Proposed Professional Information

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

VOLUTRIP (film-coated tablet)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Contains sugar: 145,37 mg mannitol

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Pink coloured, oval, biconvex, film-coated tablet debossed with ‘N33’ on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indication

The **VOLUTRIP** is a triple combination therapy which is indicated for the treatment of human immunodeficiency virus (HIV) infection in adults aged 18 years and older.

4.2 Posology and method of administration

Posology

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

Adults:

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

Special populations

Renal impairment: Significantly increased exposure occurred when tenofovir, as in **VOLUTRIP**, was administered to patients with moderate to severe renal impairment (see section 4.3).

The pharmacokinetics of tenofovir, as in **VOLUTRIP**, have not been evaluated in non-haemodialysis patients with creatinine clearance < 80 ml/min); therefore, no dosing recommendations is available for these patients.

VOLUTRIP is not suitable for use in patients with renal impairment with creatinine clearance less than 50 ml/min.

For treatment-naïve and treatment experienced patients the recommended dose of **VOLUTRIP** is one tablet once daily.

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

VOLUTRIP is contraindicated in patients with renal impairment with creatinine clearance less than 80 ml/min.

Rifampicin decreases the blood levels of dolutegravir. A supplementary dose dolutegravir should be given in patients taking **VOLUTRIP**

Rifampicin decreases the blood levels of dolutegravir. A supplementary dose dolutegravir should be given in patients taking **VOLUTRIP.**

The concentration of isoniazid is increased by concomitant administration of **VOLUTRIP**.

Paediatric population

VOLUTRIP is not recommended for use in patients younger than 18 years of age.

Method of administration

Oral use.

It is recommended that **VOLUTRIP** be swallowed whole with water.

VOLUTRIP can usually be taken with food or between meals.

4.3 Contraindications

VOLUTRIP tablets are contra-indicated in patients with known hypersensitivity to lamivudine, tenofovir or dolutegravir or to any of the components of the tablets.

Impairment of renal function.

Pregnancy and lactation (see section 4.6).

Women of child-bearing age not using highly effective contraception.

Concomitant use with adefovir dipivoxil.

Co-administration with dofetilide and pilsicainide.

Co-administration with didanosine.

Co-administration with metformin.

Patients younger than 18 years of age.

Moderate and severe hepatic impairment.

4.4 Special warnings and precautions for use

WARNING

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 WARNINGS AND SPECIAL PRECAUTIONS).

VOLUTRIP IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION. THE SAFETY AND EFFICACY OF VOLUTRIP HAS NOT BEEN ESTABLISHED IN PATIENTS CO-INFECTED WITH HBV AND HIV. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED WITH HBV AND HIV AND 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 VOLUTRIP AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS AND SPECIAL PRECAUTIONS).

Safety and efficacy of the individual active ingredients in various antiretroviral combination regimens with similar dosages as contained in **VOLUTRIP** have been established in clinical

studies for the treatmnet of HIV patients. However, safety and efficacy of the fixed-drug combination as in **VOLUTRIP** for the teatment of HIV has not been established in clinical studies. The complete professional informations of the other medicines used in combination should be consulted before initiation of therapy.

Metabolic abnormalities

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

Lipodystrophy

Combination antiretroviral therapy, including **VOLUTRIP**, has also been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat enlargement (buffalo hump), peripheral wasting, facial wasting and breast enlargement 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 reactions present 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, and cryptococcal meningitis.

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 **VOLUTRIP**. 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 **VOLUTRIP** may continue to develop opportunistic infections and other complications of HIV infection and therefore patients should remain under close clinical observation by doctors experienced in the treatment of patients with HIV associated diseases.

The risk of HIV transmission to others:

Patients should be advised that treatment with **VOLUTRIP**, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be taken.

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, such as in **VOLUTRIP**. 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 2-5 mmol/L: monitor regularly and be alert for clinical signs.
- Lactate 5-10 mmol/L without symptoms, monitor closely.
- Lactate 5-10 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).

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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 **VOLUTRIP** alone or in combination, in the treatment of HIV infection. Most cases were women. Caution should be exercised when administering **VOLUTRIP** to patients with known risk factors for liver disease.

Treatment with **VOLUTRIP** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatoxicity. Caution should be exercised when administering nucleoside analogues as contained in **VOLUTRIP** 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. Patients at increased risk should be followed closely. 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 **VOLUTRIP** on clinical progression of HIV-1.

Mitochondrial dysfunction:

Nucleoside and nucleotide analogues as contained in **VOLUTRIP** 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 hematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactatemia, hyperlipidemia). 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 **VOLUTRIP.** 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 **VOLUTRIP** until a diagnosis of pancreatitis is excluded.

Patients with renal impairment:

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

Liver disease:

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

The safety and efficacy of **VOLUTRIP** 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.

