.3).

Paediatric population

VULANTE is not recommended for use in patients younger than 18 years of age (see section 4.3).

Method of administration

For oral administration (see section 4.2)

4.3. Contraindications

VULANTE is contraindicated in:

- Patients with hypersensitivity to dolutegravir, lamivudine or tenofovir or to any of the excipients in VULANTE (see section 6.1).
- Concomitant use with adefovir dipivoxil.
- Co-administration with dofetilide and pilsicainide.

- Co-administration with didanosine.
- Co-administration with metformin (see section 4.5).
- Moderate and severe hepatic impairment.
- Impairment of renal function (see sections 4.2, 4.4 and 5.2).
- Patients younger than 18 years of age.
- Women of child-bearing age not using highly effective contraception (see section 4.6).
- Women planning to become pregnant, are pregnant or breastfeeding their babies (see section 4.6).

4.4. Special warnings and precautions for use

WARNINGS

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE, OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE SECTION 4.4).

VULANTE IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION.

THE SAFETY AND EFFICACY OF VULANTE HAVE NOT BEEN ESTABLISHED IN PATIENTS CO-INFECTED WITH HBV AND HIV.

SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS CO-INFECTED WITH HBV AND HIV WHO HAVE DISCONTINUED THE COMBINATION TABLET. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT

LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE VULANTE AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE, RESUMPTION OR INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE SECTION 4.4).

Safety and efficacy of the individual active ingredients in various antiretroviral combination regimens with similar dosages as in VULANTE have been established in clinical studies for the treatment of HIV patients. However, safety and efficacy of the fixed-drug combination, as in VULANTE for the treatment of HIV have not been established in clinical studies.

The complete professional information of the other medicines used in combination should be consulted before initiation of therapy.

Hypersensitivity reactions to dolutegravir

Hypersensitivity reactions have been reported with integrase inhibitors, such as dolutegravir included in VULANTE and were characterised by rash, constitutional findings and sometimes, organ dysfunction, including liver injury.

Discontinue VULANTE and other suspect medicines 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, hepatitis, eosinophilia, angioedema) (see section 4.8). Clinical status including liver aminotransferases and bilirubin should be monitored and appropriate therapy initiated. Delay in stopping treatment with VULANTE or other suspect medicines after the onset of hypersensitivity may result in a life-threatening allergic reaction.

Metabolic abnormalities

Combination antiretroviral therapy, including VULANTE has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia.

Lipodystrophy

Combination antiretroviral therapy, including VULANTE, has also been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and elevated serum lipid and glucose levels in HIV patients.

A higher risk of lipodystrophy has been associated with individual factors such as older age, and with medicine related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances.

Clinical examination should include evaluation for physical signs of fat redistribution. Fasting serum lipids and blood glucose levels should be monitored. Lipid disorders should be managed as clinically appropriate. Patients with evidence of lipodystrophy should also have a thorough cardiovascular risk assessment.

Immune Reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART). Typically, such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an

asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts.

Common examples of IRIS reactions to opportunistic diseases are tuberculosis, atypical mycobacterial infections, cytomegalovirus retinitis, *pneumocystis jirovecii (carinii)* pneumonia, and cryptococcal meningitis. Any inflammatory symptoms should be evaluated, and treatment instituted when necessary. Appropriate treatment of the opportunistic disease should be instituted or continued and ART continued.

Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS.

Autoimmune disorders (such as Graves' disease, Guillain-Barre Syndrome, polymyositis) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis

Although the aetiology 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 combination antiretroviral therapy (cART), including components of VULANTE.

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

Opportunistic infections

Patients receiving VULANTE should be advised that they may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by healthcare professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

The risk of HIV transmission to others

Patients must be advised that antiretroviral therapy, including VULANTE, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions must continue to be employed.

Lactic acidosis/severe hepatomegaly with steatosis

Lactic acidosis, usually associated with hepatic steatosis, including fatal cases, has been reported with the use of nucleoside analogues, as in VULANTE.

Early symptoms (symptomatic hyperlactataemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness). Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure or renal failure.

Lactic acidosis generally occurs after a few or several months of treatment. Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactataemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.

Suspicious biochemical features include mild raised transaminases, raised lactate dehydrogenase (LDH) and/or creatine kinase.

In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/L) and respond as follows:

- Lactate 2 to 5 mmol/L: monitor regularly, and be alert for clinical signs.
- Lactate 5 to 10 mmol/L without symptoms: monitor closely.
- Lactate 5 to 10 mmol/L with symptoms: STOP all therapy. Exclude other causes (e.g. sepsis, uraemia, diabetic ketoacidosis, hyperthyroidism, lymphoma).
- Lactate > 10 mmol/L: STOP all therapy (80 % mortality in case studies).

The above lactate values may not be applicable to paediatric patients.

Diagnosis of lactic acidosis is confirmed by demonstrating metabolic acidosis with an increased anion gap and raised lactate level. Therapy should be stopped in any acidotic patient with a raised lactate level.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of VULANTE alone or in combination, in the treatment of HIV infection. Most cases were women.

Caution should be exercised when administering VULANTE to patients with known risk factors for liver disease.

Treatment with VULANTE should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Caution should be exercised when administering nucleoside analogues as in VULANTE to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk

factors for liver disease and hepatic steatosis (including certain medicines and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk. However, cases have also been reported in patients with no known risk factors.

Patients at increased risk should be followed closely.

There are no study results demonstrating the effect of VULANTE on clinical progression of HIV-1.

Mitochondrial dysfunction

Nucleoside and nucleotide analogues as in VULANTE have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or postnatally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactataemia, hyperlipidaemia) (see section 4.8).

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 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.

Pancreatitis

Pancreatitis has been observed in some patients receiving lamivudine, as in VULANTE. It is unclear whether this is due to lamivudine or to underlying HIV disease. Pancreatitis

must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of VULANTE until diagnosis of pancreatitis is excluded.

Patients with renal impairment

In patients with renal impairment, the terminal half-life of VULANTE is increased due to decreased clearance (see section 4.3).

VULANTE is a combination medicine and the dose of the individual components cannot be altered. Tenofovir and lamivudine are principally eliminated by the kidney. Renal safety with tenofovir, as in VULANTE, has only been studied to a very limited degree in adult patients with impaired renal function (creatinine clearance < 80 mL/min).
VULANTE is not recommended in patients with creatinine clearance < 80 mL/min or patients who require haemodialysis.
Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphataemia) has been reported with the use of tenofovir disoproxil fumarate in clinical practice. Careful monitoring of renal function (serum creatinine and serum phosphate) is therefore recommended before taking VULANTE.

Renal function

Since VULANTE is primarily eliminated by the kidneys, co-administration of VULANTE with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of VULANTE and/or increase the concentrations of other renally eliminated medicines. Some examples include, but are not limited to adefovir dipivoxil, cidofovir, aciclovir, valaciclovir, ganciclovir and valganciclovir.

Renal safety with tenofovir has only been studied to a very limited degree in adult patients with impaired renal function (creatinine clearance < 80 mL/min).

Renal monitoring

It is recommended that renal function (creatinine clearance and serum phosphate) is assessed in all patients prior to initiating therapy with tenofovir disoproxil fumarate and that it is also monitored every four weeks during the first year of tenofovir disoproxil fumarate therapy, and then every three months.

