Proposed Clean Professional Information For PRIPREMA

SCHEDULING STATUS

S4

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). PRIPREMA is not indicated for the treatment of chronic hepatitis B virus (HBV) infections and the safety and efficacy of PRIPREMA has not been established in patients co-infected with HBV and HIV.

Severe acute exacerbations of hepatitis B (HBV) have been reported in individuals co-infected with HBV and HIV who have discontinued products containing emtricitabine and/or tenofovir and may occur with discontinuation of PRIPREMA.

Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in individuals who are co-infected with HBV and HIV who discontinue PRIPREMA. If appropriate, the initiation of anti-hepatitis B therapy may be warranted (see section 4.4).

1. NAME OF THE MEDICINE

PRIPREMA

(Emtricitabine 200 mg and tenofovir alafenamide 25 mg film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg of emtricitabine and tenofovir alafenamide fumarate equivalent to 25 mg of tenofovir alafenamide.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White to off white coloured, capsule shaped, biconvex film-coated tablet debossed with ‘Cipla’ on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of HIV-1 infection

PRIPREMA is indicated in combination with other antiretroviral medicines for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older with body weight of at least 35 kg) (see sections 4.2 and 5.1).

4.2. Posology and method of administration

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

Adults and adolescents aged 12 years and older, weighing at least 35 kg

PRIPREMA should be administered as shown in table below:

Dose of PRIPREMA	Third medicine in HIV treatment regimen (see section 4.5)
PRIPREMA 200/25 mg once daily	Dolutegravir, efavirenz, maraviroc, nevirapine, rilpivirine, raltegravir.

If the patient misses a dose of PRIPREMA within 18 hours of the time it is usually taken, the patient should take PRIPREMA as soon as possible and resume the normal dosing schedule. If a patient misses a dose of PRIPREMA by more than 18 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.
If the patient vomits within 1 hour of taking PRIPREMA, another tablet should be taken.

Special populations

Elderly (patients ≥ 65 years old)

No dose adjustment of PRIPREMA is required in elderly patients.

Renal impairment

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

No dose adjustment is required in adults or adolescents (aged at least 12 years and of at least 35 kg body weight) with estimated creatinine clearance (CrCl) ≥ 30 mL/min. PRIPREMA should be discontinued in patients with estimated CrCl that declines below 30 mL/min during treatment (see sections 4.4 and 5.2).

No dose adjustment of PRIPREMA is required in adults with end stage renal disease (estimated CrCl < 15 mL/min) on chronic haemodialysis; however, PRIPREMA should generally be avoided but may be used in these patients (see sections 4.4 and 5.2). On days of haemodialysis, PRIPREMA should be administered after completion of haemodialysis treatment.

PRIPREMA should be avoided in patients with estimated CrCl ≥ 15 mL/min and < 30 mL/min as the safety of PRIPREMA has not been established in this population. PRIPREMA should not be used in patients with CrCl < 15 mL/min who are not receiving haemodialysis (see section 4.4).

No data are available to make dose recommendations in children less than 18 years with end stage renal disease.

Hepatic impairment

No dose adjustment of PRIPREMA is required in patients with mild to moderate hepatic impairment. PRIPREMA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C); therefore, PRIPREMA is not recommended for use in patients with severe hepatic impairment as no dose recommendations can be made (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of PRIPREMA in children younger than 12 years or weighing < 35 kg have not been established. No data are available.

Method of administration

PRIPREMA should be taken orally, once daily with or without food (see section 5.2).

The film-coated tablet should not be chewed, crushed or split.

4.3. Contraindications

- Hypersensitivity to the active substances or to any of the excipients of PRIPREMA listed in **section 6.1**.
- Pregnancy and lactation.

4.4. Special warnings and precautions for use

General

Individuals should be fully informed about the use of precautionary measures including barrier contraception (condoms) that should be taken to prevent HIV-1 transmission in

accordance with the national guidelines. Treatment compliance reduces risk but does not prevent the transmission of HIV-1 as PRIPREMA is not indicated for prophylaxis.

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

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.
The safety and efficacy of PRIPREMA in patients co-infected with HIV-1 and Hepatitis C (HCV) have not been established.

Tenofovir alafenamide is active against hepatitis B virus (HBV). Discontinuation of PRIPREMA therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis. Patients co-infected with HIV and HBV who discontinue PRIPREMA should be closely monitored with both clinical and laboratory follow-up for at least several months 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.

