

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Emtricitabine/Tenofovir alafenamide Viatis 200 mg/10 mg film-coated tablets
Emtricitabine/Tenofovir alafenamide Viatis 200 mg/25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

200 mg/10 mg film-coated tablets

Each tablet contains 200 mg of emtricitabine and tenofovir alafenamide monofumarate equivalent to 10 mg of tenofovir alafenamide.

200 mg/25 mg film-coated tablets

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

200 mg/10 mg film-coated tablets

Grey, film-coated, rectangle shaped, beveled edge, biconvex tablet (approximately 15 mm x 7 mm), debossed with 'ET 1' on one side of the tablet and V on the other side.

200 mg/25 mg film-coated tablets

Blue, film-coated, rectangle shaped, beveled edge, biconvex tablet of dimensions (approximately 15 mm x 7 mm) debossed with 'ET 2' on one side of the tablet and V on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Emtricitabine/Tenofovir alafenamide Viatis is indicated in combination with other antiretroviral agents for the treatment of adults and adolescents (aged 12 years and older with body weight at least 35 kg) infected with human immunodeficiency virus type 1 (HIV-1) (see sections 4.2 and 5.1).

4.2 Posology and method of administration

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

Posology

Emtricitabine/Tenofovir alafenamide Viatis should be administered as shown in Table 1.

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

Dose of Emtricitabine/Tenofovir alafenamide Viartis	Third agent in HIV treatment regimen (see section 4.5)
Emtricitabine/Tenofovir alafenamide Viartis 200/10 mg once daily	Atazanavir with ritonavir or cobicistat Darunavir with ritonavir or cobicistat ¹ Lopinavir with ritonavir
Emtricitabine/Tenofovir alafenamide Viartis 200/25 mg once daily	Dolutegravir, efavirenz, maraviroc, nevirapine, rilpivirine, raltegravir

¹ Emtricitabine/Tenofovir alafenamide Viartis 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, see section 5.1.

Missed doses

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

Elderly

No dose adjustment of Emtricitabine/Tenofovir alafenamide Viartis is required in elderly patients (see sections 5.1 and 5.2).

Renal impairment

No dose adjustment of Emtricitabine/Tenofovir alafenamide Viartis 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/Tenofovir alafenamide Viartis should be discontinued in patients with estimated CrCl that declines below 30 mL/min during treatment (see section 5.2).

No dose adjustment of Emtricitabine/Tenofovir alafenamide Viartis is required in adults with end stage renal disease (estimated CrCl < 15 mL/min) on chronic haemodialysis; however, Emtricitabine/Tenofovir alafenamide Viartis should generally be avoided but may be used in these patients if the potential benefits are considered to outweigh the potential risks (see sections 4.4 and 5.2). On days of haemodialysis, Emtricitabine/Tenofovir alafenamide Viartis should be administered after completion of haemodialysis treatment.

Emtricitabine/Tenofovir alafenamide Viartis 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/Tenofovir alafenamide Viartis 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/Tenofovir alafenamide Viartis is required in patients with hepatic impairment.

Paediatric population

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

Method of administration

Oral use.

Emtricitabine/Tenofovir alafenamide Viatris should be taken once daily with or without food (see section 5.2). It is recommended that the film-coated tablet is not chewed or crushed due to the bitter taste.

For patients who are unable to swallow the tablet whole, the tablet may be split in half and both halves taken one after the other, ensuring that the full dose is taken immediately.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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/Tenofovir alafenamide Viatris 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/Tenofovir alafenamide Viatris 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 Emtricitabine/Tenofovir alafenamide Viatris 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/Tenofovir alafenamide Viatris in patients with significant underlying liver disorders have not been established (see sections 4.2 and 5.2).

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 aetiology, 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/Tenofovir alafenamide Viatris should be avoided 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 Emtricitabine/Tenofovir alafenamide Viatris is administered with a third nucleoside analogue.

Opportunistic infections

Patients receiving Emtricitabine/Tenofovir alafenamide Viatris 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

Post-marketing cases of renal impairment, including acute renal failure and proximal renal tubulopathy have been reported with tenofovir alafenamide-containing products. 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).

It is recommended that renal function is assessed in all patients prior to, or when initiating, therapy with Emtricitabine/Tenofovir alafenamide Viatris 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/Tenofovir alafenamide Viatris should be considered.

Patients with end stage renal disease on chronic haemodialysis

Emtricitabine/Tenofovir alafenamide Viatris 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 (see sections 4.8 and 5.2).

Co-administration of other medicinal products

The co-administration of Emtricitabine/Tenofovir alafenamide Viatris 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 (see section 4.5).

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

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Emtricitabine/Tenofovir alafenamide Viatris 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 co-administered 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/Tenofovir alafenamide and development of resistance. Co-administration of Emtricitabine/Tenofovir alafenamide 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, co-administration 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/Tenofovir alafenamide 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/Tenofovir alafenamide, or the components of Emtricitabine/Tenofovir alafenamide as individual agents and/or in combination, or are potential drug-drug interactions that may occur with Emtricitabine/Tenofovir alafenamide.

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

Medicinal product by therapeutic areas ¹	Effects on medicinal product levels. Mean percent change in AUC, C _{max} , C _{min} ²	Recommendation concerning co-administration with Emtricitabine/Tenofovir alafenamide Viartis
ANTI-INFECTIVES		
Antifungals		
Ketoconazole Itraconazole	Interaction not studied with either of the components of Emtricitabine/Tenofovir alafenamide Viartis. 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/Tenofovir alafenamide Viartis is 200/10 mg once daily.
Fluconazole Isavuconazole	Interaction not studied with either of the components of Emtricitabine/Tenofovir alafenamide Viartis. Co-administration of fluconazole or isavuconazole may increase plasma concentrations of tenofovir alafenamide.	Dose Emtricitabine/Tenofovir alafenamide Viartis according to the concomitant antiretroviral (see section 4.2).
Antimycobacterials		
Rifabutin Rifampicin Rifapentine	Interaction not studied with either of the components of Emtricitabine/Tenofovir alafenamide Viartis. 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/Tenofovir alafenamide Viartis 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% C _{max} : ↔ C _{min} : ↑ 66% Emtricitabine: AUC: ↔ C _{max} : ↔ C _{min} : ↔ Tenofovir alafenamide: AUC: ↔ C _{max} : ↔	No dose adjustment of ledipasvir or sofosbuvir is required. Dose Emtricitabine/Tenofovir alafenamide Viartis according to the concomitant antiretroviral (see section 4.2).

Medicinal product by therapeutic areas ¹	Effects on medicinal product levels. Mean percent change in AUC, C _{max} , C _{min} ²	Recommendation concerning co-administration with Emtricitabine/Tenofovir alafenamide Viatis
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/Tenofovir alafenamide Viatis according to the concomitant antiretroviral (see section 4.2).
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/Tenofovir alafenamide Viatis according to the concomitant antiretroviral (see section 4.2).

Medicinal product by therapeutic areas ¹	Effects on medicinal product levels. Mean percent change in AUC, C _{max} , C _{min} ²	Recommendation concerning co-administration with Emtricitabine/Tenofovir alafenamide Viartis
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/Tenofovir alafenamide Viartis according to the concomitant antiretroviral (see section 4.2).

Medicinal product by therapeutic areas ¹	Effects on medicinal product levels. Mean percent change in AUC, C _{max} , C _{min} ²	Recommendation concerning co-administration with Emtricitabine/Tenofovir alafenamide Viatris
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/Tenofovir alafenamide Viatris 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/Tenofovir alafenamide Viatris 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/Tenofovir alafenamide Viatris 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/Tenofovir alafenamide Viatris 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/Tenofovir alafenamide Viatris is 200/10 mg once daily.

