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 IP 200mg
Tenofovir Alafenamide Fumarate IP
Equivalent to Tenofovir Alafenamide....10mg
Excipients .....q.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 IP 200mg
Tenofovir Alafenamide Fumarate IP
Equivalent to Tenofovir Alafenamide...25mg
Excipients .....q.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- naive 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 coinfected 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 (hyperlactatemia, hyperlipasemia). 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 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 (estimaed 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, ciclosporin) 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 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}: ↔ 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)[7]/ emtricitabine (200 mg once daily)/ tenofovir alafenamide (10 mg once daily)[3]	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%	
Sofosbuvir/velpatasvir/ voxilaprevir (400 mg/100 mg/100 mg+100 mg once daily)[7]/ 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_{max}: ↑ 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		

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.

	Tenofovir alafenamide exposure is not expected to be affected by maraviroc, nevirapine or raltegravir, nor is it expected to affect the metabolic and excretion pathways relevant to maraviroc, nevirapine or raltegravir.	
ANTICONVULSANTS		
Oxcarbazepine Phenobarbital Phenytoin	Interaction not studied with either of the components of Emtricitabine and Tenofovir alafenamide fumarate. Co-administration of oxcarbazepine, phenobarbital, or phenytoin, 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 oxcarbazepine, phenobarbital or phenytoin is not recommended.
Carbamazepine (titrated from 100 mg to 300 mg twice a day), emtricitabine/tenofovir alafenamide (200 mg/25 mg once daily) [5,6]	Tenofovir alafenamide: AUC: ↓ 55% C_{max}: ↓ 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 Emtricitabine and Tenofovir alafenamide fumarate and carbamazepine is not recommended.
ANTIDEPRESSANTS		
Sertraline (50 mg once daily), tenofovir alafenamide (10 mg once daily)[3]	Tenofovir alafenamide: AUC: ↔ C_{max}: ↔ Sertraline: AUC: ↑ 9% C_{max}: ↑ 14%	No dose adjustment of sertraline is required. Dose Emtricitabine and Tenofovir alafenamide fumarate according to the concomitant antiretroviral.
HERBAL PRODUCTS		
St. John's wort (*Hypericum perforatum*)	Interaction not studied with either of the components of Emtricitabine and Tenofovir alafenamide fumarate. 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 Emtricitabine and Tenofovir alafenamide fumarate with St. John's wort is not recommended.
IMMUNOSUPPRESSANTS		
Ciclosporin	Interaction not studied with either of the components of Emtricitabine and Tenofovir alafenamide fumarate. Co-administration of ciclosporin, a potent P-gp inhibitor, is expected to increase plasma concentrations of tenofovir alafenamide.	The recommended dose of Emtricitabine and Tenofovir alafenamide fumarate is 200/10 mg once daily.
ORAL CONTRACEPTIVES		
Norgestimate (0.180/0.215/0.250 mg once daily), ethinylestradiol (0.025 mg once daily), emtricitabine/tenofovir alafenamide (200/25 mg once daily)[5]	Norelgestromin: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Norgestrel: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Ethinylestradiol: AUC: ↔ C_{min}: ↔ C_{max}: ↔	No dose adjustment of norgestimate/ethinylestradiol is required. Dose Emtricitabine and Tenofovir alafenamide fumarate according to the concomitant antiretroviral.
SEDATIVES/HYPNOTICS		
Orally administered midazolam (2.5 mg single dose), tenofovir alafenamide (25 mg once daily)	Midazolam: AUC: ↔ C_{max}: ↔	No dose adjustment of midazolam is required. Dose Emtricitabine and Tenofovir alafenamide fumarate according to the concomitant antiretroviral.
Intravenously administered midazolam (1 mg single dose), tenofovir alafenamide (25 mg once daily)	Midazolam: AUC: ↔ C_{max}: ↔	

1 When doses are provided, they are the doses used in clinical drug-drug interaction studies.
2 When data are available from drug-drug interaction studies.
3 Study conducted with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fixed-dose combination tablet.
4 Study conducted with emtricitabine/rilpivirine/tenofovir alafenamide fixed-dose combination tablet.
5 Study conducted with Emtricitabine and Tenofovir alafenamide fumarate.
6 Emtricitabine/tenofovir alafenamide was taken with food in this study.
7 Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposurers expected in HCV-infected patients.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

There are no adequate and well-controlled studies of Emtricitabine and Tenofovir alafenamide fumarate or its components in pregnant women. There are no or limited data (less than 300 pregnancy outcomes) from the use of tenofovir alafenamide in pregnant women. However, a large amount of data on pregnant women (more than 1,000 exposed outcomes) indicate no malformative nor foetal/neonatal toxicity associated with emtricitabine.

