SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PREPETAM FILM-COATED TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil) and 200 mg of emtricitabine

Contains sugar (lactose monohydrate): 80,0 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

PREPETAM film coated tablets are blue, capsule shaped, biconvex and plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of HIV-1 Infections

- PREPETAM is indicated in combination with other antiretroviral agents (example; non-nucleoside reverse transcriptase inhibitors or protease inhibitors) for the treatment of HIV-1 infection in adults.

  Pre-Exposure Prophylaxis (PrEP):

- PREPETAM is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) in proven HIV-1 uninfected adults to reduce the risk of sexually acquired HIV-1 in adults at high risk, provided maximum treatment compliance can be monitored.

4.2 Posology and method of administration

Posology

Dosage in adults for treatment of HIV-1 infection

The dose of PREPETAM is one tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) once daily.

Dosage for Pre-Exposure Prophylaxis (PrEP)

The dose of PREPETAM in HIV-1 uninfected adults is one tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) once daily.

Significantly increased medicine exposures occurred when emtricitabine or tenofovir disoproxil fumarate were administered to patients with moderate to severe renal impairment (see section 4.3).

Table 1: Dosage for HIV-1 infected adult patients with creatinine clearance ≥ 50 (mL/min).

Creatinine Clearance (mL/min)[a] ≥ 50	
Recommended Dosing Interval	Every 24 hours

[a] Calculated using ideal (lean) body weight

Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in all individuals (see section 4.3 and section 4.4)

Method of administration

Oral use.

It is recommended that PREPETAM be swallowed whole with water.

PREPETAM can usually be taken with food or without food.

4.3 Contraindications

- Hypersensitivity to the tenofovir, emtricitabine or to any of the excipients listed in section 6.1.
- Pregnancy and lactation.
- Creatinine CL < 60 mL/min when used for PrEP.
- Creatinine CL < 50 mL/min when used for treatment of HIV-1.
- PREPETAM should not be co-administered with other tenofovir-containing, or emtricitabine-containing products. PREPETAM should not be administered with lamivudine-containing products due to similarities between emtricitabine and lamivudine.
- PREPETAM should not be used for Pre-Exposure Prophylaxis (PrEP) in individuals with unknown or positive HIV-1 status.
- PREPETAM should not be used for PrEP in individuals not fully committed to full treatment compliance.

4.4 Special warnings and precautions for use

WARNING

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with other antiretrovirals (see section 4.4).

PREPETAM is not indicated for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of PREPETAM has not been established in patients co infected with HBV and HIV. Severe acute

exacerbations of hepatitis B have been reported in patients who have discontinued PREPETAM.

Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients infected with HBV who discontinue the combination tablet. If appropriate, initiation of anti-hepatitis b therapy may be warranted (see section 4.4). PREPETAM used for pre-exposure prophylaxis (PrEP) indication must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiating and periodically (at least once every 3 months) during use.
Resistant HIV-1 variants have been identified with use of PREPETAM for a pre-exposure prophylaxis (PrEP) indication following undetected acute HIV-1 infection. Do not initiate PREPETAM for a pre-exposure prophylaxis (PrEP) indication if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed (see section 4.4).

There are no study results demonstrating the effect of PREPETAM on clinical progression of HIV-1.
It is not recommended that PREPETAM be used as a component of a triple nucleoside regime.
Individuals should be warned that full compliance with treatment is essential to the efficacy in preventing HIV-1 transmission and should be fully informed about the use of other preventative measures including barrier contraception (condoms). Individuals not fully committed or trusted to be treatment-compliant should not use PREPETAM for HIV-1 transmission prophylaxis.

Lactic acidosis/severe hepatomegaly with steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues such as PREPETAM alone or in combination with other antiretrovirals. This is caused by mitochondrial dysfunction. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors.

Particular caution should be exercised when administering nucleoside analogues such as PREPETAM to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with PREPETAM should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

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 to 5 mmol/L with minimum symptoms: Switch to medicines that are less likely to cause lactic acidosis.
- Lactate 5 to 10 mmol/L with symptoms and/or with reduced standard bicarbonate: Stop PREPETAM 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 PREPETAM to patients with known risk factors for liver disease. Treatment with PREPETAM should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Pancreatitis

Pancreatitis has been observed in some patients receiving PREPETAM.

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

Liver disease

Use of PREPETAM can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of PREPETAM has not been established in patients with significant underlying liver disorders/diseases.

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.

Mitochondrial dysfunction

Nucleoside and nucleotide analogues such as PREPETAM 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-natal, 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 signs and symptoms.

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

Patients with chronic hepatitis B or C and treated with antiretroviral therapy such as PREPETAM, are at an increased risk for severe and potentially fatal hepatic adverse reactions. Patients co-infected with HBV to discontinue PREPETAM, should be closely monitored with both clinical and laboratory follow-up after stopping treatment. 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). PREPETAM is not indicated for the treatment of chronic HBV infection and the safety and efficacy of PREPETAM have not been established in patients co-infected with HBV and HIV.

In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant package inserts for these medicines. 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 PREPETAM therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis, which may lead to liver decompensation and liver failure.

It is recommended that all patients with HIV be tested for the presence of chronic hepatitis B virus (HBV) before initiating PREPETAM therapy. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are co-infected with HIV and HBV and discontinue PREPETAM. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Renal impairment

PREPETAM is principally eliminated by the kidney.