In patients at risk for renal impairment, including patients who have previously experienced renal events while receiving adefovir dipivoxil, consideration should be given to more frequent monitoring of renal function.

Co-administration and risk of renal toxicity

Use of tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic medicine (e.g. aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2). If concomitant use of tenofovir disoproxil fumarate and nephrotoxic medicines is unavoidable, renal function should be carefully monitored weekly for changes in serum creatinine and phosphorus.

Tenofovir disoproxil fumarate has not been clinically evaluated in patients receiving medicines which are secreted by the same renal pathway, including the transport proteins human organic anion transporter (hOAT) 1 and 3 or MRP 4 (e.g. cidofovir, a known nephrotoxic medicine). These renal transport proteins may be responsible for tubular secretion and in part, renal elimination of tenofovir and cidofovir.

Consequently, the pharmacokinetics of these medicines, which are secreted by the same renal pathway including transport proteins hOAT 1 and 3 or MRP 4, might be modified if they are co-administered. Unless clearly necessary, concomitant use of these medicines which are secreted by the same renal pathway is not recommended, but if such use is unavoidable, renal function should be monitored weekly.

Liver disease

Use of VULANTE can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis).

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

K65R mutation

VULANTE should be avoided in antiretroviral experienced patients with HIV-1 harbouring the K65R mutation.

Bone mineral density

Decreases in bone mineral density of spine and changes in bone biomarkers from baseline are significantly greater with tenofovir disoproxil fumarate as in VULANTE. Decreases in bone mineral density of the hip are significantly greater. Clinically relevant bone fractures are reported. If bone abnormalities are suspected then appropriate

consultation should be obtained. Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk of osteopenia.

VULANTE may cause a reduction in bone mineral density. The effects of tenofovir disoproxil fumarate-associated changes in bone mineral density on long-term bone health and future fracture risk are currently unknown.

Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained. Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy.

Patients with HIV and Hepatitis B or C virus co-infection

VULANTE is not indicated for the treatment of chronic HBV infection. The safety and efficacy of VULANTE has not been established for the treatment of patients co-infected with HBV and HIV.

Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV). In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant professional information for these medicines.

Exacerbations of hepatitis

Flares of treatment

Spontaneous exacerbations in chronic hepatitis B are relatively common and are characterised by transient increases in serum ALT. After initiating antiviral therapy, serum ALT may increase in some patients. In patients with compensated liver disease, these increases in serum ALT are generally not accompanied by an increase in serum bilirubin concentrations or hepatic decompensation.

Patients with cirrhosis may be at higher risk for hepatic decompensation following hepatitis exacerbation and therefore should be monitored closely during therapy.

Flares after treatment discontinuation

Acute exacerbations of hepatitis have been reported in patients after the discontinuation of hepatitis B therapy. Post-treatment exacerbations are usually associated with rising HBV DNA, and the majority appears to be self-limited. However, severe exacerbations, including fatalities, have been reported.

Hepatic function should be monitored at repeated intervals with both clinical and laboratory follow-up for at least 6 months after discontinuation of hepatitis B therapy. If appropriate, resumption of hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation. Liver flares are especially serious, and sometimes fatal in patients with decompensated liver disease.

Integrase class resistance of particular concern

The decision to use dolutegravir, as in VULANTE, 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). The extent to which dolutegravir provides added efficacy in the presence of such integrase class resistance, is uncertain.

Medicine interactions

Factors that decrease dolutegravir, as in VULANTE, exposure should be avoided in the presence of integrase class resistance. This includes co-administration with medicines 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 anti-epileptic medicines) (see section 4.5).

Dolutegravir, as in VULANTE, increased metformin concentrations (see section 4.3 and 4.5).

Use in the elderly

There is insufficient data regarding patients aged 65 and over to determine whether they respond differently from younger patients.

Paediatric population

Safety and effectiveness in paediatric patients and patients < 18 years of age have not been established (see section 4.2).

Excipients

Lactose monohydrate

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take VULANTE.

Mannitol

VULTANTE may have a mild laxative effect.

4.5. Interaction with other medicines and other forms of interaction

No medicine interaction studies have been conducted using VULANTE. As VULANTE contains dolutegravir, tenofovir disoproxil fumarate and lamivudine, any interactions that have been identified with these individual medicines may occur with VULANTE. Important medicine interaction information for VULANTE is summarised in Tables 2 and 3. The medicine interactions described are based on studies conducted with dolutegravir, tenofovir disoproxil fumarate or lamivudine as individual medicines, or are potential medicine interactions. While the tables include potentially significant interactions, they are not all inclusive. Based on the results of *in vitro* experiments and the known elimination pathway of tenofovir, the potential for CYP450-mediated interactions involving tenofovir with other medicines is low.

An interaction with trimethoprim, a constituent of co-trimoxazole, causes a 40 % increase in lamivudine exposure at therapeutic doses. This does not require dose adjustment unless the patient also has renal impairment. Administration of co-trimoxazole with the lamivudine/zidovudine combination in patients with renal impairment should be carefully assessed.

Renally eliminated medicines

Tenofovir, as in VULANTE, is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Co-administration of VULANTE with medicines that are eliminated by active tubular secretion may increase serum

concentrations of either tenofovir or the co-administered medicines due to competition for this elimination pathway. Medicines that decrease renal function may also increase serum concentrations of tenofovir, as in VULANTE.

Tenofovir has been evaluated in healthy volunteers in combination with abacavir, adefovir dipivoxil, atazanavir, didanosine, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, methadone, oral contraceptives and ribavirin. Tables 2 and 3 summarise pharmacokinetic effects of co-administered medicine on tenofovir pharmacokinetics and effects of tenofovir on the pharmacokinetics of co-administered medicine.

When administered with multiple doses of tenofovir, the C_{max} and AUC of didanosine 400 mg increased significantly. The mechanism of this interaction is unknown.

When didanosine 250 mg enteric-coated capsules were administered with tenofovir, systemic exposures to didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions.

Table 1: Medicine Interactions: Changes in Pharmacokinetic Parameters for Tenofovir[1] in the Presence of co-administered medicines:

Co-administered Medicine	**Dose of Co-administered Medicine (mg)**	**N**	**% Change of Tenofovir Pharmacokinetic Parameters[2] (90 % CI)**		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	⇔	⇔	NC
Adefovir dipivoxil	10 once	22	⇔	⇔	⇔
Atazanavir	400 once daily x 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Didanosine (enteric-coated)	400 once	25	⇔	⇔	⇔
Didanosine (buffered)	250 or 400 once daily x 7 days	14	⇔	⇔	⇔
Efavirenz	600 once daily	29	⇔	⇔	⇔

	x 14 days				
Emtricitabine	200 once daily x 7 days	17	⇔	⇔	⇔
Indinavir	800 three times daily x 7 days	13	↑ 14 (↓ 3 to ↑ 33)	⇔	⇔
Lamivudine	150 twice daily x 7 days	15	⇔	⇔	⇔
Lopinavir/Ritonavir	400/100 twice daily x 14 days	24	⇔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)
Saquinavir/Ritonavir	1 000/100 twice daily x 14 days	35	⇔	⇔	↑ 23 (↑ 16 to ↑ 30)

1. Patients received tenofovir DF 300 mg once daily
2. Increase = ↑; Decrease = ↓; No effect = ⇔; NC = Not calculated

Following multiple dosing to HIV-negative patients receiving either chronic methadone maintenance therapy, oral contraceptives, or single doses of ribavirin, steady-state tenofovir pharmacokinetics were similar to those observed in previous studies, indicating a lack of clinically significant medicines interactions between these medicines and tenofovir disoproxil fumarate.