Medicinal product by therapeutic areas ¹	Effects on medicinal product levels. Mean percent change in AUC, C _{max} , C _{min} ²	Recommendation concerning co-administration with Emtricitabine/Tenofovir alafenamide Viatris
Tipranavir/ritonavir	Interaction not studied with either of the components of Emtricitabine/Tenofovir alafenamide. Tipranavir/ritonavir results in P-gp induction. Tenofovir alafenamide exposure is expected to decrease when tipranavir/ritonavir is used in combination with Emtricitabine/Tenofovir alafenamide.	Co-administration with Emtricitabine/Tenofovir alafenamide Viatris 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) ³	Tenofovir alafenamide: AUC: ↔ C _{max} : ↔ Dolutegravir: AUC: ↔ C _{max} : ↔ C _{min} : ↔	The recommended dose of Emtricitabine/Tenofovir alafenamide Viatris 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/Tenofovir alafenamide Viatris 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/Tenofovir alafenamide Viatris is 200/25 mg once daily.
Maraviroc Nevirapine Raltegravir	Interaction not studied with either of the components of Emtricitabine/Tenofovir alafenamide. 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.	The recommended dose of Emtricitabine/Tenofovir alafenamide Viatris is 200/25 mg once daily.
ANTICONVULSANTS		
Oxcarbazepine Phenobarbital Phenytoin	Interaction not studied with either of the components of Emtricitabine/Tenofovir alafenamide. 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/Tenofovir alafenamide Viatris and oxcarbazepine, phenobarbital or phenytoin is not recommended.

Medicinal product by therapeutic areas ¹	Effects on medicinal product levels. Mean percent change in AUC, C _{max} , C _{min} ²	Recommendation concerning co-administration with Emtricitabine/Tenofovir alafenamide Viatris
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/Tenofovir alafenamide Viatris 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/Tenofovir alafenamide Viatris according to the concomitant antiretroviral (see section 4.2).
HERBAL PRODUCTS		
St. John's wort (<i>Hypericum perforatum</i>)	Interaction not studied with either of the components of Emtricitabine/Tenofovir alafenamide Viatris. 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/Tenofovir alafenamide Viatris with St. John's wort is not recommended.
IMMUNOSUPPRESSANTS		
Ciclosporin	Interaction not studied with either of the components of Emtricitabine/Tenofovir alafenamide Viatris. Co-administration of ciclosporin, a potent P-gp inhibitor, is expected to increase plasma concentrations of tenofovir alafenamide.	The recommended dose of Emtricitabine/Tenofovir alafenamide Viatris 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/Tenofovir alafenamide Viatris according to the concomitant antiretroviral (see section 4.2).

Medicinal product by therapeutic areas ¹	Effects on medicinal product levels. Mean percent change in AUC, C _{max} , C _{min} ²	Recommendation concerning co-administration with Emtricitabine/Tenofovir alafenamide Viatis
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/Tenofovir alafenamide Viatis according to the concomitant antiretroviral (see section 4.2).
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/Tenofovir alafenamide.

⁶ Emtricitabine/tenofovir alafenamide was taken with food in this study.

⁷ Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies of Emtricitabine/Tenofovir alafenamide 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 (see section 5.3).

Emtricitabine/Tenofovir alafenamide Viatis 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/Tenofovir alafenamide Viatis should not be used during breast-feeding.

In order to avoid transmission of HIV to the infant it is recommended that women living with HIV do not breast-feed their infants.

Fertility

There are no data on fertility from the use of Emtricitabine/Tenofovir alafenamide in humans. In animal studies there were no effects of emtricitabine and tenofovir alafenamide on mating or fertility parameters (see section 5.3).

4.7 Effects on ability to drive and use machines

Emtricitabine/Tenofovir alafenamide Viatris may have minor influence on the ability to drive and use machines. Patients should be informed that dizziness has been reported during treatment with Emtricitabine/Tenofovir alafenamide.

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 which HIV-1 infected patients received medicinal products containing emtricitabine and tenofovir alafenamide and from post-marketing experience. In clinical studies of treatment-naïve adult patients receiving emtricitabine and tenofovir alafenamide with elvitegravir and cobicistat as the fixed-dose combination tablet elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide (as fumarate) 10 mg (E/C/F/TAF) through 144 weeks, the most frequently reported adverse reactions were diarrhoea (7%), nausea (11%), and headache (6%).

Tabulated summary of adverse reactions

The adverse reactions in Table 3 are listed by system organ class and frequency. Frequencies are defined as follows: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$) and uncommon ($\geq 1/1\,000$ to $< 1/100$).

Table 3: Tabulated list of adverse reactions¹

Frequency	Adverse reaction
<i>Blood and lymphatic system disorders</i>	
Uncommon:	anaemia ²
<i>Psychiatric disorders</i>	
Common:	abnormal dreams
<i>Nervous system disorders</i>	
Common:	headache, dizziness
<i>Gastrointestinal disorders</i>	
Very common:	nausea
Common:	diarrhoea, vomiting, abdominal pain, flatulence
Uncommon:	dyspepsia
<i>Skin and subcutaneous tissue disorders</i>	
Common:	Rash
Uncommon:	angioedema ^{3, 4} , pruritus, urticaria ⁴
<i>Musculoskeletal and connective tissue disorders</i>	
Uncommon:	arthralgia
<i>General disorders and administration site conditions</i>	
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.

Description of selected adverse reactions

Immune Reactivation Syndrome

In HIV infected patients with severe immune deficiency at the time of initiation of CART, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable, and these events can occur many months after initiation of treatment (see section 4.4).

Osteonecrosis

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to CART. The frequency of this is unknown (see section 4.4).

Changes in lipid laboratory tests

In studies in treatment-naïve patients, increases from baseline were observed in both the tenofovir alafenamide fumarate and tenofovir disoproxil fumarate containing treatment groups for the fasting lipid parameters total cholesterol, direct low-density lipoprotein (LDL)- and high-density lipoprotein (HDL)-cholesterol, and triglycerides at Week 144. The median increase from baseline for those parameters was greater in the E/C/F/TAF group compared with the elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil (as fumarate) 245 mg (E/C/F/TDF) group at Week 144 ($p < 0.001$ for the difference between treatment groups for fasting total cholesterol, direct LDL- and HDL-cholesterol, and triglycerides). The median (Q1, Q3) change from baseline in total cholesterol to HDL-cholesterol ratio at Week 144 was 0.2 (-0.3, 0.7) in the E/C/F/TAF group and 0.1 (-0.4, 0.6) in the E/C/F/TDF group ($p = 0.006$ for the difference between treatment groups).

In a study of virologically suppressed patients switching from emtricitabine/tenofovir disoproxil fumarate to Emtricitabine/Tenofovir alafenamide while maintaining the third antiretroviral agent (Study GS-US-311-1089), increases from baseline were observed in the fasting lipid parameters total cholesterol, direct LDL cholesterol and triglycerides in the Emtricitabine/Tenofovir alafenamide arm compared with little change in the emtricitabine/tenofovir disoproxil fumarate arm ($p \leq 0.009$ for the difference between groups in changes from baseline). There was little change from baseline in median fasting values for HDL cholesterol and glucose, or in the fasting total cholesterol to HDL cholesterol ratio in either treatment arm at Week 96. None of the changes was considered clinically relevant.

In a study of virologically suppressed adult patients switching from abacavir/lamivudine to Emtricitabine/Tenofovir alafenamide while maintaining the third antiretroviral agent (Study GS-US-311-1717), there were minimal changes in lipid parameters.