Liver disease

Use of PRIPREMA can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of PRIPREMA 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.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids (hyperlipidaemia) and glucose may occur during antiretroviral therapy. Such changes may in part be linked to diseases control and lifestyle. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Mitochondrial dysfunction following exposure *in utero*

Nucleoside and nucleotide analogues such as PRIPREMA 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. Manifestations of mitochondrial dysfunction include haematological disorders (anaemia, neutropenia), peripheral neuropathy and metabolic disorders (hyperlactataemia, lactic acidosis, hyperlipasaemia). Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). It is not known whether the neurological disorders are transient or permanent. Possible mitochondrial dysfunction should be considered in any new-

born/infant/child exposed *in utero* to nucleoside or nucleotide analogues, including HIV negative infants/children who present with severe clinical findings of unknown etiology, particularly neurologic findings. Their babies/infants and children should have clinical, and laboratory follow up and be fully investigated for possible mitochondrial dysfunction.

Lactic acidosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including emtricitabine, a component of PRIPREMA, and tenofovir disoproxil fumarate, another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with PRIPREMA should be suspended in any individual 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 of lactic acidosis 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 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 PRIPREMA to patients with known risk factors for liver disease.

Immune reactivation syndrome (IRS) / Immune reconstitution inflammatory syndrome (IRIS)

Immune Reactivation Syndrome (IRS) 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 antiretroviral 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. IRS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4+ counts. Relevant examples include cytomegalovirus retinitis, generalised and/or focal mycobacterial and other infections such as tuberculosis, cryptococcal meningitis and *Pneumocystis jirovecii* pneumonia. Appropriate treatment of the opportunistic infections and diseases 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 IRS.

Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation however, the reported time

to onset is more variable and these events can occur many months after initiation of treatment.

Patients with HIV-1 harbouring mutations

PRIPREMA should not be started in antiretroviral-experienced patients with HIV-1 harbouring the K65R mutation (see section 5.1)

Triple nucleoside therapy

There have been reports of a high rate of virological failure and of emergence of resistance at an early stage when tenofovir disoproxil was combined with lamivudine and abacavir as well as with lamivudine and didanosine as a once daily regimen. Therefore, the same problems may be seen if PRIPREMA is administered with a third nucleoside analogue.

Opportunistic infections

Patients receiving PRIPREMA 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.

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.

Nephrotoxicity

A potential risk of nephrotoxicity resulting from chronic exposure to low levels of tenofovir due to dosing with tenofovir alafenamide cannot be excluded (see section 5.3).

Patients with end stage renal disease on chronic haemodialysis

PRIPREMA should generally be avoided but may be used in adults with end stage renal disease (estimated CrCl < 15 mL/min) on chronic haemodialysis with close monitoring for the risks (see section 4.2).

Co-administration of other medicines

The co-administration of PRIPREMA is not recommended with certain anticonvulsants (e.g., carbamazepine, oxcarbazepine, phenobarbitone and phenytoin), antimycobacterials (e.g., rifampicin, rifabutin, rifapentine), boceprevir, St. John's wort and HIV protease inhibitors (PIs) other than atazanavir, lopinavir and darunavir (see section 4.5).

PRIPREMA should not be administered concomitantly with medicines containing tenofovir alafenamide, tenofovir disoproxil, emtricitabine, lamivudine or adefovir dipivoxil.

Use in paediatrics

The safety and efficacy of PRIPREMA in children younger than 12 years of age, or weighing < 35 kg, have not been established. No data are available.

Use in elderly

Studies in the elderly have not been conducted. However, 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.

4.5. Interaction with other medicines and other forms of interaction

Interaction studies have only been performed in adults.

Emtricitabine

In vitro and clinical pharmacokinetic interaction studies have shown that the potential for CYP-mediated interactions involving emtricitabine with other medicines is low. Co-administration of emtricitabine with medicines that are eliminated by active tubular secretion may increase concentrations of emtricitabine, and/or the co-administered

medicine. Medicines that decrease renal function may increase concentrations of emtricitabine.

Tenofovir alafenamide

Tenofovir alafenamide is transported by P-glycoprotein (P-gp_ and breast cancer resistance protein (BCRP). Medicines that strongly affect P-gp and BCRP activity may lead to changes in tenofovir alafenamide absorption. Medicines that induce P-gp activity (e.g., rifampicin, rifabutin, carbamazepine, phenobarbital) are expected to decrease the absorption of tenofovir alafenamide, resulting in decreased plasma concentration of tenofovir alafenamide, which may lead to loss of therapeutic effect of PRIPREMA and development of resistance. Co-administration of PRIPREMA with other medicines that inhibit P-gp and BCRP activity (e.g., cobicistat, ritonavir, ciclosporin) is expected to increase the absorption of tenofovir alafenamide and xanthine oxidase inhibitors (e.g., febuxostat) is not expected to increase systemic exposure to tenofovir *in vivo*.