Table 2: Medicine Interactions: Changes in Pharmacokinetic Parameters for Co-administered Medicines in the Presence of Tenofovir

Co-administered Medicine	**Dose of Co-administered Medicine (mg)**	**N**	**% Change of Co-administered Medicine pharmacokinetic parameters[1]**		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	↑ 122 (↑ 1 to ↑ 26)	⇔	NA
Adefovir dipivoxil	10 once	22	⇔	⇔	N/A
Efavirenz	600 once daily x 14 days	30	⇔	⇔	⇔
Emtricitabine	200 once daily x 7 days	17	⇔	⇔	⇔
Indinavir	800 three times daily x 7 days	12	↑ 14 (↓ 3 to ↑ 33)	⇔	⇔
Lamivudine	150 twice daily x 7 days	15	⇔	⇔	⇔
Lopinavir/Ritonavir	400/100 twice daily x 14 days	21	⇔	⇔	⇔
Methadone[2]	40 to 110 once daily	13	⇔	⇔	⇔

	x 14 days[3]				
Oral contraceptives[4]	Ethinyl oestradiol/ Norgestimate Once daily x 7 days	20	⇔	⇔	⇔
Ribavirin	600 once	22	⇔	⇔	NA
Ritonavir	Lopinavir/Ritonavir 4/100 twice daily x 14 days	24	⇔	⇔	⇔
Atazanavir[5]	400 once daily x 14 days	29	⇔	⇔	⇔
Atazanavir[5]	Atazanavir/Ritonavir 300/100 once daily x 42 days	10	↑ 28 (↑ 50 to ↑ 5)	↑ 25 (↑ 42 to ↑ 3)	↑ 23[6] (↑ 46 to ↑ 10)
Saquinavir Ritonavir	Saquinavir/Ritonavir 1 000/100 twice daily x 14 days	32	↑ 22 (↑ 6 to ↑ 41) ⇔	↑ 29[7] (↑ 12 to ↑ 48) ⇔	↑ 47[7] (↑ 23 to ↑ 76) ↑ 23 (↑ 3 to ↑ 46)

1. Increase = ↑; Decrease = ↓ ; No effect = ⇔; NC = Not calculated NA = Not applicable
2. R-(active), S- and total methadone exposures were equivalent when dosed alone or with tenofovir as tenofovir disoproxil fumarate 300 mg
3. Individual patients were maintained on their stable methadone dose. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported
4. Ethinyl oestradiol and 17-deacetyl norgestimate (pharmacologically active metabolite) exposures were equivalent when dosed alone or with tenofovir as tenofovir DF 300 mg
5. REYATAZ US Prescribing Information (Bristol-Myers Squibb)
6. In HIV-infected patients, addition of tenofovir disoproxil fumarate to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2,3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.
7. Increases in AUC and C_{min} are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir DF and ritonavir-boosted saquinavir are co-

administered.

Lamivudine

The likelihood of metabolic interactions is low due to limited metabolism and plasma protein binding and almost complete renal clearance.

Zidovudine plasma levels are not significantly altered when co-administered with VULANTE. Zidovudine has no effect on the pharmacokinetics of VULANTE.

Co-administration of zidovudine results in a 13 % increase in zidovudine exposure and a 28 % increase in peak plasma levels. This is not considered to be of significance to patient safety and therefore no dosage adjustments are necessary.

VULANTE may inhibit the intracellular phosphorylation of zalcitabine when the two medicines are used concurrently. VULANTE is therefore not recommended to be used in combination with zalcitabine.

Administration of trimethoprim, a constituent of co-trimoxazole causes an increase in VULANTE plasma levels. Unless the patient has renal impairment, no dosage adjustment of VULANTE is necessary. VULANTE has no effect on the pharmacokinetics of co-trimoxazole.

When concomitant administration is warranted, patients should be monitored clinically. Co-administration of lamivudine, as in VULANTE, with high doses of co-trimoxazole for the treatment of Pneumocystis jirovecii pneumonia (PCP) and toxoplasmosis should be avoided.

The possibility of interactions with other medicines administered concurrently should be considered, particularly when the main route of elimination is active renal secretion via the organic cationic transport system e.g. trimethoprim. Other medicines (e.g. ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with VULANTE. The nucleoside analogues (e.g. didanosine) like zidovudine, are not eliminated by this mechanism and are unlikely to interact with VULANTE.

The co-administration of VULANTE with etravirine (ETR) is not recommended unless the patient is also receiving concomitant atazanavir + ritonavir (ATV + RTV), lopinavir + ritonavir (LPV + RTV) or darunavir + ritonavir (DRV +RTV).
Due to similarities, VULANTE should not be administered concomitantly with other cytidine analogues, such as emtricitabine.

Moreover, VULANTE should not be taken with any other medicines containing lamivudine or tenofovir (see section 4.2 and 4.3).
In vitro lamivudine, as in VULANTE, inhibits the intracellular phosphorylation of cladribine leading to a potential risk of cladribine loss of efficacy in case of combination in the clinical setting. Some clinical findings also support a possible interaction between lamivudine and cladribine. Therefore, the concomitant use of VULANTE with cladribine is not recommended.

Lamivudine, as in VULANTE, metabolism does not involve CYP3A, making interactions with medicines metabolised by this system (e.g. PIs) unlikely.

Dolutegravir

Effect of VULANTE on the pharmacokinetics of other medicines:

Dolutegravir, as in VULANTE, demonstrates 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, OATP1B1, OATP1B3, OCT1 or MRP2.
Dolutegravir, as in VULANTE, does not induce CYP1A2, CYP2B6 or CYP3A4.
Dolutegravir, as in VULANTE, does not have an effect on midazolam, a CYP3A4 probe.
Dolutegravir, as in VULANTE, is not expected to affect the pharmacokinetics of midazolam, reverse transcriptase and protease inhibitors, opioid analgesics, antidepressants, statins, azole antifungals (such as fluconazole, itraconazole, clotrimazole), proton pump inhibitors (such as esomeprazole, lansoprazole, omeprazole), anti-erectile dysfunction medicines (such as sildenafil, tadalafil, vardenafil), aciclovir, valaciclovir, sitagliptin, adefovir.
Dolutegravir, as in VULANTE, should not have a clinically relevant effect on the pharmacokinetics of the following: tenofovir, methadone, efavirenz, lopinavir, atazanavir, darunavir, etravirine, fosamprenavir, rilpivirine, telaprevir and oral contraceptives containing norgestimate and ethinyl estradiol.

Dolutegravir, as in VULANTE, increases plasma concentrations of medicines in which excretion is dependent upon the renal organic cation transporter 2 (OCT2) and MATE 1, such as metformin (see section 4.3).

Effect of other medicines on the pharmacokinetics of VULANTE
Rifampicin decreases the blood levels of dolutegravir. A supplementary dose of dolutegravir should be given to patients taking VULANTE.
There is evidence that the concentration of isoniazid is increased by dolutegravir, as in VULANTE.