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

Paediatric population

The safety of emtricitabine and tenofovir alafenamide was evaluated through 48 weeks in an open-label clinical study (GS-US-292-0106) in which HIV-1 infected, treatment-naïve paediatric patients aged 12 to < 18 years received emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet. The safety

profile of emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat in 50 adolescent patients was similar to that in adults (see section 5.1).

Other special populations

Patients with renal impairment

The safety of emtricitabine and tenofovir alafenamide was evaluated through 144 weeks in an open-label clinical study (GS-US-292-0112) in which 248 HIV-1 infected patients who were either treatment-naïve (n = 6) or virologically suppressed (n = 242) with mild to moderate renal impairment (estimated glomerular filtration rate by Cockcroft-Gault method [eGFR_{CG}]: 30-69 mL/min) received emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet. The safety profile in patients with mild to moderate renal impairment was similar to that in patients with normal renal function (see section 5.1).

The safety of emtricitabine and tenofovir alafenamide was evaluated through 48 weeks in a single arm, open-label clinical study (GS-US-292-1825) in which 55 virologically suppressed HIV-1 infected patients with end stage renal disease (eGFR_{CG} < 15 mL/min) on chronic haemodialysis received emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet. There were no new safety issues identified in patients with end stage renal disease on chronic haemodialysis receiving emtricitabine and tenofovir alafenamide, in combination with elvitegravir and cobicistat as a fixed-dose combination tablet (see section 5.2).

Patients co-infected with HIV and HBV

The safety of emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide [E/C/F/TAF]) was evaluated in 72 HIV/HBV co-infected patients receiving treatment for HIV in an open-label clinical study (GS-US-292-1249), through Week 48, in which patients were switched from another antiretroviral regimen (which included tenofovir disoproxil fumarate [TDF] in 69 of 72 patients) to E/C/F/TAF. Based on these limited data, the safety profile of emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet, in patients with HIV/HBV co-infection, was similar to that in patients with HIV-1 mono-infection (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

If overdose occurs the patient must be monitored for evidence of toxicity (see section 4.8). Treatment of overdose with Emtricitabine/Tenofovir alafenamide Viartis 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

5.1 Pharmacodynamic properties

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

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 was 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 μ M. 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 μ M) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.007 to 1.5 μ M).

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 EC_{50} 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 (EC_{50} values ranged from 0.10 to 12.0 nM) and showed strain specific activity against HIV-2 (EC_{50} 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 $\geq$ 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/Tenofovir alafenamide.

Clinical efficacy of Emtricitabine/Tenofovir alafenamide 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.

HIV-1 infected, treatment-naïve patients

In studies GS-US-292-0104 and GS-US-292-0111, patients were randomised in a 1:1 ratio to receive either emtricitabine 200 mg and tenofovir alafenamide 10 mg (n = 866) once daily or emtricitabine 200 mg + tenofovir disoproxil (as fumarate) 245 mg (n = 867) once daily, both given with elvitegravir 150 mg + cobicistat 150 mg as a fixed-dose combination tablet. The mean age was 36 years (range: 18-76), 85% were male, 57% were White, 25% were Black, and 10% were Asian. Nineteen percent of patients were identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.5 log₁₀ copies/mL (range: 1.3-7.0) and 23% had baseline viral loads > 100 000 copies/mL. The mean baseline CD4⁺ cell count was 427 cells/mm³ (range: 0-1,360) and 13% had a CD4⁺ cell count < 200 cells/mm³.

E/C/F/TAF demonstrated statistical superiority in achieving HIV-1 RNA < 50 copies/mL when compared to E/C/F/TDF at Week 144. The difference in percentage was 4.2% (95% CI: 0.6% to 7.8%). Pooled treatment outcomes at 48 and 144 weeks are shown in Table 4.

Table 4: Pooled virological outcomes of Studies GS-US-292-0104 and GS-US-292-0111 at Weeks 48 and 144^{a,b}

	Week 48		Week 144	
	E/C/F/TAF (n = 866)	E/C/F/TDF ^c (n = 867)	E/C/F/TAF (n = 866)	E/C/F/TDF (n = 867)
HIV-1 RNA < 50 copies/mL	92%	90%	84%	80%
Treatment difference	2.0% (95% CI: -0.7% to 4.7%)		4.2% (95% CI: 0.6% to 7.8%)	
HIV-1 RNA ≥ 50 copies/mL^c	4%	4%	5%	4%
No virologic data at Week 48 or 144 window	4%	6%	11%	16%
Discontinued study drug due to AE or death ^d	1%	2%	1%	3%
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL ^c	2%	4%	9%	11%
Missing data during window but on study drug	1%	< 1%	1%	1%
Proportion (%) of patients with HIV-1 RNA < 50 copies/mL by subgroup				
Proportion (%) of patients with HIV-1 RNA < 50 copies/mL by subgroup				
Age				
< 50 years	716/777 (92%)	680/753 (90%)	647/777 (83%)	602/753 (80%)
≥ 50 years	84/89 (94%)	104/114 (91%)	82/89 (92%)	92/114 (81%)
Sex				
Male	674/733 (92%)	673/740 (91%)	616/733 (84%)	603/740 (81%)
Female	126/133 (95%)	111/127 (87%)	113/133 (85%)	91/127 (72%)
Race				
Black	197/223 (88%)	177/213 (83%)	168/223 (75%)	152/213 (71%)
Non-black	603/643 (94%)	607/654 (93%)	561/643 (87%)	542/654 (83%)
Baseline viral load				
≤ 100 000 copies/mL	629/670 (94%)	610/672 (91%)	567/670 (85%)	537/672 (80%)
> 100 000 copies/mL	171/196 (87%)	174/195 (89%)	162/196 (83%)	157/195 (81%)
Baseline CD4+ cell count				
< 200 cells/mm ³	96/112 (86%)	104/117 (89%)	93/112 (83%)	94/117 (80%)
≥ 200 cells/mm ³	703/753 (93%)	680/750 (91%)	635/753 (84%)	600/750 (80%)
HIV-1 RNA < 20 copies/mL	84.4%	84.0%	81.1%	75.8%
Treatment difference	0.4% (95% CI: -3.0% to 3.8%)		5.4% (95% CI: 1.5% to 9.2%)	

E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide

E/C/F/TDF = elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate

^a Week 48 window was between Day 294 and 377 (inclusive); Week 144 window was between Day 966 and 1049 (inclusive).

^b In both studies, patients were stratified by baseline HIV-1 RNA (≤ 100 000 copies/mL, > 100 000 copies/mL to ≤ 400 000 copies/mL, or > 400 000 copies/mL), by CD4+ cell count (< 50 cells/μL, 50-199 cells/μL, or ≥ 200 cells/μL), and by region (US or ex-US).

^c Includes patients who had ≥ 50 copies/mL in the Week 48 or 144 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.

^d Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

^e Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy; e.g., withdrew consent, loss to follow-up, etc.

The mean increase from baseline in CD4+ cell count was 230 cells/mm³ in patients receiving E/C/F/TAF and 211 cells/mm³ in patients receiving E/C/F/TDF (p = 0.024) at Week 48, and 326 cells/mm³ in E/C/F/TAF-treated patients and 305 cells/mm³ in E/C/F/TDF-treated patients (p = 0.06) at Week 144.

