PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

EMTEN tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

tenofovir disoproxil fumarate 300 mg (which is equivalent to 245 mg of tenofovir disoproxil) and emtricitabine 200 mg.

Sugar content: Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

White to off white, modified capsule shaped, film-coated tablets, debossed with “EM” on one side and “144” on other side of the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EMTEN is indicated in combination with other anti-retroviral medicines (such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors) for the treatment of HIV-1 infection in adults.

EMTEN 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

The dose of EMTEN is one tablet once daily taken orally with or without food.

Dosage for Pre-Exposure Prophylaxis

The dose of EMTEN in HIV-1 uninfected adults is one tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) once daily taken orally with or without food.

Renal impairment:

Significantly increased exposure occurred when emtricitabine (200 mg) or tenofovir were administered to patients with moderate to severe renal impairment, therefore EMTEN (which is a fixed dose combination) should not be prescribed for patients requiring dosage adjustments (see section 4.3).

Method of administration

EMTEN is taken orally with or without food.

4.3 Contraindications

- EMTEN is contraindicated in patients with previously demonstrated hypersensitivity to tenofovir or emtricitabine or any of the components of the medicine.

- EMTEN is contraindicated in patients with moderate to severe uncontrolled renal failure.
- Creatinine CL < 60 ml/min when used for PrEP.
- Creatinine CL < 50 ml/min when used for treatment of HIV-1.
- EMTEN should not be used for Pre-Exposure Prophylaxis (PrEP) in individuals with unknown or positive HIV-1 status.
- EMTEN should not be used for PrEP in individuals not fully committed to full treatment compliance.
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

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 ANTI-RETROVIRALS.

THE COMBINATION TABLET IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF THE COMBINATION TABLET HAVE NOT BEEN ESTABLISHED IN PATIENTS COINFECTED WITH HBV AND HIV. SEVERE ACUTE EXCERBATIONS OF HEPATITIS B HAVE BEEN REPOTED IN PATIENTS WHO HAVE DISCONTINUED EMTRICITABINE (200 MG) OR TENOFOVIR. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE THE COMBINATION TABLET AND

ARE COINFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED.

Lipodystrophy and metabolic abnormalities

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

Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART). Typically, such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, cytomegalovirus retinitis, and cryptococcal meningitis.

Appropriate treatment of the opportunistic disease should be instituted 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. Tenofovir disoproxil fumarate may be associated with reduction in bone density and patients bone mineral density should be monitored for evidence of bone abnormalities. Bone monitoring should be considered for patients with a history of bone fractures or those at risk of osteopenia.

Opportunistic infections

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

The risk of HIV transmission to others

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

Lactic acidosis / hyperlactataemia

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

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

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

- Lactate 2-5 mmol/ℓ with minimum symptoms: switch to medicines that are less likely to cause lactic acidosis.
- Lactate 5-10 mmol/ℓ with symptoms and/or with reduced standard bicarbonate: Stop NRTIs and change treatment option. Once lactate has settled, use medicines that are less likely to cause lactic acidosis.

Exclude other causes, (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis and hyperthyroidism.

- Lactate > 10 mmol/ℓ: STOP all therapy (80 % mortality).

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

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

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

Mitochondrial dysfunction

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

follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant sign and symptoms.

Pancreatitis

Pancreatitis has been observed in some patients receiving EMTEN. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of EMTEN until diagnosis of pancreatitis is excluded.

Patients with moderate to severe renal impairment

In patients with moderate to severe renal impairment, the terminal half-life of EMTEN is increased due to decreased clearance as the dose of EMTEN (fixed dose combination) cannot be adjusted. EMTEN should not be taken in patients with moderate to severe renal impairment (see section 4.3).

Liver disease

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

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored. If there is evidence of worsening liver disease in such patients, temporary or permanent discontinuation of treatment must be considered.

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

Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV).

In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant package inserts for these medicines.

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

Renal impairment

Emtricitabine and tenofovir are principally eliminated by the kidney.

EMTEN should not be administered to patients with creatinine clearance < 30 ml/min or patients requiring haemodialysis.

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphataemia), has been reported in association with the use of tenofovir.

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

4.5 Interactions with other medicines and other forms of interaction

Interaction studies with EMTEN tablets have not been conducted.

Emtricitabine and tenofovir disoproxil fumarate:

The steady state pharmacokinetic properties of emtricitabine and tenofovir as in EMTEN, remained unchanged when emtricitabine and tenofovir disoproxil fumarate were administered together versus each medicine given alone.