Renal Impairment:

VOLUTRIP is a combination medicine and the dose of the individual components cannot be altered. Since **VOLUTRIP** is primarily eliminated by the kidneys, co-administration of **VOLUTRIP** with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of **VOLUTRIP** 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.

VOLUTRIP is not recommended for 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 hypophosphatemia) has been reported in association 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 **VOLUTRIP**.

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

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.

VOLUTRIP should be avoided with concurrent or recent use of a nephrotoxic medicine. Patients at risk of, or with a history of, renal dysfunction and patients receiving concomitant nephrotoxic substances should be carefully monitored for changes in serum creatinine and phosphorous.

K65R mutation:

VOLUTRIP 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 contained in **VOLUTRIP.** 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.

VOLUTRIP 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.

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

VOLUTRIP is not indicated for the treatment of chronic HBV infection. The safety and efficacy of **VOLUTRIP** 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 **VOLUTRIP** 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 informations for these medicines.

Exacerbations of hepatitis:

Flares on treatment:

Spontaneous exacerbations in chronic hepatitis B are relatively common and are characterised by transient increases in serum ALT. After initiating antiviral therapy, serum ALT may increase in some patients. In patients with compensated liver disease, these increases in serum ALT are generally not accompanied by an increase in serum bilirubin concentrations or hepatic decompensation. Patients with cirrhosis may be at a higher risk for hepatic decompensation following hepatitis exacerbation, and therefore should be monitored closely during therapy.

Flares after treatment discontinuation:

Acute 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 exacerbations of hepatitis may lead to hepatic decompensation. Liver flares are especially serious, and sometimes fatal in patients with decompensated liver disease.

Hypersensitivity reactions:

Hypersensitivity reactions have been reported with integrase inhibitors, including dolutegravir

as in **VOLUTRIP** and were characterised by rash, constitutional findings and sometimes, organ dysfunction, including liver injury. Discontinue **VOLUTRIP** and other suspect medicines immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia, angioedema). Clinical status including liver aminotransferases should be monitored and appropriate therapy initiated. Delay in stopping treatment with **VOLUTRIP** or other suspect medicines after the onset of hypersensitivity may result in a life-threatening reaction.

Interactions:

Caution should be given to co-administering medications (prescription and non-prescription) that may change the exposure of dolutegravir or medications that may have their exposure changed by dolutegravir (-see sections 4.3 and 4.5").

The co-administration of dolutegravir 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) (see- section 4.5).

The recommended dose of dolutegravir is 50 mg twice daily when co-administered with efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin (see section 4.5).

Dolutegravir should not be co-administered with polyvalent cation-containing antacids. Dolutegravir is recommended to be administered 2 hours before or 6 hours after these medicines (see section 4.5).

Metformin concentrations may be increased by dolutegravir. Metformin is contra-indicated in patients taking dolutegravir (see section 4.3).

Paediatric population

Safety and effectiveness in paediatric patients and patients < 18 years of age have not been established.

Elderly patients

Clinical studies did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

Excipients:

VOLUTRIP contains mannitol and may have a laxative effect.

4.5 Interaction with other medicines and other forms of interaction

The likelihood of interactions is low due to the limited metabolism as plasma protein binding and almost complete renal clearance. Zidovudine plasma levels are not significantly altered when co-administered with lamivudine. Zidovudine has no effect on the pharmacokinetics of lamivudine. Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicines are used concurrently. Lamivudine is therefore not recommended to be used in combination with zalcitabine.

Administration of trimethoprim, a constituent of co-trimoxazole causes an increase in lamivudine plasma levels. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary. Lamivudine has no effect on the pharmacokinetics of co-trimoxazole. The possibility of interactions with other medicines administered concurrently should be considered, particularly when the main route is renal.

No medicine interaction studies have been conducted using **VOLUTRIP.** As **VOLUTRIP** contains tenofovir disoproxil fumarate and lamivudine, any interactions that have been identified with these individual medicines may occur with **VOLUTRIP.** Important medicine

interaction information for **VOLUTRIP** is summarised in Tables 1, 2 and 3. The medicine interactions described are based on studies conducted with 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 **VOLUTRIP**, is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion.

Co-administration of **VOLUTRIP** 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 **VOLUTRIP**.