Animal studies do not indicate direct or indirect harmful effects of emtricitabine with respect to fertility parameters, pregnancy, foetal development, parturition or postnatal development. Studies of tenofovir alafenamide in animals have shown no evidence of harmful effects on fertility parameters, pregnancy, or foetal development.

Emtricitabine and Tenofovir alafenamide fumarate should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding

It is not known whether tenofovir alafenamide is excreted in human milk. Emtricitabine is excreted in human milk. In animal studies it has been shown that tenofovir is excreted in milk.

There is insufficient information on the effects of emtricitabine and tenofovir in newborns/infants. Therefore, Emtricitabine and Tenofovir alafenamide fumarate should not be used during breast-feeding.

In order to avoid transmission of HIV to the infant it is recommended that HIV infected women do not breast-feed their infants under any circumstances.

Fertility

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

Pediatric Use

Treatment of HIV-1 Infection

The safety and effectiveness of Emtricitabine and Tenofovir alafenamide fumarate, in combination with other antiretroviral agents, for the treatment of HIV-1 infection was established in pediatric patients with body weight greater than or equal to 25 kg.

Use of Emtricitabine and Tenofovir alafenamide fumarate in pediatric patients between the ages of 12 to less than 18 years weighing at least 35 kg is supported by adequate and well controlled studies of FTC+TAF with EVG+COBI in adults and by an open-label trial in antiretroviral treatment-naïve HIV-1 infected pediatric subjects ages 12 to less than 18 years and weighing at least 35 kg (N=50; cohort 1). The safety and efficacy of FTC+TAF with EVG+COBI in these pediatric subjects was similar to that of HIV-1

