SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DOLAMVIR 50 mg/300 mg /300 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect: Contains sugar: 145,37 mg mannitol.

For the full list of excipients, see section 6.1.

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 SECTION 4.4).

DOLAMVIR IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION. THE SAFETY AND EFFICACY OF DOLMVIR 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 COINFECTED 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 DOLMVIR AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE SECTION 4.4).

3. PHARMACEUTICAL FORM

Film-coated tablets.

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 indications

DOLAMVIR 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

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

Adults:

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

Special Populations:

Renal impairment:

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

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

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

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

DOLAMVIR 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 DOLAMVIR.

Paediatric Population:

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

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity reaction to dolutegravir, lamivudine or tenofovir disoproxil fumarate or to any of the excipients listed in section 6.1.
- Impairment of renal function (see section 4.4).
- 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

Safety and efficacy of the individual active ingredients in various antiretroviral combination regimens with similar dosages as contained in DOLAMVIR have been established in clinical studies for the treatment of HIV patients. However, safety and efficacy of the fixed-drug combination as in DOLAMVIR 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.

Metabolic abnormalities

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

Lipodystrophy

Combination antiretroviral therapy, including DOLAMVIR has 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.

Patients with evidence of lipodystrophy should 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, cytomegalovirus retinitis, and cryptococcal meningitis.

Appropriate treatment of the opportunistic disease should be instituted, 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) 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). 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 DOLAMVIR 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 should be advised that current antiretroviral therapy, including DOLAMVIR, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Lactic acidosis / hyperlactataemia

Use of DOLAMVIR can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction.

Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss.

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

- Lactate 2-5 mmol/L with minimum symptoms: switch to medicines that are less likely to cause lactic acidosis.
- Lactate 5-10 mmol/L with symptoms and/or with reduced standard bicarbonate: Stop NRTIs and change treatment option. Once lactate has settled, use medicines that are less likely to cause lactic acidosis. Exclude other causes, (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis and hyperthyroidism.
- Lactate > 10 mmol/L: STOP all therapy (80 % mortality).

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

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

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

Mitochondrial dysfunction

Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV negative infants exposed in utero and/or post-natally to nucleoside analogues. Apart from lactic acidosis/hyperlactataemia (see above) other manifestations of mitochondrial dysfunction include haematological disorders (anaemia, neutropenia), and peripheral neuropathy. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). It is not known whether the neurological disorders are transient or permanent. Any foetus exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative infants/children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant sign and symptoms.

Pancreatitis

Pancreatitis has been observed in some patients receiving DOLAMVIR.

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

Liver disease

Use of DOLAMVIR can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of DOLAMVIR has not been established in patients with significant underlying liver disorders/diseases. In case of concomitant antiviral therapy for hepatitis B or C, please also consult the relevant professional information for these medicines.

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. If there is evidence of worsening liver disease in such patients, temporary or permanent discontinuation of treatment must be considered.

Patients with renal impairment

In patients with moderate to severe renal impairment, the terminal half-life of DOLAMVIR is increased due to decreased clearance.

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

DOLAMVIR 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 DOLAMVIR.

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 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.

DOLAMVIR 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 phosphorus.

K65R mutation

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

Bone mineral density

Decreases in bone mineral density of the spine and changes in bone biomarkers from baseline are significantly greater with tenofovir disoproxil fumarate, as contained in DOLAMVIR. 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.

DOLAMVIR 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

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.

Patients co-infected with HIV and HBV who discontinue DOLAMVIR should be closely monitored with both clinical and laboratory follow-up after stopping treatment. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Discontinuation of DOLAMVIR therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

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 exacerbation 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 and were characterised by rash, constitutional findings and sometimes organ dysfunction, including liver injury. Discontinue DOLAMVIR 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 DOLAMVIR, 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 use

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

Use in elderly

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

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

The likelihood of interactions is low due to the limited metabolism and 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 (40 %) 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. Administration of co-trimoxazole with the lamivudine/zidovudine combination in patients with renal impairment should be carefully assessed.

