

To be sold by retail on the prescription of a specialist only.

PRESCRIBING INFORMATION

Emtricitabine 200 mg and Tenofovir Alafenamide 10 mg/25 mg Tablets

TAFERO EM 10 / TAFERO EM

For India only

1. **Generic Name**
Emtricitabine 200 mg and Tenofovir Alafenamide 10 mg/25 mg Tablets

2. **Qualitative and Quantitative Composition**
a) *Each film coated tablet contains:*
Emtricitabine IP200mg
Tenofovir Alafenamide Fumarate IP
Equivalent to Tenofovir Alafenamide...10mg
Excipientsq.s
Colours: Ferric oxide USP-NF Yellow, Ferric oxide USP-NF Red, Black iron oxide & Titanium Dioxide IP
b) *Each film coated tablet contains:*
Emtricitabine IP200mg
Tenofovir Alafenamide Fumarate IP
Equivalent to Tenofovir Alafenamide...25mg
ExcipientsQ.S
Colours: Ferric oxide USP-NF Red, Black iron oxide & Titanium Dioxide IP

3. **Dosage Form & Strength**
200/10 mg or 200/25 mg film-coated tablets.

4. **Clinical Particulars**

4.1 **Therapeutic Indications**
TAFERO EM 10 & TAFERO EM film-coated tablets is indicated in combination with other antiretroviral agents for treatment of Human Immunodeficiency Virus type-1 (HIV-1) infections in adults and adolescents with aged 12 years and older.

4.2 **Posology and Method of administration**
Therapy should be initiated by a physician experienced in the management of HIV infection.

Posology
Adults and adolescents aged 12 years and older, weighing at least 35 kg
Emtricitabine and Tenofovir alafenamide fumarate should be administered as in Table 1.

Table 1: Dose of Emtricitabine and Tenofovir alafenamide fumarate according to third agent in the HIV treatment regimen

Dose of Emtricitabine and Tenofovir alafenamide fumarate	Third agent in HIV treatment regimen
Emtricitabine and Tenofovir alafenamide fumarate 200/10 mg once daily	Atazanavir with ritonavir or cobicistat Darunavir with ritonavir or cobicistat ¹ Lopinavir with ritonavir
Emtricitabine and Tenofovir alafenamide fumarate 200/25 mg once daily	Dolutegravir, efavirenz, maraviroc, nevirapine, rilpivirine, raltegravir
¹ Emtricitabine and Tenofovir alafenamide 200/10 mg in combination with darunavir 800 mg and cobicistat 150 mg, administered as a fixed-dose combination tablet, was studied in treatment-naïve subjects.	

Missed Doses

If the patient misses a dose of Emtricitabine and Tenofovir alafenamide fumarate within 18 hours of the time it is usually taken, the patient should take Emtricitabine and Tenofovir alafenamide fumarate as soon as possible and resume the normal dosing schedule. If a patient misses a dose of Emtricitabine and Tenofovir alafenamide fumarate 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 Emtricitabine and Tenofovir alafenamide fumarate another tablet should be taken.

Elderly

No dose adjustment of Emtricitabine and Tenofovir alafenamide fumarate is required in elderly patients.

Renal Impairment

No dose adjustment of Emtricitabine and Tenofovir alafenamide fumarate 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. Emtricitabine and Tenofovir alafenamide fumarate should be discontinued in patients with estimated CrCl that declines below 30 mL/min during treatment.

No dose adjustment of Emtricitabine and Tenofovir alafenamide fumarate is required in adults with end stage renal disease (estimated CrCl < 15 mL/min) on chronic haemodialysis; however, Emtricitabine and Tenofovir alafenamide fumarate should generally be avoided but may be used in these patients if the potential benefits are considered to outweigh the potential risks. On days of haemodialysis, Emtricitabine and Tenofovir alafenamide fumarate should be administered after completion of haemodialysis treatment.