Tenofovir:

Tenofovir has been evaluated in healthy volunteers in combination with abacavir, adefovir dipivoxil, atazanavir, didanosine, efavirenz, indinavir, lamivudine, lopinavir/ritonavir, methadone, oral contraceptives and ribavirin. Tables 1 and 2 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 Cmax 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 Tenofovir1 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 mg once	8	⇔	⇔	NC
Adefovir dipivoxil	10 mg once	22	⇔	⇔	⇔
Atazanavir	400 mg once daily x 14 days	33	↑14 (↑8 to ↑20)	↑24 (↑21 to ↑28)	↑22 (↑15 to ↑30)
Didanosine (enteric-coated)	400 mg once	25	⇔	⇔	⇔
Didanosine (buffered)	250 mg or 400 mg once daily x 7 days	14	⇔	⇔	⇔

Efavirenz	600 mg once daily x14 days	29	⇔	⇔	⇔
Emtricitabine	200 mg once daily x 7 days	17	⇔	⇔	⇔
Indinavir	800 mg three times daily x 7 days	13	↑14 (↓3 to ↑33)	⇔	⇔
Lamivudine	150 mg twice daily x 7 days	15	⇔	⇔	⇔
Lopinavir/ Ritonavir	400/100 mg twice daily x 14 days	24	⇔	↑ 32 (↑25 to ↑38)	↑ 51 (↑37 to ↑66)
1. Patients received as tenofovir disoproxil fumarate 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 medicine interactions between these medicines and tenofovir disoproxil fumarate.

Table 2: Medicine interactions: Changes in pharmacokinetic parameters for co-administered medicine in the presence of tenofovir:

Co-administered medicine	Dose of co-administered medicine (mg)	N	% change of co-administered medicines Pharmacokinetic parameters[1] (90 % CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 mg once	8	↑122 (↓1 to ↑26)	⇔	NA
Adefovir dipivoxil	10 mg once	22	⇔	⇔	NA
Efavirenz	600 mg once daily x 14 days	30	⇔	⇔	⇔
Emtricitabine	200 mg once daily x 7days	17	⇔	⇔	⇔
Indinavir	800 mg three times daily x 7days	12	↑14 (↓3 to ↑33)	⇔	⇔
Lamivudine	150 mg twice daily x 7 days	15	⇔	⇔	⇔
Lopinavir/ Ritonavir	400/100 mg twice daily x 14 days	21	⇔	⇔	⇔
Methadone[2]	40-110 mg once daily x 14 days[3]	13	⇔	⇔	⇔
Oral Contraceptives[4]	Ethinyl Oestradiol/ Norgestimate	20	⇔	⇔	⇔

	(Ortho-Tricyclen®) Once daily x 7days				
Ribavirin	600 mg once daily	22	⇔	⇔	NA
Ritonavir	Lopinavir/Ritonavir 400/100 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)

1. Increase =↑; Decrease =↓; No Effect = ⇔; 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 where equivalent when dosed alone or with tenofovir as tenofovir disoproxil fumarate 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.

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 **VOLUTRIP**.

Zidovudine has no effect on the pharmacokinetics of **VOLUTRIP**.

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

Table 3: Medicine interactions study reports with lamivudine:

Concomitant medicine class: Medicine name	**Effect on concentration of lamivudine or concomitant medicine**	**Clinical comment**
Trimethoprim/ sulfamethoxazole (co-trimoxazole) (160 mg/800 mg once daily for 5 days/300 mg single dose)	Lamivudine: AUC ↑ 40 % Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔	Unless the patient has renal impairment, no do**sage adjustment of lamivudine is necessary (see "section 4.2"). Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole. The effect of co-administration of lamivudine with higher doses of co-trimoxazole used for the treatment of *Pneumocystis jirovecI* (*P. carinii*) *pneumonia* and toxoplasmosis has not been studied. VOLUTRIP should**

		not be used for patients with CLcr of < 50 ml/min (see section 4.2).
Zalcitabine		Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicines are used concurrently. **VOLUTRIP** is therefore not recommended to be used in combination with zalcitabine.
Zidovudine	AUC ↔	Co-administration of zidovudine results in a 13 % increase in zidovudine exposure and 28 % increase in peak plasma levels. This is not considered to be of significance to patient safety and therefore no dosage adjustments are necessary.

VOLUTRIP may inhibit the intracellular phosphorylation of zalcitabine when the two medicines are used concurrently. **VOLUTRIP** is therefore nor recommended to be used in combination with zalcitabine.

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

The possibility of interactions with other medicines administered concurrently should be considered, particularly when the main route is renal.

The co-administration of **VOLUTRIP** 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).

Dolutegravir:

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

There is evidence that the concentration of isoniazid is increased by dolutegravir, as contained in **VOLUTRIP.**

*Effect of dolutegravir as in **VOLUTRIP** on the pharmacokinetics of other medicines: In vitro*, dolutegravir as in **VOLUTRIP** demonstrated no direct, or weak inhibition (IC50 > 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.

In vitro, dolutegravir as in **VOLUTRIP** did not induce CYP1A2, CYP2B6 or CYP3A4. *In vivo*, dolutegravir as in **VOLUTRIP** did not have an effect on midazolam, a CYP3A4 probe. Based on these data, dolutegravir as in **VOLUTRIP** is not expected to affect the pharmacokinetics of medicines that are substrates of these enzymes or transporters (e.g., 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). In medicines interaction study reports, dolutegravir as in **VOLUTRIP** did 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.