VULANTE should not be co-administered with polyvalent cation-containing antacids. VULANTE is recommended to be administered 2 hours before or 6 hours after these medicines (see section 4.5).
Dolutegravir, as in VULANTE, is eliminated mainly through metabolism by UGT1A1. Dolutegravir, as in VULANTE, is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP; therefore medicines that induce those enzymes may theoretically decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir, as in VULANTE.

Co-administration of dolutegravir, as in VULANTE and other medicines that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or Pgp may increase dolutegravir, as in VULANTE plasma concentration (see Table 4 below).

Efavirenz, nevirapine, rifampicin and tipranavir in combination with ritonavir each reduces the plasma concentrations of dolutegravir, as in VULANTE, significantly and require an extra 50 mg dolutegravir tablet to be taken daily (see section 4.2). Etravirine also reduces plasma concentrations, but the effect of etravirine is mitigated by co-administration of the CYP3A4 inhibitors lopinavir/ritonavir, darunavir/ritonavir and is expected to be mitigated by atazanavir/ritonavir. Therefore no dolutegravir, as in VULANTE, dose adjustment is necessary when co-administered with etravirine and either lopinavir/ritonavir, darunavir/ritonavir, or atazanavir/ritonavir. Another inducer, fosamprenavir in combination with ritonavir decreases plasma concentrations of dolutegravir, as in VULANTE, but does not require a dosage adjustment of dolutegravir, as in VULANTE. Caution is warranted and clinical monitoring is recommended when these combinations are given in INI-resistant patients. Atazanavir does not result in a clinically significant increase in the plasma concentrations of VULANTE. Tenofovir, ritonavir, lopinavir/ritonavir,

darunavir/ritonavir, rilpivirine, boceprevir, telaprevir, prednisone, rifabutin, and omeprazole has no or a minimal effect on dolutegravir, as in VULANTE, pharmacokinetics, therefore no dolutegravir, as in VULANTE, dose adjustment is required when co-administered with these medicines.

The absorption of VULANTE is reduced by certain anti-acid medicines.

Table 3: Medicine interactions with dolutegravir, as in VULANTE

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of VULANTE or Concomitant Medicine**	**Clinical Comment and recommendations concerning co-administration**
HIV-1 Antiviral medicines		
Non-nucleoside Reverse Transcriptase Inhibitors		
Etravirine (ETR) without boosted PI	Dolutegravir ↓ AUC ↓ 71 % C_{max} ↓ 52 % C_T ↓ 88 % Etravirine ↔ (induction of UGT1A1 and CYP3A enzymes)	Etravirine without boosted PI decreases dolutegravir plasma concentration, which may result in loss of virologic response and possible resistance to dolutegravir. Dolutegravir should not be used with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir. The recommend adult dose of dolutegravir is 50 mg twice daily when co-administered with etravirine without boosted protease inhibitors.
Lopinavir/ritonavir + Etravirine (LPV/RTV + ETR)	Dolutegravir ↔ AUC ↑ 10 % C_{max} ↑ 7 % C_T ↑ 28 % LPV ↔ RTV ↔ ETR ↔	No dose adjustment is necessary.
Darunavir/ritonavir + Etravirine (DRV/RTV + ETR)	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 ↔ (induction of UGT1A1 and CYP3A enzymes)	Efavirenz decreases dolutegravir plasma concentrations. The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with efavirenz. Alternative combinations that do not include efavirenz should be used where possible in INI-resistant patients.
Nevirapine	Dolutegravir ↓	Co-administration with nevirapine has the potential to decrease dolutegravir plasma

		concentration due to enzyme induction and has not been studied. Effect of nevirapine on dolutegravir exposure is likely similar to or less than that of efavirenz. The recommended dose of dolutegravir is 50 mg twice daily when co-administered with nevirapine. Alternative combinations that do not include nevirapine should be used where possible in INI-resistant patients.
Rilpivirine	Dolutegravir ↔ AUC ↑ 12 % C_{max} ↑ 13 % C_T ↑ 22 % Rilpivirine ↔	No dose adjustment is necessary.
Nucleoside Reverse Transcriptase Inhibitors		
Tenofovir	Dolutegravir ↔ AUC ↑ 1 % C_{max} ↓ 3 % C_T ↓ 8 % Tenofovir ↔	No dose adjustment is necessary.
Protease Inhibitors		
Atazanavir	Dolutegravir ↑ AUC ↑ 91 % C_{max} ↑ 49% C_T ↑ 180 % Atazanavir ↔ (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 due to lack of data
Atazanavir/ritonavir	Dolutegravir ↑ AUC ↑ 62 % C_{max} ↑ 33 % 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 due to lack of data
Tipranavir/ritonavir (TPV+RTV)	Dolutegravir ↓ AUC ↓ 59 % C_{max} ↓ 47 % C_T ↓ 76 % TPV ↔ RTV ↔ (induction of UGT1A1 and CYP3A enzymes)	The recommended dose of dolutegravir is 50 mg twice daily when co-administered with tipranavir/ritonavir. Alternative combinations that do not include tipranavir/ritonavir should be used where possible in INI resistant patients. In the presence of integrase class resistance this combination should be avoided.
Fosamprenavir/ ritonavir (FPV+RTV)	Dolutegravir ↓ AUC ↓ 35 % C_{max} ↓ 24 % C_T ↓ 49 % FPV ↔ RTV ↔ (induction of UGT1A1 and	No dose adjustment is necessary in INI-naïve patients. Alternative combinations that do not include fosamprenavir/ritonavir should be used where possible in INI resistant patients.

	CYP3A enzymes)	
Nelfinavir	Dolutegravir ↔	This interaction has not been studied. Although an inhibitor of CYP3A4, based on data from other inhibitors, an increase is not expected. No dose adjustment is necessary.
Darunavir/ritonavir (DRV/RTV)	Dolutegravir ↓ AUC ↓ 22 % C_{max} ↓ 11 % C_{24} ↓ 38 % DRV ↔ RTV ↔ (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Lopinavir/ritonavir (LPV + RTV)	Dolutegravir ↔ AUC ↓ 4 % C_{max} ↔ 0 % C_{24} ↓ 6 %	No dose adjustment is necessary.
Other antiviral medicines		
Telaprevir	Dolutegravir ↑ AUC ↑ 25 % C_{max} ↑ 19 % C_T ↑ 37 % Telaprevir ↔ (inhibition of CYP3A enzyme)	No dose adjustment is necessary.
Boceprevir	Dolutegravir ↔ AUC ↑ 7 % C_{max} ↑ 5 % C_T ↑ 8 % Boceprevir ↔	No dose adjustment is necessary.
Daclatasvir	Dolutegravir ↔ AUC ↑ 33 % C_{max} ↑ 29 % C_T ↑ 45 % Daclatasvir ↔	Daclatasvir does not change dolutegravir plasma concentration to a clinically relevant extent. Dolutegravir does not change daclatasvir plasma concentration. No dose adjustment is necessary.
Anticonvulsants		
Carbamazepine	Dolutegravir ↓ AUC ↓ 49 % C_{max} ↓ 33 % C_T ↓ 73 %	The recommended adult 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 Phenobarbitone	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 adult 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. Co-administration may decrease dolutegravir plasma concentration and should be avoided.
Azole anti-fungal medicines		

