PROFESSIONAL INFORMATION

TAVIRANT

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TAVIRANT (200/25/25 mg, film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg emtricitabine, rilpivirine hydrochloride equivalent to 25 mg rilpivirine and tenofovir alafenamide fumarate equivalent to 25 mg tenofovir alafenamide.

Contains sugar: 411,055 mg anhydrous lactose and 129,450 mg lactose monohydrate per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Pink coloured, capsule shaped biconvex film-coated tablets plain on both sides.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

TAVIRANT is indicated in combination with other antiretroviral medicines for the treatment of adults infected with human immunodeficiency virus type 1 (HIV-1) (see sections 4.2 and 5.1).

4.2. Posology and method of administration

Posology

Adults, weighing at least 35 kg.

The recommended dose is one TAVIRANT tablet once a day with food.

Special Populations

Elderly patients

No dose adjustment of TAVIRANT is required in elderly patients.

Paediatric population

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

Renal impairment

No dose adjustment of TAVIRANT 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. TAVIRANT 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 TAVIRANT is required in adults with end stage renal disease (estimated CrCl < 15 mL/min) on chronic haemodialysis; however, TAVIRANT should generally be avoided but may be used in these patients (see sections 4.4 and 5.2). On days of haemodialysis, TAVIRANT should be administered after completion of haemodialysis treatment. TAVIRANT should be avoided in patients with estimated CrCl ≥ 15 mL/min and < 30 mL/min as the safety of TAVIRANT has not been established in this population. TAVIRANT 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 dosage adjustment of TAVIRANT is required in patients with mild to moderate hepatic impairment (Child-Pugh score A or B). TAVIRANT has not been studied in patients with severe hepatic impairment (Child-Pugh Class C); therefore, TAVIRANT is not recommended for use in patients with severe hepatic impairment as no dose recommendations can be made (see sections 4.4).

Method of administration

TAVIRANT should be taken orally with food. 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.
- TAVIRANT should not be co-administered with medicines that can result in significant decreases in rilpivirine plasma concentrations (due to cytochrome P450 [CYP]3A enzyme induction or gastric pH increase), which may result in loss of therapeutic effect of TAVIRANT (see section 4.5), including:
- Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampicin, rifapentine.
- Omeprazole, esomeprazole, dexlansoprazole, lansoprazole, pantoprazole, rabeprazole.
- Dexamethasone (oral and parenteral doses), except as a single dose treatment.
- St. John's wort (Hypericum perforatum).

4.4 Special warnings and precautions for use

- Patients should be advised that current antiretroviral therapy does not cure HIV and has not been proven to prevent the transmission of HIV to others through blood, other bodily secretion or sexual contact. Appropriate precautions to prevent transmission of HIV should continue to be employed.
- Virologic Failure and Development of Resistance:

  There is insufficient data to justify the use in patients with prior NNRTI failure. Resistance testing and/or historical resistance data should guide the use of TAVIRANT (see section 5.1).
- Interaction with other medicines:

  Caution should be given to prescribing TAVIRANT with other medicines that may reduce the exposure of rilpivirine (see section 4.5).

  There is limited information available on the potential for a pharmacodynamic interaction between rilpivirine and medicines that prolong the QTc interval of the electrocardiogram. In a study of healthy subjects, supratherapeutic doses of rilpivirine (75 mg daily and 300 mg daily) have been shown to prolong the QTc interval of the electrocardiogram (see section 5.1 and 4.5). TAVIRANT should be used with caution when co-administered with medicines with a known risk of Torsade de Pointes.
- Co-administration of other medicines:

  The co-administration of TAVIRANT 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 other than atazanavir, lopinavir and darunavir (see section 4.5). TAVIRANT should not be administered

concomitantly with medicines containing tenofovir alafenamide, tenofovir disoproxil, emtricitabine, lamivudine or adefovir dipivoxil.