In vitro, dolutegravir as in **VOLUTRIP** inhibited the renal organic cation transporter 2 (OCT2). Based on this report, dolutegravir as in **VOLUTRIP** may increase plasma concentrations of medicines in which excretion is dependent upon OCT2 (dofetilide, metformin) (see Table 4: Medicine Interactions - Other Medicines).

*Effect of other medicines on the pharmacokinetics of dolutegravir as in **VOLUTRIP**:* Dolutegravir as in **VOLUTRIP** is eliminated mainly through metabolism by UGT1A1. Dolutegravir as in **VOLUTRIP** 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 **VOLUTRIP**.

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

Efavirenz, nevirapine, rifampicin and tipranavir in combination with ritonavir each reduced the plasma concentrations of dolutegravir significantly and require dolutegravir dose adjustment to 50 mg twice daily. Etravirine also reduced plasma concentrations, but the effect of etravirine was 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 **VOLUTRIP** 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 decreased plasma concentrations of dolutegravir but does not require a dosage adjustment of dolutegravir as in **VOLUTRIP**. Caution is warranted and clinical monitoring is recommended when these combinations are given in INI-resistant patients (see below table: Medicine Interactions - HIV-1 Antiviral Medicines). A medicine interaction study with the UGT1A1 inhibitor, atazanavir, did not result

514 in a clinically meaningful increase in the plasma concentrations of dolutegravir. Tenofovir,
515 ritonavir, lopinavir/ritonavir, darunavir/ritonavir, rilpivirine, bocepravir, telaprevir, prednisone,
516 rifabutin, and omeprazole had no or a minimal effect on dolutegravir pharmacokinetics,
517 therefore no dolutegravir as in **VOLUTRIP** dose adjustment is required when co-administered
518 with these medicines.
519

520 **Table 4: Medicine interactions**

Concomitant medicine class: Medicine name	**Effect on concentration of dolutegravir or concomitant medicine**	**Clinical comment**
HIV-1 Antiviral Medicines		
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine (ETR)	Dolutegravir↓ AUC↓ 71% C_{max}↓52% C_T↓88% ETR↔	Etravirine decreased 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.

Non-nucleoside Reverse Transcriptase Inhibitor: Efavirenz (EFV)	Dolutegravir↓ AUC↓ 57% C_{max}↓ 39% C_T↓ 75% ETR↔	Efavirenz decreased dolutegravir plasma concentrations. The recommended 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.
Non-nucleoside Reverse Transcriptase Inhibitor: 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.

Protease Inhibitor: Atazanavir (ATV)	Dolutegravir↑ AUC↑ 91% C_{max}↑ 49% C_T↑ 180% ATV↔	Atazanavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Atazanavir/ritonavir (ATV + RTV)	Dolutegravir↑ AUC↑ 62% C_{max}↑ 33% C_T↑ 121% ATV↔ RTV↔	Atazanavir/ritonavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Tipranavir/ritonavir (TPV + RTV)	Dolutegravir↓ AUC↓ 59% C_{max}↓ 47% C_T↓ 76% TPV↔ RTV↔	Tipranavir/ritonavir decreases dolutegravir concentrations. 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.
Protease Inhibitor: Fosamprenavir/	Dolutegravir↓ AUC↓ 35% C_{max}↓ 24% C_T↓ 49%	Fosamprenavir/ritonavir decreases dolutegravir concentrations, but based on limited data, did not result in decreased efficacy in Phase III

ritonavir (FPV + RTV)	FPV↔ RTV↔	studies. 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.
Protease Inhibitor: 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.
Protease Inhibitor: Lopinavir/ritonavir (LPV + RTV)	Dolutegravir ↔ AUC↔ C_{max}↔ C_T↔ LPV↔ RTV↔	Lopinavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Darunavir/ritonavir (DRV + RTV)	Dolutegravir↓ AUC↓ 32% C_{max}↓ 11% C_T↓ 38% DRV↔	Darunavir/ritonavir did not change dolutegravir plasma concentrations to a clinically relevant extent. No dose adjustment is necessary.