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 (see section 4.3).

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with PREPETAM. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment (see section 4.3).

PREPETAM should be avoided with concurrent or recent use of a nephrotoxic agent.

PREPETAM should not be administered to patients with creatinine clearance below 50 mL/min or patients requiring haemodialysis or for pre-exposure prophylaxis in patients with creatinine clearance below 60 mL/min (see section 4.3).

If a decrease in creatinine clearance is observed in uninfected individuals while using PREPETAM for PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use (see section 4.3).

Interactions

PREPETAM is a fixed-dose combination of emtricitabine and tenofovir disoproxil fumarate. PREPETAM should not be co-administered with other medicines containing emtricitabine or tenofovir (see section 4.3).

Due to similarities between emtricitabine and lamivudine, PREPETAM should not be co-administered with other medicines containing lamivudine, including lamivudine and

zidovudine co-formulation, lamivudine for HIV, lamivudine for HBV, abacavir sulfate and lamivudine co-formulation or abacavir sulfate, lamivudine and zidovudine co-formulation (see section 4.3).

Co-administration of didanosine buffered tablet formulation with PREPETAM should be under fasted conditions (see section 4.5).

Co-administration of PREPETAM and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse events. Didanosine should be discontinued in patients who develop didanosine-associated adverse events (see section 4.8).

Patients receiving atazanavir and lopinavir/ritonavir and PREPETAM should be monitored for PREPETAM-associated adverse events. PREPETAM should be discontinued in patients who develop PREPETAM-associated adverse events (see section 4.8).

Tenofovir decreases the AUC and C_{min} of atazanavir (see section 4.5). When co-administered with PREPETAM, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Atazanavir without ritonavir should not be co-administered with PREPETAM.

Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of PREPETAM with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of emtricitabine, tenofovir, and/or other renally eliminated medicines (see section 4.5). Some examples include, but are not limited to adefovir, dipivoxil, cidofovir, aciclovir, valaciclovir, ganciclovir and valganciclovir.

Lipodystrophy and metabolic abnormalities

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and “cushingoid appearance” have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

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 pulmonary tuberculosis, cytomegalovirus retinitis, *Pneumocystis jirovecii* pneumonia (PCP), cryptococcal meningitis and other forms of tuberculosis and atypical myco-bacterial infections. Appropriate treatment of the opportunistic disease should be instituted or continued and ART continued. Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS.

Autoimmune disorders (such as Graves' disease) 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.

Bone mineral density

During therapy with PREPETAM assessment of bone mineral density (BMD) should be considered for patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. The effect of supplementation with calcium and vitamin D was not studied. If bone abnormalities are suspected then appropriate consultation should be obtained. Bone mineral density monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk for osteopenia. Tenofovir combination therapy is associated with decreased bone mineral density.

In clinical trials of HIV-1 uninfected individuals, decreases in BMD were also observed. In a pre-exposure trial of men having sex with men (MSM), a sub study of 503 subjects found mean changes from baseline in BMD ranging from -0,4 % to -1,0 % across total hip, spine, femoral neck, and trochanter in the PREPETAM group compared with the placebo group. Bone fractures were reported in 1,7 % of the PREPETAM group compared with 1,4 % in the placebo group. No correlation between BMD and fractures was noted. A pre-exposure study in heterosexual couples where

one of the partners was HIV-1 infected, found similar fracture rates between treatment and placebo groups (0,8 % and 0,6 %, respectively). No BMD evaluations were conducted during this trial.

Cases of osteomalacia (associated with proximal renal tubulopathy) have been reported in association with the use of tenofovir disoproxil fumarate (tenofovir DF), such as PREPETAM (see section 4.8).

Opportunistic infections

Patients receiving PREPETAM 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 performed.

The risk of HIV transmission to others

Patients should be advised that current antiretroviral therapy, including PREPETAM, does not prevent the risk of transmission of HIV-1 to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Comprehensive management to reduce the risk of acquiring HIV-1

Use PREPETAM for pre-exposure prophylaxis only as part of a comprehensive prevention strategy that includes other prevention measures, such as safer sex practices, because PREPETAM is not always effective in preventing the acquisition of HIV-1.

- Counsel uninfected individuals about safer sex practices that include consistent and correct use of condoms, knowledge of their HIV-1 status and that of their partner(s), and regular testing for other sexually transmitted infections that can facilitate HIV-1 transmission (such as syphilis and gonorrhoea).

- Inform uninfected individuals about and support their efforts in reducing sexual risk behaviour.

Use PREPETAM to reduce the risk of acquiring HIV-1 only in individuals confirmed to be HIV-negative. HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only PREPETAM, because PREPETAM alone does not constitute a complete treatment regime for HIV-1 treatment. Therefore, care should be taken to avoid PREPETAM exposure in HIV-infected individuals (see section 4.3).