- Fat distribution:

  Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo lump), peripheral wasting, facial wasting, breast enlargement, cushingoid appearance and elevated serum lipid and glucose levels have been observed in HIV patients and those receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

- Immune reconstitution 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 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 TAVIRANT 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 TAVIRANT 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 TAVIRANT 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 TAVIRANT can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of TAVIRANT 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 newborn/infant/child exposed *in utero* to nucleos(t)ide analogues, including HIV negative infants/children who present with severe clinical findings of unknown aetiology, 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 TAVIRANT, and tenofovir disoproxil fumarate, another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with TAVIRANT 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 to 5 mmol/L with minimum symptoms: switch to medicines that are less likely to cause lactic acidosis.

- Lactate 5 to 10 mmol/L with symptoms and/or with reduced standard Bicarbonate: stop NRTIs and change treatment option. Once 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 > 10 mmol/L: STOP all therapy (80 % mortality).

The above values may not be applicable to paediatric patients.

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

- Patients with HIV-1 harbouring mutations:

TAVIRANT 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 TAVIRANT is administered with a third nucleoside analogue.

- Opportunistic infections:

  Patients receiving TAVIRANT 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.

- Patients with end stage renal disease on chronic haemodialysis:

TAVIRANT 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).

Anhydrous lactose and lactose monohydrate

TAVIRANT contains anhydrous lactose and lactose monohydrate.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Interaction studies have only been performed in adults.

Emtricitabine and Tenofovir alafenamide

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 TAVIRANT and development of resistance. Co-administration of TAVIRANT 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, CYP286, 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 OATP183 *in vitro*. The distribution of tenofovir alafenamide in the body may be affected by the activity of OATP181 and OATP183.

Other interactions

Tenofovir alafenamide is not an inhibitor of human uridine diphosphate glucuronosyltransferase (UGT) 1A1 *in vitro*. It is not known whether tenofovir alafenamide is an inhibitor of other UGT enzymes.

Emtricitabine did not inhibit the glucuronidation reaction of a non-specific UGT substrate *in vitro*.

Interactions between the components of emtricitabine and tenofovir alafenamide and potential co-administered medicines are listed in Table 1 (increase is indicated as ↑, decrease as ↓ and no change as ↔). The interactions described are based on studies conducted with emtricitabine and tenofovir alafenamide components of TAVIRANT as individual medicines and/or in combination or are potential drug-drug interactions that may occur with TAVIRANT.

Table 1: Interactions between the individual components of TAVIRANT namely emtricitabine, tenofovir alafenamide and other medicines

Medicine by therapeutic areas	Effects on medicine levels. Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with emtricitabine and tenofovir alafenamide
ANTI-INFECTIVES		
Antifungals		
Ketoconazole Itraconazole	Interaction not studied with either of the components of emtricitabine and tenofovir alafenamide.	The recommended dose of components of emtricitabine and tenofovir alafenamide is 200/10 mg once daily.

	Co-administration of ketoconazole or itraconazole, which are potent P-gp inhibitors, is expected to increase plasma concentrations of tenofovir alafenamide.	
Fluconazole Isavuconazole	Interaction not studied with either of the components of emtricitabine and tenofovir alafenamide. Co-administration of fluconazole or isavuconazole may increase plasma concentrations of tenofovir alafenamide.	Dose TAVIRANT according to concomitant antiretroviral (see section 4.2).
Antimycobacterials		
Rifabutin Rifampicin	Interaction not studied with	Co-administration of emtricitabine, tenofovir

Rifapentine	emtricitabine or tenofovir alafenamide components. 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.	alafenamide and rifabutin rifampicin, or rifapentine is not recommended.
Anti-hepatitis C virus medicines		
Ledipasvir (90 mg once daily)/ sofosbuvir (400 mg once dally), emtricitabine (200 mg once daily)/ tenofovir alafenamide (10 mg once daily)	Ledipasvir: AUC: ↑ 79 % C_{max} ↑ 65 % C_{min} ↑ 93 % Sofosbuvir: AUC: ↑ 47% Cmax ↑ 29 %	No dose adjustment of ledipasvir or sofosbuvir is required. Dose of TAVIRANT according to the concomitant antiretroviral (see section 4.2).