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 adult 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 VULANTE (minimum 2 hours before or 6 hours after).
Calcium supplements	Dolutegravir ↓ AUC ↓ 39 % C_{max} ↓ 37 % C_{24} ↓ 39 % (Complex binding to polyvalent ions)	Calcium supplements, iron supplements or multivitamins should be taken well separated in time from the administration of dolutegravir (minimum 2 hours before or 6 hours after).
Iron supplements	Dolutegravir ↓ AUC ↓ 54 % C_{max} ↓ 57 % C_{24} ↓ 56 % (Complex binding to polyvalent ions)	
Multivitamin	Dolutegravir ↓ AUC ↓ 33 % C_{max} ↓ 35 % C_{24} ↓ 32 % (Complex binding to polyvalent ions)	
Corticosteroids		
Prednisone	Dolutegravir ↔ AUC ↑ 11 % C_{max} ↑ 6 % C_T ↑ 17 %	No dose adjustment is necessary.
Antidiabetics		
Metformin	Metformin ↑ When co-administered with dolutegravir 50 mg once daily: Metformin AUC ↑ 79 %	Co-administration with VULANTE is contraindicated (see section 4.3). Note that co-administration with VULANTE increased the risk for lactic acidosis in patients with moderate renal impairment due

	C_{max} ↑ 66 % When co-administered with dolutegravir 50 mg twice daily: Metformin AUC ↑ 145 % C_{max} ↑ 111 %	to increased metformin concentration.
Antimycobacterials		
Rifampicin	Dolutegravir ↓ AUC ↓ 54 % C_{max} ↓ 43 % C_T ↓ 72 % (induction of UGT1A1 and CYP3A enzymes)	The recommended adult 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 has 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 VULANTE.
Analgesics		
Methadone	Dolutegravir ↔ Methadone ↔ AUC ↓ 2 % C_{max} ↔ 0 % C_T ↓ 1 %	No dose adjustment is necessary of either medicine.
Increase is indicated as "↑", decrease as "↓", no change as "↔", area under the concentration versus time curve as "AUC", maximum observed concentration as "C_{max}", concentration at end of dosing interval as "C_T")		

4.6. Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be counselled about the potential risk of neural tube defects with dolutegravir (see below), as in VULANTE, including consideration of using effective contraceptive measures.

Perform pregnancy testing before initiation of VULANTE in women of childbearing potential to exclude inadvertent (unintentional) use of VULANTE during the first trimester of pregnancy.

If a woman plans pregnancy, the benefits and the risks of starting or continuing treatment with dolutegravir, as in VULANTE, versus using another antiretroviral regimen should be discussed with her.

Pregnancy

Use of dolutegravir, as in VULANTE, during pregnancy was associated with a small increase in the prevalence of neural tube defects (0,19 %) compared to non-dolutegravir regimens (0,11 %). Most neural tube defects occur within the first 4 weeks of embryonic development after conception (approximately 6 weeks after the last menstrual period).

If a pregnancy is confirmed in the first trimester while on dolutegravir, as in VULANTE, the benefits and risks of continuing dolutegravir, as in VULANTE, versus switching to another antiretroviral regimen should be discussed with the patient, taking the gestational age and the critical time period of neural tube defect development into account.

Dolutegravir, as in VULANTE, may be used during the second and third trimester of pregnancy when the expected benefit outweighs the potential risk to the foetus.

Dolutegravir, as in VULANTE, was shown to cross the placenta in humans, leading to significant exposure to the foetus, but the implications of such exposure are not yet known.

Tenofovir, dolutegravir and lamivudine, as in VULANTE, were shown to cross the placenta in reproductive toxicity studies in animals. Late onset neurological disorders, including seizures, have been observed in children who have been exposed *in utero* to nucleoside analogues such as tenofovir and lamivudine (see section 4.4).

Breastfeeding

HIV infected women should not breastfeed their infants in order to avoid transmission of HIV to the baby or follow appropriate guidelines.

Dolutegravir, as in VULANTE, is excreted in human breast milk, and there is significant exposure to the neonate/infants due to slow elimination; the half-life of dolutegravir in the newborn was 33 hr compared to 14 hr in the adults. There is insufficient information on the effects of dolutegravir, as in VULANTE, in neonates/infants.

Women on treatment with dolutegravir, as in VULANTE, or dolutegravir containing anti-retroviral combinations containing a nucleoside analogue should not breastfeed their babies.

Lamuvidine, as in VULANTE, passes into breastmilk. It is expected that dolutegravir, as in VULANTE, will pass into breastmilk. It is unknown whether tenofovir, as in VULANTE, passes into breastmilk. HIV infected women should not breastfeed their babies in order to avoid transmission of HIV to the baby.

Fertility

There are no data on the effects of dolutegravir, as in VULANTE, on human fertility, male or female. Animal studies indicate no effects of dolutegravir on male or female fertility. Studies in animals showed that lamivudine had no effect on fertility.

4.7. Effects on ability to drive and use machines

VULANTE has a minor influence on the ability to drive and use machines.

VULANTE may affect the ability to drive and use machines. Patients should ensure that they do not engage in driving or operating machines until they know how VULANTE affects them.

Since adverse reactions such as dizziness have been reported in patients receiving VULANTE, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that VULANTE does not adversely affect their ability to do so (see section 4.8).

4.8. Undesirable effects

a) Tabulated list of adverse reactions

VULANTE adverse reactions:

System organ class	Frequent	Less frequent	Frequency unknown
Blood and the lymphatic system disorders		Neutropenia, anaemia, thrombocytopenia	Pure red cell aplasia,
Immune system disorders		Hypersensitivity, immune reconstitution inflammatory syndrome, angioedema	Allergy, allergic reactions.
Metabolism and nutrition disorders	Hypophosphataemia	Lactic acidosis, lipodystrophy (including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorso-cervical fat accumulation (buffalo hump)), metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactatemia, hypokalaemia	

Psychiatric disorders	Insomnia, abnormal dreams, depression, anxiety	Suicidal ideation, suicide attempt	
Nervous system disorders	Headache, dizziness	Peripheral neuropathy (or paraesthesia), late onset neurological disorders in children exposed *in utero,* convulsions	
Ear and labyrinth disorders			Vertigo
Respiratory, thoracic and mediastinal disorders	Cough, nasal symptoms		Dyspnoea
Gastrointestinal disorders	Nausea, diarrhoea, vomiting, flatulence, upper abdominal pain or cramps, abdominal pain, abdominal discomfort, abdominal distension, dyspepsia, anorexia	Pancreatitis, elevations in serum amylase	
Hepato-biliary disorders		Hepatitis, acute hepatic failure, hepatic steatosis	Hepatomegaly
Skin and subcutaneous tissue disorders	Rash, pruritus, alopecia		
Musculoskeletal and connective tissue disorders	Arthralgia, muscle disorders, musculoskeletal pain	Rhabdomyolysis, decrease in bone mineral density, osteopenia, fractures, myalgia, myositis, muscular weakness, osteomalacia (manifested as bone pain and infrequently contributing to fractures), hypertonia, myopathy, osteomalacia (both associated with proximal renal tubulopathy)	Osteonecrosis
Renal and urinary disorders		Renal impairment, Increased creatinine, proximal renal tubulopathy (including Fanconi syndrome), renal insufficiency, acute renal failure, renal failure, acute tubular necrosis, nephritis (including	

		acute interstitial nephritis), nephrogenic diabetes insipidus, proteinuria, polyuria	
Pregnancy, puerperium and perinatal conditions			Neural tube defects
General disorders and administrative site conditions	Fatigue, malaise, fever, asthenia, pyrexia		
Investigations	Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations, creatine phosphokinase (CPK) elevations, bilirubin (without clinical jaundice)		