- Many HIV-1 tests, such as rapid tests, detect anti-HIV antibodies and may not identify HIV-1 during the acute stage of infection. Prior to initiating PREPETAM for a PrEP indication, evaluate seronegative individuals for current or recent signs or symptoms consistent with acute viral infections (e.g., fever, fatigue, myalgia, skin rash, etc.) and ask about potential exposure events (e.g. unprotected sex, or condom broken during sex with an HIV-1 infected partner) that may have occurred within the last month.
- If clinical symptoms consistent with acute viral infection are present and recent (< 1 month) exposures are suspected, delay starting PrEP for at least one month and reconfirm HIV-1 status or use an approved test as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection.
- While using PREPETAM for a PrEP indication, HIV-1 screening tests should be repeated at least once every 3 months. If symptoms consistent with acute HIV-1 infection develop following a potential exposure event, PrEP should be discontinued until negative infection status is confirmed using an approved test as an aid in the diagnosis of HIV-1, including acute or primary HIV-1 infection.

Counsel uninfected individuals to strictly adhere to the recommended PREPETAM dosing schedule. The effectiveness of PREPETAM in reducing the risk of acquiring

HIV-1 is correlated, strongly, with adherence as demonstrated by measurable medicine levels in clinical trials.

Early virologic failure

Clinical trials in HIV-1 infected patients have demonstrated that certain regimes that only contain three nucleoside reverse transcriptase inhibitors (NRTIs) are generally less effective than regimes containing two NRTIs in combination with either a non-nucleoside reverse transcriptase inhibitor or a HIV-1 protease inhibitor. In particular, early virological failure and high rates of resistance substitutions have been reported.

Triple nucleoside regimes should therefore be used with caution. Patients on a therapy utilising a triple nucleoside-only regime should be carefully monitored and considered for treatment modification.

Paediatric use

Safety and effectiveness in paediatric patients have not been established.

Geriatric use

Clinical studies of emtricitabine (200 mg) or tenofovir DF did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patients should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other medicine therapy.

Lactose warning

PREPETAM contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been conducted using PREPETAM tablets.

The steady state pharmacokinetics of emtricitabine and tenofovir were unaffected when administered together versus each medicine dosed alone.

In vitro and clinical pharmacokinetic interaction studies have shown that the potential for CYP450 mediated interactions involving emtricitabine and tenofovir with other medicines is low.

PREPETAM is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No interactions due to competition for renal excretion have been observed. However, co-administration of PREPETAM with medicines that are eliminated by active tubular secretion may increase concentrations of emtricitabine, tenofovir, and/or the co-administered medicine, and is therefore not recommended.

Medicine that decrease renal function may increase concentrations of emtricitabine and/or tenofovir.

Co-administration of tenofovir DF and ledipasvir/sofosbuvir or sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir has been shown to increase tenofovir exposure. Patients receiving a regimen containing tenofovir DF concomitantly with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir should be monitored for adverse reactions associated with tenofovir DF.

No clinically significant interactions have been observed between emtricitabine and famciclovir, indinavir, zidovudine, stavudine, and tenofovir disoproxil fumarate as an individual medicine (see Tables 2 and 3). Similarly, no clinically significant interactions

have been observed between tenofovir disoproxil fumarate and abacavir, ribavirin, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, saquinavir/ritonavir, sofosbuvir, and tacrolimus in studies conducted in healthy volunteers (see Tables 4 and 5).

Table 2: Medicine interactions: Changes in pharmacokinetic parameters for emtricitabine in the presence of the co-administered medicine[1].

Co-administered medicine	**Dose of co-administered medicine (mg)**	**Emtricitabine Dose (mg)**	**N**	**% Change of emtricitabine pharmacokinetic parameters[2] (90 % CI)**		
				C_{max}	**AUC**	**C_{min}**
Tenofovir DF	300 once daily x 7 days	200 once daily x 7 days	17	⇔	⇔	↑ 20 (↑ 12 to ↑29)
Zidovudine	300 twice daily x 7 days	200 once daily x 7 days	27	⇔	⇔	⇔
Indinavir	800 x 1	200 x 1	12	⇔	⇔	N/A
Famciclovir	500 x 1	200 x 1	12	⇔	⇔	N/A
Stavudine	40 x 1	200 x 1	6	⇔	⇔	N/A

1. All interaction studies conducted in healthy volunteers.

2. ↑ = Increase; ↓= Decrease; ⇔ = No Effect; NA = Not Applicable

Table 3: Medicine interactions: Changes in pharmacokinetic parameters for co-administered medicine in the presence of emtricitabine[1].

Co-administered medicine	**Dose of co-administered medicine (mg)**	**Emtricitabine Dose (mg)**	**N**	**% Change of co-administered medicine pharmacokinetic**

				parameters[2] (90 % CI)		
				C_{max}	**AUC**	**C_{min}**
Tenofovir DF	300 once daily x 7 days	200 once daily x 7 days	17	⇔	⇔	⇔
Zidovudine	300 twice daily x 7 days	200 once daily x 7 days	27	↑ 17 (↑ 0 to ↑38)	↑ 13 (↑ 5 to ↑20)	⇔
Indinavir	800 x 1	200 x 1	12	⇔	⇔	N/A
Famciclovir	500 x 1	200 x 1	12	⇔	⇔	N/A
Stavudine	40 x 1	200 x 1	6	⇔	⇔	N/A

[1.] All interaction studies conducted in healthy volunteers.

[2.] = ↑ Increase; = ↓ Decrease; ⇔ = No Effect; NA = Not Applicable

Table 4: Medicine interactions: Changes in pharmacokinetic parameters for tenofovir[1] in the presence of the co-administered medicine.