	RTV↔	
Nucleoside Reverse Transcriptase Inhibitor: Tenofovir (TDF)	Dolutegravir↔ TFV↔	Tenofovir did not change dolutegravir plasma concentration to clinically relevant extent. No dose adjustment is necessary
Protease Inhibitor: Lopinavir/ritonavir + Etravirine (LPV/RTV + ETR)	Dolutegravir↔ AUC↑ 10% C_{max}↑ 7% C_T↑ 28% LPV↔ RTV↔ ETR↔	Lopinavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Darunavir/ritonavir + Etravirine (DRV/RTV+ETR)	Dolutegravir↓ AUC↓ 25% C_{max}↓ 12% C_T↓ 36% DRV↔ RTV↔	Darunavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Other Medicines		

Dofetilide Pilsicainide	Dofetilide↑ Pilsicainide↑	Co-administration of dolutegravir has the potential to increase dofetilide or pilsicainide plasma concentration via inhibition of OCT2 transporter; co-administration has not been studied. Dofetilide or pilsicainide co-administration with dolutegravir is contraindicated due to the potential life-threatening toxicity caused by high dofetilide or pilsicainide concentration (see section 4.3).
Oxcarbazepine Phenytoin Phenobarbitone Carbamazepine St.John's wort	Dolutegravir↓	Co-administration may decrease dolutegravir plasma concentration and has not been studied. Co-administration with these metabolic inducers should be avoided.
Antacids containing polyvalent cations (e.g. Mg, Al or Ca)	Dolutegravir↓ AUC↓ 74% C_{max}↓ 72% C_{24}↓ 74%	Co-administration of antacids containing polyvalent cations decreased dolutegravir plasma concentration. Dolutegravir is recommended to be administered 2 hours before or 6 hours after taking antacid products containing polyvalent cations.

Calcium supplements	Dolutegravir↓ AUC↓ 39% C_{max}↓ 37% C_{24}↓ 39%	Dolutegravir is recommended to be administered 2 hours before or 6 hours after taking products containing calcium, or alternatively, administer with food.
Iron supplements	Dolutegravir↓ AUC↓ 54% C_{max}↓ 57% C_{24}↓ 56%	Dolutegravir is recommended to be administered 2 hours before or 6 hours after taking products containing iron, or alternatively, administer with food.
Metformin	Metformin↑	Co-administration of dolutegravir increased metformin plasma concentration. Metformin is contraindicated in patients taking dolutegravir (see section 4.3).
Rifampicin	Dolutegravir↓ AUC↓ 54% C_{max}↓ 43% C_T↓ 72%	Rifampicin decreased dolutegravir plasma concentration. The recommended dose of dolutegravir is 50 mg twice daily when co-administered with rifampicin. Alternatives to rifampicin should be used where possible for INI-resistant patients.

Oral contraceptives (Ethinyl estradiol (EE) and Norgestromin (NGMN)	Effect of dolutegravir: EE↔ AUC↑ 3% C_{max}↓ 1% C_T↑ 2% Effect of dolutegravir: NGMN↔ AUC↓ 2% C_{max}↓ 2% C_T↓ 7%	Dolutegravir did not change ethinyl estradiol and norgestromin plasma concentrations to clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with dolutegravir.
Methadone	Effect of dolutegravir: Methadone↔ AUC↓ 2% C_{max} ↔ 0% C_T↓ 1%	Dolutegravir did not change methadone plasma concentrations to a clinically relevant extent. No dose adjustment of methadone is necessary when co-administered with dolutegravir.
Azole anti-fungals: Ketoconazole Fluconazole Itraconazole Posaconazole	Dolutegravir ↔ (Not studied)	No dose adjustment is necessary. Based on data from other CYP3A4 inhibitors, a marked increase is not expected.

Voriconazole		

Abbreviations: ↑ = increase; ↓ = decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; C_{max} = maximum observed concentration; CT = concentration at the end of dosing interval.

VOLUTRIP should not be co-administered with polyvalent cation-containing antacids. **VOLUTRIP** is recommended to be administered 2 hours before or 6 hours after these medicines (see section 4.5).

Metformin concentrations may be increased by **VOLUTRIP**. Metformin is contra-indicated in patients taking **VOLUTRIP** (see section 4.3).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Women of childbearing potential should be counselled about the potential risk of neural tube defects with dolutegravir (see below), including consideration of using effective contraceptive measures. Perform pregnancy testing before initiation of **VOLUTRIP** in women of childbearing potential to exclude inadvertent (unintentional) use of **VOLUTRIP** during the first trimester of pregnancy. If a woman plans pregnancy, the benefits and the risks of starting or continuing treatment with dolutegravir versus using another antiretroviral regimen should be discussed with her.

Pregnancy

VOLUTRIP is contraindicated in pregnancy and lactation (see section 4.3). Use of dolutegravir 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, the benefits and risks of continuing dolutegravir 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 may be used during the second and third trimester of pregnancy when the expected benefit outweighs the potential risk to the foetus. Dolutegravir 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 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 to nucleoside analogues *in utero* such as tenofovir and lamivudine, (see Mitochondrial Dysfunction under section 4.4).

