SCHEDULING STATUS

S4

WARNING:

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION WITH OTHER ANITRETROVIRALS (SEE SECTION 4.4.)

TAFICITA IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF TAFICITA HAS NOT BEEN ESTABLISHED IN PATIENTS CO-INFECTED WITH HBV AND HIV. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED WITH HBV AND HIV AND HAVE DISCONTINUED TENOFOVIR AND EMTRICITABINE, WHICH ARE COMPONENTS OF TAFICITA. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS INFECTED WITH HBV WHO DISCONTINUE THE COMBINATION TABLET AND ARE CO-INFECTED WITH HIV AND HBV.

IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE SECTION 4.4,

1 NAME OF THE MEDICINE

TAFICITA 200 mg/25 mg Film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg of emtricitabine and 28.0 mg tenofovir alafenamide hemifumarate equivalent to 25 mg of tenofovir alafenamide.

Sugar free

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

A blue, film-coated, rectangular, biconvex, bevelled edge tablet debossed with M on one side of the tablet and EA I on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TAFICITA is indicated in combination with other antiretroviral medicines 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 medical practitioner experienced in the management of HIV infection.

Posology

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

TAFICITA should be administered as shown in Table 1.

Table 1: Dose of TAFICITA according to third agent in the HIV treatment regimen

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

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

Elderly

No dose adjustment of TAFICITA is required in elderly patients (see sections 5.1 and 5.2).

Renal impairment

No dose adjustment of TAFICITA 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. TAFICITA should be discontinued in patients with estimated CrCl that declines below 30 mL/min during treatment (see sections 4.4 and 5.2).

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

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

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

Hepatic impairment

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

Paediatric population

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

Method of administration

TAFICITA should be taken orally, once daily with or without food (see section 5.2). The film-coated tablet should not be chewed, crushed, or split.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

While effective viral suppression with antiretroviral therapy has been proven to reduce the risk of sexual transmission or blood contamination, the risk of transmission remains present.

Precautions to prevent transmission should be taken in accordance with national guidelines.

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

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

The safety and efficacy of TAFICITA 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 TAFICITA 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 TAFICITA should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment.

In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since.

post treatment exacerbation of hepatitis may lead to hepatic decompensation.

Liver disease

Use of TAFICITA can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of TAFICITA has not been established in patients with significant underlying liver disorders/diseases. In case of concomitant antiviral therapy for hepatitis B or C, please also consult the Professional Information of these medicines. Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored. If there is evidence of worsening liver disease in such patients, temporary or permanent discontinuation of treatment must be considered.

Weight and metabolic parameters

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

Mitochondrial dysfunction following exposure in *utero.*

Nucleos(t)ide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial dysfunction/ damage. There have been reports of mitochondrial dysfunction in HIV negative infants exposed in utero and/or postnatally to nucleoside analogues.

Manifestations of mitochondrial dysfunction include haematological disorders (anaemia, neutropenia), peripheral neuropathy and metabolic disorders (hyperlactataemia, lactic acidosis, hyperlipasaemia). Late onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is

unknown. Possible mitochondrial dysfunction should be considered in any new-born/infant/child exposed in utero to nucleos(t)ide analogues, including HIV negative infants/children who present with severe clinical findings of unknown etiology, particularly neurologic findings. These babies/infants and children should have clinical, and laboratory follow up and be fully investigated for possible mitochondrial dysfunction

Lactic acidosis:

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including emtricitabine, a component of TAFICITA, and tenofovir DF, another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with TAFICITA should be suspended in any individual who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

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

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

- Lactate 2-5 mmol/L with minimum symptoms: switch to medicines that are less likely to cause lactic acidosis

- Lactate 5-10 mmol/L with symptoms and/or with reduced standard bicarbonate. Stop NRTIs and change treatment option. Once the lactate has settled, use medicines that are less likely to cause lactic acidosis. Exclude other causes (e.g., sepsis, uraemia, diabetic keto acidosis, thyrotoxicosis/hyperthyroidism

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

The above values may not be applicable to paediatric patients.