	Sofosbuvir metabolite GS-331007: AUC: ↑ 48 % C_{max} ↔ C_{min} ↑ 66 % Emtricitabine: AUC: ↔ C_{max} ↔ C_{min} ↔ Tenofovir alafenamide: AUC: ↔ C_{max} ↔	
Ledipasvir (90 mg once daily), sofosbuvir (400 mg once daily), emtricitabine (200 mg once dally)/ tenofovir alafenamide (25 mg once daily)	Ledipasvir: AUC: ↔ C_{max} ↔ C_{min} ↔ Sofosbuvir: AUC: ↔ C_{max} ↔ Sofosbuvir metabolite G5-331 007: AUC: ↔ C_{max} ↔ C_{min} ↔	No dose adjustment of ledipasvir or sofosbuvir is required. Dose TAVIRANT according to the concomitant antiretroviral (see section 4.2).

	Emtricitabine: AUC: ↔ C_{max} ↔ C_{min} ↔ Tenofovir alafenamide: AUC: ↑ 32 % C_{max} ↔	
Sofosbuvir (400 mg once daily)/ velpatasvir (100 mg once daily), emtricitabine (200 mg once dally)/ tenofovir alafenamide (10 mg once daily)	Sofosbuvir: AUC: ↑ 37% Cmax ↔ 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} ↔	No dose adjustment of sofosbuvir, velpatasvir or voxilaprevir is required. Dose TAVIRANT according to the concomitant antiretroviral (see section 4.2).

	Tenofovir alafenamide: AUC: ↔ C_{max} ↓ 21%	
Sofosbuvir/velpatasvir/ voxilaprevir (400 mg/100 mg/100 mg + 100 mg once daily)/ emtricitabine (200 mg once daily)/ tenofovir alafenamide (10 mg once daily)	Sofosbuvir: AUC: ↔ C_{max} ↑ 27 % C_{min} ↔ Sofosbuvir metabolite GS-331007: AUC: ↑ 43 % C_{max} ↔ Velpatasvir: AUC: ↔ C_{max} ↑ 46 % C_{min} ↔ Voxilaprevir: AUC: ↑ 171 % C_{max} ↑ 350 % C_{min} ↑ 92 % Emtricitabine: AUC: ↔ C_{max} ↔ C_{min} ↔	

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

	AUC: ↑ 52 % C_{max} ↑ 32 %	
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 components containing emtricitabine and tenofovir alafenamide is 200/10 mg once daily.
Atazanavir/ritonavir (300 mg/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 components containing emtricitabine and tenofovir alafenamide is 200/10 mg once daily.
Atazanavir/cobicistat (800 mg/150 mg once daily), tenofovir alafenamide (25 mg)	Tenofovir alafenamide: AUC: ↔ C_{max} ↔ Tenofovir:	The recommended dose of components containing emtricitabine and tenofovir alafenamide is 200/10 mg once daily.

	AUC: ↑ 224 % C_{max} ↑ 216 % C_{min} ↑ 221 % Darunavir: AUC: ↔ Cmax ↔ Cmin ↔	
Darunavir/ritonavir (800 mg/100 mg once daily), tenofovir alafenamide (10 mg once daily)	Tenofovir alafenamide: AUC: ↔ C_{max} ↔ Tenofovir: AUC: ↑ 105 % C_{max} ↑ 142 % Darunavir: AUC: ↔ Cmax ↔ Cmin ↔	The recommended dose of components containing emtricitabine and tenofovir alafenamide is 200/10 mg once daily.
Lopinavir/ritonavir (800 mg/200 mg once daily), tenofovir alafenamide (10 mg once daily)	Tenofovir alafenamide: AUC: ↑ 47 % C_{max} ↑ 119 % Lopinavir: AUC: ↔ Cmax ↔	The recommended dose of components containing emtricitabine and tenofovir alafenamide is 200/10 mg once daily.