In vitro and clinical pharmacokinetic medicine interaction studies have found that the potential of CYP450 mediated interactions involving emtricitabine and tenofovir, as in EMTEN, with other medicines is low.

The kidneys are primarily responsible for the excretion of emtricitabine and tenofovir through a combination of glomerular filtration and active tubular secretion. Although no interactions due to competition for renal excretion have been observed, it is possible that, when EMTEN is co-administered with medicines that are eliminated by active tubular secretion, the concentrations of emtricitabine, tenofovir and/or the concomitant medicine may increase.

Medicines that reduce renal function may increase emtricitabine and/or tenofovir concentrations.

The use of tenofovir disoproxil fumarate with nephrotic medicines or with medicines eliminated by active tubular secretion is not recommended. If such use is unavoidable, renal function should be monitored weekly.

Clinically significant medicine interactions have not been observed between emtricitabine, one of the active ingredients in EMTEN, and famciclovir, indinavir, stavudine and tenofovir disoproxil fumarate.

Co-administration of tenofovir disoproxil fumarate 300 mg once daily for 7 days with emtricitabine, 200 mg once daily for 7 days, caused no changes in the C_{max} or AUC of emtricitabine. However, C_{max} of emtricitabine increased by 20 % [90 % confidence interval (CI) + 12 % to + 29 %]. The C_{max}, AUC and C_{min} of tenofovir were unchanged.

Co-administration of single doses of indinavir 800 mg, famciclovir 500 mg and stavudine 40 mg with a single dose of emtricitabine 200 mg did not alter the C_{max} or AUC of emtricitabine or the co-administered medicine.

Similarly, clinically significant interactions have not been observed between tenofovir disoproxil fumarate, one of the active ingredients in EMTEN, and abacavir, adefovir dipivoxil,

ribavirin, efavirenz, indinavir, lamivudine, lopinavir/ritonavir, methadone and oral contraceptives.

Co-administration of a single dose abacavir 300 mg with tenofovir caused no changes in the C_{max} or AUC of tenofovir. However, C_{max} of abacavir increased by 12 % (90 % CI – 1 % to + 26 %), while the AUC remained unchanged.

Concomitant administration of a single dose of adefovir dipivoxil 10 mg with tenofovir 300 mg did not result in any changes in the C_{max} or AUC of tenofovir nor in the C_{max}, C_{min} or AUC of tenofovir nor in the C_{max} or AUC of adefovir dipivoxil.

Co-administration of atazanavir 400 mg once daily for 14 days with tenofovir 300 mg once daily resulted in a 14 % increase (90 % CI + 8 % to + 20 %) in tenofovir C_{max} 24 % increase (+ 21 % to + 28 %) in tenofovir AUC and 22 % increase (+ 15 % to + 30 %) in tenofovir C_{min}. Corresponding parameters for atazanavir showed a 21 % decrease (- 27 to – 14 %) in C_{max} 25 % decrease (- 30 % to -19 %) in AUC and 40 % decrease (- 48 % to – 32 %) in C_{min}. In HIV-infected patients, addition of tenofovir disoproxil fumarate to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2,3- and 4- fold higher than the respective values observed for atazanavir 400 mg when given alone.

Concomitant administration of a single dose of enteric-coated didanosine 400 mg with tenofovir 300 mg did not result in any changes in the C_{max} C_{min} or AUC of tenofovir. The same holds true for the combination of buffered didanosine 250 or 400 mg once daily for 7 days with tenofovir 300 mg once daily.

When administered with multiple doses of tenofovir, the C_{max} and AUC of didanosine 400 mg increased significantly.The mechanism of the interaction has not been identified.

Concomitant administration of didanosine 250 mg enteric-coated capsules with tenofovir resulted in systematic exposures similar to those observed with the 400 mg enteric-coated capsules alone under fasted conditions.

Tenofovir disoproxil fumarate:

When tenofovir disoproxil fumarate was administered with didanosine the Cmax and AUC of didanosine administered as either the buffered or enteric-coated formulation increased significantly. The mechanism of this action is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse events, including pancreatitis, and neuropathy. In adults weighing > 60 kg, the didanosine dose should be reduced to 250 mg when it is co-administered with EMTEN. Data are not available to recommend a dose adjustment of didansine for patients weighing < 60 kg. When co-administered, EMTEN and didanosine may be taken under fasted conditions or with a light meal (< 400 kcal, 20 % fat).

Co-administration of didanosine buffered tablet formulation with EMTEN should be under fasted conditions.

Co-administration of EMTEN and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosin-associated adverse events. Didanosine should be discontinued in patients who develop didansine-associated adverse events.

