APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

VIRLAM, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each VIRLAM film-coated tablet contains 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate, equivalent to 245 mg of tenofovir disoproxil.

VIRLAM contains sugar (lactose - 39,4 mg)

For the full list of excipients, see section 6.1

LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS

There have been reports of lactic acidosis and severe hepatomegaly with steatosis, which were fatal in some instances, with the use of nucleoside analogues alone or in combination with other antiretrovirals (see section 4.4). Early symptoms (symptomatic hyperlactataemia) include benign symptoms of the digestive tract (abdominal pain, nausea and vomiting), loss of weight or appetite, malaise that is non-specific, Neurological symptoms (including motor weakness) or respiratory symptoms (deep and/or rapid breathing). Lactic acidosis is linked to a high mortality rate and may be associated with pancreatitis, renal failure, or liver failure. Generally,

lactic acidosis arose following a few or several months of therapy.

In the case of symptomatic hyperlactataemia and metabolic/lactic acidosis, progressive hepatomegaly or rapidly increasing levels of aminotransferase, VIRLAM treatment should be stopped.

When administering VIRLAM to any patient (obese women in particular) with hepatitis, hepatomegaly or other known risk factors for liver disease and hepatic steatosis (including use of certain medicines and alcohol), caution should be exercised.

Patients with hepatitis C co-infection receiving treatment with ribavirin and alpha-interferon may pose a special risk.

Patients at great risk must be monitored carefully.

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, thyrotoxicosis, lymphoma).**
- **Lactate > 10 mmol/l: STOP all therapy (80 % mortality in case studies).**

Demonstrating metabolic acidosis with an increased anion gap and a raised lactate level confirms the diagnosis of lactic acidosis. Therapy should be discontinued in any acidotic patient with a raised lactate level.

Blood for lactate assays should be heparinised and stored on ice.

After recovery, use of NRTIs should be avoided. Seek expert advice on medicine selection.

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

HEPATITIS B AND HIV-1 INFECTION:

VIRLAM is not indicated in the treatment of chronic infection with the hepatitis B virus (HBV). The safety and efficacy of VIRLAM have not been determined in patients with HBV and HIV co-infection. Acute severe exacerbations of hepatitis B infection have been observed in individuals who are HBV and HIV co-infection and have stopped taking VIRLAM.

Patients with HIV and HBV co-infection who have stopped taking VIRLAM require close monitoring of their hepatic function for no less than several months; this should include both laboratory and clinical follow-up. If appropriate, initiation of treatment for hepatitis B infection may be necessary.

HBV antibody testing should be offered to all individuals before initiating therapy with lamivudine and tenofovir disoproxil (see below Co-infection with HIV-1 and hepatitis B).

3. PHARMACEUTICAL FORM

Oral film coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VIRLAM, in combination with other antiretroviral medicines, is indicated for the treatment of HIV-infected adults over the age of 18 years

4.2 Posology and method of administration

A healthcare provider with experience in the management of HIV infection should initiate VIRLAM treatment.

Posology

Adults and adolescents older than 18 years:

The recommended dosage in one VIRLAM tablet taken orally with food once daily.

Special populations

Elderly:

VIRLAM should be used with caution in patients > 65 years of age (see section 4.4 and 4.8).

Renal impairment:

Patients with moderate to severe impairment of renal function should not use VIRLAM (see section 4.3).

Hepatic impairment:

Patients with impaired hepatic function do not require dose adjustments.

Paediatric population

The use of VIRLAM is not recommended in children younger than 18 years of age.

Method of administration

It is recommended that VIRLAM be swallowed whole with water.

VIRLAM can be taken with food or between meals.

4.3 Contraindications

- Hypersensitivity to lamivudine or tenofovir, or to any of the ingredients of VIRLAM
- Patients with moderate to severe renal function impairment (CrCl < 50 ml/min) (see section 5.2), since dose adjustments are not possible with a fixed dose combination such as VIRLAM
- Pregnancy and lactation (see section 4.6)
- Patients under the age of 18 years
- Combination with zalcitabine (see section 4.5)

4.4 Special warnings and precautions for use

Metabolic abnormalities

Combination antiretroviral therapy is also associated with metabolic disturbances, including hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia.

Renal disease:

See section 4.3, 4.4 and 4.8.

Elimination of the tenofovir and lamivudine is principally via the renal route. In all patients with creatinine clearance < 50 ml/min adjustment of the dosing interval is recommended. In addition, due to reduced renal clearance in patients with moderate to severe renal function impairment, the lamivudine terminal half-life is increased, and dose adjustment is therefore necessary. As this is not possible with a fixed dose combination such as VIRLAM, use of appropriate formulations of the individual components are recommended (see section 4.3).

There have been reports of impaired renal function, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphataemia) in association with tenofovir use as in VIRLAM (see section 4.4 and 4.8).

Nephrotoxic medicines should not be used in combination with VIRLAM. Careful monitoring for changes in serum creatinine and phosphorus is required in patients at risk of, or with a history of, kidney dysfunction and in patients receiving concomitant nephrotoxic medicines.