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

Immune Reactivation Syndrome (IRS) / Immune Reconstitution Inflammatory Syndrome (IRIS)

Immune Reactivation Syndrome (IRS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination antiretroviral therapy (CART). Typically, such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRS usually develops within the first 3 months of initiation of ART and occurs more commonly in patients with low CD4+ counts Relevant examples include cytomegalovirus retinitis, generalised and/or focal mycobacterial and other infections, such as tuberculosis, cryptococcal meningitis and *Pneumocystis jirovecii pneumonia*. Appropriate treatment of the opportunistic disease(s) should be instituted or continued, and ART continued. Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRS.

Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable, and these events can occur many months after initiation of treatment.

Patients with HIV-1 harbouring mutations

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

Triple nucleoside therapy

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

Opportunistic infections

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

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV disease and/or long-term exposure to cART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Nephrotoxicity

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

Patients with end stage renal disease on chronic haemodialysis

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

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

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

4.5 Interaction with other medicines and other forms of interaction

Interaction studies have only been performed in adults.

Emtricitabine

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

Tenofovir alafenamide

Tenofovir alafenamide is transported by P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Medicines that strongly affect P-gp and BCRP activity may lead to changes in tenofovir alafenamide absorption. Medicines that induce P-gp activity (e.g., rifampicin, rifabutin, carbamazepine, phenobarbital) are expected to decrease the absorption of tenofovir alafenamide, resulting in decreased plasma concentration of tenofovir alafenamide, which may lead to loss of therapeutic effect of TAFICITA and development of resistance. Co-administration of TAFICITA with other medicines 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 TAFICITA and potential co-administered medicines are listed in Table 2 (increase is indicated as "↑", decrease as "↓", no change as "↔"). The interactions described are based on studies conducted with TAFICITA, or the components of TAFICITA as individual agents and/or in combination or are potential drug-drug interactions that may occur with TAFICITA.

Table 2: Interactions between the individual components of TAFICITA and other medicines

Medicine by therapeutic areas[1]	**Effects on medicine levels. Mean percent change in AUC, C_{max}, C_{min}[2]**	**Recommendation concerning co-administration with TAFICITA**
ANTI-INFECTIVES		
Antifungals		
Ketoconazole Itraconazole	Interaction not studied with either of the components of TAFICITA. 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 TAFICITA is 200/10 mg once daily.
Fluconazole Isavuconazole	Interaction not studied with either of the components of TAFICITA. Co-administration of fluconazole or isavuconazole may increase plasma concentrations of tenofovir alafenamide.	Dose TAFICITA according to the concomitant antiretroviral (see section 4.2).
Antimycobacterials		

Rifabutin Rifampicin Rifapentine	Interaction not studied with either of the components of TAFICITA. 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 TAFICITA and rifabutin rifampicin, or rifapentine is not recommended.
Anti-hepatitis C virus medicines		
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 % Cmax: ↑ 65 % Cmin: ↑ 93 % Sofosbuvir: AUC: ↑ 47 % Cmax: ↑ 29 % Sofosbuvir metabolite GS-331007: AUC: ↑ 48 % Cmax: ↔ Cmin: ↑ 66 % Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir alafenamide: AUC: ↔ Cmax: ↔	No dose adjustment of ledipasvir or sofosbuvir is required. Dose TAFICITA according to the concomitant antiretroviral (see section 4.2).
Ledipasvir (90 mg once daily)/ sofosbuvir (400 mg once daily), emtricitabine (200 mg once daily)/ tenofovir alafenamide (25 mg once daily) [4]	Ledipasvir: AUC: ↔ Cmax: ↔ Cmin: ↔ Sofosbuvir: AUC: ↔ Cmax: ↔ Sofosbuvir metabolite GS-331007: AUC: ↔ Cmax: ↔ Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔	No dose adjustment of ledipasvir or sofosbuvir is required. Dose TAFICITA 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 % Cmax: ↔ Sofosbuvir metabolite GS-331007: AUC: ↑ 48 % Cmax: ↔ Cmin: ↑ 58 % Velpatasvir: AUC: ↑ 50 % Cmax: ↑ 30 % Cmin: ↑ 60 % Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔	No dose adjustment of sofosbuvir, velpatasvir or voxilaprevir is required. Dose TAFICITA according to the concomitant antiretroviral (see section 4.2).