infected adults on this regimen.
Use of Emtricitabine and Tenofovir alafenamide fumarate in pediatric patients weighing at least 25 kg is supported by adequate and well controlled studies of FTC+TAF with EVG+COBI in adults and by an open-label trial in virologically-suppressed pediatric subjects between the ages of 6 to less than 12 years weighing at least 25 kg, in which subjects were switched from their antiretroviral regimen to FTC+TAF with EVG+COBI (N=23; cohort 2). The safety in these subjects through 24 weeks of FTC+TAF with EVG+COBI was similar to that of HIV-1 infected adults on this regimen, with the exception of a decrease in mean change from baseline in CD4+ cell count.
Safety and effectiveness of Emtricitabine and Tenofovir alafenamide fumarate coadministered with an HIV-1 protease inhibitor that is administered with either ritonavir or cobicistat have not been established in pediatric subjects weighing less than 35 kg.
Safety and effectiveness of Emtricitabine and Tenofovir alafenamide fumarate for treatment of HIV-1 infection in pediatric patients less than 25 kg have not been established.
HIV-1 PrEP
Safety and effectiveness of Emtricitabine and Tenofovir alafenamide fumarate for HIV-1 PrEP in at-risk adolescents weighing at least 35 kg, excluding individuals at risk from receptive vaginal sex, is supported by data from an adequate and well-controlled trial of Emtricitabine and Tenofovir alafenamide fumarate for HIV-1 PrEP in adults with additional data from safety and pharmacokinetic studies in previously conducted trials with the individual drug products, FTC and TAF, with EVG+COBI, in HIV-1 infected adults and pediatric subjects.
While using Emtricitabine and Tenofovir alafenamide fumarate for HIV-1 PrEP, HIV-1 testing should be repeated at least every 3 months, and upon diagnosis of any other STIs. Previous studies in at-risk adolescents indicated waning adherence to a daily oral PrEP regimen once visits were switched from monthly to quarterly visits. Adolescents may therefore benefit from more frequent visits and counseling.
Safety and effectiveness of Emtricitabine and Tenofovir alafenamide fumarate for HIV-1 PrEP in pediatric patients less than 35 kg have not been established.
Geriatric Use
In clinical trials of an FTC+TAF-containing regimen for treatment of HIV-1, 80 of the 97 subjects enrolled aged 65 years and over received FTC+TAF and EVG+COBI. No differences in safety or efficacy have been observed between elderly subjects and adults between 18 and less than 65 years of age.
Renal Impairment
No dosage adjustment of Emtricitabine and Tenofovir alafenamide fumarate is recommended in individuals with estimated creatinine clearance greater than or equal to 30 mL per minute, or in adults with ESRD (estimated creatinine clearance below 15 mL per minute) who are receiving chronic hemodialysis. On days of hemodialysis, administer the daily dose of Emtricitabine and Tenofovir alafenamide fumarate after completion of hemodialysis treatment.
Safety and effectiveness of Emtricitabine and Tenofovir alafenamide fumarate coadministered with an HIV-1 protease inhibitor that is administered with either ritonavir or cobicistat have not been established in patients with ESRD.
Emtricitabine and Tenofovir alafenamide fumarate is not recommended in individuals with severe renal impairment (estimated creatinine clearance of 15 to below 30 mL per minute), or in individuals with ESRD who are not receiving chronic hemodialysis, as the safety of Emtricitabine and Tenofovir alafenamide fumarate has not been established in these populations.
Hepatic Impairment
No dosage adjustment of Emtricitabine and Tenofovir alafenamide fumarate is recommended in individuals with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.
Emtricitabine and Tenofovir alafenamide fumarate has not been studied in individuals with severe hepatic impairment (Child-Pugh Class C).
4.7 Effects on ability to drive and use machines
Patients should be informed that dizziness has been reported during treatment with Emtricitabine and Tenofovir alafenamide fumarate.
4.8 Undesirable Effects
Summary of the safety profile
Assessment of adverse reactions is based on safety data from across all Phase 2 and 3 studies in HIV-1 infected patients received medicinal products containing emtricitabine and tenofovir alafenamide and from postmarketing experience.
Tabulated summary of adverse reactions[1]
The adverse reactions are listed by system organ class and frequency. Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100).
Blood and lymphatic system disorders
Uncommon: anaemia[2]
Psychiatric disorders
Common: abnormal dreams
Nervous system disorders
Common: headache, dizziness
Gastrointestinal disorders
Very common: nausea
Common: diarrhoea, vomiting, abdominal pain, flatulence
Uncommon: dyspepsia
Skin and subcutaneous tissue disorders
Common: Rash
Uncommon: angioedema,[3,4] pruritus, urticaria [4]
Musculoskeletal and connective tissue disorders
Uncommon: arthralgia
General disorders and administration site conditions
Common: fatigue
1 With the exception of angioedema, anaemia and urticaria (see footnotes 2, 3 and 4), all adverse reactions were identified from clinical studies of F/TAF containing products. The frequencies were derived from Phase 3 E/C/F/TAF clinical studies in 866 treatment-naïve adult patients through 144 weeks of treatment (GS-US-292-0104 and GS-US-292-0111).
2 This adverse reaction was not observed in the clinical studies of F/TAF-containing products but identified from clinical studies or post-marketing experience for emtricitabine when used with other antiretrovirals.
3 This adverse reaction was identified through post-marketing surveillance for emtricitabine-containing products.
4 This adverse reaction was identified through post-marketing surveillance for tenofovir alafenamide-containing products.
Reporting of suspected adverse reactions
Health care professionals, patients/consumers are advised to closely monitor the possibility of the above ADRs associated with the use of the above drugs. If such reactions are encountered, please report to the Hetero either by filling of Suspect Adverse Drug Reactions Reporting Form **(form.heteroworld.com)** or by **Hetero Helpline No. 1800-120-8689.** Also for all India safety cases and complaints, pls write to **drugsafetyindia@heterodrugs.com**.
4.9 Overdose
If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with Emtricitabine and Tenofovir alafenamide fumarate consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient.
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. Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54%. It is not known whether emtricitabine or tenofovir can be removed by peritoneal dialysis.
5. Pharmacological Properties
Pharmacotherapeutic group: Antiviral for systemic use; antivirals for treatment of HIV infections, combinations. ATC code: J05AR17.
5.1 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 triphosphate. Emtricitabine triphosphate inhibits HIV replication through incorporation into viral deoxyribonucleic acid (DNA) by the HIV reverse transcriptase (RT), which results in DNA chain-termination. Emtricitabine has activity against HIV-1, HIV-2, and HBV.
Tenofovir alafenamide is a nucleotide reverse transcriptase inhibitor (NtRTI) and phosphonamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). Tenofovir alafenamide is permeable into cells and due to increased plasma stability and intracellular activation through hydrolysis by cathepsin A, tenofovir alafenamide is more efficient than tenofovir disoproxil fumarate in concentrating tenofovir in peripheral blood mononuclear cells (PBMCs) or HIV target cells including lymphocytes and macrophages. Intracellular tenofovir is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV 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.
Pharmacodynamics
Antiviral activity in vitro
Emtricitabine and tenofovir alafenamide demonstrated synergistic antiviral activity in cell culture. No antagonism was observed with emtricitabine or tenofovir alafenamide when combined with other antiretroviral agents.
The antiviral activity of emtricitabine against laboratory and clinical isolates of HIV-1 had been assessed in lymphoblastoid cell lines, the MAGI CCR5 cell line, and PBMCs. The 50% effective concentration (EC_{50}) values for emtricitabine were in the range of 0.0013 to 0.64 μM. Emtricitabine displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007 to 0.075 μM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.007 to 1.5 μM).
The antiviral activity of tenofovir alafenamide against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells and CD4+-T lymphocytes. The EC50 values for tenofovir alafenamide were in the range of 2.0 to 14.7 nM. Tenofovir alafenamide displayed antiviral activity in cell culture against all HIV-1 groups (M, N, and O), including subtypes A, B, C, D, E, F, and G (EC50 values ranged from 0.10 to 12.0 nM) and showed strain specific activity against HIV-2 (EC50 values ranged from 0.91 to 2.63 nM).
Resistance