Emtricitabine and Tenofovir alafenamide fumarate should be avoided in patients with estimated CrCl ≥ 15 mL/min and < 30 mL/min, or < 15 mL/min who are not on chronic haemodialysis, as the safety of Emtricitabine and Tenofovir alafenamide fumarate has not been established in these populations.

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 Emtricitabine and Tenofovir alafenamide fumarate is required in patients with hepatic impairment.

Method of administration

Emtricitabine and Tenofovir alafenamide fumarate should be taken orally, once daily with or without food. The film-coated tablet should not be chewed, crushed, or split.

4.3 Contraindications

Emtricitabine and Tenofovir alafenamide fumarate is contraindicated in:

- Hypersensitivity to the active substances or to any of the excipients

4.4 Special warnings and precautions for use

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

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

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

The safety and efficacy of Emtricitabine and Tenofovir alafenamide fumarate in patients co-infected with HIV-1 and hepatitis C virus (HCV) have not been established.

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

Liver disease

The safety and efficacy of Emtricitabine and Tenofovir alafenamide fumarate in patients with significant underlying liver disorders have not been established.

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

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. 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*

Nucleos(t)ide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or postnatally to nucleoside analogues; these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactataemia, hyperlipasaemia). These events have often been transitory. Late onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed *in utero* to nucleos(t)ide analogues, who present with severe clinical findings of unknown etiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Immune Reactivation Syndrome

In HIV infected patients with severe immune deficiency at the time of institution of CART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples include cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. 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

Emtricitabine and Tenofovir alafenamide fumarate should be avoided in antiretroviral-experienced patients with HIV-1 harbouring the K65R mutation.

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 Emtricitabine and Tenofovir alafenamide fumarate is administered with a third nucleoside analogue.

Opportunistic infections

Patients receiving Emtricitabine and Tenofovir alafenamide fumarate or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and, therefore, should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.

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 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.

It is recommended that renal function is assessed in all patients prior to, or when initiating, therapy with Emtricitabine and Tenofovir alafenamide fumarate and that it is also monitored during therapy in all patients as clinically appropriate. In patients who develop clinically significant decreases in renal function, or evidence of proximal renal tubulopathy, discontinuation of Emtricitabine and Tenofovir alafenamide should be considered.

Patients with end stage renal disease on chronic haemodialysis

Emtricitabine and Tenofovir alafenamide fumarate should generally be avoided but may be used in adults with end stage renal disease (estimated CrCl < 15 mL/min) on chronic haemodialysis if the potential benefits outweigh the potential risks (see section 4.2). In a study of emtricitabine + tenofovir alafenamide in combination with elvitegravir + cobicistat as a fixed-dose combination tablet (E/C/F/TAF) in HIV-1 infected adults with end stage renal disease (estimated CrCl < 15 mL/min) on chronic haemodialysis, efficacy was maintained through 48 weeks but emtricitabine exposure was significantly higher than in patients with normal renal function. Although there were no new safety issues identified, the implications of increased emtricitabine exposure remain uncertain.

Co-administration of other medicinal products

The co-administration of Emtricitabine and Tenofovir alafenamide fumarate is not recommended with certain anticonvulsants (e.g., carbamazepine, oxcarbazepine, phenobarbital and phenytoin), antimycobacterials (e.g., rifampicin, rifabutin, rifapentine), St. John's wort and HIV protease inhibitors (PIs) other than atazanavir, lopinavir and darunavir.

Emtricitabine and Tenofovir alafenamide fumarate should not be administered concomitantly with medicinal products containing tenofovir alafenamide, tenofovir disoproxil, emtricitabine, lamivudine or adefovir dipivoxil.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults. Emtricitabine and Tenofovir alafenamide fumarate should not be administered concomitantly with medicinal products containing tenofovir alafenamide, tenofovir disoproxil, emtricitabine, lamivudine or adefovir dipivoxil.