Co-administered medicine	**Dose of co-administered medicine (mg)**	**N**	**% Change of tenofovir pharmacokinetic parameters[2] (90 % CI)**		
			C_{max}	**AUC**	**C_{min}**
Abacavir	300 once	8	⇔	⇔	NC
Atazanavir[3]	400 once daily x 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Didanosine (enteric-coated)	400 once	25	⇔	⇔	⇔

Didanosine (buffered)	250 or 400 once daily x 7 days	14	⇔	⇔	⇔
Efavirenz	600 once daily x 14 days	29	⇔	⇔	⇔
Emtricitabine	200 once daily x 7 days	17	⇔	⇔	⇔
Indinavir	800 three times daily x 7 days	13	↑ 14 (↓ 3 to ↑ 33)	⇔	⇔
Lamivudine	150 twice daily x 7 days	15	⇔	⇔	⇔
Ledipasvir/ Sofosbuvir [4,5]	90/400 once daily x 10 days	24	↑ 47 (↑ 37 to ↑ 58)	↑ 35 (↑ 29 to ↑ 42)	↑ 47 (↑ 38 to ↑ 57)
Ledipasvir/ Sofosbuvir [4,6]		23	↑ 64 (↑ 54 to ↑ 74)	↑ 50 (↑ 42 to ↑ 59)	↑ 59 (↑ 49 to ↑ 70)
Ledipasvir/ Sofosbuvir [7]	90/400 once daily x 14 days	15	↑ 79 (↑ 56 to ↑ 104)	↑ 98 (↑ 77 to ↑ 123)	↑ 163 (↑ 132 to ↑ 197)
Ledipasvir/ Sofosbuvir [8]	90/400 once daily x 10 days	14	↑ 32 (↑ 25 to ↑ 39)	↑ 40 (↑ 31 to ↑ 50)	↑ 91 (↑ 74 to ↑ 110)

Ledipasvir/ Sofosbuvir [9]	90/400 once daily x 10 days	29	↑ 61 (↑ 51 to ↑ 72)	↑ 65 (↑ 59 to ↑ 71)	↑ 115 (↑ 105 to ↑ 126)
Lopinavir/ Ritonavir	400/100 twice daily x 14 days	24	⇔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)
Nelfinavir	1 250 twice daily X 14 days	29	⇔	⇔	⇔
Saquinavir/ Ritonavir	1 000/100 twice daily x 14 days	35	⇔	⇔	↑ 23 (↑ 16 to ↑ 30)
Sofosbuvir[10]	400 single dose	16	↑ 25 (↑ 8 to ↑ 45)	⇔	⇔
Sofosbuvir/ Velpatasvir[11]	400/100 once daily	24	↑ 55 (↑ 43 to ↑ 68)	↑ 30 (↑ 24 to ↑ 36)	↑ 39 (↑ 31 to ↑ 48)
Sofosbuvir/ Velpatasvir[12]	400/100 once daily	29	↑ 55 (↑ 45 to ↑ 66)	↑ 39 (↑ 33 to ↑ 44)	↑ 52 (↑ 45 to ↑ 59)
Sofosbuvir/ Velpatasvir[13]	400/100 once daily	15	↑ 77 (↑ 53 to ↑ 104)	↑ 81 (↑ 68 to ↑ 94)	↑ 121 (↑ 100 to ↑ 143)
Sofosbuvir/ Velpatasvir[14]	400/100 once daily	24	↑ 36 (↑ 25 to ↑ 47)	↑ 35 (↑ 29 to ↑ 42)	↑ 45 (↑ 39 to ↑ 51)
Sofosbuvir/ Velpatasvir[15]	400/100 once daily	24	↑ 44 (↑ 33 to ↑ 55)	↑ 40 (↑ 34 to ↑ 46)	↑ 84 (↑ 76 to ↑ 92)

Sofosbuvir/ Velpatasvir[16]	400/100 once daily	30	↑ 46 (↑ 39 to ↑ 54)	↑ 40 (↑ 34 to ↑ 45)	↑ 70 (↑ 61 to ↑ 79)
Sofosbuvir/ Velpatasvir/ Voxilaprevir[17]	400/100/100 + Voxilaprevir[18] 100 once daily	29	↑ 48 (↑ 36 to ↑ 61)	↑ 39 (↑ 32 to ↑ 46)	↑ 47 (↑ 38 to ↑ 56)
Tacrolimus	0,05 mg/kg twice daily x 7 days	21	↑ 13 (↑ 1 to ↑ 27)	⇔	⇔

1. Patients received tenofovir DF 300 mg once daily.

2. Increase = ↑; Decrease = ↓; No Effect = ⇔; NC = Not calculated

3. Atazanavir South African Prescribing Information

4. Data generated from simultaneous dosing with ledipasvir/sofosbuvir. Staggered administration (12 hours apart) provided similar results.

5. Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir DF.

6. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir DF.

7. Study conducted with efavirenz/emtricitabine/tenofovir DF co-administered with ledipasvir/sofosbuvir.

8. Study conducted with emtricitabine/rilpivirine/tenofovir DF co-administered with ledipasvir/sofosbuvir.

9. Study conducted with emtricitabine/tenofovir DF + dolutegravir co administered with ledipasvir/sofosbuvir.

10. Study conducted with efavirenz/emtricitabine/tenofovir DF co-administered with sofosbuvir.

[11.] Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir DF.

[12.] Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir DF.