Tenofovir alafenamide is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6 *in vitro*. It is not an inhibitor or inducer of CYP3A *in vivo*. Tenofovir alafenamide is a substrate of OATP1B1 and OATP1B3 *in vitro*. The distribution of tenofovir alafenamide in the body may be affected by the activity of OATP1B1 and OATP1B3.

Other interactions

Tenofovir alafenamide is not an inhibitor of human uridine diphosphate glucuronosyltransferase (UGT) 1A1 *in vitro*. It is not known whether tenofovir alafenamide is an inhibitor of other UGT enzymes. Emtricitabine did not inhibit the glucuronidation reaction of a non-specific UGT substrate *in vitro*.

Interactions between the individual components of PRIPREMA and other medicines

Medicine by therapeutic area	**Effect on medicine levels**	**Recommendation concerning co-administration with PRIPREMA**
ANTI-INFECTIVES		
Antifungals		
Ketoconazole Itraconazole	Interaction not studied with either of the components of PRIPREMA. Co-administration of ketoconazole or itraconazole, which are potent P-gp inhibitors, is expected to increase plasma concentrations of tenofovir alafenamide.	The recommended dose of PRIPREMA is 200 mg/10 mg once daily.

Fluconazole Isavuconazole	Interaction not studied with either of the components of PRIPREMA. Co-administration of fluconazole or isavuconazole may increase plasma concentrations of tenofovir alafenamide.	Dose PRIPREMA according to the concomitant antiretroviral (see section 4.2).
Antimycobacterials		
Rifabutin Rifampicin Rifapentine	Interaction not studied with either of the components of PRIPREMA. Co-administration of rifampicin, rifabutin and rifapentine, all of which are P-gp inducers, may decrease tenofovir alafenamide plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	Co-administration of PRIPREMA and rifabutin, rifampicin or rifapentine is not recommended.
Anti-hepatitis C virus medicines		
Ledipasvir (90 mg once daily)	Ledipasvir: AUC: Increases 79 %	No dose adjustment of ledipasvir or sofosbuvir is

Sofosbuvir (400 mg once daily) Emtricitabine (200 mg once daily) Alafenamide (10 mg once daily)	C_{max}: Increases 65 % C_{min}: Increases 93 % Sofosbuvir: AUC: Increases 47 % C_{max}: Increases 29 % Sofosbuvir metabolite GS-331007: AUC: Increases 48 % C_{max}: No change C_{min}: Increases 66 % Emtricitabine: AUC: No change C_{max}: No change C_{min}: No change Tenofovir alafenamide: AUC: No change C_{max}: No change	required. Dose PRIPREMA according to the concomitant antiretroviral (see section 4.2).
Ledipasvir (90 mg once daily)	Ledipasvir: AUC: No change	No dose adjustment of ledipasvir or sofosbuvir is

Sofosbuvir (400 mg once daily) Emtricitabine (200 mg once daily) Alafenamide (25 mg once daily)	C_{max}: No change C_{min}: No change Sofosbuvir: AUC: No change C_{max}: No change Sofosbuvir metabolite GS-331007: AUC: No change C_{max}: No change C_{min}: No change Emtricitabine: AUC: No change C_{max}: No change C_{min}: No change Tenofovir alafenamide: AUC: Increases 32 % C_{max}: No change	required. Dose PRIPREMA according to the concomitant antiretroviral (see section 4.2).
Sofosbuvir (400 mg once daily)	Sofosbuvir: AUC: Increases 37 %	No dose adjustment of sofosbuvir, velpatasvir or

Velpatasvir (100 mg once daily) Emtricitabine (200 mg once daily) Alafenamide (10 mg once daily)	C_{max}: No change Sofosbuvir metabolite GS-331007: AUC: Increases 48 % C_{max}: No change C_{min}: Increases 58 % Velpatasvir: AUC: Increases 50 % C_{max}: Increases 30 % C_{min}: Increases 60 % Emtricitabine: AUC: No change C_{max}: No change C_{min}: No change Tenofovir alafenamide: AUC: No change C_{max}: Decreases 20 %	voxilaprevir is required. Dose PRIPREMA according to the concomitant antiretroviral (see section 4.2).
Sofosbuvir/ Velpatasvir/	Sofosbuvir: AUC: No change	No dose adjustment of sofosbuvir, velpatasvir or