	Cmin ↔	
Tipranavir/ritonavir	Interaction not studied with either of the components containing emtricitabine and 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 and tenofovir alafenamide.	Co-administration with TAVIRANT containing emtricitabine and tenofovir alafenamide is not recommended.
Other protease inhibitors	Effect is unknown.	There are no data available to make dosing recommendations for co-administration with other protease inhibitors.
Other HIV antiretrovirals		

Dolutegravir (50 mg once daily), tenofovir alafenamide (10 mg once daily)	Tenofovir alafenamide: AUC: ↔ C_{max} ↔ Dolutegravir: AUC: ↔ Cmax ↔ Cmin ↔	The recommended dose of components containing emtricitabine and tenofovir alafenamide is 200/25 mg once daily.
Rilpivirine (25 mg once daily), tenofovir alafenamide (25 mg once daily)	Tenofovir alafenamide: AUC: ↔ C_{max} ↔ Rilpivirine: AUC: ↔ Cmax ↔ Cmin ↔	The recommended dose of components containing emtricitabine and tenofovir alafenamide is 200/25 mg once daily.
Efavirenz (600 mg once daily), tenofovir alafenamide (40 mg once daily)	Tenofovir alafenamide: AUC: ↓ 14 % C_{max}: ↓ 22 %	The recommended dose of components containing emtricitabine and tenofovir alafenamide is 200/25 mg once daily.
Maraviroc Nevirapine Raltegravir	Interaction not studied with either of the components of emtricitabine or	The recommended dose of components containing emtricitabine and tenofovir

	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.	alafenamide is 200/25 mg once daily.
ANTICONVULSANTS		
Oxcarbazepine Phenobarbitone Phenytoin	Interaction not studied with either of the components of emtricitabine or tenofovir alafenamide. Co-administration of oxcarbazepine,	Co-administration of TAVIRANT containing emtricitabine and tenofovir alafenamide with oxcarbazepine, phenobarbitone or phenytoin is not recommended.

	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.	
Carbamazepine (titrated from 1 00 mg to 300 mg twice a day), emtricitabine/ tenofovir alafenamide (200 mg/25 mg once daily)	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	Co-administration of TAVIRANT containing emtricitabine and tenofovir alafenamide with carbamazepine is not recommended.

	development of resistance.	
ANTIDEPRESSANTS		
Sertraline (50 mg once daily), tenofovir alafenamide (10 mg once daily)	Tenofovir alafenamide: AUC: ↔ C_{max}: ↔ Sertraline: AUC: ↑ 9 % C_{max}: ↑ 14 %	No dose adjustment of sertraline is required. Dose TAVIRANT containing emtricitabine and tenofovir alafenamide 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 TAVIRANT containing emtricitabine and tenofovir alafenamide. Co-administration of St. John's wort, a P-gp inducer, may decrease tenofovir alafenamide plasma concentrations,	Co-administration of TAVIRANT containing emtricitabine and tenofovir alafenamide with St. John's wort is not recommended.

	which may result in loss of therapeutic effect and development of resistance.	
IMMUNOSUPPRESSANTS		
Ciclosporin	Interaction not studied with either of the components of emtricitabine and tenofovir alafenamide. Co-administration of ciclosporin, a potent P-gp inhibitor. is expected to increase plasma concentrations of tenofovir alafenamide.	The recommended dose of TAVIRANT containing emtricitabine and tenofovir alafenamide is 200/10 mg once daily.
ORAL CONTRACEPTIVES		
Norgestimate (0,180/ 0,215/ 0,250 mg once daily) Ethinylestradiol	Norelgestromin: AUC: ↔ Cmax ↔ Cmin ↔	No dose adjustment of norgestimate/ethinylestradiol is required. Dose TAVIRANT containing emtricitabine and

(0,025 mg once daily), emtricitabine/ tenofovir alafenamide (200/25 mg once daily)	Norgestrel: AUC: ↔ Cmax ↔ Cmin ↔ Ethinylestradiol: AUC: ↔ Cmax ↔ Cmin ↔	tenofovir alafenamide 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)	Midazolam: AUC: ↔ Cmax ↔	No dose adjustment of midazolam is required. Dose TAVIRANT containing emtricitabine and tenofovir alafenamide according to the concomitant antiretroviral (see section 4.2).
Intravenously administered midazolam (1 mg single dose) tenofovir alafenamide (25 mg once daily)	Midazolam: AUC: ↔ Cmax ↔	