In vitro

Reduced susceptibility to emtricitabine is associated with M184V/I mutations in HIV-1 RT.

HIV-1 isolates with reduced susceptibility to tenofovir alafenamide express a K65R mutation in HIV-1 RT; in addition, a K70E mutation in HIV-1 RT has been transiently observed.

In treatment-naïve patients

In a pooled analysis of antiretroviral-naïve patients receiving emtricitabine and tenofovir alafenamide (10 mg) given with elvitegravir and cobicistat as a fixed-dose combination tablet in Phase 3 studies GS-US-292-0104 and GS-US-292-0111, genotyping was performed on plasma HIV-1 isolates from all patients with HIV-1 RNA ≥ 400 copies/mL at confirmed virological failure, at Week 144, or at the time of early study drug discontinuation. Through Week 144, the development of one or more primary emtricitabine, tenofovir alafenamide, or elvitegravir resistance-associated mutations was observed in HIV-1 isolates from 12 of 22 patients with evaluable genotypic data from paired baseline and E/C/F/TAF treatment-failure isolates (12 of 866 patients [1.4%]) compared with 12 of 20 treatment-failure isolates from patients with evaluable genotypic data in the E/C/F/TDF group (12 of 867 patients [1.4%]). In the E/C/F/TAF group, the mutations that emerged were M184V/I (n = 11) and K65R/N (n = 2) in RT and T66T/A/I/V (n = 2), E92Q (n = 4), Q148Q/R (n = 1), and N155H (n = 2) in integrase. Of the HIV-1 isolates from 12 patients with resistance development in the E/C/F/TDF group, the mutations that emerged were M184V/I (n = 9), K65R/N (n = 4), and L210W (n = 1) in RT and E92Q/V (n = 4) and Q148R (n = 2), and N155H/S (n=3) in integrase. Most HIV-1 isolates from patients in both treatment groups who developed resistance mutations to elvitegravir in integrase also developed resistance mutations to emtricitabine in RT.