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 metabolite GS-331007: AUC: ↑ 43 % Cmax: ↔ Velpatasvir: AUC: ↔ Cmin: ↑ 46 % Cmax: ↔ Voxilaprevir: AUC: ↑ 171 % Cmin: ↑ 350 % Cmax: ↑ 92 % Emtricitabine: AUC: ↔ Cmin: ↔ Cmax: ↔ Tenofovir alafenamide: AUC: ↔ Cmax: ↓ 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: ↔ Cmax: ↔ Sofosbuvir metabolite GS-331007: AUC: ↔ Cmin: ↔ Velpatasvir: AUC: ↔ Cmin: ↔ Cmax: ↔ Voxilaprevir: AUC: ↔ Cmin: ↔ Cmax: ↔ Emtricitabine: AUC: ↔ Cmin: ↔ Cmax: ↔ Tenofovir alafenamide: AUC: ↑ 52 % Cmax: ↑ 32 %	No dose adjustment of sofosbuvir, velpatasvir or voxilaprevir is required. Dose TAFICITA according to the concomitant antiretroviral (see section 4.2).
ANTIRETROVIRALS		
HIV protease inhibitors		

Atazanavir/cobicistat (300 mg/150 mg once daily), tenofovir alafenamide (10 mg)	Tenofovir alafenamide: AUC: ↑ 75 % Cmax: ↑ 80 % Atazanavir: AUC: ↔ Cmax: ↔ Cmin: ↔	The recommended dose of TAFICITA is 200/10 mg once daily.
Atazanavir/ritonavir (300/100 mg once daily), tenofovir alafenamide (10 mg)	Tenofovir alafenamide: AUC: ↑ 91 % Cmax: ↑ 77 % Atazanavir: AUC: ↔ Cmax: ↔ Cmin: ↔	The recommended dose of TAFICITA is 200/10 mg once daily.
Darunavir/cobicistat (800/150 mg once daily), tenofovir alafenamide (25 mg once daily)[5]	Tenofovir alafenamide: AUC: ↔ Cmax: ↔ Tenofovir: AUC: ↑ 224 % Cmax: ↑ 216 % Cmin: ↑ 221 % Darunavir: AUC: ↔ Cmax: ↔ Cmin: ↔	The recommended dose of TAFICITA is 200/10 mg once daily.
Darunavir/ritonavir (800/100 mg once daily), tenofovir alafenamide (10 mg once daily)	Tenofovir alafenamide: AUC: ↔ Cmax: ↔ Tenofovir: AUC: ↑ 105 % Cmax: ↑ 142 % Darunavir: AUC: ↔ Cmax: ↔ Cmin: ↔	The recommended dose of TAFICITA is 200/10 mg once daily.
Lopinavir/ritonavir (800/200 mg once daily), tenofovir alafenamide (10 mg once daily)	Tenofovir alafenamide: AUC: ↑ 47 % Cmax: ↑ 119 % Lopinavir: AUC: ↔ Cmax: ↔ Cmin: ↔	The recommended dose of TAFICITA is 200/10 mg once daily.
Tipranavir/ritonavir	Interaction not studied with either of the components of TAFICITA. Tipranavir/ritonavir results in P-gp induction. Tenofovir alafenamide exposure is expected to decrease when tipranavir/ritonavir is used in combination with TAFICITA.	Co-administration with TAFICITA 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: ↔ Cmax: ↔ Dolutegravir: AUC: ↔ Cmax: ↔ Cmin: ↔	The recommended dose of TAFICITA is 200/25 mg once daily.
Rilpivirine (25 mg once daily), tenofovir alafenamide (25 mg once daily)	Tenofovir alafenamide: AUC: ↔ Cmax: ↔ Rilpivirine: AUC: ↔ Cmax: ↔ Cmin: ↔	The recommended dose of TAFICITA is 200/25 mg once daily.
Efavirenz (600 mg once daily), tenofovir alafenamide (40 mg once daily)[4]	Tenofovir alafenamide: AUC: ↓ 14 % Cmax: ↓ 22 %	The recommended dose of TAFICITA is 200/25 mg once daily.
Maraviroc Nevirapine Raltegravir	Interaction not studied with either of the components of TAFICITA. 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 TAFICITA is 200/25 mg once daily.
ANTICONVULSANTS		
Oxcarbazepine Phenobarbitone Phenytoin	Interaction not studied with either of the components of TAFICITA. 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 TAFICITA and oxcarbazepine, Phenobarbitone or phenytoin is not recommended.