Dolutegravir

System organ class	Frequent	Less frequent	Frequency unknown
Immune system disorders		Hypersensitivity, immune reconstitution inflammatory syndrome (IRIS)	
Psychiatric disorders	Insomnia, abnormal dreams, depression, anxiety.	Suicidal ideation, suicide attempt.[1]	
Nervous system disorders	Headache, dizziness.		
Ear and labyrinth disorders			Vertigo.
Gastrointestinal disorders	Nausea, diarrhoea, vomiting, flatulence, upper abdominal pain, abdominal pain, abdominal discomfort		
Hepato-biliary disorders		Hepatitis, acute hepatic failure.	
Skin and subcutaneous tissue disorders	Rash, pruritus.		
Musculoskeletal and connective tissue disorders		Arthralgia, myalgia.	Myopathy, rhabdomyolysis.

Renal and urinary disorders		Renal impairment.	
Pregnancy, puerperium and perinatal conditions			Neural tube defects.[2]
General disorders and administrative site conditions	Fatigue.		
Investigations	Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations. Creatine phosphokinase (CPK) elevations, bilirubin (without clinical jaundice).		

Dolutegravir

[1]Suicidal ideation and suicide attempt particularly in patients with a pre-existing history of depression or psychiatric illness.

[2]Neural tube defects in babies born to women taking dolutegravir, as in VULANTE, at the time of conception (see section 4.6).

Lamivudine

The following side effects have been reported during therapy for HIV disease with VULANTE alone and in combination with other antiretrovirals.

System organ class	Frequent	Less frequent	Frequency unknown
Blood and the lymphatic system disorders		Neutropenia, anaemia, thrombocytopenia.	Pure red cell aplasia.
Immune system disorders		Angioedema, immune reconstitution inflammatory syndrome (IRIS).	
Metabolism and nutrition disorders	Hyperlactataemia.[4]	Lactic acidosis, lipodystrophy[3], metabolic abnormalites.[4]	
Nervous system disorders	Headache, insomnia.	Peripheral neuropathy (or paraesthesia), late onset neurological disorders in children	

		exposed *in utero,* convulsions.	
Respiratory, thoracic and mediastinal disorders	Cough, nasal symptoms.		
Gastrointestinal disorders	Nausea, vomiting, upper abdominal pain or cramps, diarrhoea.	Pancreatitis, elevations in serum amylase.	
Hepato-biliary disorders		Transient elevations in liver enzymes (AST, ALT), hepatitis.	Hepatomegaly, hepatic steatosis.
Skin and subcutaneous tissue disorders	Rash, alopecia.		
Musculoskeletal and connective tissue disorders	Arthralgia, muscle disorders, musculoskeletal pain.	Rhabdomyolysis, myalgia, decrease in bone mineral density, osteopenia, fractures, myositis.	Osteonecrosis.
General disorders and administrative site conditions	Fatigue, malaise, fever.		

Lamivudine

[3]Lypodystrophy (including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorso-cervical fat accumulation (buffalo hump)).

[4]Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactatemia.

Tenofovir

System organ class	Frequent	Less frequent	Frequency unknown
Blood and the lymphatic system disorders			Neutropenia.
Immune system disorders		Angioedema.	Allergy, allergic reactions, Immune reconstitution inflammatory syndrome.
Metabolism and nutrition disorders	Hypophosphataemia[6].	Hypokalaemia[6].	Lactic acidosis.

Nervous system disorders	Headache, dizziness, insomnia.		Convulsions.
Respiratory, thoracic and mediastinal disorders			Dyspnoea.
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, abdominal pain, abdominal distension, flatulence, dyspepsia, anorexia.	Raised serum amylase concentrations, pancreatitis.	
Hepato-biliary disorders	Increased transaminases (raised liver enzymes: ALT, AST, Gamma GT).	Hepatic steatosis hepatitis.	
Skin and subcutaneous tissue disorders	Rash, pruritus		
Musculoskeletal and connective tissue disorders		Rhabdomyolysis, muscular weakness, osteomalacia[5] hypertonia, myopathy.	
Renal and urinary disorders		Increased creatinine, proximal renal tubulopathy(including Fanconi syndrome), renal insufficiency, acute renal failure, renal failure, acute tubular necrosis, nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus, proteinuria, polyuria.	
General disorders and administrative site conditions	Asthenia, fatigue, pyrexia.		

Tenofovir

[5]Osteomalacia (manifested as bone pain and infrequently contributing to fractures and associated with proximal renal tubulopathy).

[6]Hypophosphataemia, hypokalaemia, may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil in the absence of this condition.

Description of selected adverse reactions

Immune Reconstitution Inflammatory Syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) 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).

Metabolic parameters

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

In overdose, side effects can be precipitated and/or of increased severity.

Treatment

Tenofovir

If overdose occurs the patient must be monitored for evidence of toxicity and palliative supportive treatment be applied as necessary. Tenofovir can be removed by haemodialysis, the median haemodialysis clearance of tenofovir is 134 mL/min. The elimination of tenofovir by peritoneal dialysis has not been studied.

Lamivudine

Limited data are available on the consequences of ingestion of acute overdoses in humans.

If overdosage occurs the patient should be monitored, and palliative supportive treatment applied as required.

Dolutegravir

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 VULANTE. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. As VULANTE is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class: A 20.2.8 Antimicrobial (Chemotherapeutic) Medicines. Antiviral

agents.

Pharmacotherapeutic group: Antivirals for treatment of HIV infections

ATC code: J05AR27

Mechanism of action

VULANTE is a fixed-dose combination tablet containing tenofovir disoproxil fumarate (tenofovir DF), a nucleoside reverse transcriptase inhibitor (NRTI), dolutegravir, an integrase strand transfer inhibitor (INSTI), and lamivudine, a nucleoside reverse transcriptase inhibitor (NRTI).

Lamivudine

Lamivudine, a nucleoside reverse transcriptase inhibitor (NRTI), is a selective inhibitor of HIV-1 and HIV-2 replication *in vitro*. Lamivudine is metabolised intracellularly to the 5'-triphosphate which has an intracellular half-life of 16 to 19 hours.

Lamivudine 5'-triphosphate is a weak inhibitor of the RNA and DNA dependent activities of HIV reverse transcriptase, its mode of action is a chain terminator of HIV reverse transcription.

Reduced *in vitro* sensitivity to lamivudine has been reported for HIV isolates from patients who have received lamivudine therapy.

Lamivudine-resistant HIV-1 mutants are cross-resistant to didanosine and zalcitabine. In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

Lamivudine does not interfere with cellular deoxynucleotide metabolism and has little effect on mammalian cell and mitochondrial DNA content.

Tenofovir

Tenofovir disoproxil fumarate, also known as tenofovir DF, is an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate and is converted *in vivo* to tenofovir. It is a nucleoside reverse transcriptase inhibitor.

Tenofovir is phosphorylated by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase, by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation in DNA, by chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β and mitochondrial DNA polymerase γ.