Voxilaprevir (400 mg/ 100 mg/ 100 mg + 100 mg once daily) Emtricitabine (200 mg once daily)/ Tenofovir alafenamide (10 mg once daily)	C_{max}: Increases 27 % Sofosbuvir metabolite GS-331007: AUC: Increases 43 % C_{max}: No change Velpatasvir: AUC: No change C_{min}: Increases 46 % C_{max}: No change Voxilaprevir: AUC: Increases 171 % C_{min}: Increases 350 % C_{max}: Increases 92 % Emtricitabine: AUC: No change C_{min}: No change C_{max}: No change Tenofovir alafenamide:	voxilaprevir is required. Dose PRIPREMA according to the concomitant antiretroviral (see section 4.2).

	AUC: No change C_{max}: Decreases 21 %	
Sofosbuvir/ Velpatasvir/ Voxilaprevir (400 mg/ 100 mg/ 100 mg + 100 mg once daily) Emtricitabine (200 mg once daily)/ Tenofovir alafenamide (25 mg once daily)	Sofosbuvir: AUC: No change C_{max}: No change Sofosbuvir metabolite GS-331007: AUC: No change C_{max}: No change Velpatasvir: AUC: No change C_{min}: No change C_{max}: No change Voxilaprevir: AUC: No change C_{min}: No change C_{max}: No change Emtricitabine: AUC: No change	No dose adjustment of sofosbuvir, velpatasvir pr voxilaprevir is required. Dose PRIPREMA according to the concomitant antiretroviral (see section 4.2).

	C_{min}: No change C_{max}: No change Tenofovir alafenamide: AUC: Increases 52 % C_{max}: Increases 32 %	
ANTIRETROVIRALS		
HIV protease inhibitors		
Atazanavir/Cobicistat (300 mg/ 150 mg once daily), Tenofovir alafenamide (10 mg)	Tenofovir alafenamide: AUC: Increases 75 % C_{max}: Increases 80 % Atazanavir: AUC: No change C_{max}: No change C_{min}: No change	The recommended dose of PRIPREMA is 200 mg/10 mg once daily.
Atazanavir/Ritonavir (300 mg/100 mg once daily), Tenofovir alafenamide (10 mg once daily)	Tenofovir alafenamide: AUC: Increases 91 % C_{max}: Increases 77 % Atazanavir: AUC: No change C_{max}: No change	The recommended dose of PRIPREMA is 200 mg/10 mg once daily)

	C_{min}: No change	
Darunavir/Cobicistat (800 mg/150 mg once daily), Tenofovir alafenamide (25 mg once daily)	Tenofovir alafenamide: AUC: No change C_{max}: No change Tenofovir: AUC: Increases 224 % C_{max}: Increases 216 % C_{min}: Increases 221 % Darunavir: AUC: No change C_{max}: No change C_{min}: No change	The recommended dose of PRIPREMA is 200 mg/10 mg once daily.
Darunavir/Ritonavir (800 mg/100 mg once daily), Tenofovir alafenamide (10 mg once daily)	Tenofovir alafenamide: AUC: No change C_{max}: No change Tenofovir: AUC: Increases 105 % C_{max}: Increases 142 % Darunavir:	The recommended dose of PRIPREMA is 200 mg/10 mg once daily.

	AUC: No change C_{max}: No change C_{min}: No change	
Lopinavir/Ritonavir (800 mg/200 mg once daily), Tenofovir alafenamide (10 mg once daily)	Tenofovir alafenamide: AUC: Increases 47 % C_{max}: Increases 119 % Lopinavir: AUC: No change C_{max}: No change C_{min}: No change	The recommended dose of PRIPREMA is 200 mg/10 mg once daily.
Tipranavir/Ritonavir	Interaction not studied with either of the components of PRIPREMA. Tipranavir/Ritonavir results in P-gp induction. Tenofovir alafenamide exposure is expected to decrease when tipranavir/ritonavir is used in combination with PRIPREMA.	Co-administration with PRIPREMA is not recommended.
Other protease inhibitors	Effect is unknown.	There are no data available to make dosing