Fat redistribution:

Some patients receiving combination antiretroviral therapy, such as VIRLAM, demonstrated redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, "cushingoid appearance", and elevated serum lipid and glucose levels either separately or together (see section 4.4 and 4.8).

The aetiology of this lipodystrophy syndrome is multi-factorial with, for example, HIV disease status, duration of antiretroviral therapy, and older age all playing important, possibly synergistic, roles.

The long-term consequences of these events are not known at present. Physical signs of fat redistribution should be evaluated during clinical examination. Determination of fasting serum lipid and blood glucose levels should be considered, and lipid disorders should be managed as clinically appropriate.

Pancreatitis:

Pancreatitis has been seen in patients who were treated with lamivudine, as in VIRLAM.

Consideration should be given to the possibility of pancreatitis whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. VIRLAM should be discontinued until diagnosis of pancreatitis is excluded.

Opportunistic infections:

Patients treated with VIRLAM may continue to develop infections with opportunistic pathogens and other complications of HIV infection. They therefore should remain under close observation by medical practitioners with experience in the management of patients with associated HIV disease.

The risk of HIV transmission to others:

Patients should be advised that there is no proof that current antiretroviral therapy, including VIRLAM, can prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Patients should continue to employ appropriate precautions to prevent transmission.

Immune reconstitution syndrome:

There have been reports of immune reconstitution syndrome in patients who received combination antiretroviral therapy, including VIRLAM. During the early phase of combination antiretroviral treatment, patients whose immune systems respond may experience an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia or tuberculosis). Such inflammatory responses may necessitate further evaluation and treatment.

Bone mineral density:

Tenofovir-based treatment, such as VIRLAM, have been associated with decreases in bone mineral density of the hip and spine. However, no increased risk of fracture is apparent nor is there evidence of clinically relevant bone abnormalities. If bone abnormalities are suspected, appropriate consultation should be sought.

Consider bone monitoring for HIV infected patients with a history of pathologic bone fracture or those at risk for osteopenia. Although the effect of calcium and vitamin D supplementation was not studied, all patients may benefit from such supplementation.

There may be an association between bone abnormalities (infrequently contributing to fractures) and proximal renal tubulopathy.

Liver disease:

There are very limited safety and efficacy data in liver transplant patients.

There is a paucity of data on the safety and efficacy of the tenofovir disoproxil fumarate in VIRLAM in HBV infected patients with decompensated liver disease and with Child-Pugh-C (moderate to severe) liver impairment. These patients may have a greater risk of developing serious hepatic or renal adverse reactions. Therefore, this patient population requires close monitoring of hepatobiliary and renal parameters.

VIRLAM should be administered with caution to patients with advanced cirrhotic liver disease due to chronic hepatitis B infection, because there is a risk of rebound hepatitis post-treatment.

Osteonecrosis:

There have been reports of cases of osteonecrosis, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to obtain medical advice if they develop joint aches and pain, joint stiffness or difficulty in movement.

Paediatric use:

Safety and effectiveness in children and patients younger than 18 years of age have not been established.

Elderly use:

Since elderly patients have a greater frequency of decreased liver, kidney or cardiac function, and of concomitant disease or treatment with other medicines, dose selection for the elderly patient requires caution.

Mitochondrial dysfunction:

It has been demonstrated *in vitro* and *in vivo* that nucleoside and nucleotide analogues, such as contained in VIRLAM, cause a variable degree of mitochondrial damage. Mitochondrial dysfunction has been reported in HIV negative infants exposed *in utero* and/or postnatally to nucleoside analogues. The chief adverse events reported are haematological disorders (neutropenia, anaemia) and metabolic disorders (hyperlactataemia, hyperlipasaemia). These events are often temporary. There have been a few reports of late-onset neurological disorders (convulsions, hypertonia, abnormal

behaviour). It is currently not known whether the neurological disorders are transient or permanent. Any child who were exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative children, requires clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in the presence of relevant signs or symptoms.

Lactose:

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

4.5 Interaction with other medicines and other forms of interaction

VIRLAM should not be administered with any other medicines containing lamivudine or tenofovir disoproxil fumarate.

Table 1: Interactions between tenofovir disoproxil fumarate and other medicinal products