Rilpivirine

Medicines that affect rilpivirine exposure

Rilpivirine is primarily metabolised by cytochrome P450 (CYP3A), and medicines that induce or inhibit CYP3A may thus affect the clearance of rilpivirine. Co-

administration of rilpivirine and medicines that induce CYP3A may result in decreased plasma concentrations of rilpivirine (exposure) which could potentially reduce the therapeutic effect of rilpivirine. Co-administration of rilpivirine and medicines that inhibit CYP3A may result in increased plasma concentrations of rilpivirine. Co-administration of rilpivirine with medicines that increase gastric pH such as PPIs, may result in decreased plasma concentrations of rilpivirine which could potentially reduce the therapeutic effect of TAVIRANT.

Medicines that are affected by the use of rilpivirine

Rilpivirine at a dose of 25 mg (once daily) is not likely to have a clinically relevant effect on the exposure of medicines metabolised by CYP enzymes. Established and theoretical interactions with selected antiretrovirals and non-antiretroviral medicines are listed in Table 1 and Table 2, respectively.

Interaction table

Interactions between rilpivirine and co-administered medicines are listed in Table 2 and Table 3 below (increase is indicated as ↑, decrease as ↓, no change as ↔, not applicable as NA.

Table 2: Medicine interactions - Rilpivirine co-administered with antiretroviral and antiviral medicines

Co-administered medicine	Dose of co-administered medicine	Medicine assessed	C_{max}	AUC	C_{min}
NUCLEOSIDE OR NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs/N(t)RTIs)					
Didanosine*#	400 mg daily	Didanosine	↔	↑ 12 %	NA
		Rilpivirine	↔	↔	↔

	No dose-adjustment is required when TAVIRANT is co-administered with didanosine. As didanosine is administered on an empty stomach, didanosine should be administered at least one hour before or two hours after rilpivirine (which should be administered with a meal).

Tenofovir disoproxil fumarate*#	300 mg daily	Tenofovir	↑ 19 %	↑ 23 %	↑ 24 %
		Rilpivirine	↔	↔	↔
	No dose-adjustment is required when rilpivirine is co-administered with tenofovir disoproxil fumarate.				
Other NRTIs (abacavir, emtricitabine, lamivudine, stavudine and zidovudine)	Based on the different elimination routes for rilpivirine and these other NRTIs, no clinically relevant interactions are expected between these medicines and rilpivirine.				

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)					
NNRTIs (delavirdine, efavirenz, etravirine, nevirapine)	It is not recommended to co administer rilpivirine with NNRTIs.				
PROTEASE INHIBITORS (PIs) with co-administration of low-dose ritonavir					
Darunavir/ritonavir*#	800/ 100 mg daily	Darunavir	↔	↔	↓ 11 %
		Rilpivirine	↑ 79 %	↑ 130 %	↑ 178 %
	Concomitant use of rilpivirine with darunavir/ritonavir may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). No dose adjustment is				

	required when rilpivirine is co administered with darunavir/ ritonavir.

Lopinavir/ritonavir (soft gel capsules) *#	400/100 mg twice daily	Lopinavir	↔	↔	↓ 11 %
		Rilpivirine	↑ 29 %	↑ 52 %	↑ 74 %
	Concomitant use of rilpivirine with lopinavir/ ritonavir may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). No dose adjustment is required when rilpivirine is co-administered with lopinavir/ ritonavir.				
Other boosted PIs (atazanavir/ ritonavir, fosamprenavir/ ritonavir, saquinavir/ ritonavir, tipranavir/ ritonavir	Concomitant use of rilpivirine with boosted PIs may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.				

PROTEASE INHIBITORS (PIs) – without co-administration of low dose ritonavir	
Unboosted PIs (atazanavir, Fosamprenavir, indinavir, nelfinavir)	Concomitant use of rilpivirine with unboosted PIs may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). Rilpivirine is not expected to affect the plasma concentrations of co-administered PIs.
CCR5 ANTAGONISTS	
Maraviroc	No clinically relevant interaction is expected when rilpivirine is co-administered with maraviroc.
INTEGRASE STRAND TRANSFER INHIBITORS	

Raltegravir	No clinically relevant interaction is expected when rilpivirine is co-administered with raltegravir.
OTHER ANTIVIRAL MEDICINES	
Ribavirin	No clinically relevant interaction is expected when TAVIRANT is co-administered with ribavirin.
	*The Interaction between rilpivirine and the medicine was evaluated in a clinical study. All other medicine interactions shown may have been predicted. #This interaction study was performed with a dose higher than the recommended dose for rilpivirine assessing the maximal effect on the co-administered medicine. The dosing recommendation is applicable to the recommended dose of 25 mg rilpivirine daily.