In patients co-infected with HIV and HBV

In a clinical study of HIV virologically suppressed patients co-infected with chronic hepatitis B, who received emtricitabine and tenofovir alafenamide, given with elvitegravir and cobicistat as a fixed-dose combination tablet (E/C/F/TAF), for 48 weeks (GS-US-292-1249, n = 72), 2 patients qualified for resistance analysis. In these 2 patients, no amino acid substitutions associated with resistance to any of the components of E/C/F/TAF were identified in HIV-1 or HBV.

Cross-resistance in HIV-1 infected, treatment-naïve or virologically suppressed patients

Emtricitabine-resistant viruses with the M184V/I substitution were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir, and zidovudine. The K65R and K70E mutations result in reduced susceptibility to abacavir, didanosine, lamivudine, emtricitabine, and tenofovir, but retain sensitivity to zidovudine. Multinucleoside-resistant HIV-1 with a T69S double insertion mutation or with a Q151M mutation complex including K65R showed reduced susceptibility to tenofovir alafenamide.

Clinical data

There are no efficacy and safety studies conducted in treatment-naïve patients with emtricitabine, and tenofovir.

Clinical efficacy of emtricitabine, and tenofovir was established from studies conducted with emtricitabine and tenofovir alafenamide when given with elvitegravir and cobicistat as the fixed-dose combination tablet E/C/F/TAF.

Cardiac Electrophysiology

In a thorough QT/QTc study in 48 healthy subjects, TAF at the recommended dose or at a dose approximately 5 times the recommended dose, did not affect the QT/QTc interval and did not prolong the PR interval. The effect of the other component of FTC, or the combination of FTC and TAF on the QT interval is not known.

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. Following multiple dose oral administration of emtricitabine to 20 HIV-1 infected subjects, the (mean ± SD) steady state plasma emtricitabine peak concentrations (C_{max}) were 1.8 ± 0.7 µg/mL and the area-under the plasma concentration-time curve over a 24-hour dosing interval (AUC) was 10.0 ± 3.1 µg•h/mL. The mean steady state plasma trough concentration at 24 hours post-dose was equal to or greater than the mean *in vitro* IC_{90} value for anti-HIV-1 activity.

Emtricitabine systemic exposure was unaffected when emtricitabine was administered with food.

Following administration of food in healthy subjects, peak plasma concentrations were observed approximately 1-hour post-dose for tenofovir alafenamide administered as F/TAF (25 mg) or E/C/F/TAF (10 mg). The mean C_{max} and AUC_{last}, (mean ± SD) under fed conditions following a single 25 mg dose of tenofovir alafenamide administered in Emtricitabine and Tenofovir alafenamide fumarate were 0.21 ± 0.13 µg/mL and 0.25 ± 0.11 µg•h/mL, respectively. The mean C_{max} and AUC_{last} following a single 10 mg dose of tenofovir alafenamide administered in E/C/F/TAF were 0.21 ± 0.10 µg/mL and 0.25 ± 0.08 µg•h/mL, respectively.

Relative to fasting conditions, the administration of tenofovir alafenamide with a high fat meal (~800 kcal, 50% fat) resulted in a decrease in tenofovir alafenamide C_{max} (15-37%) and an increase in AUC_{last} (17-77%).

Distribution

In vitro binding of emtricitabine to human plasma proteins was < 4% and independent of concentration over the range of 0.02-200 µg/mL. At peak plasma concentration, the mean plasma to blood drug concentration ratio was ~1.0 and the mean semen to plasma drug concentration ratio was ~4.0.

In vitro binding of tenofovir to human plasma proteins is < 0.7% and is independent of concentration over the range of 0.01-25 µg/mL. *Ex vivo* binding of tenofovir alafenamide to human plasma proteins in samples collected during clinical studies was approximately 80%.

Biotransformation

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 (~86%) and faeces (~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 (~9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (~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. *In vitro* studies have shown 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 carboxylesterase-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 human clinical studies, a 10 mg oral dose of tenofovir alafenamide (given with emtricitabine and elvitegravir and cobicistat) resulted in tenofovir diphosphate concentrations > 4-fold higher in PBMCs and > 90% lower concentrations of tenofovir in plasma as compared to a 245 mg oral dose of tenofovir disoproxil (as fumarate) (given with emtricitabine and elvitegravir and cobicistat).