Atazanavir and lopinavir/ritonavir have been shown to increase tenofovir concentrations. The mechanism of this action is unknown.

Patients receiving atazanavir and lopinavir/ritonavir and EMTEN should be monitored for EMTEN-associated adverse events.

EMTEN should be discontinued in patients who develop EMTEN associated adverse events.

Tenofovir decreases the AUC and Cmin of atazanavir. When co-administered with EMTEN, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg.

Atazanavir without ritonavir should not be co-administered with EMTEN.

Emtricitabine and tenofovir disoproxil fumarate:

Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of EMTEN 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. Some examples include, but are not limited to adefovir, dipivoxil, cidofovir, acyclovir, valacyclovir, ganciclovir and valganciclovir.

EMTEN is a fixed-dose combination of emtricitabine and tenofovir disoproxil fumarate. EMTEN should not be co-administered with (emtricitabine 200 mg) or tenofovir. Due to similarities between emtricitabine and lamivudine, EMTEN should not be co-administered with other medicines containing lamivudine, including lamivudine and zidovudine co-formulation, lamivudine for HIV, lamivudine for HBV, abacavir sulphate and lamivudine co-formulation or abacavir sulphate, lamivudine and zidovudine co-formulation.

For a detailed summary of the changes in pharmacokinetic parameters for didanosine, please refer to the table below.

Table 1: *Medicine interactions: Pharmacokinetic parameters for didanosine when co-administered with tenofovir:*

Didanosine dose (mg)/ Method of Administration[1]	Tenofovir method of administration	N	% Difference (90 % CI) vs. didanosine 400 mg alone, fasted[2]	
			C_{max}	AUC
Buffered tablets				
400 once daily[3] X 7 days	Fasted 1 hour before didanosine	14	↑28 (↑11 - ↑48)	↑44 (↑31 - ↑59)
Enteric-coated capsules				

400 once, fasted	With food, 2 hour after didanosine	26	↑48 (↑25 -↑76)	↑48 (↑31 -↑67)
400 once, with food	Simultaneously with didanosine	26	↑64 (↑41 -↑89)	↑60 (↑44 -↑79)
250 once, fasted	With food, 2 hour after didanosine	28	↓10 (↓22 -↑3)	↔
250 once, fasted	Simultaneously with didanosine	28	↔	↑14 (0 - ↑31)
250 once, with food	Simaltenously with didanosine	28	↓29 (↓39 -↓18)	↓11 (↓23 - ↑2)

1. Administration with food was with a light meal
2. ↑ = increase; ↓ = decrease; ↔ = no difference.
3. Includes 4 subjects weighing < 60 kg receiving ddl 250 mg.

Concomitant administration of efavirenz 600mg once daily for 14 days with tenofovir 300 mg once daily did not result in any changes in the C_{max}, C_{min} or AUC of either efavirenz or tenofovir. There was a 14 % increase (90 % CI – 3 % to + 33 %) in the C_{max} of tenofovir when indinavir 800 mg three times daily for 7 days was co- administered with tenofovir 300 mg once daily. The C_{min} and AUC of tenofovir remained unchanged as did the C_{min} and AUC of indinavir.

Indinavir C_{max} decreased by 11 % (- 30 % to + 12 %). Coadministration of lamivudine 150 mg twice daily for 7 days with tenofovir 300 mg once daily did not result in any changes in the C_{max} C_{min} or AUC of tenofovir. While the C_{min} and AUC of lamivudine were unchanged, the C_{max} decreased by 24 % (90 % CI – 34 % to – 12 %).

Co-administration of a combination of lopinavir 400 mg and ritonavir 100 mg twice daily for 14 days with tenofovir 300 mg once daily resulted in a 32 % increase (90 % CI + 26 % to + 38 %) in tenofovir AUC and 29 % increase (+23 % to + 66 %) in tenofovir C_{min} while tenofovir C_{max} remained changed. There were no changes in C_{max}, C_{min} or AUC of lopinavir and ritonavir.

There appears to be a lack of clinically significant interactions between tenofovir and methadone, oral contraceptives and ribavirin. Steady state tenofovir pharmacokinetics were similar following multiple dosing to HIV-negative individuals receiving either chronic methadone maintenance therapy or oral contraceptives, or single doses of ribavirin, to those observed previously.

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

Co-administration of tenofovir and didanosine results in a 40 – 60 % increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions.

4.6 Fertility, pregnancy and lactation

Pregnancy

A reliable method of contraceptive should be used to avoid pregnancy while taking EMTEN.

There are no adequate and well-controlled studies of EMTEN in pregnant women. EMTEN should not be used during pregnancy (see section 4.3).