Emtricitabine

In vitro and clinical pharmacokinetic drug-drug interaction studies have shown that the potential for CYP-mediated interactions involving emtricitabine with other medicinal products is low. Co-administration of emtricitabine with medicinal products that are eliminated by active tubular secretion may increase concentrations of emtricitabine, and/or the coadministered medicinal product. Medicinal products 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). Medicinal products that strongly affect P-gp and BCRP activity may lead to changes in tenofovir alafenamide absorption. Medicinal products 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 Emtricitabine and Tenofovir alafenamide fumarate and development of resistance. Co-administration of Emtricitabine and Tenofovir alafenamide fumarate with other medicinal products that inhibit P-gp and BCRP activity (e.g., cobicistat, ritonavir, diltiazem) is expected to increase the absorption and plasma concentration of tenofovir alafenamide. Based on data from an *in vitro* study, coadministration 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 components of Emtricitabine and Tenofovir alafenamide fumarate and potential co-administered medicinal products are listed in Table 2 (increase interactions between the components of Emtricitabine and Tenofovir alafenamide fumarate as "+/-"). The interactions described are based on studies conducted with Emtricitabine and Tenofovir alafenamide fumarate, is indicated as "+", decrease as "-", no change as "+/-". The interactions described are based on studies conducted with Emtricitabine and Tenofovir alafenamide fumarate, or the components of Emtricitabine and Tenofovir alafenamide fumarate as individual agents and/or in combination, or are potential drug-drug interactions that may occur with Emtricitabine and Tenofovir alafenamide fumarate.

Table 2: Interactions between the individual components of Emtricitabine and Tenofovir alafenamide fumarate and other medicinal products

Medicinal products by therapeutic areas ¹	Effects on medicinal product levels. Mean percent change in AUC, C _{max} , C _{min} ²	Recommendations concerning coadministration with Emtricitabine and Tenofovir alafenamide fumarate
ANTI-INFECTIVES		
Antifungals		
Ketoconazole Itraconazole	Interaction not studied with either of the components of Emtricitabine and Tenofovir alafenamide fumarate. 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 Emtricitabine and Tenofovir alafenamide fumarate is 200/10 mg once daily.
Fluconazole Isavuconazole	Interaction not studied with either of the components of Emtricitabine and Tenofovir alafenamide fumarate. Co-administration of fluconazole or isavuconazole may increase plasma concentrations of tenofovir alafenamide.	Dose Emtricitabine and Tenofovir alafenamide fumarate according to the concomitant antiretroviral.
Antimycobacterials		
Rifabutin Rifampicin Rifapentine	Interaction not studied with either of the components of Emtricitabine and Tenofovir alafenamide fumarate. 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 Emtricitabine and Tenofovir alafenamide fumarate and rifabutin, rifampicin, or rifapentine is not recommended.
Anti-hepatitis C virus medicinal products		
Ledipasvir (90 mg once daily)/sofosbuvir (400 mg once daily), emtricitabine (200 mg once daily)/tenofovir alafenamide (10 mg once daily). ³	Ledipasvir: AUC: ↑79% C _{max} : ↑65% C _{min} : ↑93% Sofosbuvir: AUC: ↑47% C _{max} : ↑29% Sofosbuvir metabolite GS-331007: AUC: ↑ 48%	No dose adjustment of ledipasvir or sofosbuvir is required. Dose Emtricitabine and Tenofovir alafenamide fumarate according to the concomitant antiretroviral.