VOLUTRIP should not be prescribed in women who plan to become pregnant. Women of childbearing age should not use **VOLUTRIP** unless they are reliably using highly effective contraception. Treatment with **VOLUTRIP** should not be initiated without a medically supervised negative pregnancy test.

This test should be repeated at frequent intervals during treatment with **VOLUTRIP**; and especially in the event that pregnancy is suspected.

Breastfeeding

HIV infected women should not breast-feed their infants in order to avoid transmission of

Tenofovir

Tenofovir is excreted in breast milk

HIV or follow appropriate guidelines. breastfeeding their infants should not use **VOLUTRIP**.

Dolutegravir

Dolutegravir 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 in neonates/infants.

Lamivudine

Lamivudine is excreted in human milk at similar concentrations to those found in serum

Fertility

There are no data on the effects of dolutegravir on human male or female fertility. Animal studies indicate no effects of dolutegravir on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

VOLUTRIP may affect the ability to drive and use machines as it may cause dizziness and drowsiness. Patients should ensure that they do not engage in driving or using machines until they know how **VOLUTRIP** affects them.

4.8 Undesirable effects

a) Summary of the safety profile

Studies revealed the most severe adverse reactions linked to dolutegravir treatment are

hypersensitivity reactions that include rash and severe liver effects.

The most common adverse reactions of dolutegravir are nausea (13 %), diarrhoea (18 %) and headache (13%).

Renal impairment, renal failure and proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have been reported rarely in patients receiving tenofovir disoproxil. Monitoring of renal function is recommended for patients receiving **VOLUTRIP** (see section 4.4).

b) Tabulated list of adverse reactions

- Frequency not known- cannot be estimated from the available data.

Lamivudine

System Organ Class	Adverse effect	Frequency
Blood and the lymphatic system disorders:	Anaemia, neutropenia, thrombocytopaenia	Less frequent
	pure red cell aplasia.	Frequency unknown
Metabolism and nutrition disorders:	Hyperlactataemia	Frequent
	Lactic acidosis; lipodystrophy (redistribution/accumulation of body fat)	Less frequent
Nervous system disorders:	Headache, insomnia	Frequent
	Peripheral neuropathy (or paraesthesia), late onset neurological disorders in children exposed in utero.	Less frequent
Gastrointestinal disorders	Nausea, vomiting; upper abdominal pain or cramps; diarrhoea; stomatitis	Frequent
	Pancreatitis, elevations in serum amylase	Less frequent
Hepato-biliary disorders	Transient rises in liver enzymes (AST, ALT)	Less frequent
Skin and subcutaneous tissue disorders:	Rash, alopecia	Frequent:
Musculoskeletal, connective tissue and bone disorders:	Arthralgia, muscle disorders	Frequent:
	Rhabdomyolysis, decrease in bone mineral density, osteopenia, fractures	Less frequent
General disorders and administrative site conditions:	Fatigue, malaise, fever	Frequent

609 **Tenofovir disoproxil fumarate:**

Organ Class	Adverse effect	Frequency
Immune system disorders:	allergic reaction	Less frequent:
Gastrointestinal disorders:	Abdominal pain, anorexia, dyspepsia, flatulence	Frequent:
	Increased amylase, pancreatitis	Less frequent
Hepato-biliary disorders:	Increased liver enzymes, hepatitis	Less frequent
Metabolism and nutrition disorders	Hypophosphatemia	Frequent
	Lactic acidosis	Less frequent
Renal and urinary disorders	Renal insufficiency, renal failure, proximal tubulopathy, proteinuria, increased creatinine, acute tubular necrosis, nephrogenic diabetes insipidus, Fanconi syndrome, polyuria, interstitial nephritis.	Frequent

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Respiratory, thoracic and mediastinal disorders:	Dyspnoea	Frequency unknown
Nervous system disorders:	Dizziness	Frequent
Musculoskeletal, connective tissue and bone disorders:	Rhabdomyolysis [1]; muscular weakness[1]; osteomalacia (manifested as bone pain and infrequently contributing to fractures)[1, 2,] myopathy[1]	Less frequent:
[1]This side effect may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil fumarate in the absence of this condition. [2]This side effect was identified through post-marketing surveillance.		
General disorders and administration site conditions:	Asthenia	Frequent

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614 **Dolutegravir:**

Organ Class	Adverse effect	Frequency
Immune system disorders:	Hypersensitivity, immune reconstitution syndrome	Less frequent:
Psychiatric disorders	Insomnia	Frequent
Nervous system disorders	Headache, dizziness, abnormal dreams	Frequent
Gastrointestinal disorders:	Nausea, diarrhoea	Frequent:
	Vomiting, flatulence, upper abdominal pain	Less frequent:
	Abdominal pain, abdominal discomfort	Frequency unknown
Hepatobiliary disorders	Hepatitis	Frequency unknown:
Skin and subcutaneous tissue disorders:	Rash, pruritus	Frequent:
General disorders and administration site conditions:	Fatigue	Frequent

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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 asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website

4.9 Overdose

Signs and symptoms:

If overdose occurs the patient must be monitored for evidence of toxicity (see sections 4.8 and 5.3), and standard supportive treatment applied as necessary.