In vitro, tenofovir alafenamide 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. Following administration of tenofovir alafenamide, plasma [^{14}C]-radioactivity showed a time-dependent profile with tenofovir alafenamide as the most abundant species in the initial few hours and uric acid in the remaining period.

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 the emtricitabine dose was recovered in urine as three metabolites. 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.

6. Nonclinical Properties

6.1 Animal Toxicology or Pharmacology

Non-clinical data on emtricitabine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. Emtricitabine has demonstrated low carcinogenic potential in mice and rats.

Non-clinical studies of tenofovir alafenamide in rats and dogs revealed bone and kidney as the primary target organs of toxicity. Bone toxicity was observed as reduced BMD in rats and dogs at tenofovir exposures at least four times greater than those expected after administration of Emtricitabine and Tenofovir alafenamide fumarate. A minimal infiltration of histiocytes was present in the eye in dogs at tenofovir alafenamide and tenofovir exposures of approximately 4 and 17 times greater, respectively, than those expected after administration of Emtricitabine and Tenofovir alafenamide fumarate.

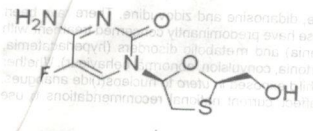
Tenofovir alafenamide was not mutagenic or clastogenic in conventional genotoxicity assays.

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. No special hazard for humans was revealed in conventional studies of 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, tenofovir disoproxil fumarate reduced the viability index and weight of pups in a peri-postnatal toxicity study at maternally toxic doses.

7. Description

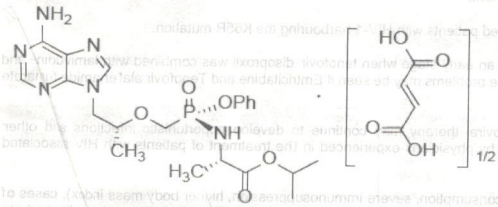
Emtricitabine (FTC)

Emtricitabine (FTC), a synthetic nucleoside analog of cytidine, is an HIV nucleoside analog reverse transcriptase inhibitor (HIV NRTI). It is chemically described as 4-amino-5-fluoro-1-(2*R*hydroxymethyl-1,3-oxathiolan-5S-yl)-(1H)-pyrimidin-2-one with a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24 g/mol. The structural formula as



Tenofovir Alafenamide (TAF)

TAF, an HIV NRTI, is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. It is chemically described as L-alanine, N-[(S)-[[(1R)-2-(6-amino-9H-purin-9-yl)-1methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester, (2E)-2butenedioate (2:1) with a molecular formula of $C_{21}H_{29}O_5N_6P \cdot ½(C_4H_4O_4)$ and a molecular weight of 534.50 g/mol. The structural formula as:



8. Pharmaceutical Particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

24 months

8.3 Packing Information

HDPE Container Pack of 30 tablets

8.4 Storage and handling instructions

Store protected from moisture, at a temperature not exceeding 30°C.

Keep out of reach of children

Dispense in original container.

Keep container tightly closed.

9. Patient Counselling Information

Important Information for Uninfected Individuals Taking Emtricitabine and Tenofovir alafenamide fumarate for HIV-1 PrEP

Advise HIV-1 uninfected individuals about the following:

- The need to confirm that they are HIV-negative before starting to take Emtricitabine and Tenofovir alafenamide fumarate to reduce the risk of acquiring HIV-1.
- That HIV-1 resistance substitution may emerge in individuals with undetected HIV-1 infection who are taking Emtricitabine and Tenofovir alafenamide fumarate, because Emtricitabine and Tenofovir alafenamide fumarate alone does not constitute a complete regimen for HIV-1 treatment.
- The importance of taking Emtricitabine and Tenofovir alafenamide fumarate on a regular dosing schedule and strict adherence to the recommended dosing schedule to reduce the risk of acquiring HIV-1. Uninfected individuals who miss doses are at greater risk of acquiring HIV-1 than those who do not miss doses.
- That Emtricitabine and Tenofovir alafenamide fumarate does not prevent other sexually acquired infections and should be used as part of a complete prevention strategy including other prevention measures.
- To use condoms consistently and correctly to lower the chances of sexual contact with any body fluids such as semen, vaginal secretions, or blood.
- The importance of knowing their HIV-1 status and the HIV-1 status of their partner(s).
- The importance of virologic suppression in their partner(s) with HIV-1.
- The need to get tested regularly for HIV-1 (at least every 3 months, or more frequently for some individuals such as adolescents) and to ask their partner(s) to get tested as well.
- To report any symptoms of acute HIV-1 infection (flu-like symptoms) to their healthcare provider immediately.
- That the signs and symptoms of acute infection include fever, headache, fatigue, arthralgia, vomiting, myalgia, diarrhea, pharyngitis, rash, night sweats, and adenopathy (cervical and inguinal).
- To get tested for other sexually transmitted infections, such as syphilis, chlamydia, and gonorrhea, that may facilitate HIV-1 transmission.
- To assess their sexual risk behavior and get support to help reduce sexual risk behavior.

Post-treatment Acute Exacerbation of Hepatitis B in Patients with HBV Infection

Inform individuals that severe acute exacerbations of hepatitis B have been reported in patients who are infected with HBV and have discontinued products containing FTC and/or TDF and may likewise occur with discontinuation of Emtricitabine and Tenofovir alafenamide fumarate. Advise HBV-infected individuals to not discontinue Emtricitabine and Tenofovir alafenamide fumarate without first informing their healthcare provider.

Immune Reconstitution Syndrome

Advice HIV-1 infected patients to inform their healthcare provider immediately of any symptoms of infection. In some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started.

New Onset or Worsening Renal Impairment

Postmarketing cases of renal impairment, including acute renal failure, proximal renal tubulopathy (PRT), and Fanconi syndrome have been reported with TAF containing products; while most of these cases were characterized by potential confounders that may have contributed to the reported renal events, it is also possible these factors may have predisposed patients to tenofovir-related adverse events. Emtricitabine and TAF is not recommended in individuals with estimated creatinine clearance of 15 to below 30 mL per minute, or in individuals with estimated creatinine clearance below 15 mL per minute who are not receiving chronic hemodialysis.

Individuals taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents including non-steroidal anti-inflammatory drugs are at increased risk of developing renal-related adverse reactions. Prior to or when initiating Emtricitabine and TAF, and during treatment on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all individuals. In individuals with chronic kidney disease, also assess serum phosphorus. Discontinue Emtricitabine and TAF in individuals who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

Lactic Acidosis and Severe Hepatomegaly

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with use of drugs similar to Emtricitabine and Tenofovir alafenamide fumarate. Advice HIV-1 infected patients and uninfected individuals that they should stop Emtricitabine and Tenofovir alafenamide fumarate if they develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity.

Dosage Recommendations for Treatment of HIV-1 Infection

Inform HIV-1 infected patients that it is important to take Emtricitabine and Tenofovir alafenamide fumarate with other antiretroviral drugs for the treatment of HIV-1 on a regular dosing schedule with or without food and to avoid missing doses as it can result in development of resistance.

Pregnancy Registry

Inform individuals using Emtricitabine and Tenofovir alafenamide fumarate that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant women exposed to Emtricitabine and Tenofovir alafenamide fumarate.

Lactation

Instruct mothers with HIV-1 infection not to breastfeed because of the risk of passing the HIV-1 virus to the baby.

10. Details of Manufacturer

Hetero Labs Limited (Unit II)

Village: Kalyanpur, Chakkan Road, Tehsil: Baddi,

Distt.: Solan, Himachal Pradesh – 173 205.

11. Details of permission or licence number with date

MF-ND-04/2018 dated: 10-01-2018

12. Date of revision

17-02-2022

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HETERO HEALTHCARE LIMITED

7-2-A 2, Hetero Corporate, Industrial Estate,

Sanath Nagar, Hyderabad - 500 018.

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