	C _{max} : ↔ C _{min} : ↑ 66% Emtricitabine: AUC: ↔ C _{max} : ↔ C _{min} : ↔ Tenofovir alafenamide: AUC: ↔ C _{max} : ↔	
Ledipasvir (90 mg once daily)/sofosbuvir (400 mg once daily), emtricitabine (200 mg once daily)/tenofovir alafenamide (25 mg once daily) ⁴	Ledipasvir: AUC: ↔ C _{max} : ↔ C _{min} : ↔ Sofosbuvir: AUC: ↔ C _{max} : ↔ C _{min} : ↔ Sofosbuvir metabolite GS-331007: AUC: ↔ C _{max} : ↔ C _{min} : ↔ Emtricitabine: AUC: ↔ C _{max} : ↔ C _{min} : ↔ Tenofovir alafenamide: AUC: ↑ 32% C _{max} : ↔	No dose adjustment of ledipasvir or sofosbuvir is required. Dose Emtricitabine and Tenofovir alafenamide fumarate according to the concomitant antiretroviral.
Sofosbuvir (400 mg once daily)/velpatasvir (100 mg once daily), emtricitabine (200 mg once daily)/tenofovir alafenamide (10 mg once daily) ³	Sofosbuvir: AUC: ↑ 37% C _{max} : ↔ Sofosbuvir metabolite GS-331007: AUC: ↑ 48% C _{max} : ↔ C _{min} : ↑ 58% Velpatasvir: AUC: ↑ 50% C _{max} : ↑ 30% C _{min} : ↑ 60% Emtricitabine: AUC: ↔ C _{max} : ↔ C _{min} : ↔ Tenofovir alafenamide: AUC: ↔ C _{max} : ↓ 20%	No dose adjustment of sofosbuvir, velpatasvir or voxilaprevir is required. Dose Emtricitabine and Tenofovir alafenamide fumarate according to the concomitant antiretroviral.
Sofosbuvir/velpatasvir/ voxilaprevir (400 mg/100 mg/100 mg+100 mg once daily) ¹ / emtricitabine (200 mg once daily)/ tenofovir alafenamide (10 mg once daily) ¹	Sofosbuvir: AUC: ↔ C _{max} : ↑ 27% Sofosbuvir metabolite GS-331007: AUC: ↑ 43% C _{max} : ↔ Velpatasvir: AUC: ↔ C _{min} : ↑ 46% C _{max} : ↔ Voxilaprevir: AUC: ↑ 171% C _{min} : ↑ 350% C _{max} : ↑ 92% Emtricitabine: AUC: ↔ C _{min} : ↔ C _{max} : ↔ Tenofovir alafenamide: AUC: ↔ C _{max} : ↑ 21%	No dose adjustment of sofosbuvir, velpatasvir or voxilaprevir is required. Dose Emtricitabine and Tenofovir alafenamide fumarate according to the concomitant antiretroviral.
Sofosbuvir/velpatasvir/ voxilaprevir (400 mg/100 mg/100 mg+100 mg once daily) ¹ / emtricitabine (200 mg once daily)/ tenofovir alafenamide (25 mg once daily) ⁴	Sofosbuvir: AUC: ↔ C _{max} : ↔ Sofosbuvir metabolite GS-331007: AUC: ↔ C _{min} : ↔ Velpatasvir: AUC: ↔ C _{min} : ↔ C _{max} : ↔ Voxilaprevir: AUC: ↔ C _{min} : ↔ C _{max} : ↔ Emtricitabine: AUC: ↔ C _{min} : ↔ C _{max} : ↔ Tenofovir alafenamide: AUC: ↑ 52% C _{min} : ↑ 32%	No dose adjustment of sofosbuvir, velpatasvir or voxilaprevir is required. Dose Emtricitabine and Tenofovir alafenamide fumarate according to the concomitant antiretroviral.