		recommendations for co-administration with other protease inhibitors.
Other HIV antiretrovirals		
Dolutegravir (50 mg once daily), tenofovir alafenamide (10 mg once daily)	Tenofovir alafenamide: AUC: No change C_{max}: No change Dolutegravir: AUC: No change C_{max}: No change C_{min}: No change	The recommended dose of PRIPREMA is 200 mg/25 mg once daily.
Rilpivirine (25 mg once daily), Tenofovir alafenamide (25 mg once daily)	Tenofovir alafenamide: AUC: No change C_{max}: No change Rilpivirine: AUC: No change C_{max}: No change C_{min}: No change	The recommended dose of PRIPREMA is 200 mg/25 mg once daily.
Efavirenz (600 mg once daily), Tenofovir	Tenofovir alafenamide: AUC: Decreases 14 % C_{max}: Decreases 22 %	The recommended dose of PRIPREMA is 200 mg/25 mg once daily.

alafenamide (40 mg once daily)		
Maraviroc Nevirapine Raltegravir	Interaction not studied with either of the components of PRIPREMA. Tenofovir alafenamide exposure is not expected to be affected by maraviroc, nevirapine or raltegravir, nor is it expected to affect the metabolic pathways relevant to maraviroc, nevirapine or raltegravir.	The recommended dose of PRIPREMA is 200 mg/25 mg once daily.
ANTICONVULSANTS		
Oxcarbazepine Phenobarbitone Phenytoin	Interaction not studied with either of the components of PRIPREMA. Co-administration of oxcarbazepine, phenobarbitone or phenytoin, all of which are P-gp inducers, may decrease	Co-administration of PRIPREMA and oxcarbazepine, phenobarbitone or phenytoin is not recommended

	Tenofovir alafenamide plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	
Carbamazepine (Titrated from 100 mg to 300 mg twice a day), Emtricitabine/ Tenofovir alafenamide (200 mg/25 mg once daily)	Tenofovir alafenamide: AUC: Decreases 55 % C_{max}: Decreases 57 % Co-administration of carbamazepine, a P-gp inducer, decreases tenofovir alafenamide plasma concentrations which may result in loss of therapeutic effect and development of resistance.	Co-administration of PRIPREMA and carbamazepine is not recommended.
ANTIDEPRESSANTS		
Sertraline (50 mg once daily), Tenofovir alafenamide (10 mg once daily)	Tenofovir alafenamide: AUC: No change C_{max}: No change Sertraline:	No dose adjustment of Sertraline is required. Dose PRIPREMA according to the

	AUC: Increases 9 % C_{max}: Increases 14 %	concomitant antiretroviral (see section 4.2)
HERBAL PRODUCTS		
St. John's wort (*Hypericum perforatum)*	Interaction not studied with either of the components of PRIPREMA. Co-administration of St. John's wort, a P-gp inducer, may decrease tenofovir alafenamide plasma concentrations which may result in loss of therapeutic effect and development of resistance.	Co-administration of PRIPREMA with St. John's wort is not recommended.
IMMUNOSUPRESSANTS		
Ciclosporin	Interaction not studied with either of the components of PRIPREMA. Co-administration of ciclosporin, a potent P-gp inhibitor, is expected to	The recommended dose of PRIPREMA is 200 mg/10 mg once daily.

	increase plasma concentrations of tenofovir alafenamide.	
ORAL CONTRACEPTIVES		
Norgestimate (0,180/ 0,215/ 0,250 mg once daily), Ethinylestradiol (0,025 mg once daily), Emtricitabine/ Tenofovir alafenamide (200 mg/25 mg once daily)	Norelgestromin: AUC: No change C_{min}: No change C_{max}: No change Norgestrel: AUC: No change C_{min}: No change C_{max}: No change Ethinylestradiol: AUC: No change C_{min}: No change C_{max}: No change	No dose adjustment of norgestimate/ ethinylestradiol is required. Dose PRIPREMA according to the concomitant antiretroviral (see section 4.2).
SEDATIVE/HYPNOTICS		
Orally administered Midazolam (2,5 mg single dose), Tenofovir alafenamide (25 mg once daily)	Midazolam: AUC: No change C_{max}: No change	No dose adjustment of midazolam is required. Dose PRIPREMA according to the

Intravenously administered Midazolam (1 mg single dose), Tenofovir alafenamide (25 mg once daily)	Midazolam: AUC: No change C_{max}: No change	concomitant antiretroviral (see section 4.2)

4.6. Fertility, pregnancy and lactation

Pregnancy

There are limited data in pregnant women. PRIPREMA should not be used during pregnancy (see section 4.3).