Medicine by therapeutic area	**Interaction**	**Recommendations**
Antiretrovirals		
Nucleoside reverse transcriptase inhibitors		
Abacavir / tenofovir	A high rate of virological failure and the emergence of resistance at an early	Abacavir and VIRLAM should not be co-administered, as

	stage were reported when tenofovir disoproxil fumarate and lamivudine, as contained in VIRLAM, were combined with abacavir as a once-daily regimen.	the additive effect of abacavir is expected to be limited or absent.
Emtricitabine	No changes in the C_{max}, C_{min} or AUC for tenofovir Emtricitabine C_{min} ↑ 20 %	VIRLAM should not be co-administered, due to the similarity between emtricitabine and lamivudine, and consequently expected additive toxicity and no benefit in efficacy. (see

		section 4.4.)
Didanosine (400 mg q.d.) / tenofovir	Didanosine AUC ↑ 40-60 %	The risk of didanosine-related adverse effects (e.g., pancreatitis, lactic acidosis) appears to be increased, and CD4-cells may decrease significantly on co-administration. Also didanosine at 250 mg co-administered with tenofovir within several different antiretroviral combination

		regimens has been associated with a high rate of virological failure. Co-administration of VIRLAM and didanosine is not recommended (see section 4.4).
Efavirenz	No effect on C_{max}, C_{min} or AUC	
Zalzitabine	The lamivudine in VIRLAM may inhibit the intracellular phosphorylation of zalcitabine when the two medicines are given concomitantly	It is recommended that VIRLAM is not used in combination with zalcitabine
Zidovudine	Zidovudine plasma levels are not	Zidovudine has no effect on the

	significantly altered by concomitant administration with the lamivudine in VIRLAM.	pharmacokinetic characteristics of lamivudine.
Protease inhibitors		
Atazanavir (400 mg once daily)	Atazanavir: AUC: ↓ 25 % C_{max}: ↓ 21 % C_{min}: ↓ 40 % Tenofovir: AUC: ↑ 24 % C_{max}: ↑ 14 % C_{min}: ↑ 22 %	If atazanavir and VIRLAM are co-administered, the dose of atazanavir should be 300 mg once daily together with ritonavir 100 mg once daily ("ritonavir-boosting", see below). Co-administration of atazanavir/ritona

		vir with tenofovir, as contained in VIRLAM, results in increased tenofovir exposure. Higher tenofovir concentrations could potentiate tenofovir-associated adverse effects, including kidney disorders. Renal function requires close monitoring
Atazanavir/Ritonavir (300 mg/100 mg once daily)	Atazanavir: AUC: ↓ 25 % (↓ 42 to↓ 3) C_{max}: ↓ 28 % (↓ 50 to ↑ 5) C_{min}: ↓ 26 % (↓ 46 to	No dose adjustment is recommended. The increased exposure of tenofovir could

	↑ 10) Tenofovir: AUC: ↑ 37 % C_{max}: ↑ 34 % C_{min}: ↑ 29 %	potentiate tenofovir adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
Indinavir	Indinavir 800 mg 3 x daily for 7 days was co-administered with tenofovir 300 mg once daily: Tenofovir C_{max} ↑ 14 % Indinavir C_{max} ↓ 11 %	
Lopinavir/Ritonavir (400 mg/100 mg twice	Lopinavir/ritonavir: No significant effect On lopinavir/ritonavir	No dose adjustment is recommended.

daily)	Tenofovir: AUC: ↑ 32 % C_{max}: ↔ C_{min}: ↑ 51 %	The increased exposure of tenofovir could potentiate tenofovir adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
Darunavir/Ritonavir (300 mg/100 mg twice daily)	Darunavir: No significant effect on darunavir/ritonavir Tenofovir: AUC: ↑ 22 % C_{min}: ↑ 37 %	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir adverse events, including renal

		disorders. Renal function should be closely monitored (see section 4.4).
Antiretrovirals: NRTIs		
Didanosine (400 mg once daily)	Didanosine AUC ↑ 40–60 %	The risk of didanosine-related adverse effects (e.g., pancreatitis, lactic acidosis appears to be increased, and CD4 cells may decrease significantly on co-administration. Also, didanosine at 250 mg co-administered

		with tenofovir in several different antiretroviral combination regimens has been associated with a high rate of virological failure. Co-administration of VIRLAM and didanosine is not recommended (see section 4.4).
Adefovir dipivoxil	AUC: ↔ C_{max}: ↔	VIRLAM should not be administered concurrently with adefovir dipivoxil (see section 4.4).

Entecavir (1 mg once daily)	AUC: ↔ C_{max}: ↔	No clinically significant pharmacokinetic interactions when VIRLAM is co-administered with entecavir
Hepatitis C virus antiviral medicines		
Sofosbuvir/tenofovir disoproxil	Tenofovir ↑ C_{max} 1,25 (1,08;1,45) ↔ AUC 0,98 (0,91;1,05) ↔ C_{min} 0,99 (0,91;1,07) Sofosbuvir ↓ C_{max} 0,81 (0,60;1,10) ↔ AUC 0,94 (0,76;1,16) C_{min} (NA) GS-331007	No dose adjustment of sofosbuvir or VIRLAM is required when sofosbuvir and VIRLAM are used concomitantly.