[13.] Study conducted with efavirenz/emtricitabine/tenofovir DF co-administered with sofosbuvir/velpatasvir.

[14.] Study conducted with elvitegravir/cobicistat/emtricitabine/tenofovir DF co-administered with sofosbuvir/velpatasvir.

[15.] Study conducted with emtricitabine/rilpivirine/tenofovir DF co-administered with sofosbuvir/velpatasvir.

[16.] Administered as raltegravir + emtricitabine/tenofovir DF

[17.] Comparison based on exposures when administered as darunavir + ritonavir + emtricitabine/tenofovir DF.

[18.] Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposure expected in HCV-infected patients.

Table 5: Medicine interactions: Changes in pharmacokinetic parameters for co-administered medicine in the presence of tenofovir.

Co-administered medicine	**Dose of co-administered medicine (mg)**	**N**	**% Change of co-administered medicine pharmacokinetic parameters[1] (90 % CI)**		
			C_{max}	**AUC**	**C_{min}**
Abacavir	300 once	8	↑ 12 (↓ 1 to ↑ 26)	⇔	N/A
Atazanavir[2]	400 once daily x 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)

Atazanavir[2]	Atazanavir/Ritonavir 300/100 once daily x 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓ 25[3] (↓ 42 to ↓ 3)	↓ 23[3] (↓ 46 to ↑ 10)
Efavirenz	600 once daily x 14 days	30	⇔	⇔	⇔
Emtricitabine	200 once daily x 14 days	17	⇔	⇔	↑ 20 (↑ 12 to ↑ 29)
Indinavir	800 three times daily x 7 days	12	↓ 11 (↓ 30 to ↑ 12)	⇔	⇔
Lamivudine	150 twice daily X 7 days	15	↓ 24 (↓ 34 to ↓ 12)	⇔	⇔
Lopinavir Ritonavir	Lopinavir/ Ritonavir 400/100 twice daily x 14 days	24	⇔	⇔	⇔
Methadone[4]	40 to 110 once daily x 14 days[5]	13	⇔	⇔	⇔
Nelfinavir M8 metabolite	1 250 twice daily x 14 days	29	⇔ ⇔	⇔ ⇔	⇔ ⇔
Oral Contraceptives[6]	Ethinyl Estradiol 0,035 mg/ Norgestimate 0,25 mg once	20	⇔	⇔	⇔

	daily x 7 days				
Ribavirin	600 once daily	22	⇔	⇔	N/A
Saquinavir Ritonavir	Saquinavir/ Ritonavir 1 000/100 twice daily x 14 days	32	↑ 22 (↑ 6 to ↑ 41) ⇔	↑ 29[7] (↑ 12 to ↑ 48) ⇔	↑ 47[7] (↑ 23 to ↑ 76) ↑ 23 (↑ 3 to ↑ 46)
Sofosbuvir GS-331007 Velpatasvir Voxilaprevir	Sofosbuvir/ Velpatasvir/ Voxilaprevir 400/100/100 + Voxilaprevir[8] 100 once daily	29	↓ 30[9] (↓ 38 to ↓ 22) ⇔[9] ⇔[9] ↑ 72[9] (↑ 51 to ↑ 97)	⇔[9] ⇔[9] ⇔[9] ↑ 143[9] (↑ 115 to ↑ 175)	N/A N/A ⇔[9] ↑ 300[9] (↑ 244 to ↑ 365)

[1.] Increase = ↑; Decrease = ↓; No Effect = ⇔; NA = Not Applicable

[2.] Atazanavir South African Prescribing Information

[3.] In HIV-infected patients, addition of tenofovir DF 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.

[4.] R-(active), S- and total methadone exposures were equivalent when dosed alone or with tenofovir DF.

[5.] Individual subjects were maintained on their stable methadone dose. No pharmacodynamics alterations (opiate toxicity or withdrawal signs or symptoms) were reported.

[6.] Ethinyl estradiol 0,035 mg and 17-deacetyl norgestimate 0,25 mg (pharmacologically active metabolite) exposures were equivalent when dosed alone or with tenofovir DF.

[7.] Increases in AUC and C_{min} are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir DF and ritonavir-boosted saquinavir are co-administered.

[8.] Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

[9.] Comparison based on exposures when administered as darunavir + ritonavir + emtricitabine/tenofovir DF.

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

Co-administration of tenofovir DF with didanosine results in changes in the pharmacokinetics of didanosine that may be of clinical significance. Table 6 summarises the effects of tenofovir DF on the pharmacokinetics of didanosine. Concomitant dosing of tenofovir DF with didanosine buffered tablets or enteric coated capsules significantly increases the C_{max} and AUC of didanosine. When didanosine 250 mg enteric-coated capsules were administered with tenofovir DF, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions. The mechanism of this interaction is unknown.

Table 6: Medicine interactions: Pharmacokinetic parameters for didanosine in the presence of tenofovir.