Lactation

PRIPREMA should not be used by women breastfeeding their babies as possible harm to their babies cannot be excluded (see section 4.3). Emtricitabine is excreted in human milk and animal studies show that tenofovir is excreted in milk. In order to avoid transmission of HIV to the infant it is recommended that HIV infected women do not breastfeed their infants under any circumstances.

Fertility

There are no data on fertility from the use of PRIPREMA in humans. In animal studies there were no effects of emtricitabine and tenofovir alafenamide on mating or fertility parameters.

4.7. Effects on ability to drive and use machines

PRIPREMA has a moderate influence on the ability to drive and use machines.

PRIPREMA may affect the ability to drive and use machines. Patients should not drive and use machines until they know how treatment with PRIPREMA affects them. Patients should be informed that dizziness and fatigue have been reported during treatment with PRIPREMA.

4.8. Undesirable effects

Summary of the safety profile

Assessment of adverse reactions based on safety data from studies performed in HIV infected patients who received medicines containing emtricitabine and tenofovir alafenamide, as in PRIPREMA, and from post-marketing experience showed that the most frequently reported adverse reactions were diarrhoea, nausea and headache.

Tabulated summary of adverse reactions

Blood and lymphatic system disorders	
Less frequent	Anaemia.
Psychiatric disorders	
Frequent	Abnormal dreams.
Nervous system disorders	
Frequent	Headache, dizziness.
Gastrointestinal disorders	

Frequent	Nausea, diarrhoea, vomiting, abdominal pain, flatulence.
Less frequent	Dyspepsia.
Skin and subcutaneous tissue disorders	
Frequent	Rash.
Musculoskeletal and connective tissue disorders	
Less frequent	Arthralgia.
General disorders and administration site conditions	
Frequent	Fatigue.

Post marketing reported side effects

Blood and lymphatic system disorders
Anaemia.
Psychiatric disorders
Angiodema.

Description of selected adverse reactions

Metabolic parameters – Weight and levels of blood lipids and glucose may increase during PRIPREMA therapy.

Paediatric population

According to studies performed, the safety profile of emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat to adolescents was similar to that in adults.

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 359 Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8, or to Cipla Medpro (Pty) Ltd. by email (drugsafetysa@cipla.com) or telephone: 080 222 6662 (toll free).

4.9. Overdose

If overdose occurs the patient must be monitored for evidence of toxicity (see section 4.8). Treatment of overdose with PRIPREMA consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient.

Emtricitabine

Emtricitabine can be removed by haemodialysis, which 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 dialysate flow rate of 600 mL/min). it is not known whether emtricitabine can be removed by peritoneal dialysis.

Tenofovir alafenamide fumarate

Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54 %.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological class:

A 20.2.8 Antimicrobial (chemotherapeutic) agents - Antiviral agents

ATC code: J05AR17

Mechanism of action:

Emtricitabine is a nucleoside reverse transcriptase inhibitor (NRTI) and nucleoside analogue of 2'-deoxycytidine. Emtricitabine is phosphorylated by cellular enzymes to form emtricitabine 5’-triphosphate. Emtricitabine 5’-triphosphate inhibits HIV replication through incorporation into viral deoxyribonucleic acid (DNA) by the HIV reverse transcriptase (RT), which results in DNA chain-termination. Emtricitabine 5’-triphosphate is a weak inhibitor of mammalian DNA polymerase α, β, ε and mitochondrial DNA polymerase γ.

Tenofovir alafenamide is a phosphonamidite prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). Plasma exposure to tenofovir alafenamide allows for permeation into cells and then tenofovir alafenamide is intracellularly converted to tenofovir through hydrolysis by cathepsin A. Tenofovir is intracellularly phosphorylated by cellular kinases to the active metabolite tenofovir diphosphate. Tenofovir

diphosphate inhibits HIV-1 replication through incorporation into viral DNA by the HIV RT, which results in DNA chain termination.

Tenofovir has activity against HIV-1, HIV-2 and HBV. *In vitro* studies have shown that both tenofovir and emtricitabine can be fully phosphorylated when combined into cells. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of toxicity to mitochondria in cell culture.

Resistance:
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 RT has been selected by tenofovir and results in reduced susceptibility to tenofovir.

In a clinical study of treatment-naïve patients (emtricitabine + tenofovir + efavirenz vs zidovudine + lamivudine + efavirenz), resistance analysis was performed on HIV isolates from all virologic failures with greater than 400 copies/mL of HIV-1 RNA at week 144 or early discontinuation. Development of efavirenz resistance-associated mutations occurred most frequently and was similar between the treatment groups.