Carbamazepine (titrated from 100 mg to 300 mg twice a day), emtricitabine/tenofovir alafenamide (200 mg/25 mg once daily) [5,6]	Tenofovir alafenamide: AUC: ↓ 55 % Cmax: ↓ 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 TAFICITA and carbamazepine is not recommended.
ANTIDEPRESSANTS		
Sertraline (50 mg once daily), tenofovir alafenamide (10 mg once daily)[3]	Tenofovir alafenamide: AUC: ↔ Cmax: ↔ Sertraline: AUC: ↑ 9 % Cmax: ↑ 14 %	No dose adjustment of sertraline is required. Dose TAFICITA according to the concomitant antiretroviral (see section 4.2).
HERBAL PRODUCTS		
St. John's wort (*Hypericum perforatum*)	Interaction not studied with either of the components of TAFICITA. 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 TAFICITA with St. John's wort is not recommended.
IMMUNOSUPPRESSANTS		
Ciclosporin	Interaction not studied with either of the components of TAFICITA. Co-administration of ciclosporin, a potent P-gp inhibitor, is expected to increase plasma concentrations of tenofovir alafenamide.	The recommended dose of TAFICITA 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: ↔ Cmin: ↔ Cmax: ↔ Norgestrel: AUC: ↔ Cmin: ↔ Cmax: ↔ Ethinylestradiol: AUC: ↔ Cmin: ↔ Cmax: ↔	No dose adjustment of norgestimate/ethinylestradiol is required. Dose TAFICITA according to the concomitant antiretroviral (see section 4.2).
SEDATIVES/HYPNOTICS		

Orally administered midazolam (2.5 mg single dose) tenofovir alafenamide (25 mg once daily) Intravenously administered midazolam (1 mg single dose) tenofovir alafenamide (25 mg once daily)	Midazolam: AUC: ↔ Cmax: ↔ Midazolam: AUC: ↔ Cmax: ↔	No dose adjustment of midazolam is required. Dose TAFICITA according to the concomitant antiretroviral (see section 4.2).

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 TAFICITA.

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

Women of childbearing potential / contraception in males and females

The use of TAFICITA should be accompanied by the use of effective contraception.

Pregnancy

The use of TAFICITA is not recommended in pregnancy unless no other appropriate medicine that is known to be safe in pregnancy is available, not tolerated or has failed.

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.

There are no or limited data (less than 300 pregnancy outcomes) from the use of tenofovir alafenamide in pregnant women.

Studies of tenofovir alafenamide in animals have shown no evidence of harmful effects on fertility parameters, pregnancy, or foetal development (see section 5.3).

Nucleos(t)ide analogues, as in TAFICITA, may impact on mitochondrial function to a variable degree. There have been reports of mitochondrial dysfunction in HIV negative infants exposed in utero and/or postnatally to nucleoside analogues The main adverse reactions reported are haematological disorders (anaemia, neutropenia), peripheral neuropathy and metabolic disorders (hyperlactataemia, hyperlipasaemia). These events have often been transitory. Late onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is unknown. These findings should be considered and investigated for any baby/ infant/child exposed in utero to nucleos(t)ide analogues, who present with severe clinical findings of unknown etiology, particularly neurologic findings.