Medicine resistance

HIV-1 isolates with reduced susceptibility to tenofovir have been selected *in vitro* and a K65R mutation in reverse transcriptase have been selected *in vitro* and in some patients treated with tenofovir in combination with certain antiretroviral medicines.

In treatment-naïve patients treated with tenofovir + lamivudine + efavirenz, viral isolates from 17 % of patients with virologic failure showed reduced susceptibility to tenofovir.

In treatment-experienced patients, some of the tenofovir-treated patients with virologic failure through week 96 showed reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a mutation in the HIV-1 reverse transcriptase gene resulting in the K65R amino acid substitution.

Cross-resistance

Cross-resistance among certain reverse transcriptase inhibitors has been recognised. The K65R mutation can also be selected by abacavir, didanosine, or zalcitabine and results in reduced susceptibility to these medicines plus lamivudine, emtricitabine and tenofovir. Tenofovir disoproxil fumarate should be avoided in antiretroviral experienced patients with strains harbouring the K65R mutation. Patients with HIV-1 expressing three or more thymidine analogue associated mutations (TAMs) that included either the M41L or L210W reverse transcriptase mutation showed reduced susceptibility to tenofovir disoproxil fumarate.

Antiviral activity

The *in vitro* antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 has been assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The IC_{50} (50 % inhibitory concentration) values for tenofovir were in the range of 0,04 µM to 8,5 µM. In medicine combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Tenofovir displayed antiviral activity *in vitro* against HIV-1 clades A, B, C, D, E, F, G, and O (IC_{50} values ranged from 0,5 µM to 2,2 µM). The IC_{50} values of tenofovir against HIV-2 ranged from 1,6 µM to 4,9 µM.

Dolutegravir

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. *In vitro*, dolutegravir dissociates slowly from the active site of the wild-type integrase-DNA complex ($t_{½}$ 71 hours).

Resistance in vitro:

Isolation from wild-type HIV-1: Viruses highly resistant to dolutegravir have not been observed during HIV-1 passage. During wild-type HIV-1 passage in the presence of dolutegravir integrase substitutions observed were S153Y and S153F with FCs ≤ 4,1 for strain IIIB, or E92Q with FC = 3,1 and G193E with FC = 3,2 for strain NL432. Additional passage of wild-type subtype B, C, and A/G viruses in the presence of dolutegravir selected for R263K, G118R and S153T.

Anti-HIV activity Against Resistant Strains: Reverse Transcriptase Inhibitor-and Protease Inhibitor-Resistant Strains: Dolutegravir demonstrated equivalent potency against 2 non-nucleoside (NN)-RTI-resistant, 3 nucleoside (N)-RTI-resistant and 2 PI-resistant HIV-1 mutant clones (1 triple and 1 sextuple) compared to the wild-type strain.

Integrase Inhibitor-Resistant HIV-1 Strains: Dolutegravir showed anti-HIV activity (susceptibility) with FC < 5 against 27 of 28 integrase inhibitor resistant mutant viruses with single substitutions including T66A/I/K, E92Q/V, Y143C/H/R, Q148H/K/R, and N155H.

Integrase Inhibitor-Resistant HIV-2 Strains: Site directed mutant HIV-2 viruses were constructed based on patients infected with HIV-2 and treated with raltegravir who showed virologic failure. Overall the HIV-2 FCs observed were similar to HIV-1 FCs observed for similar pathway mutations.

Resistance in vivo: integrase inhibitor naïve patients: No integrase inhibitor (INI) resistant mutations or treatment emergent resistance to the NRTI backbone therapy were isolated with dolutegravir 50 mg once daily in treatment – naïve studies.

Effects on Renal Function: The effect of dolutegravir on serum creatinine clearance (CrCl),

glomerular filtration rate (GFR) using iohexol as the probe and effective renal plasma flow (ERPF) using para-aminohippurate (PAH) as the probe was evaluated. A small decrease of 10 to 14 % in mean serum creatinine clearance (CrCl) was observed with dolutegravir within the first week of treatment. Dolutegravir had no significant effect on glomerular filtration rate (GFR) or the effective renal plasma flow (ERPF). *In vitro* studies suggest that the increases in creatinine observed in clinical studies are due to the non-pathologic inhibition of the organic cation transporter 2 (OCT2) in the proximal renal tubules, which mediates the tubular secretion of creatinine.

5.2. Pharmacokinetic properties

Dolutegravir

Absorption

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

The linearity of dolutegravir pharmacokinetics is dependent on the dose and formulation. Following oral administration of tablet formulations, dolutegravir exhibits non-linear 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.

Dolutegravir may be administered with or without food. Food increases the extent and slows the rate of absorption of dolutegravir. Bioavailability of dolutegravir depends on meal content: low, moderate and high fat meals increases dolutegravir AUC (0-∞) by 34 %, 41 %, and 66 %, increases C_{max} by 46 %, 52 %, and 67 %, prolongs T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively. These increases are not clinically significant. The absolute bioavailability of dolutegravir has not been established.

Distribution

Dolutegravir is highly bound (approximately 99,3 %) to human plasma proteins *in vitro* data.

The apparent volume of distribution is estimated at 17 L to 20 L in HIV-infected patients, based on a population pharmacokinetic analysis. Binding of dolutegravir to plasma proteins is independent of concentration. Total blood and plasma drug-related radioactivity concentration ratios averages between 0,441 to 0,535 indicating minimal association of radioactivity with blood cellular components. Free fraction of dolutegravir in plasma is estimated at approximately 0,2 to 1,1 % in healthy patients, approximately 0,4 to 0,5 % in patients with moderate hepatic impairment, and 0,8 to 1,0 % in patients with severe renal impairment and 0,5 % in HIV-1 infected patients. 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 IC50).

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

Biotransformation

Dolutegravir is primarily metabolised through glucuronidation via UGT1A1 with a minor CYP3A component. Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged medicine 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 medicine or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. Thirty-one 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).

Elimination

Dolutegravir has a terminal half-life of approximately 14 hours and an apparent clearance (CL/F) of approximately 1L/hr based on population pharmacokinetic analysis.

Special populations

Adolescents

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 dosage resulted in dolutegravir exposure comparable to that observed in adults who received dolutegravir 50 mg once daily.

Due to a lack of data, dolutegravir, as in VULANTE, is not recommended for use in patients under 18 years of age (see section 4.2).

Table 4: Adolescent pharmacokinetic parameters

Age/weight	**Dolutegravir Dose**	**Dolutegravir Pharmacokinetic Parameter Estimates Geometric Mean (CV %)**		
		$AUC_{(0-24)}$ µg.hr/mL	**C_{max} µg/mL**	**C_{24} µg/mL**
12 to < 18 years ≥ 40 kg[a]	50 mg once daily[a]	46 (43)	3,49 (38)	0,90 (59)

[a] One patient weighing 37 kg received 35 mg once daily

Elderly

Population pharmacokinetic analysis of dolutegravir using data in HIV-1 infected adults showed that there was no clinically relevant effect of age on dolutegravir exposure.

Pharmacokinetic data for dolutegravir in patients of > 65 years old are limited.