	(predominant inactive metabolite of sofosbuvir) ↓ C_{max} 0,77 (0,70;0,84) ↔ AUC 0,84 (0,76;0,92) C_{min} (NA)	
Ledipasvir (90 mg once daily) /sofosbuvir (400 mg once daily) / tenofovir disoproxil	Tenofovir ↑ C_{max} 1,79 (1,56;2,04) ↑ AUC 1,98 (1,77;2,23) ↑ C_{min} 2,63 (2,32;2,97) Ledipasvir ↓ C_{max} 0,66 (0,59;0,75) ↓ AUC 0,66 (0,59;0,75) ↓ C_{min} 0,66 (0,57;0,76)	Monitor for tenofovir-associated adverse reactions in patients receiving ledipasvir/sofosbuvir concomitantly with VIRLAM

	Sofosbuvir ↔ C_{max} 1,03 (0,87;1,23) ↔ AUC 0,94 (0,81;1,10) GS-331007 ↔ C_{max} 0,86 (0,76;0,96) ↔ AUC 0,90 (0,83;0,97) ↔ C_{min} 1,07 (1,02;1,13)	
Daclatasvir/ tenofovir disoproxil	↔ Daclatasvir AUC: 1,10 (1,01;1,21) C_{max}: 1,06 (0,98; 1,15) C_{min}: 1,15 (1,02; 1,30) ↔ Tenofovir AUC: 1,10 (1,05;1,15)	No dose adjustment of. Daclatasvir VIRLAM is required

	C_{max}: 0,95 (0,89; 1,02) C_{min}: 1,17 (1,10; 1,24)	

Interactions relevant to lamivudine:

The likelihood of other medicines adversely interacting with the lamivudine in VIRLAM is small due to the limited metabolism and plasma protein binding and almost complete renal clearance of lamivudine.

Trimethoprim/sulphametoxazole (co-trimoxazole)

Co-administration with trimethoprim/sulfamethoxazole (co-trimoxazole) 160 mg/800 mg results in a 40 % increase in lamivudine exposure, because of the trimethoprim component; the sulfamethoxazole component did not interact. However, unless the patient has renal impairment, no dose adjustment of lamivudine/tenofovir disoproxil fumarate is necessary. Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole. When concomitant administration is warranted, patients should be monitored clinically. Co-administration of lamivudine with high doses of co-trimoxazole for the treatment of *Pneumocystis carinii* pneumonia (PCP) and toxoplasmosis should be avoided.

The possibility of interactions with other medicinal products administered concurrently should be considered, particularly when the main route of elimination is active renal secretion via the organic cationic transport system e.g. trimethoprim. Other medicinal

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

Interactions relevant to tenofovir:

At concentrations considerably higher (~ 300-fold) than those seen *in vivo*, tenofovir did not inhibit *in vitro* medicine metabolism mediated by any of the following human CYP450 isoforms: CYP3A4, CYP2D6, CYP2C9 or CYP2E1. However, there was a small (6 %) but statistically significant reduction in metabolism of CYP1A substrate. The potential for CYP450 mediated interactions involving tenofovir and other medicinal products is small, given the results of *in vitro* experiments and the known elimination pathway of tenofovir.

Tenofovir, as contained in VIRLAM, is primarily excreted via the renal route through a combination of glomerular filtration and active tubular secretion. Concomitant administration of VIRLAM with medicines that are eliminated through active tubular secretion may increase serum concentrations of either tenofovir or of the co-administered medicine, as a result of competition via transport proteins hOAT 1, hOAT 2 or MRP 4 (e.g cidofovir), for this elimination pathway.

Medicines that reduce renal function may also produce an increase in the serum concentration of the tenofovir in VIRLAM.

Other:

After multiple dosing to HIV-negative individuals receiving either chronic methadone

maintenance therapy or oral contraceptives, or single doses of ribavirin, steady-state tenofovir pharmacokinetic characteristics were similar to those documented in previous studies, indicating lack of clinically significant medicine interactions between these [~~agents~~] medicines and the tenofovir in VIRLAM.

Specifically, when methadone 40 - 110 mg once daily for 14 days was given in combination with tenofovir 300 mg, as in VIRLAM, once daily, R-(active), S- and total methadone exposures were equivalent when dosed alone or with tenofovir. Individual subjects were maintained on their stable methadone dose. There were no reports of pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms).

Administration of VIRLAM should be avoided with concomitant or recent use of a nephrotoxic medicinal product (see section 4.3). Some examples include, but are not limited to, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2.

Since tacrolimus may influence kidney function, close monitoring is recommended when it is co-administered with the tenofovir in VIRLAM.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / contraception in males and females

Women of childbearing potential should make use of effective contraception while undergoing treatment with VIRLAM.

Pregnancy

The safety and efficacy of VIRLAM in pregnancy have not been determined. Therefore, VIRLAM should not be used in pregnancy (see section 4.3).

Breastfeeding

Mothers receiving treatment with VIRLAM should not breastfeed their babies (see section 4.3).

To avoid transmission of HIV to the infant, it is recommended that women infected with HIV do not breastfeed their babies.

4.7 Effects on ability to drive and use machines:

VIRLAM may cause dizziness. Patients should be instructed not to drive a car or operate machinery until they know their individual susceptibility

4.8 Undesirable effects

Summary of the safety profile

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

Co-administration of tenofovir disoproxil and didanosine is not recommended as this may result in an increased risk of adverse reactions (see section 4.5). Pancreatitis and lactic acidosis, sometimes fatal, have been reported (see section 4.4).