Didanosine1 dose (mg)/Method of administration[2]	**Tenofovir method of administration[2]**	**N**	**% Difference (90 % CI) vs. didanosine 400 mg alone, fasted[3]**	
			C_{max}	**AUC**
Buffered tablets				
400 once daily[4] x 7 days	Fasted 1 hour after didanosine	14	↑ 28 (↑ 11 to ↑ 48)	↑ 44 (↑ 31 to ↑ 59)
Enteric-coated capsules				
400 once, fasted	With food, 2 hr after didanosine	26	↑ 48 (↑ 25 to ↑ 76)	↑ 48 (↑ 31 to ↑ 67)
400 once, with food	Simultaneously with didanosine	26	↑ 64 (↑ 41 to ↑ 89)	↑ 60 (↑ 44 to ↑ 79)
250 once, fasted	With food, 2 hr after didanosine	28	↓ 10 (↓ 22 to ↑ 3)	⇔
250 once, fasted	Simultaneously with didanosine	28	⇔	↑ 14 (0 to ↑ 31)
250 once, with food	Simultaneously with didanosine	28	↓ 29 (↓ 39 to ↓ 18)	↓ 11 (↓ 23 to ↑ 2)

[1.] See section 4.4 for use regarding use of didanosine with tenofovir.

[2.] Administration with food was with a light meal (~ 373 kcal, 20 % fat).

[3.] Increase = ↑; Decrease = ↓; No Effect = ⇔

[4.] Includes 4 subjects weighing < 60 kg receiving ddL 250 mg.

4.6 Fertility, pregnancy and lactation

The safety of PREPETAM in pregnancy and lactation has not been established (see section 4.3).

A reliable method of contraception should be used to avoid pregnancy while taking PREPETAM.

Pregnancy

There are no adequate and well-controlled studies in pregnant women. PREPETAM should not be used in pregnancy (see section 4.3). Animal studies on emtricitabine and tenofovir disoproxil do not indicate reproductive toxicity (see section 5.3).

Breastfeeding

Nursing Mothers: HIV-infected mothers should not breastfeed their infants, to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that tenofovir is secreted in milk. It is not known whether tenofovir or emtricitabine is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving PREPETAM.

Fertility

No human data on the effect of PREPETAM are available. Reported animal studies do not indicate harmful effects of emtricitabine or tenofovir disoproxil on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects of either tenofovir DF or emtricitabine on the ability to drive and use machines have been performed. However, dizziness has been reported during treatment with both tenofovir DF and emtricitabine.
If dizziness occurs, patients should be advised not to drive or operate machinery.

4.8 Undesirable effects

HIV-1 infection: The most frequently reported adverse reactions considered possibly or probably related to emtricitabine and/or tenofovir disoproxil were nausea and diarrhoea in a clinical study in adults. The safety profile of emtricitabine and tenofovir disoproxil in this study was consistent with the previous experience with these medicines when each was administered with other antiretroviral agents.

Pre-exposure prophylaxis: No new adverse reactions to tenofovir DF/emtricitabine as contained in PREPETAM were identified from reported studies in which HIV-1 uninfected adults received tenofovir DF/emtricitabine as contained in PREPETAM once daily for pre-exposure prophylaxis. The most frequent adverse reaction reported in the study was headache.

Tabulated summary of adverse reactions: Emtricitabine and Tenofovir DF

Frequency	**Emtricitabine**	**Tenofovir disoproxil**
Blood and lymphatic system disorders		
Frequent:	neutropenia	
Less frequent:	anaemia[2]	
Immune system disorders		
Frequent:	allergic reaction, angioedema	angioedema
Metabolism and nutrition disorders		

Frequent:	hyperglycaemia, hypertriglyceridaemia	hypophosphataemia[1]
Less frequent:		hypokalaemia[1] lactic acidosis
Psychiatric disorders		
Frequent:	insomnia, abnormal dreams	
Nervous system disorders		
Frequent:	headache dizziness	headache dizziness
Respiratory, thoracic and mediastinal disorders		
Frequent:	dyspnoea	dyspnoea
Gastrointestinal disorders		
Frequent:	diarrhoea, nausea, elevated amylase including elevated pancreatic amylase, elevated serum lipase, vomiting, abdominal pain, dyspepsia	diarrhoea, vomiting, nausea, abdominal pain, abdominal distension, flatulence
Less frequent:		pancreatitis
Hepatobiliary disorders		
Frequent:	elevated serum aspartate aminotransferase (AST) and/or elevated serum alanine aminotransferase (ALT),	increased transaminases

	hyperbilirubinaemia	
Less frequent:		hepatic steatosis, hepatitis
Skin and subcutaneous tissue disorders		
Frequent:	vesiculobullous rash, pustular rash, maculopapular rash, rash, pruritus, urticaria, skin discolouration (increased pigmentation)[2]	rash
Musculoskeletal and connective tissue disorders		
Frequent:	elevated creatine kinase	
Less frequent:		rhabdomyolysis[1], muscular weakness[1], osteomalacia (manifested as bone pain and infrequently contributing to fractures)[1,3,] myopathy[1]
Renal and urinary disorders		

Less frequent:		increased creatinine, proteinuria, proximal renal tubulopathy including Fanconi syndrome, renal failure (acute and chronic), acute tubular necrosis, nephritis (including acute interstitial nephritis)[3], nephrogenic diabetes insipidus
General disorders and administration site conditions		
Frequent:	pain, asthenia	asthenia

[1] This adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil in the absence of this condition.

[2] Anaemia was common and skin discolouration (increased pigmentation).

[3] This adverse reaction was identified through reported post-marketing surveillance.

Renal impairment

As PREPETAM may cause renal damage monitoring of renal function is recommended (see section 4.4).