No medicine interaction studies have been conducted using DOLAMVIR. As DOLAMVIR contains tenofovir disoproxil fumarate and lamivudine, any interactions that have been identified with these individual medicines may occur with DOLAMVIR. Important medicine interaction information for DOLAMVIR is summarised in Table 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.

Renally eliminated medicines

Tenofovir, as in DOLAMVIR, is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Co-administration of DOLAMVIR 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 DOLAMVIR.

Tenofovir

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 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 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 % Cl)**		
			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 x 14 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 tenofovir DF 300 mg once daily

2. Increase = ↑; Decrease = ↓; No effect = ↔; NC = Not calculated

Following multiple dosing to HIV-negative subjects 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 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)	↔	N/A
Adefovir dipivoxil	10 once	22	↔	↔	N/A
Efavirenz	600 mg once daily x 14 days	30	↔	↔	↔
Emtricitabine	200 mg once daily	17	↔	↔	↔
Indinavir	800 mg three times daily x 7 days	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 once daily x 14 days[3]	13	↔	↔	↔
Oral contraceptives[4]	Ethinyl oestradiol/ norgestimate (Ortho-Tricyclen®) Once daily x 7 days	20	↔	↔	↔
Ribavirin	600 once	22	↔	↔	N/A
Ritonavir	Lopinavir/ritonavir 400/100	24	↔	↔	↔

	twice daily x 14 days				
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 subjects 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 disoproxil fumarate 300 mg.
5. Reyataz US prescribing information (Bristol-Meyers 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 DOLAMVIR. Zidovudine has no effect on the pharmacokinetics of DOLAMVIR.

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 (cotrimoxazole) (160 mg/800 mg once daily for 5 days/300 mg single dose)	Lamivudine: AUC ↑ Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔	Unless the patient has renal impairment, no dosage adjustment, of lamivudine is necessary. Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole. The effect of coadministration of lamivudine with higher doses of cotrimoxazole used for the treatment of *Pneumocystis jirovecl* (*P. carinii*) *pneumonia* and toxoplasmosis has not been studied. DOLAMVIR should not be used for patients with CLcr of < 50 mL/min (see section 4.3).

Zalcitabine		Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicines are used concurrently. DOLAMVIR 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.

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

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

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

Effects of DOLAMVIR on the pharmacokinetics of other medicines:

In vitro, dolutegravir as in DOLAMVIR demonstrated no direct, or weak inhibition (lC50 > 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 DOLAMVIR did not induce CYP1A2, CYP2B6 or CYP3A4. *In vivo*, dolutegravir as in DOLAMVIR did not have an effect on midazolam, a CYP3A4 probe. Based on these data, dolutegravir as in DOLAMVIR 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 DOLAMVIR 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 DOLAMVIR inhibited the renal organic cation transporter 2 (OCT2). Based on this report, dolutegravir as in DOLAMVIR may increase plasma concentrations of medicines in which excretion is dependent upon OCT2 (dofetilide, metformin) (see Table 4: Medicine Interactions - Other Medicines).

Effects of other medicines on the pharmacokinetics of dolutegravir, as in DOLAMVIR:

Dolutegravir, as in DOLAMVIR, is eliminated mainly through metabolism by UGT1A1. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp and BCRP; therefore, medicines that induce those enzymes may theoretically decrease dolutegravir plasma concentrations and reduce the therapeutic effect of dolutegravir in DOLAMVIR. Co-administration of DOLAMVIR and other medicines that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or Pgp may increase dolutegravir plasma concentration.

Efavirenz, nevirapine, rifampicin and tipranavir in combination with ritonavir each reduces the plasma concentrations of dolutegravir significantly and requires dolutegravir dose adjustment of 50 mg twice daily. Etravirine also reduces 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 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. Caution is warranted, and clinical monitoring is recommended when these combinations are given in INI-resistant patients. A medicine interaction study with the UGT1A1 inhibitor, atazanavir, did not result in a clinically meaningful increase in the plasma concentrations of dolutegravir. Tenofovir, ritonavir, lopinavir/ritonavir, darunavir/ritonavir, rilpivirine, bocepravir, telaprevir, prednisone, rifabutin and omeprazole had no or a minimal effect on dolutegravir pharmacokinetics, therefore no dose adjustment of dolutegravir as contained in DOLAMVIR is required when co- administered with these medicines.