Renal impairment

Renal clearance of unchanged medicine is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of dolutegravir was performed in patients with severe renal impairment (CLcr < 30 mL/min). No clinically important pharmacokinetic differences between patients with severe renal impairment (CLcr < 30 mL/min) and matching healthy patients were observed, AUC, C_{max}, and C_{24} of dolutegravir were decreased by 40 %, 23 %, and 43 %, respectively, compared with those in matched healthy patients. No dosage adjustment is necessary for patients with renal impairment. Dolutegravir has not been studied in patients on dialysis, though differences in exposure are not expected.

Hepatic impairment

Dolutegravir is primarily metabolised and eliminated by the liver. In a study comparing 8 patients with moderate hepatic impairment (Child-Pugh category B score 7 to 9) to 8 matched healthy adult controls, the single 50 mg dose exposure of dolutegravir was similar between the two groups. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of dolutegravir has not been studied.

Polymorphisms in metabolising enzymes

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

associated with normal metabolism via UGT1A1 (n = 41). Polymorphisms in CYP3A4, CYP3A5, and NR1I2 were not associated with differences in the pharmacokinetics of dolutegravir.

Co-infection with Hepatitis B or C

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

Lamivudine

Absorption

Lamivudine is well absorbed from the gastrointestinal tract and the bioavailability of oral lamivudine in adults is normally between 80 % and 85 %. Following oral administration, the mean time (T_{max}) to maximum serum concentration (C_{max}) is about an hour. At therapeutic dose levels i.e. 4 mg/kg/day (as 12 hourly doses), C_{max} is in the order of 1 to 1,5 µg/mL. No dose adjustment is needed when co-administered with food as lamivudine bioavailability is not altered, although a delay in T_{max} and a reduction in C_{max} have been observed.

Distribution

Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin.

Binding of lamivudine to human plasma proteins is low (less than 36 %). *In vitro* studies showed that over the concentration range of 0,1 to 100 mcg per mL, the amount of lamivudine associated with erythrocytes ranged from 53 % to 57 % and was independent

of concentration.

Limited data shows lamivudine penetrates the central nervous system and reaches the CSF. The mean ratio CSF/serum lamivudine concentration 2 to 4 hours after oral administration was approximately 0,12. The true extent of penetration or relationship with any clinical efficacy is unknown.

Biotransformation

Lamivudine undergoes predominantly renal clearance (> 70 %) via active tubular secretion, but little (< 10 %) hepatic metabolism.

Lamivudine is not significantly metabolized by CYP450 enzymes.

The likelihood of metabolic interactions of lamivudine with other medicines is low due to the small extent of hepatic metabolism (5 to10 %) and low plasma protein binding.

Elimination

The mean terminal half-life of elimination is 5 to 7 hours. In HIV-1-infected patients, total clearance was 398,5 ± 69,1 mL per min (mean ± SD). Oral clearance and elimination half-life were independent of dose and body weight over an oral dosing range of 0,25 to 10 mg per kg. The mean systemic clearance of lamivudine is approximately 0,32 L/kg/h. Lamivudine elimination will be affected by renal impairment, whether it is disease- or age-related. Dosage for patients with creatinine clearance below 80 mL/min should be avoided (see section 4.2).

An interaction with trimethoprim, a constituent of co-trimoxazole, causes a 40 % increase in lamivudine exposure at therapeutic doses. This does not require dose adjustment unless the patient also has renal impairment (see sections 4.5 and 4.2). Administration of co-trimoxazole with lamivudine in patients with renal impairment should be carefully

assessed.

Tenofovir

Absorption

Tenofovir disoproxil fumarate is a water-soluble diester pro-drug of the active ingredient tenofovir. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted patients is approximately 25 %. Following oral administration of a single dose of tenofovir DF 300 mg to HIV-1 infected patients in the fasted state, maximum serum concentrations (C_{max}) are achieved in 1,0 ± 0,4 hrs. C_{max} and AUC values are 296 ± 90 ng/mL and 2 287 ± 685 ng·h/mL, respectively.

The pharmacokinetics of tenofovir DF are dose proportional over a dose range of 75 mg to 600 mg and are not affected by repeated dosing.

Administration of tenofovir disoproxil fumarate following a high-fat meal (~700 to 1 000 kcal containing 40 to 50 % fat) increases the oral bioavailability, with an increase in tenofovir $AUC_{0-\infty}$ of approximately 40 % and an increase in C_{max} of approximately 14 %. However, administration of tenofovir disoproxil fumarate with a light meal does not have a significant effect on the pharmacokinetics of tenofovir when compared to fasted administration of the medicine. Food delays the time to tenofovir C_{max} by approximately 1 hour. C_{max} and AUC of tenofovir are 326 ± 119 ng/mL and 3 324 ± 1 370 ng·h/mL following multiple doses of tenofovir disoproxil fumarate 300 mg once daily in the fed state, when meal content was not controlled (see section 4.2).

Distribution

In vitro binding of tenofovir to human plasma or serum proteins is less than 0,7 % and 7,2 % respectively, over the tenofovir concentration range 0,01 to 25 μg/mL. The volume

of distribution at steady-state is 1,3 ± 0,6 L/kg and 1,2 ± 0,4 L/kg, following intravenous administration of tenofovir 1,0 mg/kg and 3,0 mg/kg.

Biotransformation

Data indicate that neither tenofovir disoproxil nor tenofovir are substrates of CYP450 enzymes.

Following a single oral dose, the terminal elimination half-life of tenofovir is approximately 17 hours. After multiple oral doses of tenofovir 300 mg once daily (under fed conditions), 32 ± 10 % of the administered dose is recovered in urine over 24 hours.

Elimination

Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion with a renal clearance in adults with normal renal function of 243 ± 33 mL/min (mean ± SD). There may be competition for elimination with other compounds that are also renally eliminated.

Special populations

Paediatrics and the elderly:

Pharmacokinetic studies have not been performed in children (< 18 years) or in the elderly (> 65 years).

Hepatic impairment:

Tenofovir pharmacokinetics after a 300 mg single dose have been studied in non-HIV infected patients with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. Change in tenofovir dosing is not required in patients with hepatic impairment.

Renal impairment:

Tenofovir pharmacokinetics are altered in patients with renal impairment. In patients with creatinine clearance < 50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, C_{max}, and $AUC_{0-\infty}$ of tenofovir were increased. It is recommended that the dosing interval for tenofovir be modified in patients with creatinine clearance < 50 mL/min or in patients with ESRD who require dialysis (see section 4.2). Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54 %. Following a single 300 mg dose of tenofovir, a four-hour haemodialysis session removed approximately 10 % of the administered tenofovir dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients:

Croscarmellose sodium, lactose monohydrate, macrogol, mannitol, microcrystalline cellulose, polyvinyl alcohol part hydrolysed, povidone, pregelatinised starch, sodium starch glycolate, sodium stearyl fumarate, talc, titanium dioxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the bottle tightly closed. Protect from moisture.

Keep the desiccant in the container. Do not remove the desiccant.

Keep in original packaging until required for use.

6.5 Nature and Contents of Container

28, 30 or 84 tablets packed in a white, round, high density polyethylene bottle with a silica gel desiccant and closed with a white polypropylene cap with heat seal liner. The bottle may be packed in an outer cardboard carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

53/20.2.8/0082

9. DATE OF FIRST AUTHORISATION

10 ctober 2018

10. DATE OF REVISION OF TEXT

03 October 2024

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

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