ANTIRETROVIRALS		
HIV protease inhibitors		
Atazanavir/cobicistat (300 mg/150 mg once daily), tenofovir alafenamide (10 mg)	Tenofovir alafenamide: AUC: ↑ 75% C _{max} : ↑ 80% Atazanavir: AUC: ↔ C _{max} : ↔ C _{min} : ↔	The recommended dose of Emtricitabine and Tenofovir alafenamide fumarate is 200/10 mg once daily.
Atazanavir/ritonavir (300/100 mg once daily), tenofovir alafenamide (10 mg)	Tenofovir alafenamide: AUC: ↑ 91% C _{max} : ↑ 77% Atazanavir: AUC: ↔ C _{max} : ↔ C _{min} : ↔	The recommended dose of Emtricitabine and Tenofovir alafenamide fumarate is 200/10 mg once daily.
Darunavir/cobicistat (800/150 mg once daily), tenofovir alafenamide (25 mg once daily) ⁵	Tenofovir alafenamide: AUC: ↔ C _{max} : ↔ Tenofovir: AUC: ↑ 224% C _{max} : ↑ 216% C _{min} : ↑ 221% Darunavir: AUC: ↔ C _{max} : ↔ C _{min} : ↔	The recommended dose of Emtricitabine and Tenofovir alafenamide fumarate is 200/10 mg once daily.
Darunavir/cobicistat (800/150 mg once daily), tenofovir alafenamide (25 mg once daily) ⁵	Tenofovir alafenamide: AUC: ↔ C _{max} : ↔ Tenofovir: AUC: ↑ 224% C _{max} : ↑ 216% C _{min} : ↑ 221% Darunavir: AUC: ↔ C _{max} : ↔ C _{min} : ↔	The recommended dose of Emtricitabine and Tenofovir alafenamide fumarate is 200/10 mg once daily.
Darunavir/ritonavir (800/100 mg once daily), tenofovir alafenamide (10 mg once daily)	Tenofovir alafenamide: AUC: ↔ C _{max} : ↔ Tenofovir: AUC: ↑ 105% C _{max} : ↑ 142% Darunavir: AUC: ↔ C _{max} : ↔ C _{min} : ↔	The recommended dose of Emtricitabine and Tenofovir alafenamide fumarate is 200/10 mg once daily.
Lopinavir/ritonavir (800/200 mg once daily), tenofovir alafenamide (10 mg once daily)	Tenofovir alafenamide: AUC: ↑ 47% C _{max} : ↑ 119% Lopinavir: AUC: ↔ C _{max} : ↔ C _{min} : ↔	The recommended dose of Emtricitabine and Tenofovir alafenamide fumarate is 200/10 mg once daily.
Tipranavir/ritonavir	Interaction not studied with either of the components of Emtricitabine and Tenofovir alafenamide fumarate. Tipranavir/ritonavir results in P-gp induction. Tenofovir alafenamide exposure is expected to decrease when tipranavir/ritonavir is used in combination with Emtricitabine and Tenofovir alafenamide fumarate.	Co-administration with Emtricitabine and Tenofovir alafenamide fumarate is not recommended.
Other protease inhibitors	Effect is unknown	There are no data available to make dosing recommendations for coadministration with other protease inhibitors.
Other HIV antiretrovirals		
Dolutegravir (50 mg once daily), tenofovir alafenamide (10 mg once daily) ³	Tenofovir alafenamide: AUC: ↔ C _{max} : ↔ Dolutegravir: AUC: ↔ C _{max} : ↔ C _{min} : ↔	The recommended dose of Emtricitabine and Tenofovir alafenamide fumarate is 200/25 mg once daily.
Rilpivirine (25 mg once daily), tenofovir alafenamide (25 mg once daily)	Tenofovir alafenamide: AUC: ↔ C _{max} : ↔ Rilpivirine: AUC: ↔ C _{max} : ↔ C _{min} : ↔	The recommended dose of Emtricitabine and Tenofovir alafenamide fumarate is 200/25 mg once daily.
Efavirenz (600 mg once daily), tenofovir alafenamide (40 mg once daily) ⁴	Tenofovir alafenamide: AUC: ↓ 14% C _{max} : ↓ 22%	The recommended dose of Emtricitabine and Tenofovir alafenamide fumarate is 200/25 mg once daily.
Maraviroc Nevirapine Raltegravir	Interaction not studied with either of the components of Emtricitabine and Tenofovir alafenamide fumarate.	The recommended dose of Emtricitabine and Tenofovir alafenamide fumarate is 200/25 mg once daily.