The M184V amino acid mutation, associated with resistance to emtricitabine and lamivudine, was observed in 2/19 analysed subject isolates in the emtricitabine/tenofovir group and in 10/29 analysed subject isolates in the zidovudine/lamivudine group. Through 144 weeks of this study, no subjects have developed a detectable K65R or K70E substitution in their HIV-1 as analysed through standard genotypic analysis.

The M184V amino acid substitution, associated with resistance to emtricitabine and lamivudine, was observed in 2/12 (17 %) analyses patient isolates in the emtricitabine/tenofovir group and in 7/22 (32 %) analysed patient isolates in the zidovudine/lamivudine group.

Emtricitabine

Emtricitabine resistant isolates were selected *in vivo* and *in vitro*. Genotypic analysis of these isolated showed that reduced susceptibility to emtricitabine was associated with a RT mutation at codon 184 which resulted in an amino acid substitution from methionine to 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 antiretrovirals. Viral isolates from treatment-naïve patients with virologic failure showed > 20-fold reduced susceptibility to emtricitabine. These isolates were showed that the resistance was due to M184V/I mutation in the HIV RT gene.

Tenofovir

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 harbours the K65R or K70E mutations.

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 isolated of HIV-1 have also been recovered from some patients treated with tenofovir in combination with certain antiretrovirals. In treatment-naïve patients, 8/47 (17 %) isolates from patients on tenofovir + lamivudine + efavirenz through week 144 showed greater than 1,4-fold (median 3,7) reduced susceptibility in cell culture to tenofovir. Isolates from treatment-experienced patients failing tenofovir through week 96 showed greater 1,4-fold (median 2,7) reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a mutation in the HIV-1 RT gene resulting in the K65R amino acid substitution.

Cross-resistance

Cross-resistance among certain NRTIs has been recognised. The M184V/I and/or K65R mutations selected in cell culture by the combination of emtricitabine and tenofovir are also observed in some HIV-1 isolates from patients 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 amino acid substitutions.

Emtricitabine

Emtricitabine-resistant isolates (M184V/I) were resistant to lamivudine and zalcitabine but retained susceptibility to didanosine, stavudine, tenofovir, zidovudine and NNRTIs (delavirdine, efavirenz and nevirapine), *in vitro*. Isolates from heavily treatment-experienced patients containing the M184V/I amino acid substitution in the context of other NRTI resistance associated substitution 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 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

HIV-1 isolates from patients 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

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

5.2. Pharmacokinetic properties

Absorption

Emtricitabine is rapidly and extensively absorbed following oral administration with peak plasma concentrations occurring at 1 to 2 hours post-dose.

According to studies performed, emtricitabine systemic exposure was unaffected when administered with food. Following administration of food in healthy subjects, peak plasma concentrations were observed approximately 1-hour post-dose for tenofovir alafenamide. Relative to fasting conditions, the administration of tenofovir alafenamide with a high fat meat resulted in a decrease in tenofovir alafenamide C_{max} and an increase in AUC.

Distribution

According to studies, the *in vitro* binding of emtricitabine to human plasma proteins was < 4 % and independent of concentration over the range of 0,02 – 200 ug/mL. At peak plasma concentration, the mean plasma to blood drug concentration ratio was

approximately 1,0 and the mean semen to plasma drug concentration was approximately 4,0.

According to studies, the *in vitro* binding of tenofovir to human plasma proteins is < 0,7 % and is independent of concentration over the range of 0,01 – 25 ug/mL. *Ex vivo* binding of tenofovir alafenamide to human plasma proteins in samples collected during clinical studies performed was approximately 80 %.

Biotransformation

Data from *in vitro* studies indicate that emtricitabine is not an inhibitor of human CYP enzymes. Following administration of [^{14}C]-emtricitabine, complete recovery of the emtricitabine dose was achieved in urine (approximately 86 %) and faeces (approximately 14 %). Thirteen percent of the dose was recovered in the urine as three putative metabolites. The biotransformation of emtricitabine includes oxidation of the thiol moiety to form the 3'-sulfoxide diastereomers (approximately 9 % of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (approximately 4 % of dose). No other metabolites were identifiable.