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 % Cmax↓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:	Dolutegravir↓	Fosamprenavir/ritonavir decreases dolutegravir

Fosamprenavir/ ritonavir (FPV + RTV)	AUC↓ 35 % C_{max}↓ 24 % C_T↓ 49 % FPV↔ RTV↔	concentrations, but based on limited data, did not result in decreased efficacy in Phase III 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↔ RTV↔	Darunavir/ritonavir did not change dolutegravir plasma concentrations to a clinically relevant extent. No dose adjustment is necessary.
Nucleoside Reverse	Dolutegravir↔	Tenofovir did not change dolutegravir plasma

Transcriptase Inhibitor: Tenofovir (TDF)	TFV↔	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; coadministration 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 % C24↓ 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 % C24↓ 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 % C24↓ 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 %	Rifampicin decreased dolutegravir plasma concentration. The recommended dose of dolutegravir

	C_{max}↓ 43 % C_T↓ 72 %	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.

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.

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

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

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

DOLAMVIR should not be prescribed in women who plan to become pregnant. Women of child-bearing age should not use DOLAMVIR unless they are reliably using highly effective contraception. Treatment with DOLAMVIR should not be initiated without a medically supervised negative pregnancy test. This test should be repeated at frequent intervals during treatment with DOLAMVIR, and especially in the event that pregnancy is suspected.

Pregnancy

DOLAMVIR is contraindicated in pregnancy and lactation. Neural tube defects have been noted in an observational study in humans, where DTG-bases regimens were used at the time of conception and early pregnancy, (see section 4.3).

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 section 4.4).

Breastfeeding

Mothers breastfeeding their infants should not use DOLAMVIR. Lamivudine is excreted in human milk at similar concentrations to those found in serum; tenofovir is excreted in breast milk and it is not known whether dolutegravir is excreted in human milk.

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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Table 5:

Tabulated summary of adverse reactions associated with the individual components of DOLAMVIR.

Lamivudine

System organ class	**Frequent**	**Less frequent**	**Frequency unknown**
Blood and the lymphatic system disorders		Neutropenia, anaemia, thrombocytopenia	Pure red cell aplasia
Endocrine disorders			Hyperglycaemia
Metabolism and nutrition disorders	Hyperlactataemia	Lactic acidosis, lipodystrophy	

		(redistribution/ accumulation of body fat) (see section 4.4)	
Nervous system disorders	Headache, insomnia	Peripheral neuropathy (or paraesthesia), late onset neurological disorders in children exposed *in utero*	
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, upper abdominal pain or cramps, stomatitis	Pancreatitis, elevations in serum amylase.	
Hepato-biliary disorders		Transient rises in liver enzymes (AST, ALT)	
Hepato-biliary disorders			Hepatic steatosis, hepatitis
Skin and subcutaneous tissue disorders	Rash, alopecia		Anaphylaxis, urticaria, pruritus
Musculoskeletal, connective tissue and bone disorders	Arthralgia, muscle disorders	Rhabdomyolysis, decrease in bone mineral density, osteopenia, fractures	Myasthenia, CPK elevation

General disorders and administration site conditions	Fatigue, malaise, fever		

Tenofovir disoproxil fumarate

System organ class	Frequent	Less frequent	Frequency unknown
Immune system disorders		Allergic reactions, including angioedema	
Metabolism and nutrition disorders			Hypophosphatemia, lactic acidosis, hypokalaemia
Respiratory, thoracic and mediastinal disorders			Dyspnoea
Gastrointestinal disorders	Anorexia, dyspepsia, flatulence, abdominal pain	Pancreatitis, increased amylase	
Hepato-biliary disorders		Increased liver enzymes, hepatitis	Hepatic steatosis
Skin and subcutaneous tissue disorders			Rash
Musculoskeletal, connective tissue and bone disorders			Rhabdomyolysis, osteomalacia (manifested as bone

			pain and which may contribute to fractures), myasthenia, myopathy
Renal and urinary disorders	Renal insufficiency, renal failure, proximal tubulopathy, proteinuria, increased creatinine, acute tubular necrosis, nephrogenic diabetes insipidus		Interstitial nephritis (including acute cases), polyuria
General disorders and administration site conditions			Asthenia