Clinical efficacy of Emtricitabine/Tenofovir alafenamide in treatment-naïve patients was also established from a study conducted with emtricitabine and tenofovir alafenamide (10 mg) when given with darunavir (800 mg) and cobicistat as a fixed-dose combination tablet (D/C/F/TAF). In Study GS-US-299-0102, patients were randomised in a 2:1 ratio to receive either fixed-dose combination D/C/F/TAF once daily (n = 103) or darunavir and cobicistat and emtricitabine/tenofovir disoproxil fumarate once daily (n = 50). The proportions of patients with plasma HIV-1 RNA < 50 copies/mL and < 20 copies/mL are shown in Table 5.

Table 5: Virological outcomes of Study GS-US-299-0102 at Week 24 and 48^a

	Week 24		Week 48	
	D/C/F/TAF (n = 103)	Darunavir, cobicistat and emtricitabine/tenofovir disoproxil fumarate (n = 50)	D/C/F/TAF (n = 103)	Darunavir, cobicistat and emtricitabine/tenofovir disoproxil fumarate (n = 50)
HIV-1 RNA < 50 copies/mL	75%	74%	77%	84%
Treatment difference	3.3% (95% CI: -11.4% to 18.1%)		-6.2% (95% CI: -19.9% to 7.4%)	
HIV-1 RNA ≥ 50 copies/mL^b	20%	24%	16%	12%
No virologic data at Week 48 window	5%	2%	8%	4%
Discontinued study drug due to AE or death ^c	1%	0	1%	2%
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL ^d	4%	2%	7%	2%
Missing data during window but on study drug	0	0	0	0
HIV-1 RNA < 20 copies/mL	55%	62%	63%	76%
Treatment difference	-3.5% (95% CI: -19.8% to 12.7%)		-10.7% (95% CI: -26.3% to 4.8%)	

D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide

^a Week 48 window was between Day 294 and 377 (inclusive).

^b Includes patients who had ≥ 50 copies/mL in the Week 48 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.

^c Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

^d Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy; e.g., withdrew consent, loss to follow-up, etc.

HIV-1 infected virologically suppressed patients

In Study GS-US-311-1089, the efficacy and safety of switching from emtricitabine/tenofovir disoproxil fumarate to Emtricitabine/Tenofovir alafenamide while maintaining the third antiretroviral agent were evaluated in a randomised, double-blind study of virologically suppressed HIV-1 infected adults (n = 663). Patients must have been stably suppressed (HIV-1 RNA < 50 copies/mL) on their baseline regimen for at least 6 months and had HIV-1 with no resistance mutations to emtricitabine or tenofovir alafenamide prior to study entry. Patients were randomised in a 1:1 ratio to either switch to Emtricitabine/Tenofovir alafenamide (n = 333), or stay on their baseline emtricitabine/tenofovir disoproxil fumarate containing regimen (n = 330). Patients were stratified by the class of the third agent in their prior treatment regimen. At baseline, 46% of patients were receiving emtricitabine/tenofovir disoproxil fumarate in combination with a boosted PI and 54% of patients were receiving emtricitabine/tenofovir disoproxil fumarate in combination with an unboosted third agent.

Treatment outcomes of Study GS-US-311-1089 through 48 and 96 weeks are presented in Table 6.

Table 6: Virological outcomes of Study GS-US-311-1089 at Weeks 48^a and 96^b

	Week 48		Week 96	
	Emtricitabine/ Tenofovir alafenamide containing regimen (n = 333)	Emtricitabine/ tenofovir disoproxil fumarate containing regimen (n = 330)	Emtricitabine/ Tenofovir alafenamide containing regimen (n = 333)	Emtricitabine/ tenofovir disoproxil fumarate containing regimen (n = 330)
HIV-1 RNA < 50 copies/mL	94%	93%	89%	89%
Treatment difference	1.3% (95% CI: -2.5% to 5.1%)		-0.5% (95% CI: -5.3% to 4.4%)	
HIV-1 RNA ≥ 50 copies/mL^c	< 1%	2%	2%	1%
No virologic data at Week 48 or 96 window	5%	5%	9%	10%
Discontinued study drug due to AE or death ^d	2%	1%	2%	2%
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL ^e	3%	5%	7%	9%
Missing data during window but on study drug	< 1%	0	0	<1%
Proportion (%) of patients with HIV-1 RNA < 50 copies/mL by prior treatment regimen				
Boosted PIs	142/155 (92%)	140/151 (93%)	133/155 (86%)	133/151 (88%)
Other third agents	172/178 (97%)	167/179 (93%)	162/178 (91%)	161/179 (90%)

PI = protease inhibitor

^a Week 48 window was between Day 294 and 377 (inclusive).

^b Week 96 window was between Day 630 and 713 (inclusive).

^c Includes patients who had ≥ 50 copies/mL in the Week 48 or Week 96 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.

^d Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

^e Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy; e.g., withdrew consent, loss to follow-up, etc.

In Study GS-US-311-1717, patients who were virologically suppressed (HIV-1 RNA <50 copies/mL) on their abacavir/lamivudine containing regimen for at least 6 months were randomised in a 1:1 ratio to either switch to Emtricitabine/Tenofovir alafenamide (N=280) while maintaining their third agent at baseline or stay on their baseline abacavir/lamivudine - containing regimen (N=276).

Patients were stratified by the class of the third agent in their prior treatment regimen. At baseline, 30% of patients were receiving abacavir/lamivudine in combination with a boosted protease inhibitor and 70% of patients were receiving abacavir/lamivudine in combination with an unboosted third agent. Virologic success rates at Week 48 were:

Emtricitabine/Tenofovir alafenamide Containing Regimen: 89.7% (227 of 253 subjects);

Abacavir/lamivudine Containing Regimen: 92.7% (230 of 248 subjects). At Week 48, switching to a Emtricitabine/Tenofovir alafenamide-containing regimen was non-inferior to staying on a baseline abacavir/lamivudine-containing regimen in maintaining HIV-1 RNA < 50 copies/mL.

HIV-1 infected patients with mild to moderate renal impairment

In Study GS-US-292-0112, the efficacy and safety of emtricitabine and tenofovir alafenamide were evaluated in an open-label clinical study in which 242 HIV-1 infected patients with mild to moderate renal impairment (eGFR_{CG}: 30-69 mL/min) were switched to emtricitabine and tenofovir alafenamide (10 mg) given with elvitegravir and cobicistat as a fixed-dose

combination tablet. Patients were virologically suppressed (HIV-1 RNA < 50 copies/mL) for at least 6 months before switching.

The mean age was 58 years (range: 24-82), with 63 patients (26%) who were ≥ 65 years of age. Seventy-nine percent were male, 63% were White, 18% were Black, and 14% were Asian. Thirteen percent of patients were identified as Hispanic/Latino. At baseline, median eGFR was 56 mL/min, and 33% of patients had an eGFR from 30 to 49 mL/min. The mean baseline CD4+ cell count was 664 cells/mm³ (range: 126-1,813).

At Week 144, 83.1% (197/237 patients) maintained HIV-1 RNA < 50 copies/mL after switching to emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat as a fixed-dose combination tablet.

In Study GS-US-292-1825, the efficacy and safety of emtricitabine and tenofovir alafenamide, given with elvitegravir and cobicistat as a fixed-dose combination tablet were evaluated in a single arm, open-label clinical study in which 55 HIV-1 infected adults with end stage renal disease (eGFR_{CG} < 15 mL/min) on chronic haemodialysis for at least 6 months before switching to emtricitabine and tenofovir alafenamide, given with elvitegravir and cobicistat as a fixed-dose combination tablet. Patients were virologically suppressed (HIV-1 RNA < 50 copies/mL) for at least 6 months before switching.