Proximal renal tubulopathy generally resolved or improved after tenofovir disoproxil discontinuation. However, in some HIV-1 infected 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).

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). Rarely, 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 and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

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).

Other special populations

Individuals with renal impairment

Since tenofovir disoproxil can cause renal toxicity, close monitoring of renal function is recommended in any adults with renal impairment receiving PREPETAM (see sections 4.2, 4.4 and 5.2). The use of PREPETAM is not recommended in individuals under the age of 18 years with renal impairment (see sections 4.2 and 4.4).

HIV/HBV or HCV co-infected patients

The adverse reaction profile of emtricitabine and tenofovir disoproxil in a reported HIV-infected patient study who were co-infected with HBV or HCV was similar to that observed in patients infected with HIV without co-infection. However, as would be expected in this patient population, elevations in AST and ALT occurred more frequently than in the general HIV infected population.

Exacerbations of hepatitis after discontinuation of treatment

In HBV infected patients, clinical and laboratory evidence of hepatitis have occurred after discontinuation of treatment (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. 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

Symptoms

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

Emtricitabine

Haemodialysis treatment removes approximately 30 % of the emtricitabine dose over a 3-hour dialysis period starting within 1,5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

Tenofovir DF

Tenofovir is poorly removed by haemodialysis. Following a single 300 mg dose of tenofovir DF, a four-hour haemodialysis session removed only approximately 10 % of the administered tenofovir dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification/ Category and Class:

A 20.2.8 Antimicrobial (Chemotherapeutic) Agents. Antiviral Agents

ATC Classification: Antiviral for systemic use; antivirals for treatment of HIV infections, combinations.

ATC Code: J05AR03

Emtricitabine

Emtricitabine, a synthetic nucleoside analogue of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase (RT) by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5'-triphosphate is a weak inhibitor of mammalian DNA polymerase α, β, ε and mitochondrial DNA polymerase γ.

Tenofovir DF

Tenofovir DF also known as tenofovir DF is an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate. Tenofovir DF requires initial diester

hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 RT by competing with the natural substrate deoxyadenosine 5'- triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Resistance

Emtricitabine and tenofovir DF

HIV-1 isolates with reduced susceptibility to the combination of emtricitabine and tenofovir have been selected in cell culture. Genotypic analysis of these isolates identified the M184I/V and/or K65R amino acid substitutions in the viral RT.
In addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in reduced susceptibility to tenofovir.

Emtricitabine-resistant isolates of HIV have been recovered from some patients treated with emtricitabine alone or in combination with other antiretroviral medicines. In a clinical study, viral isolates from 6/16 (37,5 %) treatment-naïve patients with virological failure showed > 20-fold reduced susceptibility to emtricitabine. Genotypic analysis of these isolates showed that the resistance was due to M184V/I mutations in the HIV RT gene.

Tenofovir DF

The K65R and K70E substitutions selected by tenofovir are also selected in some HIV-1-infected patients treated with abacavir or didanosine.

HIV-1 isolates with the K65R and K70E substitutions also showed reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among

these NRTIs may occur in patients whose virus harbors the K65R or K70E substitutions.

HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R mutation in RT and showed a 2 to 4-fold reduction in susceptibility to tenofovir.

Tenofovir-resistant isolates of HIV-1 have also been recovered from some patients treated with tenofovir in combination with certain antiretroviral medicines.

Cross-resistance

Emtricitabine and tenofovir DF

Cross-resistance among certain nucleoside reverse transcriptase inhibitors (NRTIs) has been recognised. The M184V/I and/or K65R substitutions selected in cell culture by the combination of emtricitabine and tenofovir are also observed in some HIV-1 isolates from subjects failing treatment with tenofovir in combination with either lamivudine or emtricitabine, and either abacavir or didanosine. Therefore, cross-resistance among these medicines may occur in patients whose virus harbours either or both of these amino acid substitutions.

Emtricitabine

Emtricitabine-resistant isolates (M184V/I) were cross resistant to lamivudine and zalcitabine but retained susceptibility *in vitro* to didanosine, stavudine, tenofovir, zidovudine, and NNRTIs (delavirdine, efavirenz, and nevirapine). Isolates from heavily treatment experienced patients containing the M184V/I amino acid substitution in the context of other NRTI resistance associated substitutions may retain susceptibility to tenofovir. HIV-1 isolates containing the K65R substitution, selected in vivo by abacavir, didanosine, tenofovir, and zalcitabine, demonstrated reduced susceptibility to inhibition by emtricitabine. Viruses harbouring mutations conferring reduced susceptibility to

stavudine and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to emtricitabine. HIV-1 containing the K103N substitution associated with resistance to NNRTIs was susceptible to emtricitabine.

Tenofovir DF

HIV-1 isolates from patients (N = 20) whose HIV-1 expressed a mean of 3' zidovudine-associated RT amino acid substitutions (M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N) showed a 3,1-fold decrease in the susceptibility to tenofovir. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the RT showed reduced susceptibility to tenofovir.

Antiviral Activity

Emtricitabine and tenofovir DF

In combination studies evaluating the in-cell culture antiviral activity of emtricitabine and tenofovir together, synergistic antiviral effects were observed.

5.2 Pharmacokinetic properties

Adults

One combination tablet was bioequivalent to one emtricitabine capsule (200 mg) plus one tenofovir DF tablet (300 mg) following single-dose administration to fasting healthy subjects (N = 39).