Lactation

It is recommended that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV.

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 EMTEN.

4.7 Effects on ability to drive and use machines

Dizziness has been reported during treatment with both emtricitabine and tenofovir disoproxil fumarate, therefore caution should be exercised when driving or operating machinery.

4.8 Undesirable effects

a. Summary of the safety profile

Not Applicable

b. Tabulated summary of adverse reactions

Side-effects which have been associated with the individual components of EMTEN are listed below:

	Emtricitabine	**Tenofovir disoproxil fumarate**
Nervous system disorders		
Frequent:	headache, dizziness.	headache, dizziness.
Psychiatric disorders		
Frequent:	sleep disturbances (abnormal dreams, insomnia), depressive disorder.	

	Emtricitabine	**Tenofovir disoproxil fumarate**
Frequency unknown:	neuropathy, paraesthesia, peripheral neuritis, asthenia.	depression, asthenia, insomnia, peripheral neuropathy (including peripheral neuritis and neuropathy), anxiety.
Gastrointestinal disorders		
Frequent:	nausea, vomiting, diarrhoea, elevated amylase including elevated pancreatic amylase, elevated serum lipase, abdominal pain, dyspepsia.	nausea, vomiting, diarrhoea, abdominal pain, flatulence, abdominal distension, dyspepsia, anorexia.
Less frequent:		pancreatitis, serum-amylase concentrations may be raised.
Frequency unknown:	abdominal pain.	
Skin and subcutaneous tissue disorders		
Frequent:	rash event (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash and allergic reaction).	

	Emtricitabine	**Tenofovir disoproxil fumarate**
Frequency unknown:	skin discolouration manifested by hyperpigmentation on the palms and/or sole, but is generally mild.	skin rashes (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash and pustular rash).
Musculoskeletal, connective tissue and bone disorders		
Less frequent:		rhabdomyolysis, muscular weakness, osteomalacia (manifested as bone pain and infrequently contributing to fractures), myopathy.
Frequency unknown:	myalgia, arthralgia.	back pain, myalgia, arthralgia.
Blood and lymphatic system disorders		
Frequent:	neutropenia.	
Less frequent:	anaemia.	
Frequency unknown:		neutropenia, haematuria.
Renal and urinary disorders		
Frequent:	elevated creatinine kinase.	
Less frequent:		increased creatinine, proteinuria, renal failure (acute and chronic), acute tubular

	Emtricitabine	**Tenofovir disoproxil fumarate**
		necrosis, proximal renal tubulopathy including Fanconi syndrome, nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus.
Hepato-biliary disorders		
Frequent:	elevated serum aspartate aminotransferase (AST) and/or elevated serum alanine aminotransferase (ALT), hyperbilirubinaemia .	increased transaminases.
Less frequent:		hepatic steatosis, hepatitis.
Frequency unknown:	**hepatic steatosis.**	
Respiratory, thoracic and mediastinal disorders		
Frequency unknown:	increased cough and rhinitis.	chest pain, pneumonia, dyspnoea.
Metabolism and nutrition disorders		
Frequent:	hyperglycaemia, hypertriglyceridaemia.	hypophosphataemia.
Less frequent:		hypokalaemia.
Frequency unknown:	lactic acidosis, usually associated with severe	lactic acidosis, usually associated with severe

	Emtricitabine	**Tenofovir disoproxil fumarate**
	hepatomegaly and steatosis, has been associated with nucleoside reverse transcriptase inhibitors.	hepatomegaly and steatosis, has been associated with nucleoside reverse transcriptase inhibitors, hypertriglyceridaemia, hyperglycaemia.
Immune system disorders		
Frequent:	allergic reaction.	
Less frequent:	angioedema.	angioedema.
Frequency unknown:		allergy.
General disorders and administrative site conditions		
Frequent:	pain, asthenia.	asthenia.
Frequency unknown:		fever, sweating, weight loss.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

If overdose occurs, the patient should be monitored for evidence of toxicity, including monitoring of vital signs and observation of the patient's clinical status. Standard supportive treatment should then be 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 disoproxil fumarate:

Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54 %. Following a single 300 mg dose of tenofovir DF, a 4-hour haemodialysis session can remove approximately 10 % of the administered tenofovir dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral for systemic use; antivirals for treatment of HIV infections, combinations. ATC code: J05AR03

<u>Antiviral activity:</u>

Emtricitabine and tenofovir disoproxil fumarate:

Combination studies that evaluated the *in vitro* antiviral activity of emtricitabine and tenofovir together, demonstrated synergistic effects.