The mean age was 48 years (range 23-64). Seventy-six percent were male, 82% were Black and 18% were White. Fifteen percent of patients identified as Hispanic/Latino. The mean baseline CD4+ cell count was 545 cells/mm³ (range 205-1473). At Week 48, 81.8% (45/55 patients) maintained HIV-1 RNA < 50 copies/mL after switching to emtricitabine and tenofovir alafenamide, given with elvitegravir and cobicistat as a fixed-dose combination tablet. There were no clinically significant changes in fasting lipid laboratory tests in patients who switched.

Patients co-infected with HIV and HBV

In open-label Study GS-US-292-1249, the efficacy and safety of emtricitabine and tenofovir alafenamide, given with elvitegravir and cobicistat as a fixed-dose combination tablet (E/C/F/TAF), were evaluated in adult patients co-infected with HIV-1 and chronic hepatitis B. Sixty-nine of the 72 patients were on prior TDF-containing antiretroviral therapy. At the start of treatment with E/C/F/TAF, the 72 patients had been HIV-suppressed (HIV-1 RNA < 50 copies/mL) for at least 6 months with or without suppression of HBV DNA and had compensated liver function. The mean age was 50 years (range 28-67), 92% of patients were male, 69% were White, 18% were Black, and 10% were Asian. The mean baseline CD4+ cell count was 636 cells/mm³ (range 263-1498). Eighty-six percent of patients (62/72) were HBV suppressed (HBV DNA < 29 IU/mL) and 42% (30/72) were HBeAg positive at baseline.

Of the patients who were HBeAg positive at baseline, 1/30 (3.3%) achieved seroconversion to anti-HBe at Week 48. Of the patients who were HBsAg positive at baseline, 3/70 (4.3%) achieved seroconversion to anti-HBs Week 48.

At Week 48, 92% of patients (66/72) maintained HIV-1 RNA < 50 copies/mL after switching to emtricitabine and tenofovir alafenamide, given with elvitegravir and cobicistat as a fixed-dose combination tablet. The mean change from baseline in CD4+ cell count at Week 48 was -2 cells/mm³. Ninety-two percent (66/72 patients) had HBV DNA < 29 IU/mL using missing = failure analysis at Week 48. Of the 62 patients who were HBV suppressed at baseline, 59 remained suppressed and 3 had missing data. Of the 10 patients who were not HBV suppressed at baseline (HBV DNA ≥ 29 IU/mL), 7 became suppressed, 2 remained detectable, and 1 had missing data.

There are limited clinical data on the use of E/C/F/TAF in HIV/HBV co-infected patients who are treatment-naïve.

Changes in measures of bone mineral density

In studies in treatment-naïve patients, emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat as a fixed-dose combination tablet was associated with smaller reductions in bone mineral density (BMD) compared to E/C/F/TDF through 144 weeks of treatment as measured by dual energy X ray absorptiometry (DXA) analysis of hip (mean change: -0.8% vs -3.4%, $p < 0.001$) and lumbar spine (mean change: -0.9% vs -3.0%, $p < 0.001$). In a separate study, emtricitabine and tenofovir alafenamide given with darunavir and cobicistat as a fixed-dose combination tablet was also associated with smaller reductions in BMD (as measured by hip and lumbar spine DXA analysis) through 48 weeks of treatment compared to darunavir, cobicistat, emtricitabine and tenofovir disoproxil fumarate.

In a study in virologically suppressed adult patients, improvements in BMD were noted through 96 weeks after switching to Emtricitabine/Tenofovir alafenamide from a TDF containing regimen compared to minimal changes with maintaining the TDF containing regimen as measured by DXA analysis of hip (mean change from baseline of 1.9% vs -0.3%, $p < 0.001$) and lumbar spine (mean change from baseline of 2.2% vs -0.2%, $p < 0.001$).

In a study in virologically suppressed adult patients, BMD did not change significantly through 48 weeks after switching to Emtricitabine/Tenofovir alafenamide from an abacavir/lamivudine containing regimen compared to maintaining the abacavir/lamivudine containing regimen as measured by DXA analysis of hip (mean change from baseline of 0.3% vs 0.2%, $p = 0.55$) and lumbar spine (mean change from baseline of 0.1% vs < 0.1%, $p = 0.78$).

Changes in measures of renal function

In studies in treatment-naïve patients, emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat as a fixed-dose combination tablet through 144 weeks was associated with a lower impact on renal safety parameters (as measured after 144 weeks treatment by eGFR_{CG} and urine protein to creatinine ratio and after 96 weeks treatment by urine albumin to creatinine ratio) compared to E/C/F/TDF. Through 144 weeks of treatment, no subject discontinued E/C/F/TAF due to a treatment-emergent renal adverse event compared with 12 subjects who discontinued E/C/F/TDF ($p < 0.001$).

In a separate study in treatment-naïve patients, emtricitabine and tenofovir alafenamide given with darunavir and cobicistat as a fixed-dose combination tablet was associated with a lower impact on renal safety parameters through 48 weeks of treatment compared to darunavir and cobicistat given with emtricitabine/tenofovir disoproxil fumarate (see also section 4.4).

In a study in virologically suppressed adult patients measures of tubular proteinuria were similar in patients switching to a regimen containing Emtricitabine/Tenofovir alafenamide compared to patients who stayed on an abacavir/lamivudine containing regimen at baseline. At Week 48, the median percentage change in urine retinol binding protein to creatinine ratio was 4% in the Emtricitabine/Tenofovir alafenamide group and 16% in those remaining on an abacavir/lamivudine containing regimen; and in urine beta-2 microglobulin to creatinine ratio it was 4% vs. 5%.

Paediatric population

In Study GS-US-292-0106, the efficacy, safety, and pharmacokinetics of emtricitabine and tenofovir alafenamide were evaluated in an open-label study in which 50 HIV-1 infected, treatment-naïve adolescents received emtricitabine and tenofovir alafenamide (10 mg) given with elvitegravir and cobicistat as a fixed-dose combination tablet. Patients had a mean age of 15 years (range: 12-17), and 56% were female, 12% were Asian, and 88% were Black. At baseline, median plasma HIV-1 RNA was 4.7 log₁₀ copies/mL, median CD4⁺ cell count was 456 cells/mm³ (range: 95-1,110), and median CD4⁺% was 23% (range: 7-45%). Overall, 22% had baseline plasma HIV-1 RNA > 100 000 copies/mL. At 48 weeks, 92% (46/50) achieved HIV-1 RNA < 50 copies/mL, similar to response rates in studies of treatment-naïve

HIV-1 infected adults. The mean increase from baseline in CD4+ cell count at Week 48 was 224 cells/mm³. No emergent resistance to E/C/F/TAF was detected through Week 48.

The European Medicines Agency has deferred the obligation to submit the results of studies with the reference medicinal product containing Emtricitabine/Tenofovir alafenamide in one or more subsets of the paediatric population in the treatment of HIV-1 infection (see section 4.2 for information on paediatric use).

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 $\pm$ SD) steady state plasma emtricitabine peak concentrations ($C_{\max}$) were 1.8 ± 0.7 $\mu\text{g/mL}$ and the area-under the plasma concentration-time curve over a 24-hour dosing interval (AUC) was 10.0 ± 3.1 $\mu\text{g}\cdot\text{h/mL}$. The mean steady state plasma trough concentration at 24 hours post-dose was equal to or greater than the mean *in vitro* IC₉₀ 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 $\pm$ SD) under fed conditions following a single 25 mg dose of tenofovir alafenamide administered in Emtricitabine/Tenofovir alafenamide were 0.21 ± 0.13 $\mu\text{g/mL}$ and 0.25 ± 0.11 $\mu\text{g}\cdot\text{h/mL}$, 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 $\mu\text{g/mL}$ and 0.25 ± 0.08 $\mu\text{g}\cdot\text{h/mL}$, 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 $\mu\text{g/mL}$. 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 $\mu\text{g/mL}$. *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 [¹⁴C]-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 [14C]-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.