Discontinuation of VIRLAM therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis (see section 4.4).

Tabulated list of adverse effects

Adverse effects for VIRLAM:

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Less frequent	Neutropenia, anaemia (occasionally severe), thrombocytopenia, pure red cell aplasia
Metabolism and nutrition disorders	Frequent Less frequent Frequency unknown	Hypophosphataemia Lactic acidosis Hypokalaemia
Nervous system disorders	Frequent Less frequent	Dizziness, headache and insomnia Peripheral neuropathy (paraesthesia)

Respiratory, thoracic and mediastinal disorders	Frequent Less frequent	Cough and nasal symptoms Dyspnoea
Gastrointestinal disorders	Frequent Less frequent	Diarrhoea, nausea, vomiting, abdominal pain/cramps and flatulence Pancreatitis and elevated serum amylases
Hepatobiliary disorders	Less frequent Frequency unknown	Transient elevation in liver enzymes and hepatitis Hepatic steatosis
Skin and subcutaneous tissue disorders	Frequent	Rash and hair loss

Musculoskeletal, connective tissue and bone disorders	Frequent Frequency unknown	Arthralgia and muscle disorder Rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), muscular weakness, myopathy and osteonecrosis
Renal and urinary disorders	Less frequent Frequency unknown	Acute renal failure, renal failure, proximal renal tubulopathy (including Fanconi syndrome), increased serum creatinine, and acute tubular necrosis Nephritis (including acute interstitial nephritis) and nephronic diabetes insipidus

General disorders and administrative site conditions	Frequent Less frequent Frequency unknown	Fatigue, malaise and fever Asthenia Immune reconstitution syndrome

Adverse effects for Lamivudine:

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Less frequent	Anaemia, neutropenia, thrombocytopenia, pure red cell aplasia
Immune system disorders	Less frequent	Angioedema
Metabolism and nutrition disorders	Frequent Less frequent	Hyperlactataemia Lactic acidosis (see section 4.4), lipodystrophy (accumulation/redistribution of body fat) (see section 4.4).

Nervous system disorders	Frequent Less frequent	Insomnia, headache Peripheral neuropathy, paraesthesia
Respiratory, thoracic and mediastinal disorders	Frequent	Cough, nasal symptoms
Gastrointestinal disorders	Frequent Less frequent	Nausea, abdominal cramps or pain, vomiting, diarrhoea Pancreatitis, increase in serum amylase
Hepatobiliary disorders	Less frequent	Hepatitis, transient hepatic enzyme increases (ALT, AST).
Skin and subcutaneous tissue disorders	Frequent	Rash, alopecia
Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent	Arthralgia, muscle disorders Rhabdomyosis

General disorders and administrative site conditions	Frequent	Fever, malaise, fatigue

Adverse effects of Tenofovir disoproxil fumarate:

System Organ Class	**Frequency**	**Side effects**
Infections and Infestations	Frequent	Pneumonia
Immune system disorders	Less frequent Frequency unknown	Angioedema Allergic reaction
Metabolism and nutrition disorders	Frequent Less frequent Frequency unknown	Weight loss, lipodystrophy Lactic acidosis Hypophosphataemia
Psychiatric disorders	Frequent	Depression, anxiety

Nervous system disorders	Frequent	Peripheral neuropathy (including neuropathy and peripheral neuritis), headache, insomnia, anorexia, dizziness
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Dyspnoea
Gastrointestinal disorders	Frequent Less frequent	Abdominal pain or distension, nausea, vomiting, diarrhoea, dyspepsia, flatulence Pancreatitis
Hepatobiliary disorders	Frequent Less frequent Frequency unknown	Raised transaminases Hepatitis, hepatic steatosis Raised liver enzymes

Skin and subcutaneous tissue disorders	Frequent	Maculopapular, vesiculobullous, or pustular rash, urticaria, pruritus, sweating
Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent	Myalgia, arthralgia Rhabdomyolysis, muscular weakness, osteomalacia and myopathy due to proximal renal tubulopathy
Renal and urinary disorders	Less frequent	Raised creatinine, renal insufficiency or failure, Fanconi syndrome, acute renal syndrome, proximal tubulopathy, acute tubular necrosis, nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus, proteinuria

General disorders and administrative site conditions	Frequent	Pain, fever, asthenia, back or chest pain, fatigue
Investigations	Frequent	Increased total cholesterol or triglyceride levels, increased serum amylase, raised ALT and AST, increased creatine kinase, haematuria, elevated neutrophil count, increased serum glucose, glycosuria, hypophosphataemia due to proximal renal tubulopathy
	Less frequent	Hypokalaemia due to proximal renal tubulopathy

Description of selected adverse reactions

a. *Renal toxicity*

As VIRLAM may cause renal damage, monitoring of renal function is recommended (see

sections 4.4 and 4.8). Proximal renal tubulopathy generally resolved or improved after tenofovir disoproxil discontinuation. However, in some patients, declines in creatinine clearance did not completely resolve despite tenofovir disoproxil discontinuation. Patients at risk of renal impairment (such as patients with baseline renal risk factors, advanced HIV disease, or patients receiving concomitant nephrotoxic medications) are at increased risk of experiencing incomplete recovery of renal function despite tenofovir disoproxil discontinuation (see section 4.4).