Dolutegravir:

System organ class	**Frequent**	**Less frequent**	**Frequency unknown**
Immune system disorder		Hypersensitivity, immune reconstitution syndrome	
Endocrine disorders		Hyperglycaemia	
Psychiatric disorders	Insomnia, depression	Suicidal ideation, attempt, behaviour, or completion. (These	

		events were observed primarily in subjects with a pre-existing history of depression or other psychiatric illness.)	
Nervous system disorders	Headache, dizziness, abnormal dreams		
Ear and labyrinth disorders	Vertigo		
Gastrointestinal disorders	Nausea, diarrhoea	Vomiting, flatulence, upper abdominal pain	Abdominal pain and discomfort
Hepato-biliary disorders		Transient rises in liver enzymes (AST, ALT)	Hepatitis
Skin and subcutaneous tissue disorders	Rash, pruritus		
Musculoskeletal and connective tissue disorders		Myositis	Arthralgia, myalgia
Renal and urinary disorders		Renal impairment, increase in serum creatinine	

General disorders and administration site conditions	Fatigue		

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. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Tenofovir disoproxil fumarate

If overdose occurs, the patient must be monitored for evidence of toxicity, and standard supportive treatment 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 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 dolutegravir as contained in DOLAMVIR. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaceutical classification: A 20.2.8 Antiviral Medicines.

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.

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 IC50 (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 (IC50 values ranged from 0,5 μM to 2,2 μM). The IC50 values of tenofovir against HIV-2 ranged from 1,6 μM to 4,9 μM.

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, Cmax, and AUC0-∞ of tenofovir were increased. 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

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 (t½ 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 S135Y 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 1sextuple) 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 paraaminohippurate (PAH) as the probe was evaluated. A small decrease of 10-14 % 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 increase 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.

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 6: 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, C_{max} 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 coinfection.

5.2 Pharmacokinetic properties

Lamivudine

Pharmacokinetics in adults: 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. 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. 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.

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 CT 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-∞) 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 IC50); 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 either 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

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 ($C_{max)}$ are achieved in 1,0 ± 0,4 hrs. C_{max} 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 AUC $_{0-\infty}$ of approximately 40 % and an increase in C_{max} 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 C_{max} by approximately 1 hour. C_{max} 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.

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.

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.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Colloidal silicon dioxide

Croscarmellose sodium

Ferric oxide

Hypromellose

Magnesium stearate

Mannitol

Microcrystalline Cellulose

Povidone USP

Sodium starch glycollate

Sodium stearyl fumarate

Tablet coating

Opadry II Pink 85F94172 containing:

Ferrosoferric oxide / Black Iron Oxide

Iron oxide red

Macrogol

Polyvinyl alcohol – part hydrolysed

Talc

Titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 30 °C in HDPE container packs.

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

DOLAMVIR are packed in round wide mouth white opaque 100 mL HDPE container closed with white opaque polypropylene 38 mm - 400 polypropylene child resistant closure with wad having induction sealing liner. The HDPE container also contains 3 g of silica gel sachet. This HDPE container will be further packed in preprinted carton with package leaflet.

Each container contains 30 tablets.

Pack size: 30’s - One HDPE container contains 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novagen Pharma (Pty) Ltd

Office 2

100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Drive

Irene

Pretoria

0157

8. REGISTRATION NUMBER(S)

56/20.2.8/0342

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 October 2023

10. DATE OF REVISION OF THE TEXT

10 October 2023