Pharmacokinetics in 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.

Paediatric population

Exposures of emtricitabine and tenofovir alafenamide (given with elvitegravir and cobicistat) achieved in 24 paediatric patients aged 12 to < 18 years who received emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat in Study GS-US-292-0106 were similar to exposures achieved in treatment-naïve adults (Table 7).

Table 7: Pharmacokinetics of emtricitabine and tenofovir alafenamide in antiretroviral-naïve adolescents and adults

	Adolescents			Adults		
	FTC ^a	TAF ^b	TFV ^b	FTC ^a	TAF ^c	TFV ^c
AUC_{tau} (ng•h/mL)	14,424.4 (23.9)	242.8 (57.8)	275.8 (18.4)	11,714.1 (16.6)	206.4 (71.8)	292.6 (27.4)
C_{max} (ng/mL)	2,265.0 (22.5)	121.7 (46.2)	14.6 (20.0)	2,056.3 (20.2)	162.2 (51.1)	15.2 (26.1)
C_{tau} (ng/mL)	102.4 (38.9) ^b	N/A	10.0 (19.6)	95.2 (46.7)	N/A	10.6 (28.5)

E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate

FTC = emtricitabine; TAF = tenofovir alafenamide fumarate; TFV = tenofovir

N/A = not applicable

Data are presented as mean (%CV).

^a n = 24 adolescents (GS-US-292-0106); n = 19 adults (GS-US-292-0102)

^b n = 23 adolescents (GS-US-292-0106, population PK analysis)

^c n = 539 (TAF) or 841 (TFV) adults (GS-US-292-0111 and GS-US-292-0104, population PK analysis)

Renal impairment

No clinically relevant differences in tenofovir alafenamide, or tenofovir pharmacokinetics were observed between healthy subjects and patients with severe renal impairment (estimated CrCl ≥ 15 mL/min and < 30 mL/min) in a Phase 1 study of tenofovir alafenamide. In a separate Phase 1 study of emtricitabine alone, mean systemic emtricitabine exposure was higher in patients with severe renal impairment (estimated CrCl < 30 mL/min) ($33.7 \mu\text{g}\cdot\text{h/mL}$) than in subjects with normal renal function ($11.8 \mu\text{g}\cdot\text{h/mL}$). The safety of emtricitabine and tenofovir alafenamide has not been established in patients with severe renal impairment (estimated CrCl ≥ 15 mL/min and < 30 mL/min).

Exposures of emtricitabine and tenofovir in 12 patients with end stage renal disease (estimated CrCl < 15 mL/min) on chronic haemodialysis who received emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet (E/C/F/TAF) in Study GS-US-292-1825 were significantly higher than in patients with normal renal function. 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. There were no new safety issues identified in patients with end stage renal disease on chronic haemodialysis receiving emtricitabine and tenofovir alafenamide, in combination with elvitegravir and cobicistat as a fixed-dose combination tablet (see section 4.8).

There are no pharmacokinetic data on emtricitabine or tenofovir alafenamide in patients with end stage renal disease (estimated CrCl < 15 mL/min) not on chronic haemodialysis. The safety of emtricitabine and tenofovir alafenamide has not been established in these patients.

Hepatic impairment

The pharmacokinetics of emtricitabine have not been studied in subjects with hepatic impairment; however, emtricitabine is not significantly metabolised by liver enzymes, so the impact of liver impairment should be limited.

Clinically relevant changes in the pharmacokinetics of tenofovir alafenamide or its metabolite tenofovir were not observed in patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, total plasma concentrations of tenofovir alafenamide and tenofovir are lower than those seen in subjects with normal hepatic function. When corrected for protein binding, unbound (free) plasma concentrations of tenofovir alafenamide in severe hepatic impairment and normal hepatic function are similar.

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.

5.3 Preclinical safety data

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/Tenofovir alafenamide. 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/Tenofovir alafenamide.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

200 mg/10 mg film-coated tablets

Tablet core

Cellulose, microcrystalline
Croscarmellose sodium
Magnesium stearate

Film-coating

Poly (vinyl alcohol) partially hydrolyzed
Titanium dioxide (E171)
Macrogol
Talc
Black Iron Oxide (E172)

200 mg/25 mg film-coated tablets

Tablet core

Cellulose, microcrystalline
Croscarmellose sodium
Magnesium stearate

Film-coating

Poly (vinyl alcohol) partially hydrolyzed
Titanium dioxide (E171)
Macrogol
Talc
Indigo carmine Aluminum lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blisters

2 years

HDPE Bottle

2 years.

6.4 Special precautions for storage

Blisters

Do not store above 30°C.

HDPE bottle

This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

200 mg/10 mg film-coated tablets

High density polyethylene (HDPE) bottle with white opaque polypropylene (PP) child-resistant closure along with a desiccant containing 30 and 90 film-coated tablets.

200 mg/25 mg film-coated tablets

Blister (OPA/alu/PE/desiccant/HDPE-alu/PE) containing 30 and 90 film-coated tablets.

Perforated unit dose blister (OPA/alu/PE/desiccant/HDPE-alu/PE) containing 30 x 1 and 90 x 1 film-coated tablets.

High density polyethylene (HDPE) bottle with white opaque polypropylene (PP) child-resistant closure along with a desiccant containing 30 and 90 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Viatrix Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

200 mg/10 mg film-coated tablets

EU/1/25/1952/001

EU/1/25/1952/002

200 mg/25 mg film-coated tablets

EU/1/25/1952/003
EU/1/25/1952/004
EU/1/25/1952/005
EU/1/25/1952/006
EU/1/25/1952/007
EU/1/25/1952/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 July 2025

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Mylan Hungary Kft.
Mylan utca 1., 2900 Komárom,
Hungary

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**BOTTLE CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Emtricitabine/Tenofovir alafenamide Viatris 200 mg/10 mg film-coated tablets
emtricitabine/tenofovir alafenamide

2. STATEMENT OF ACTIVE SUBSTANCE

Each film coated tablet contains 200 mg of emtricitabine and tenofovir alafenamide monofumarate equivalent to 10 mg of tenofovir alafenamide.

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

30 film-coated tablets

90 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viartis Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1952/001
EU/1/25/1952/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Emtricitabine/Tenofovir alafenamide Viartis 200 mg/10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**BOTTLE LABEL****1. NAME OF THE MEDICINAL PRODUCT**

Emtricitabine/Tenofovir alafenamide Viatris 200 mg/10 mg film-coated tablets
emtricitabine/tenofovir alafenamide

2. STATEMENT OF ACTIVE SUBSTANCE

Each film coated tablet contains 200 mg of emtricitabine and tenofovir alafenamide monofumarate equivalent to 10 mg of tenofovir alafenamide.

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

30 film-coated tablets

90 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viartis Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1952/001
EU/1/25/1952/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**BLISTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Emtricitabine/Tenofovir alafenamide Viatris 200 mg/25 mg film-coated tablets
emtricitabine/tenofovir alafenamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film coated tablet contains 200 mg of emtricitabine and tenofovir alafenamide monofumarate equivalent to 25 mg of tenofovir alafenamide

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

30 film-coated tablets
90 film-coated tablets
30 x 1 film-coated tablets
90 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viartis Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/25/1952/003
EU/1/25/1952/004
EU/1/25/1952/005
EU/1/25/1952/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Emtricitabine/Tenofovir alafenamide Viartis 200 mg/25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Emtricitabine/Tenofovir alafenamide Viatris 200 mg/25 mg film-coated tablets
emtricitabine/tenofovir alafenamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Viatris Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

BUD: Oral use

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**BOTTLE CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Emtricitabine/Tenofovir alafenamide Viatris 200 mg/25 mg film-coated tablets
emtricitabine/tenofovir alafenamide

2. STATEMENT OF ACTIVE SUBSTANCE

Each film coated tablet contains 200 mg of emtricitabine and tenofovir alafenamide monofumarate equivalent to 25 mg of tenofovir alafenamide.