Tenofovir disoproxil fumarate:

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 overdose in humans.

If overdosage occurs the patient should be monitored, and palliative supportive treatment applied are 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 **VOLUTRIP**. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. As **VOLUTRIP** is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A.20.2.8 Antiviral agents.

Pharmacotherapeutic group: Direct acting antivirals, Antivirals for treatment of HIV

ATC Code: J05AR12

Mechanism of action

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 active 5'-triphosphate which has an intracellular half-life of 16-19 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 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 DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Drug 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 and 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 selected by tenofovir is also selected in some HIV-1 infected patients treated

with 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 reported. 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.

5.2 Pharmacokinetic properties

Lamivudine:

Absorption:

Lamivudine is well absorbed from the gastrointestinal tract and the bioavailability of oral lamivudine in adults is normally between 80 % and 85 %. 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 two 12-hourly doses), C_{max} is in the order of 1-1,5 µg/ml.

Distribution and elimination:

The mean volume of distribution is 1,3 L/kg and the mean terminal half-life of elimination is 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0,32 L/kg/h, with predominantly renal clearance (> 70 %) via active tubular secretion, but little (< 10 %) hepatic metabolism. No dose adjustment is needed when co-administered with food as lamivudine bioavailability is not altered, although a delay in T_{max} and reduction in C_{max} have been reported.

Linearity:

Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin. Lamivudine elimination will be affected by renal impairment, whether it is disease- or age-related.

Interactions:

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. The likelihood of adverse interactions with lamivudine is low due to the limited metabolism and plasma protein binding and almost complete renal clearance.

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

Dolutegravir

Dolutegravir pharmacokinetics are reported as similar between healthy and HIV-infected patients. The PK variability of dolutegravir is between low to moderate. In Phase 1 studies in healthy patients, interpatient CVb % for AUC and C_{max} ranged from ~20 to 40 % and C_T from 30 to 65 % across studies. The interpatient PK variability of dolutegravir was higher in HIV-infected patients than healthy patients. Intrapatient variability (CVw %) is lower than interpatient variability.

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 dose and formulation. Following oral administration of tablet formulations, dolutegravir exhibited non-linear pharmacokinetics with less than dose-proportional increases in plasma exposure from 2 to 100 mg; however an increase in dolutegravir exposure appears dose proportional from 25 mg to 50 mg.

Dolutegravir may be administered with or without food. 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 34 %, 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 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 based on *in vitro* data.

The apparent volume of distribution (following oral administration of suspension formulation, Vd/F) is estimated at 12,5 L. Binding of dolutegravir to plasma proteins was independent of concentration. Total blood and plasma medicine-related radioactivity concentration ratios averaged 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 patients 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}); CSF: plasma concentration ratio of dolutegravir ranged from 0,11 to 0,66 %. Dolutegravir concentrations in CSF exceeded the IC_{50}, supporting the median reduction from baseline in CSF HIV-1 RNA of 2,1 log after 2 weeks of therapy (see section 5.1).

Metabolism:

Dolutegravir is primarily metabolised via UGT1A1 with a minor CYP3A component (9,7 % of total dose administered in a human mass balance study). 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 ~14 hours and an apparent clearance (Cl/F) of 0,56 L/hr.

Tenofovir disoproxil fumarate

Absorption:

Tenofovir disoproxil fumarate is a water soluble diester prodrug 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 300

mg to HIV-1 infected patients in the fasted state, maximum serum concentrations (Cmax) are achieved in 1,0 ± 0,4 hrs. Cmax and AUC values are 296 ± 90 ng/ml and 2287 ± 685 ng h/ml, respectively.

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

Administration of tenofovir following a high-fat meal (~ 700 to 1000 kcal containing 40 to 50 % fat) increases the oral bioavailability, with an increase in tenofovir AUC0-∞ of approximately 40 % and an increase in Cmax of approximately 14 %. However, administration of tenofovir with a light meal did not have a significant effect on the pharmacokinetics of tenofovir when compared to fasted administration of the medicine. Food delays the time to tenofovir Cmax by approximately 1 hour. Cmax and AUC of tenofovir are 326 ± 119 ng/ml and 3324 ± 1370 ng h/ml following multiple doses of tenofovir 300 mg once daily in the fed state, when meal content was not controlled.

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:

In vitro studies reported that neither tenofovir disoproxil nor tenofovir are substrates of CYP450 enzymes. Following single dose, oral administration of tenofovir, 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. There may be competition for elimination with other compounds that are also renally eliminated.