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

Interaction with didanosine

Co-administration of tenofovir disoproxil and didanosine is not recommended as it results in a 40-60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse

reactions. (see section 4.5). Pancreatitis and lactic acidosis, sometimes fatal, have been reported.

Metabolic parameters

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

Immune Reactivation Syndrome

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

Osteonecrosis

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

b. Other special populations

Elderly

Lamivudine/tenofovir disoproxil has not been studied in patients over the age of 65. Elderly patients are more likely to have decreased renal function; therefore, caution should be exercised when treating elderly patients with emtricitabine/tenofovir disoproxil.

HIV/HBV or HCV co-infected patients

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

In HIV-negative individuals limited data indicate that the adverse reaction profile of lamivudine and tenofovir disoproxil was similar in individuals with and without hepatitis B/C infection.

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 professionals 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

Signs and symptoms:

In the event of overdosage, the patient must be monitored for evidence of toxicity and supportive treatment instituted as necessary.

The tenofovir in VIRLAM is haemodialysable, with the median haemodialysis clearance of tenofovir 134 ml/min. Elimination of tenofovir via peritoneal dialysis has not been

investigated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Antivirals for treatment of HIV infections, combinations

ATC code: J05AR12

Pharmacological classification:

A 20.2.8 antimicrobial (chemotherapeutic) agents. Antiviral agents

Lamivudine:

In vitro, lamivudine is a selective inhibitor of the replication of Human Immunodeficiency Virus-1 (HIV-1) and HIV-2. In addition, lamivudine is active against HIV clinical isolates that are resistant to zidovudine.

Intracellularly, lamivudine is metabolised to the active 5'-triphosphate with an intracellular $t_{1/2}$ of 16 - 19 hours. Lamivudine 5'-triphosphate weakly inhibits HIV reverse transcriptase's DNA and RNA-dependent activities. The mechanism of action is by chain termination of HIV reverse transcription.

It has been shown that lamivudine acts synergistically or additively with other anti-HIV medicines, especially zidovudine, to inhibit HIV replication in cell culture.

Lamivudine sparsely affects the mitochondrial and cellular DNA content of mammalian cells and does not interfere with cellular deoxynucleotide metabolism.

Lamivudine demonstrates little *in vitro* cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines, and to a range of bone marrow progenitor cells

Resistance:

In vitro, HIV-1 variants have been selected that are resistant to lamivudine. Genotypic analysis demonstrated that this resistance was caused by substitution of a specific amino acid at codon 184 in the HIV-1 reverse transcriptase, exchanging the methionine residue with either valine or isoleucine. HIV-1 strains that demonstrated resistance to both lamivudine and zidovudine have been isolated from patients. Controlled clinical trials were employed to monitor the susceptibility of clinical isolates to zidovudine and lamivudine. Within 12 weeks, HIV-1 isolates from the majority of patients who received either monotherapy with lamivudine or lamivudine-zidovudine combination therapy became genotypically and phenotypically resistant to lamivudine. In some patients harbouring viral strains resistant to zidovudine at baseline, phenotypic sensitivity to zidovudine was restored after 12 weeks of therapy with lamivudine and zidovudine. The emergence of mutations providing resistance to zidovudine was delayed by combination therapy with lamivudine plus zidovudine.

Cross-resistance:

HIV-1 mutants resistant to lamivudine were cross-resistant to zalcitabine and didanosine. Isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine,

emerged in some patients who received treatment with zidovudine plus didanosine or zalcitabine.

There have been reports of reduced *in vitro* sensitivity to lamivudine for HIV isolates from patients who were treated with lamivudine. Clinical studies in subjects with no previous antiretroviral treatment have provided evidence that zidovudine plus lamivudine therapy delays the emergence of isolates resistant to zidovudine.

The relationship between the clinical response to lamivudine therapy and HIV-susceptibility to lamivudine *in vitro* remain to be examined.

Tenofovir disoproxil fumarate:

Tenofovir disoproxil fumarate, an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate, requires initial hydrolysis of the diester for conversion to tenofovir. Subsequently, phosphorylations by cellular enzymes produce tenofovir disphosphate. The activity of HIV-1 reverse transcriptase is inhibited by tenofovir diphosphate through competition with the naturally occurring deoxyadenosine 5' - triphosphate and, after incorporation into DNA, by termination of the DNA chain.