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

Film coated tablet

30 film-coated tablets

90 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viartis Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1952/007
EU/1/25/1952/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Emtricitabine/Tenofovir alafenamide Viartis 200 mg/25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Emtricitabine/Tenofovir alafenamide Viatris 200 mg/25 mg film-coated tablets
emtricitabine/tenofovir alafenamide

2. STATEMENT OF ACTIVE SUBSTANCE

Each film coated tablet contains 200 mg of emtricitabine and tenofovir alafenamide monofumarate equivalent to 25 mg of tenofovir alafenamide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film coated tablet

30 film-coated tablets

90 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viartis Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1952/007
EU/1/25/1952/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Emtricitabine/Tenofovir alafenamide Viatris 200 mg/10 mg film-coated tablets
Emtricitabine/Tenofovir alafenamide Viatris 200 mg/25 mg film-coated tablets
emtricitabine/tenofovir alafenamide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Emtricitabine/Tenofovir alafenamide Viatris is and what it is used for
2. What you need to know before you take Emtricitabine/Tenofovir alafenamide Viatris
3. How to take Emtricitabine/Tenofovir alafenamide Viatris
4. Possible side effects
5. How to store Emtricitabine/Tenofovir alafenamide Viatris
6. Contents of the pack and other information

1. What Emtricitabine/Tenofovir alafenamide Viatris is and what it is used for

Emtricitabine/Tenofovir alafenamide Viatris contains two active substances:

- **emtricitabine**, an antiretroviral medicine of a type known as a nucleoside reverse transcriptase inhibitor (NRTI)
- **tenofovir alafenamide**, an antiretroviral medicine of a type known as a nucleotide reverse transcriptase inhibitor (NtRTI)

Emtricitabine/Tenofovir alafenamide Viatris blocks the action of the reverse transcriptase enzyme, which is essential for the virus to multiply. Emtricitabine/Tenofovir alafenamide Viatris, therefore, reduces the amount of HIV in your body.

Emtricitabine/Tenofovir alafenamide Viatris in combination with other medicines is for the **treatment of human immunodeficiency virus 1 (HIV-1) infection** in adults and adolescents 12 years of age and older, who weigh at least 35 kg.

2. What you need to know before you take Emtricitabine/Tenofovir alafenamide Viatris

Do not take Emtricitabine/Tenofovir alafenamide Viatris

- **If you are allergic to emtricitabine, tenofovir alafenamide** or any of the other ingredients of this medicine (listed in section 6 of this leaflet).

Warnings and precautions

You must remain under the care of your doctor while taking Emtricitabine/Tenofovir alafenamide Viatris.

This medicine is not a cure for HIV infection. While taking Emtricitabine/Tenofovir alafenamide Viatris you may still develop infections or other illnesses associated with HIV infection.

Talk to your doctor before taking Emtricitabine/Tenofovir alafenamide Viatris:

- **If you have liver problems or have suffered liver disease, including hepatitis.**
Patients with liver disease including chronic hepatitis B or C, who are treated with antiretrovirals, have a higher risk of severe and potentially fatal liver complications. If you have hepatitis B infection, your doctor will carefully consider the best treatment regimen for you.

If you have hepatitis B infection, liver problems may become worse after you stop taking Emtricitabine/Tenofovir alafenamide Viatris. Do not stop taking Emtricitabine/Tenofovir alafenamide Viatris without talking to your doctor: see section 3, *Do not stop taking Emtricitabine/Tenofovir alafenamide Viatris*.
- Your doctor may choose to not prescribe Emtricitabine/Tenofovir alafenamide Viatris to you if your virus has a certain resistance mutation, as Emtricitabine/Tenofovir alafenamide Viatris may not be able to reduce the amount of HIV in your body as effectively.
- **If you have had kidney disease or if tests have shown problems with your kidneys.**
Your doctor may order blood tests to monitor how your kidneys work when starting and during treatment with Emtricitabine/Tenofovir alafenamide Viatris.

While you are taking Emtricitabine/Tenofovir alafenamide Viatris

Once you start taking Emtricitabine/Tenofovir alafenamide Viatris, look out for:

- **Signs of inflammation or infection**
- **Joint pain, stiffness or bone problems**

→ **If you notice any of these symptoms, tell your doctor immediately.** For more information see section 4, *Possible side effects*.

There is a possibility that you may experience kidney problems when taking Emtricitabine/Tenofovir alafenamide Viatris over a long period of time (see *Warnings and precautions*).

Children and adolescents

Do not give this medicine to children aged 11 years or under, or weighing less than 35 kg. The use of Emtricitabine/Tenofovir alafenamide Viatris in children aged 11 years or under has not yet been studied.

Other medicines and Emtricitabine/Tenofovir alafenamide Viatris

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Emtricitabine/Tenofovir alafenamide Viatris may interact with other medicines. As a result, the amounts of Emtricitabine/Tenofovir alafenamide Viatris or other medicines in your blood may change. This may stop your medicines from working properly, or may make any side effects worse. In some cases, your doctor may need to adjust your dose or check your blood levels.

Medicines used in treating hepatitis B infection:

You should not take Emtricitabine/Tenofovir alafenamide Viartis with medicines containing:

- **tenofovir alafenamide**
- **tenofovir disoproxil**
- **lamivudine**
- **adefovir dipivoxil**

→ **Tell your doctor** if you are taking any of these medicines.

Other types of medicine:

Talk to your doctor if you are taking:

- **antibiotics**, used to treat bacterial infections including tuberculosis, containing:
 - rifabutin, rifampicin, and rifapentine
- **antiviral medicines used to treat HIV:**
 - emtricitabine and tipranavir
- **anticonvulsants**, used to treat epilepsy, such as:
 - carbamazepine, oxcarbazepine, phenobarbital and phenytoin
- **herbal remedies** used to treat depression and anxiety containing:
 - St. John's wort (*Hypericum perforatum*)

→ **Tell your doctor if you are taking these or any other medicines.** Do not stop your treatment without contacting your doctor.

Pregnancy and breast-feeding

- If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
- Tell your doctor immediately if you become pregnant and ask about the potential benefits and risks of your antiretroviral therapy to you and your child.

If you have taken Emtricitabine/Tenofovir alafenamide Viartis during your pregnancy, your doctor may request regular blood tests and other diagnostic tests to monitor the development of your child. In children whose mothers took NRTIs during pregnancy, the benefit from the protection against HIV outweighed the risk of side effects.

Do not breast-feed during treatment with Emtricitabine/Tenofovir alafenamide Viartis.

This is because one of the active substances in this medicine passes into breast milk.

Breast-feeding is not recommended in women living with HIV because HIV infection can be passed on to the baby in breast milk.

If you are breast-feeding, or thinking about breast-feeding, you should **discuss it with your doctor as soon as possible**.

Driving and using machines

Emtricitabine/Tenofovir alafenamide Viartis can cause dizziness. If you feel dizzy when taking Emtricitabine/Tenofovir alafenamide Viartis, do not drive and do not use any tools or machines.