Emtricitabine

The pharmacokinetic properties of emtricitabine are summarised in Table 1. Following oral administration of emtricitabine (200 mg), emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1 to 2 hours post-dose. *In vitro* binding of emtricitabine to human plasma proteins is < 4 % and is independent of concentration over the range of 0,02 to 200 µg/mL. Following administration of radiolabelled emtricitabine, approximately 86 % is recovered in the urine and 13 % is recovered as

metabolites. The metabolites of emtricitabine include 3'-sulfoxide diastereomers and their glucuronic acid conjugate.

Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of emtricitabine (200 mg), the plasma emtricitabine half-life is approximately 10 hours.

Tenofovir DF

The pharmacokinetic properties of tenofovir DF are summarised in Table 7. Following oral administration of tenofovir, maximum tenofovir serum concentrations are achieved in 1,0 ± 0,4 hours. In cell culture binding of tenofovir to human plasma proteins is < 0,7 % and is independent of concentration over the range of 0,01 to 25 µg/mL. Approximately 70 to 80 % of the intravenous dose of tenofovir is recovered as unchanged medicine in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of tenofovir DF, the terminal elimination half-life is approximately 17 hours.

Table 7: Single Dose Pharmacokinetic Parameters for Emtricitabine and Tenofovir in Adults[1]

	Emtricitabine	Tenofovir
Fasted Oral Bioavailability[2] (%)	92 (83,1 to 106,4)	25 (NC to 45,0)
Plasma Terminal Elimination Half-Life[2] (hr)	10 (7,4 to 18,0)	17 (12,0 to 25,7)
C_{max}[3] (µg/mL)	1,8 ± 0,72[4]	0,30 ± 0,09
AUC[3] (µg·hr/mL)	10,0 ± 3,12[4]	2,29 ± 0,69
CL/F[3] (mL/min)	302 ± 94	1043 ± 115
CL_{renal}[3] (mL/min)	213 ± 89	243 ± 33

1. NC = Not calculated

2. Median (range)

[3.] Mean (± SD)

[4.] Data presented as steady state values

Effects of food on oral absorption

The combination tablet may be administered with or without food. Administration of the combination tablet following a high fat meal (784 kcal; 49 grams of fat) or a light meal (373 kcal; 8 grams of fat) delayed the time of tenofovir C_{max} by approximately 0,75 hour. The mean increases in tenofovir AUC and C_{max} were approximately 35 % and 15 %, respectively, when administered with a high fat or light meal, compared to administration in the fasted state. In previous safety and efficacy studies, tenofovir was taken under fed conditions. Emtricitabine systemic exposures (AUC and C_{max}) were unaffected when the combination tablet was administered with either a high fat or a light meal.

Special populations

Race

Emtricitabine

No pharmacokinetic differences due to race have been identified following the administration of emtricitabine (200 mg).

Tenofovir DF

There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations following the administration of tenofovir DF.

Paediatric and elderly patients

Pharmacokinetics of emtricitabine and tenofovir have not been fully evaluated in children (< 12 years weighing less than 35 kg) or in the elderly (> 65 years) (see section 4.4).

Patients with impaired renal function

The pharmacokinetics of emtricitabine and tenofovir are altered in patients with renal impairment (see section 4.3 and 4.4). In patients with creatinine clearance < 50 mL/min, C_{max}, and $AUC_{0-\infty}$ of emtricitabine and tenofovir were significantly increased. It is recommended that PREPETAM not be used in patients with creatinine clearance < 50 mL/min or in patients with end-stage renal disease requiring dialysis (see section 4.3 and 4.4).

Do not use PREPETAM for a Pre-exposure Prophylaxis (PrEP) indication in HIV-1 uninfected individuals with a creatinine clearance < 60 mL/min (see section 4.3 and 4.4).

Patients with hepatic impairment

The pharmacokinetics of tenofovir following a 300 mg dose of tenofovir DF 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. The pharmacokinetics of PREPETAM or emtricitabine has not been studied in patients with hepatic impairment; however, emtricitabine is not significantly metabolised by liver enzymes, so the impact of liver impairment should be limited.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose,

Lactose monohydrate,

Croscarmellose sodium,

Magnesium stearate,

Pregelatinized Starch,

Hydroxypropyl methyl cellulose,

Titanium dioxide,

Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 30 °C.

Protect from light.

Do not use if seal over bottle opening is broken or missing.

Keep in original container until required for use.

Keep bottle tightly closed.

6.5 Nature and contents of container

Bottle with silica gel sachet

30 Tablets - 120 CC White HDPE Bottle with 5 g silica gel desiccant sachet and white 38 mm non CR closure. Seal the bottle by an Induction sealing process

Bottle with molecular sieve

30 Tablets - 120 CC White HDPE Bottle with 5 g molecular sieve desiccant sachet and white 38 mm non CR closure. Seal the bottle by an Induction sealing process.

Pack size of 30’s

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown

JOHANNESBURG

2193

South Africa

Tel: 0860287835

Manufactured by

Lupin Ltd

Imported and distributed by

Austell Pharmaceuticals (Pty) Ltd

8. REGISTRATION NUMBER

55/20.2.8/0350

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07 December 2021

10. DATE OF REVISION OF THE TEXT

10 February 2023