Tenofovir diphosphate weakly inhibits mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Tenofovir *in vitro* antiviral activity against clinical and laboratory isolates of HIV-1 was examined in macrophage cells, primary monocytes, peripheral blood lymphocytes and lymphoblastoid cell lines. Tenofovir IC_{50} values are between 0,04 µM and 8,5 µM. Additive to synergistic actions were detected in studies of tenofovir in combination with nucleoside

reverse transcriptase inhibitors (zidovudine, zalcitabine, stavudine, lamivudine, didanosine, abacavir), non-nucleoside reverse transcriptase inhibitors (nevirapine, efavirenz, delavirdine), and protease inhibitors (saquinavir, ritonavir, nelfinavir, indinavir, amprenavir). *In vitro*, tenofovir exhibited antiviral effects (IC50 values between 0,5 µM and 2,2 µM) against HIV-1 clades A, B, C, D, E, F, G, and O and against HIV-2 (IC_{50} values between 1,6 µM and 4,9 µM).

Resistance:

In vitro, HIV-1 strains with reduced susceptibility to tenofovir have been selected. The viruses from these isolates expressed a K65R mutation in reverse transcriptase and demonstrated a 2- to 4-fold reduced susceptibility to tenofovir.

Tenofovir-resistant strains of HIV-1 have also been isolated from some patients who received treatment with tenofovir in combination with certain antiretroviral medicines.

Genotypic analysis of the resistant isolates demonstrated a mutation in the HIV-1 reverse transcriptase gene giving rise to the K65R amino acid substitution.

Cross-resistance:

It has been recognised that there is cross-resistance among certain reverse transcriptase inhibitors. The K65R mutation selected by tenofovir is also selected in some HIV-1 infected individuals who received treatment with abacavir, didanosine, or zalcitabine. HIV strains with this mutation also demonstrated reduced susceptibility to lamivudine and emtricitabine. Consequently, individuals infected with viruses harbouring the K65R

mutation may experience cross-resistance between these medicines. A 3,1-fold reduction in sensitivity to tenofovir was observed in HIV-1 isolates from individuals whose HIV-1 expressed a mean of 3 reverse transcriptase mutations associated with zidovudine (D67N, M41L, L210W, K70R, K219Q/E/N or T215Y/F). Decreased sensitivity to tenofovir was observed in multinucleoside resistant HIV-1 with a reverse transcriptase containing a T69S double insertion mutation.

5.2 Pharmacokinetic properties

Lamivudine:

Absorption:

Lamivudine is well absorbed from the gut with an oral bioavailability in adults of normally between 80 – 85 %.

The mean time (T_{max}) to maximum serum concentration (C_{max}) is approximately one hour after oral administration. At therapeutic dose levels of 4 mg/kg/day (administered as two 12-hourly doses). C_{max} is approximately 1 - 1,5 µg/ml.

Co-administration with food does not alter lamivudine bioavailability and therefore no dose adjustment is required. However, co-administration with food caused a delay in T_{max} and reduction in C_{max}.

Distribution:

Lamivudine has a mean volume of distribution of 1,3 l/kg with a mean terminal half-life of elimination of 5 - 7 hours.

Lamivudine displays limited binding to albumin, the main plasma protein, and pharmacokinetics are linear over the therapeutic dose range.

Limited data indicates that lamivudine enters the central nervous system (CNS) and reaches the cerebrospinal fluid (CSF). Two to four hours after oral administration, the mean CSF/serum concentration ratio is about 0,12. Neither the true extent of penetration nor the relationship with any clinical efficacy is known.

Biotransformation and elimination:

Clearance of lamivudine is predominantly via the renal route (> 70 %) through active tubular secretion and, to a small extent, via hepatic metabolism (< 10 %) with a mean systemic clearance of about 0,32 l/kg/h.

Tenofovir disoproxil fumarate:

Tenofovir disoproxil fumarate displays similar pharmacokinetics in HIV-1 infected patients and healthy volunteers, as demonstrated by assessments of both these populations.

Absorption:

Tenofovir, the active compound, is formulated as a water-soluble prodrug in the form of tenofovir disoproxil fumarate. The bioavailability of tenofovir from tenofovir disoproxil fumarate following oral administration in fasted patients is approximately 25 %. Maximum serum concentrations are reached in 1,0 ± 0,4 hours after administration of a single 300 mg oral dose of tenofovir disoproxil fumarate to fasted HIV-1 infected patients. The AUC is

2287 ± 685 ng*h/ml and maximum serum concentration (C_{max}) is 296 ± 90 ng/ml.

Tenofovir pharmacokinetics are dose proportional, are not influenced by repeated dosing and is independent of the tenofovir disoproxil fumarate dose over the 75 - 600 mg dose range.

Oral bioavailability of tenofovir is increased following administration after a high fat meal, with an approximate 14 % increase in tenofovir C_{max} and an approximate 40 % increase $AUC_{0-\infty}$.

Nevertheless, co-administration of tenofovir disoproxil fumarate with a light meal did not have a notable influence on the pharmacokinetics of tenofovir when compared with fasted administration.

The time to tenofovir C_{max} is delayed by about 1 hour following administration with food. In the fed state, when meal content was not controlled, C_{max} of tenofovir was 326 ± 119 ng/ml and AUC was 3324 ± 1370 ng*h/ml following multiple once-daily doses of tenofovir 300 mg.