Breast-feeding

TAFICITA should not be used by women breast-feeding their babies as possible harm to their babies cannot be excluded.

Emtricitabine is excreted in human milk. In animal studies it has been shown that tenofovir is excreted in milk.

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

Fertility

There are no data on fertility from the use of TAFICITA 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

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

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 3,112 HIV-1 infected patients received medicines containing emtricitabine and tenofovir alafenamide and from post-marketing experience. In clinical studies of 866 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 (≥ 1/10) common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100)

Table 3: Tabulated list of adverse reactions reported in Clinical Trials

Frequency	Adverse reaction
Blood and lymphatic system disorders	
Uncommon:	Anaemia[2]
Psychiatric disorders	
Common:	abnormal dreams
Nervous system disorders	
Common:	headache, dizziness
Gastrointestinal disorders	
Very common:	nausea
Common:	diarrhoea, vomiting, abdominal pain, flatulence
Uncommon:	dyspepsia
Skin and subcutaneous tissue disorders	
Common:	Rash
Musculoskeletal and connective tissue disorders	
Uncommon:	arthralgia
General disorders and administration site conditions	
Common:	fatigue

1. 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.

Table 4: Tabulated list of Post marketing reported side effects

Adverse reaction
Blood and lymphatic system disorders
Anaemia[1]
Skin and subcutaneous tissue disorders
Angioedema,[2,3] urticaria[3]

1.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.

2 This adverse reaction was identified through post-marketing surveillance for emtricitabine- containing products.

3 This adverse reaction was identified through post-marketing surveillance for tenofovir alafenamide-containing products.

Description of selected adverse reactions

Changes in lipid laboratory tests

In studies in treatment-naïve patients, increases from baseline were

observed 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 (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.

In a study of virologically suppressed patients switching from emtricitabine/tenofovir disoproxil fumarate to TAFICITA while maintaining the third antiretroviral agent, increases from baseline were observed in the fasting lipid parameters total cholesterol, direct LDL cholesterol and triglycerides in the TAFICITA arm. None of the changes was considered clinically relevant.

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during TAFICITA therapy.

Paediatric population

The safety of emtricitabine and tenofovir alafenamide was evaluated through 48 weeks in an open-label clinical study 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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of TAFICITA is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse

reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity.

If overdose occurs the patient must be monitored for evidence of toxicity (see section 4.8). Treatment of overdose with TAFICITA consists of general symptomatic and 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 3hour 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

Pharmacological classification: A.20.2.8 Antiviral Agents

Pharmacotherapeutic group: Antiviral for systemic use; antivirals for treatment of HIV infections, combinations. ATC code: J05AR17.

<u>Mechanism of action</u>

Emtricitabine is a nucleoside reverse transcriptase inhibitor (NRTI) and nucleoside analogue of 2'-deoxycytidine. Emtricitabine is phosphorylated by cellular enzymes to form emtricitabine triphosphate.

Emtricitabine triphosphate inhibits HIV replication through incorporation into viral deoxyribonucleic acid (DNA) by the HIV reverse transcriptase (RT), which results in DNA chain-termination. Emtricitabine has activity against HIV-1, HIV-2, and HBV.

Tenofovir alafenamide is a nucleotide reverse transcriptase inhibitor (NtRTI) and phosphonamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). Tenofovir alafenamide is permeable into cells and due to increased plasma stability and intracellular activation through hydrolysis by cathepsin A, tenofovir alafenamide is more efficient than tenofovir disoproxil fumarate in concentrating tenofovir in peripheral blood mononuclear cells (PBMCs) or HIV target cells including lymphocytes and macrophages. Intracellular tenofovir is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV replication through incorporation into viral DNA by the HIV RT, which results in DNA chain-termination.

Tenofovir has activity against HIV-1, HIV-2 and HBV.

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 (EC50) values for emtricitabine were in the range of 0,0013 to 0,64 µm. Emtricitabine displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC50 values ranged from 0,007 to 0,075 µm) and showed strain specific activity against HIV-2 (EC50 values ranged from 0,007 to 1,5 µm).