Table 3: Medicine interactions - Rilpivirine co-administered with non-antiretroviral medicines

Co-administered medicine	Dose of co-administered medicine	Medicine assessed	C_{max}	AUC	C_{min}
ANTICONVULSANTS					
Carbamazepine, Oxcarbazepine, Phenobarbital Phenytoin	Rilpivirine should not be used in combination with these anticonvulsants as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of TAVIRANT, see section 4.3.				

AZOLE ANTIFUNGAL MEDICINES

Ketoconazole *#	400 mg daily	Ketoconazole Rilpivirine	↔ ↑ 30 %	↓ 24 % ↑ 49 %	↓ 66 % ↑ 76 %
Fluconazole, Itraconazole, Posaconazole, Voriconazole	Concomitant use of rilpivirine with azole antifungal medicines may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). No dose adjustment is required when rilpivirine is co-administered with azole antifungal medicines.				

ANTIMYCOBACTERIALS					
Rifabutin *#	300 mg daily	Rifabutin 25-*O*-desacetyl-rifabutin Rilpivirine	↔ ↔ ↓ 35 %	↔ ↔ ↓ 46 %	↔ ↔ ↓ 49 %
	Rilpivirine should not be used in combination with rifabutin as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of TAVIRANT.				

Rifampicin*#	600 mg daily	Rifampicin 25-desacetyl-rifampicin Rilpivirine	↔ ↔ ↓ 69 %	↔ ↓ 9 % ↓ 80 %	NA NA ↓ 89 %
Rifapentine	Rilpivirine should not be used in combination with rifampicin as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of TAVIRANT (see section 4.3).				

MACROLIDE ANTIBIOTICS	
Clarithromycin, Erythromycin, Troleandomycin	Concomitant use of rilpivirine with clarithromycin, erythromycin and troleandomycin may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). Where possible, alternatives such as azithromycin should be considered.
GLUCOCORTICOIDS	
Dexamethasone (systemic)	Rilpivirine should not be used in combination with systemic dexamethasone as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of rilpivirine. Alternatives should be considered, particularly for long-term use (see section 4.3).

PROTON PUMP INHIBITORS					
Omeprazole *#	20 mg daily	Omeprazole Rilpivirine	↓ 14 % ↓ 40 %	↓ 14 % ↓ 40 %	NA ↓ 33 %
Lansoprazole, Rabeprazole Pantoprazole Esomeprazole	Rilpivirine should not be used in combination with proton pump inhibitors as co-administration may cause significant decreases in rilpivirine plasma concentrations (gastric pH increase). This may result in loss of therapeutic effect of TAVIRANT (see section 4.3).				

H_2-RECEPTOR ANTAGONISTS					
Famotidine *#	40 mg single dose taken 12	Rilpivirine	↔	↓ 9 %	NA

	hours before rilpivirine				
	40 mg single dose taken 2 hours before rilpivirine	Rilpivirine	↓ 85 %	↓ 76 %	NA
	40 mg single dose taken 4 hours after rilpivirine	Rilpivirine	↑ 21 %	↑ 13 %	NA

Cimetidine, Nizatidine Ranitidine	The combination of rilpivirine and H_2-receptor antagonists should be used with caution as co-administration may cause significant decreases in rilpivirine plasma concentrations (gastric pH increase). H_2-receptor antagonists should only be administered atleast12 hours before or at least four hours after TAVIRANT.
ANTACIDS	
Antacids (e.g., aluminium or magnesium hydroxide, calcium carbonate)	The combination of rilpivirine and antacids should be used with caution as co-administration may cause significant decreases in rilpivirine plasma concentrations (gastric pH increase). Antacids should only be administered either at least two hours before or at least four hours after TAVIRANT.