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 disoproxil fumarate (DF):

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 disoproxil fumarate:

HIV-1 isolates with reduced susceptibility to the combination of emtricitabine and tenofovir have been selected *in vitro*.

Genotypic analysis of these isolates identified the M184I/V and/or K65R amino acid substitutions in the viral RT.

Emtricitabine:

Emtricitabine-resistant isolates of HIV have been selected *in vitro*.

Genotypic analysis of these isolates showed that the reduced susceptibility to emtricitabine was associated with a mutation in the HIV RT gene at codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I).

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 virologic 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 disoproxil fumarate:

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

Cross-resistance

Efavirenz and tenofovir disoproxil fumarate:

Cross-resistance among certain nucleoside reverse transcriptase inhibitors (NRTIs) has been recognised. The M184V/I and/or K65R substitutions selected *in vitro* 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). 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 and K219Q/E) or didanosine (L74V) remained sensitive to emtricitabine.

Tenofovir disoproxil fumarate:

Multi-nucleoside resistant HIV-1 with a T68S double insertion mutation in the RT showed reduced susceptibility to tenofovir.

5.2 Pharmacokinetic properties

Adults:

Emtricitabine:

Following oral administration of emtricitabine (200 mg), emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1-2 hours post dose. *In vitro* binding of emtricitabine to human plasma proteins is less than 4 % and is independent of concentration over the range of 0,02 to 200 µg/ml. Following administration of radio-labelled 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, the plasma emtricitabine half-life is between 8 and 10 hours.

Tenofovir disoproxil fumarate:

Subsequent to oral administration of tenofovir maximum serum concentrations (C_{max}) were achieved in 1,0 ± 0,4 hours. *In vitro* binding of tenofovir to human plasma proteins is less than 0,7 % and is independent of concentration over the range of 0,01 to 25 µg/ml.

Tenofovir undergoes both glomerular filtration and active tubular secretion. Between 70 % and 80 % of an intravenous dose is recovered unchanged in the urine. Following a single oral dose of tenofovir, the terminal elimination half-life is approximately 17 hours.

Effects of food on oral absorption

The combination tablet may be administered with or without food. The time to tenofovir C_{max} was delayed by approximately 0,75 hours following administration of the combination tablet with a high fat meal or a light meal. 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

Paediatric and geriatric patients

Emtricitabine and tenofovir pharmacokinetic studies have not been evaluated in paediatric patients (less than 18 years) or in the elderly (more than 65 years).

Patients with impaired renal function

The pharmacokinetics of emtricitabine and tenofovir are altered in patients with renal impairment (see section 4.4, Renal Impairment). The C_{MAX} and AUC0-∞ of emtricitabine and tenofovir are increased in patients with creatinine clearance < 50 ml/min.

The combination tablet should not be used in patients with creatinine clearance < 30 ml/min and in patients with end-stage renal disease requiring dialysis (see section 4.4, Renal Impairment).

Patients with Hepatic Impairment

The pharmacokinetic properties of tenofovir following a 300 mg dose of tenofovir disoproxil fumarate have been evaluated in non-HIV infected individuals with moderate to severe impairment of liver function.

Tenofovir pharmacokinetics were not substantially altered in patients with hepatic impairment compared with unimpaired patients.

Pharmacokinetic properties of the combination tablet or emtricitabine have not been evaluated in patients with impaired liver function. Since emtricitabine is not metabolised by liver enzymes to a significant extent, the impact of liver impairment should be limited.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The tablets include the following inactive ingredients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose and pregelatinized starch.

The tablets are coated with a coating material opadry AMB white 80W68912; which contains polyvinyl alcohol, soya lecithin, talc, titanium dioxide (CI 77891) and xanthan gum.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep HDPE containers tightly closed.

Keep the blisters in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

HDPE containers:

28 or 30 tablets are packed in a 75 cc, white opaque, wide mouth round, HDPE container and closed with a 38 mm, white opaque, polypropylene child resistant closure. Each HDPE container contains a HDPE canister containing silica gel.

Pack size: 28's or 30's

Blisters:

Silver aluminium- aluminium foil blisters containing 10 tablets per blister strip.

Pack size: 30's - Three blister strips are packed in a cardboard carton.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Emcure Pharmaceuticals SA (Pty) Ltd.

Arizona House, First floor, South Wing, Aspen Business Park

1 Madison Avenue, Aspen Lakes, Extension 13

Johannesburg South

2190

8. REGISTRATION NUMBER(S)

50/20.2.8/0243

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 2 June 2017

10. DATE OF REVISION OF THE TEXT

02 February 2023