Pharmacokinetics in special patient groups

Tenofovir

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, Cmax, and AUC0-∞ 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 hemodialysis with an extraction coefficient of approximately 54 %. Following a single 300 mg dose of tenofovir, a four-hour hemodialysis session removed approximately 10 % of the administered tenofovir dose.

Dolutegravir

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.

Table 1: 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 > 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, Cmax and C24 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 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

Paediatric population:

The absolute bioavailability of lamivudine (approximately 55 - 65 %) was reduced in paediatric patients below 12 years of age. In addition, systemic clearance values were greater in younger paediatric patients and decreased with age approaching adult values around 12 years of age. Recent findings indicate that exposure in children 2 to < 6 years of age may be reduced by about 30 % compared with other age groups. At present, the available data do not suggest that lamivudine is less efficacious in this group. There are limited pharmacokinetic data for patients < 3 months of age. In neonates one week of age, lamivudine oral clearance was reduced when compared to paediatric patients and is likely due to immature renal function and variable absorption.

Pharmacokinetics in pregnancy:

Pharmacokinetics in pregnancy: Lamivudine pharmacokinetics in late-pregnancy were similar to non-pregnant adults. Administration of lamivudine in animal toxicity studies at very high doses was not associated with any major organ toxicity. The clinically relevant effects noted were a reduction in red blood cell count and neutropenia. Lamivudine was not mutagenic in bacterial tests but, like many nucleoside analogues, showed activity in an in vitro cytogenic assay. Lamivudine was not genotoxic in vivo at doses that gave plasma concentrations around 30-40 times higher than the anticipated clinical plasma levels. As the in vitro mutagenic activity of lamivudine could not be confirmed in in vivo tests it is concluded that lamivudine should not represent a genotoxic hazard to patients undergoing treatment. There is as yet no information on the tumorigenic risk in animals, and therefore any potential risk to man must be balanced against the expected benefits of treatment.

5.3 Preclinical safety data

N/A

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

- croscarmellose sodium,
- ferric oxide, hypromellose,
- magnesium stearate,
- mannitol,
- microcrystalline cellulose,
- opadry II pink 85F94172,
- povidone,
- sodium starch glycolate
- sodium stearyl fumarate.

Tablet coating: opadry II pink 85F94172

- iron oxide red (C.I. No: 77491)
- oxide black (C.I. No: 77499),
- polyethylene glycol
- talc
- titanium dioxide (C.I. No: 77891)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the desiccant sachet in the container. Do not remove the desiccant sachet. Keep the tablets in the original container.

Keep HDPE containers tightly closed.

6.5 Nature and contents of container

Pack size: 28s.Tablets are packed in white opaque round 75 ml HDPE container with 38 mm neck finish closed with white opaque polypropylene 38 mm - 400 child resistant closure with wad having induction sealing liner. The HDPE container also contains 3 g of silica gel sachet. Each container contains 28 tablets and is packed in an outer cardboard carton.

Pack size: 30s

Tablets are packed in white opaque round 100 ml HDPE container with 38 mm neck finish closed with white opaque polypropylene 38 mm - 400 child resistant closure with wad having induction sealing liner. The HDPE container also contains 3 g of silica gel sachet. Each container contains 30 tablets and is packed in an outer cardboard carton.

Pack size: 30's –

Tablets are packed in white opaque round 100 ml HDPE container with 38 mm neck finish closed with white opaque polypropylene 38 mm - 400 child resistant closure with wad having induction sealing liner. The HDPE container also contains two 3 g of silica gel sachet. One HDPE container contains 30 tablets.

Pack size: 84's-Tablets are packed in white, opaque, round 200 mL HDPE container with 38 mm neck finish closed with white opaque polypropylene 38 mm - 400 mm child resistant closure with wad having induction sealing liner. The HDPE container also contains two 3 g silica gel sachets.

One HDPE container contains 84 tablets

Pack size: 90's

Tablets are packed in white opaque round 400 ml HDPE container with 38 mm neck finish closed with white opaque polypropylene 38 mm - 400 child resistant closure with wad having induction sealing liner. The HDPE container also contains three 3 g of silica gel sachet.

One HDPE container contains 90 tablets

Pack size: 180's – Tablets are packed in white, opaque, round 400 mL HDPE container with 53 mm neck finish closed with white opaque polypropylene 53 mm - 400 mm child resistant closure with wad having induction sealing liner. The HDPE container also contains three 3 g silica gel sachet.

One HDPE container contains 180 tablets

6.6 Special precautions for disposal and other handling

This medicine does not require any special storage conditions.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Aurobindo Pharma (Pty) Ltd
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8 REGISTRATION NUMBER(S)

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10 DATE OF REVISION OF THE TEXT

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