Emtricitabine/Tenofovir alafenamide Viartis contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Emtricitabine/Tenofovir alafenamide Viatris

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is:

Adults: one tablet each day, with or without food

Adolescents 12 years of age and older, who weigh at least 35 kg: one tablet each day with or without food

It is recommended not to chew or crush the tablet due to the bitter taste.

If you have difficulty swallowing the tablet whole, you can split it in half. Take both halves of the tablet one after the other to get the full dose. Do not store the split tablet.

Always take the dose recommended by your doctor. This is to make sure that your medicine is fully effective, and to reduce the risk of developing resistance to the treatment. Do not change the dose unless your doctor tells you to.

If you are on dialysis, take your daily dose of Emtricitabine/Tenofovir alafenamide Viatris following completion of dialysis.

If you take more Emtricitabine/Tenofovir alafenamide Viatris than you should

If you take more than the recommended dose of Emtricitabine/Tenofovir alafenamide Viatris you may be at higher risk of side effects of this medicine (see section 4, *Possible side effects*).

Contact your doctor or nearest emergency department immediately for advice. Keep the tablet bottle with you so that you can show what you have taken.

If you forget to take Emtricitabine/Tenofovir alafenamide Viatris

It is important not to miss a dose of Emtricitabine/Tenofovir alafenamide Viatris.

If you do miss a dose:

- **If you notice within 18 hours** of the time you usually take Emtricitabine/Tenofovir alafenamide Viatris, you must take the tablet as soon as possible. Then take the next dose as usual.
- **If you notice 18 hours or more** after the time you usually take Emtricitabine/Tenofovir alafenamide Viatris, then do not take the missed dose. Wait and take the next dose at your usual time.

If you vomit less than 1 hour after taking Emtricitabine/Tenofovir alafenamide Viatris, take another tablet.

Do not stop taking Emtricitabine/Tenofovir alafenamide Viatris

Do not stop taking Emtricitabine/Tenofovir alafenamide Viatris without talking to your doctor. Stopping Emtricitabine/Tenofovir alafenamide Viatris can seriously affect how well future treatment works. If Emtricitabine/Tenofovir alafenamide Viatris is stopped for any reason, speak to your doctor before you restart taking Emtricitabine/Tenofovir alafenamide Viatris tablets.

When your supply of Emtricitabine/Tenofovir alafenamide Viatris starts to run low, get more from your doctor or pharmacist. This is very important because the amount of virus may start to increase if the medicine is stopped for even a few days. The disease may then become harder to treat.

If you have both HIV infection and hepatitis B, it is very important not to stop taking Emtricitabine/Tenofovir alafenamide Viatris without talking to your doctor first. You may require blood tests for several months after stopping treatment. In some patients with advanced liver disease or cirrhosis, stopping treatment may lead to worsening of hepatitis, which may be life-threatening.

→ **Tell your doctor immediately** about new or unusual symptoms after you stop treatment, particularly symptoms you associate with hepatitis B infection.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Possible serious side effects: tell a doctor immediately

- **Any signs of inflammation or infection.** In some patients with advanced HIV infection (AIDS) and who have had opportunistic infections in the past (infections that occur in people with a weak immune system), signs and symptoms of inflammation from previous infections may occur soon after antiretroviral treatment is started. It is thought that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms.
- **Autoimmune disorders** (the immune system attacks healthy body tissue), may also occur after you start taking medicines for HIV infection. Autoimmune disorders may occur many months after the start of treatment. Look out for any symptoms of infection or other symptoms such as:
 - muscle weakness
 - weakness beginning in the hands and feet and moving up towards the trunk of the body
 - palpitations, tremor or hyperactivity

→ **If you notice the side effects described above, tell your doctor immediately.**

Very common side effects

(may affect more than 1 in 10 people)

- feeling sick (*nausea*)

Common side effects

(may affect up to 1 in 10 people)

- abnormal dreams
- headache
- dizziness
- diarrhoea
- vomiting
- stomach pain
- wind (*flatulence*)
- rash
- tiredness (*fatigue*)

Uncommon side effects

(may affect up to 1 in 100 people)

- low red blood cell count (*anaemia*)
- problems with digestion resulting in discomfort after meals (*dyspepsia*)
- swelling of the face, lips, tongue or throat (*angioedema*)
- itching (*pruritus*)
- hives (*urticaria*)
- joint pain (*arthralgia*)

→ If any of the side effects get serious tell your doctor.

Other effects that may be seen during HIV treatment

The frequency of the following side effects is not known (frequency cannot be estimated from the available data).

- **Bone problems.** Some patients taking combination antiretroviral medicines such as Emtricitabine/Tenofovir alafenamide Viatris may develop a bone disease called *osteonecrosis* (death of bone tissue caused by loss of blood supply to the bone). Taking this type of medicine for a long time, taking corticosteroids, drinking alcohol, having a very weak immune system, and being overweight, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are:
 - joint stiffness
 - joint aches and pains (especially of the hip, knee and shoulder)
 - difficulty with movement

→ If you notice any of these symptoms tell your doctor.

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Reporting of side effects

If you get any side effects, talk to your doctor, or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Emtricitabine/Tenofovir alafenamide Viatris

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and bottle after "EXP". The expiry date refers to the last day of that month.

Blisters: Do not store above 30°C.

Bottles: This medicine does not require any special temperature storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Emtricitabine/Tenofovir alafenamide Viatris contains

The active substances are emtricitabine and tenofovir alafenamide.

Each Emtricitabine/Tenofovir alafenamide Viatris film-coated tablet contains 200 mg of emtricitabine and tenofovir alafenamide monofumarate equivalent to 10 mg of tenofovir alafenamide or 200 mg of emtricitabine and tenofovir alafenamide monofumarate equivalent to 25 mg of tenofovir alafenamide.

The other ingredients are

Tablet core:

Microcrystalline cellulose, croscarmellose sodium, magnesium stearate.

Film-coating:

Poly (vinyl alcohol) partially hydrolyzed, Titanium dioxide (E171), Black iron oxide (E172) (200 mg/10 mg film-coated tablets only), Macrogol, Talc, Indigo carmine Aluminum lake (E132) (200 mg/25 mg film-coated tablets only).

What Emtricitabine/Tenofovir alafenamide Viatris looks like and contents of the pack

Emtricitabine/Tenofovir alafenamide Viatris 200 mg/10 mg film-coated tablets (tablets) are grey, film-coated, rectangle shaped, beveled edge, biconvex of dimensions (approximately 15 mm x 7 mm) debossed with 'ET 1' on one side of the tablet and V on the other side.

Emtricitabine/Tenofovir alafenamide Viatris 200 mg/25 mg film-coated tablets (tablets) are blue, film-coated, rectangle shaped, beveled edge, biconvex of dimensions (approximately 15 mm x 7 mm) debossed with 'ET 2' on one side of the tablet and V on the other side.

Emtricitabine/Tenofovir alafenamide Viatris comes in bottles of 30 and 90 film-coated tablets (with a silica gel desiccant that must be kept in the bottle to help protect your tablets). The silica gel desiccant is contained in a separate sachet or canister and should not be swallowed.

The following pack sizes are available: outer cartons containing 1 bottle of 30 and 90 film-coated tablets.

200 mg/25 mg film-coated tablets are available also in outer cartons containing blisters of 30 and 90 film-coated tablets and perforated unit dose blisters of 30 x 1 and 90 x 1 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder:

Viatris Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

Manufacturer:

Mylan Hungary Kft.
Mylan utca. 1, H-2900 Komárom,
Hungary

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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Luxembourg/Luxemburg

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This leaflet was last revised in <{month YYYY}>.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website <http://www.ema.europa.eu>