Metabolism is a major elimination pathway for tenofovir alafenamide in humans, accounting for > 80 % of an oral dose. Data from *In vitro* studies show that tenofovir alafenamide is metabolised to tenofovir (major metabolite) by cathepsin A in PBMCs (including lymphocytes and other HIV target cells) and macrophages; and by caboxylesterase-1 in hepatocytes. *In vivo*, tenofovir alafenamide is hydrolysed within

cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite tenofovir diphosphate.

In vitro, tenofovir is not metabolised by CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Tenofovir alafenamide is minimally metabolised by CYP3A4. Upon co-administration with the moderate CYP3A inducer probe efavirenz, tenofovir alafenamide exposure was not significantly affected.

Elimination

Emtricitabine is primarily excreted by the kidneys with complete recovery of the dose achieved in urine (approximately 86 %) and faeces (approximately 14 %). Thirteen percent of emtricitabine is recovered in urine as three metabolites. According to studies, the systemic clearance of emtricitabine averaged 307 mL/min. Following oral administration, the elimination half-life of emtricitabine is approximately 10 hours.

Renal excretion of intact tenofovir alafenamide is a minor pathway with < 1 % of the dose eliminated in urine. Tenofovir alafenamide is mainly eliminated following metabolism to tenofovir. Tenofovir alafenamide and tenofovir have a median plasma half-life of 0,51 and 32,37 hours, respectively. Tenofovir is renally eliminated by both glomerular filtration and active tubular secretion.

Special Populations

Age, gender and ethnicity

No clinically relevant pharmacokinetic differences due to age, gender or ethnicity have been identified for emtricitabine, or tenofovir alafenamide.

Renal Impairment

No clinically relevant differences in tenofovir alafenamide, or tenofovir alafenamide pharmacokinetics were observed between healthy subjects and patients with severe renal impairment (estimated CrCl ≥ 15 mL/min and < 30 mL/min).

No clinically relevant differences in tenofovir alafenamide pharmacokinetics were observed in patients with end stage renal disease on chronic haemodialysis as compared to those with normal renal function.

Hepatic impairment

The pharmacokinetics of emtricitabine have 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.

Hepatitis B and/or hepatitis C virus co-infection

The pharmacokinetics of emtricitabine and tenofovir alafenamide have not been fully evaluated in patients co-infected with HBV and/or HCV.

Elderly (≥ 65 years old)

PRIPREMA pharmacokinetics have not been evaluated in the elderly.

Children

PRIPREMA pharmacokinetics have not been evaluated in children.

5.3 Preclinical safety data

Non-clinical date on emtricitabine reveal no genotoxicity, carcinogenic potential, or toxicity to reproduction and development relevant to humans.

Non-clinical studies of tenofovir alafenamide in rats and dogs revealed bone and kidneys as the primary target organs of toxicity. Bone toxicity was observed as reduced BMD. A minimal infiltration of histocytes was observed in the eye of dogs at high exposure to tenofovir alafenamide.

Tenofovir alafenamide was not mutagenic or clastogenic.

Because there is a lower tenofovir exposure in rats and mice after the administration of tenofovir alafenamide compared to tenofovir disoproxil fumarate, carcinogenicity studies and a rat peri-postnatal study were conducted only with tenofovir disoproxil fumarate which revealed no relevant carcinogenic potential and toxicity to reproduction and development. Reproductive toxicity studies in rats and rabbits showed no effects on mating, fertility, pregnancy or foetal parameters. However, the viability index and weight of pups were reduced in a peri-postnatal toxicity study at maternally toxic doses.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

- Croscarmellose sodium
- Magnesium stearate
- Microcrystalline cellulose
- Opadry II white 85F18422.

Contents of the Opadry White II 85F18422 film-coating solution:

- Macrogol (polyethylene glycol) (E1521)
- Polyvinyl alcohol-part hydrolysed (E1203)
- Talc (E553b)
- Titanium dioxide (E171).

6.2. Incompatibilities

Not applicable.

6.3. Shelf Life

24 months.

6.4. Special precautions for storage

Store in the original container at or below 30 °C.

Keep the bottle tightly closed.

6.5. Nature and contents of container

PRIPREMA is packed in a white high-density polyethylene (HDPE) bottle that is fitted with a white HDPE closure, containing 28, 30 or 90 film-coated tablets and silica gel desiccants.

6.6. Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements**.**

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Bellville

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Customer Care: 080 222 6662

8. REGISTRATION NUMBER

PRIPREMA: 55/20.2.8/0079

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 November 2021

10. DATE OF REVISION OF THE TEXT

25 May 2022