Distribution:

In vitro, over a concentration range of 0,01 - 25 µg/ml, tenofovir is < 0,7 % bound to plasma proteins and < 7,2 % to serum proteins. After intravenous administration of 3,0 mg/kg and 1,0 mg/kg tenofovir, the steady-state volume of distribution was 1,2 ± 0,4 l/kg and 1,3 ± 0,6 l/kg, respectively.

Biotransformation:

Neither tenofovir nor tenofovir disoproxil fumarate are CYP450 enzyme substrates, as demonstrated by *in vitro* studies.

Elimination:

Within 72 hours 9J intravenous tenofovir administration, about 70 - 80 % of the dose is recovered as unchanged tenofovir in the urine. The terminal elimination half-life of tenofovir is about 17 hours following oral administration of a single dose. Following multiple once daily oral doses of tenofovir 300 mg (under fed conditions), 32 ± 10 % of the administered dose is recovered in urine over a 24-hour period.

Tenofovir is eliminated via both active tubular secretion and glomerular filtration and may compete for elimination with other compounds that are also renally eliminated.

Pharmacokinetics in special patient groups

Age:

Pharmacokinetic studies for tenofovir have not been performed in the elderly (> 65 years) or in children younger than 18 years of age.

Renal impairment:

Tenofovir pharmacokinetics are altered in patients with impairment of renal function. AUC and C_{max} of tenofovir are increased in patients with creatinine clearance < 50 ml/min or with end-stage renal disease (ESRD) receiving dialysis; and it is recommended that the tenofovir dosing interval be modified in these patients. As this is not possible with a fixed

dose combination, use of appropriate formulations of the individual components is recommended (see section 4.3).

Tenofovir may effectively be removed by haemodialysis (extraction coefficient about 54 %). A haemodialysis session of 4 hours removed about 10 % of a single 300 mg dose of tenofovir.

Age- or disease-related renal impairment will influence lamivudine elimination (see section 4.3)

Hepatic impairment:

Patients with impaired hepatic function do not experience significant changes in tenofovir pharmacokinetics compared to patients with no liver function impairment; therefore, these patients do not require a dosage adjustment.

Paediatric population

Lamivudine pharmacokinetics are generally similar in paediatric and adult patients. However, in paediatric patients aged < 12 years the absolute bioavailability (about 55 - 65 %) was decreased. Furthermore, greater systemic clearance is seen in younger paediatric patients, decreasing with increasing age, until about the age of 12 years, when systemic clearance values approach that of adults. As a consequence of these age-related differences, the recommended dose for children aged 3 months to 12 years is 8 mg/kg/day, which will afford comparable exposure to the recommended adult dose.

Pharmacokinetic data for paediatric patients < 3 months of age are limited.

5.3 Preclinical safety data

Lamivudine:

Administration of lamivudine in animal toxicity studies at high doses was not associated with any major organ toxicity.

Lamivudine was not mutagenic in bacterial tests but showed activity in an *in vitro* cytogenetic assay and the mouse lymphoma assay. Lamivudine was not genotoxic *in vitro* at doses that gave plasma concentrations around 40–50 times higher than the expected clinical plasma levels. As the *in vitro* mutagenic activity of lamivudine could not be confirmed *in vivo*, it is concluded that lamivudine should not represent a genotoxic hazard to patients undergoing treatment.

The results of long-term carcinogenicity studies in rats and mice did not show any carcinogenic potential relevant for humans.

Tenofovir:

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

mechanism(s) underlying these toxicities.

Reproductive studies were conducted in rats and rabbits. There were no effects on mating or fertility parameters or on any pregnancy or fetal parameter. There were no gross fetal alterations of soft or skeletal tissues. Tenofovir disoproxil reduced the viability index and weight of pups in peri-post-natal toxicity studies. Genotoxicity studies have shown that tenofovir disoproxil was negative in the *in vivo* mouse bone marrow micronucleus assay but was positive for inducing forward mutations in the *in vitro* L5178Y mouse lymphoma cell assay in the presence or absence of S9 metabolic activation. Tenofovir disoproxil was positive in the Ames test (strain TA 1535) in two out of three studies, once in the presence of S9 mix (6.2- to 6.8-fold increase) and once without S9 mix. Tenofovir disoproxil was also weakly positive in an *in vivo/in vitro* unscheduled DNA synthesis test in primary rat hepatocytes.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Corn starch

Croscarmellose sodium

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 30 °C.

Keep container tightly closed.

6.5 Nature and contents of container

30 Tablets shall be fill into a 120CC white HDPE Bottle along with 5 g silica gel desiccant sachet and close a bottle with 38 mm non-CR closure.

30 Tablets shall be fill into a 120CC white HDPE Bottle along with 5 g molecular sieve desiccant sachet and close a bottle with 38 mm non-CR closure.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION:

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, SOUTH AFRICA

8. REGISTRATION NUMBER(S)

A55/20.2.8/0111

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

9 February 2021

10. DATE OF REVISION OF THE TEXT

Not applicable