The antiviral activity of tenofovir alafenamide against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells and CD4+-T lymphocytes. The EC50 values for tenofovir alafenamide were in the range of 2,0 to 14,7 nm. Tenofovir alafenamide displayed antiviral activity in cell culture against all HIV-1 groups (M, N, and O), including subtypes A, B, C, D, E, F, and G (EC50 values ranged from 0,10 to 12,0 nm) and showed strain specific activity against HIV-2 (EC50 values ranged from 0,91 to 2,63 nm).

Resistance

In vitro

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

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

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 TAFICITA.

Clinical efficacy of TAFICITA 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.

5.2 Pharmacokinetic properties

Absorption

Emtricitabine is rapidly and extensively absorbed following oral administration

with peak plasma concentrations occurring at 1 to 2 hours post-dose. Following multiple dose oral administration of emtricitabine to 20 HIV-1 infected subjects, the (mean ± SD) steady state plasma emtricitabine peak concentrations (Cmax) were 1,8 ± 0,7 µg/ml and the area-under the plasma concentration-time curve over a 24-hour dosing interval (AUC) was 10,0 ± 3,1 µg•h/ml. The mean steady state plasma trough concentration at 24 hours post-dose was equal to or greater than the mean in vitro 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 1hour post-dose for tenofovir alafenamide administered as F/TAF (25 mg) or E/C/F/TAF (10 mg). The mean Cmax and AUClast, (mean ± SD) under fed conditions following a single 25 mg dose of tenofovir alafenamide administered in TAFICITA were 0,21 ± 0,13 µg/ml and 0,25 ± 0,11 µg•h/ml, respectively. The mean Cmax and AUClast following a single 10 mg dose of tenofovir alafenamide administered in E/C/F/TAF were 0,21 ± 0,10 µg/ml and 0,25 ± 0,08 µg•h/ml, respectively.

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

Distribution

In vitro binding of emtricitabine to human plasma proteins was < 4 % and independent of concentration over the range of 0.02-200 µg/ml. At peak plasma concentration, the mean plasma to blood drug concentration ratio was ~1,0 and the mean semen to plasma drug concentration ratio was ~4,0.

In vitro binding of tenofovir to human plasma proteins is < 0,7 % and is independent of concentration over the range of 0,01-25 µg/ml. Ex vivo binding of tenofovir alafenamide to human plasma proteins in samples collected during

clinical studies was approximately 80 %.

Biotransformation

In vitro studies indicate that emtricitabine is not an inhibitor of human CYP enzymes. Following administration of [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 were similar to exposures achieved in treatment-naïve adults (Table 5).

Table 5: 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]**
AUCtau (ng•h/ml)	14,424,4	242,8 (57,8)	275,8	11,714,1 (16,6)	206,4 (71,8)	292,6 (27.4)
Cmax (ng/ml)	2,265,0	121,7 (46.2)	14,6 (20,0	2,056,3 (20,2)	162,2 (51,1)	15,2 (26,1)
Ctau (ng/ml)	102.4 (38,9)	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 µg•h/ml) than in subjects with normal renal function (11,8 µg•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) 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.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core Microcrystalline cellulose Croscarmellose sodium Magnesium stearate

Film-coating

TAFICITA 200mg/25 mg Polyvinyl alcohol Titanium dioxide Macrogol 3350
Talc
FD&C Blue # 2

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

36 months

6.4 Special precautions for storage

Store at or below 30 °C

Store in the original package in order to protect from moisture. Keep the bottle tightly closed.

6.5 Nature and contents of container

Blue High-density polyethylene (HDPE) bottle with a blue opaque polypropylene screw closure with wad containing aluminium induction sealing line containing 30 film-coated tablets. Each bottle contains silica gel desiccant.

6.6 Special precautions for disposal

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd
4 Brewery Street
Isando
Gauteng
1609

8 REGISTRATION NUMBERS

To be allocated.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be confirmed.

10 DATE OF REVISION OF THE TEXT

N/A