NARCOTIC ANALGESICS					
Methadone *	60 -100 mg daily, individualised dose	R (-) methadone S (+) methadone	↓ 14 % ↓ 13 %	↓ 16 % ↓ 16 %	↓ 22 % ↓ 21 %
	No dose adjustments are required when initiating co-administration of methadone with rilpivirine. However, clinical				

	monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.
HERBAL PRODUCTS	
St John's Wort (Hypericum perforatum)	Rilpivirine should not be used in combination with products containing St John's wort as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of TAVIRANT (see section 4.3).

ANALGESICS					
Acetaminophen *# (paracetamol)	500 mg single dose	Acetaminophen Rilpivirine	↔ ↔	↔ ↔	NA ↑ 26 %
	No dose-adjustments are required when rilpivirine is co-administered with acetaminophen (paracetamol).				
OESTROGEN-BASED CONTRACEPTIVES					
Ethinyloestradiol* Norethindrone•	0,035 mg daily 1 mg daily	Ethinyloestradiol Norethindrone	↑ 17 % ↔	↔ ↔	↔ ↔
	No dose adjustment is required for the concomitant use of rilpivirine and oestrogen and/or progesterone-based contraceptives.				

HMG CO-A REDUCTASE INHIBITORS					
Atorvastatin *#	40 mg daily	Atorvastatin Rilpivirine	↑ 35 % ↓ 9 %	↔ ↔	↓ 15 % ↔

Ruvastatin Lovastatin Pitavastatin Pravastatin Rosuvastatin Simvastatin	No dose-adjustment is required when rilpivirine is co-administered with an HMG co-A reductase inhibitor.

PHOSPHODIESTERASE TYPE 5 (PDE-5) INHIBITOR					
Sildenafil *#	50 mg single dose	Sildenafil Rilpivirine	↔ ↔	↔ ↔	NA ↔
Vardenafil Tadalafil	No dose-adjustment is required when rilpivirine is co-administered with a PDE-5 inhibitor.				

*The interaction between rilpivirine and the medicine was evaluated in a clinical study. All other interactions shown are predicted.

This interaction study has been performed with a dose higher that the recommended dose for rilpivirine assessing the maximal effect on the co-administered medicine. The dosing recommendation is applicable to the recommended dose of rilpivirine 25 mg daily.

4.6. Fertility, pregnancy and lactation

Women of childbearing potential/ contraception in males and females

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

Pregnancy

Safe use during pregnancy and lactation has not been established.

The use of TAVIRANT containing emtricitabine and tenofovir alafenamide is not recommended in pregnancy.

Data on pregnant women (more than 1,000 exposed outcomes) indicate no malformities 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. Nucleos(t)ide analogues, as in TAVIRANT, 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 aetiology, particularly neurologic findings.

Breastfeeding

Mothers should not breastfeed their infants when taking TAVIRANT.
Emtricitabine is excreted in human milk. In animal studies it has been shown that tenofovir is excreted in milk. It is not known whether rilpivirine is secreted in human milk.

Fertility

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

4.7. Effects on ability to drive and use machines

TAVIRANT may influence the ability to drive and use machines. Patients should not drive and use machines until they know how treatment with TAVIRANT affects them. Dizziness and somnolence may occur.

4.8. Undesirable effects

a) Summary of the safety profile

Emtricitabine and tenofovir alafenamide

The most frequently reported adverse reactions in clinical studies of treatment-naïve patients taking emtricitabine +tenofovir alafenamide in combination with elvitegravir + cobicistat were nausea (11 %), diarrhoea (7 %), and headache (6 %). The most frequently reported adverse reactions in clinical studies of treatment-naïve patients taking rilpivirine hydrochloride in combination with emtricitabine + tenofovir disoproxil fumarate were nausea (9 %), dizziness (8 %), abnormal dreams (8 %), headache (6 %), diarrhoea (5 %) and insomnia (5 %).

b) Tabulated (or structured listing) summary of adverse reactions for emtricitabine and tenofovir alafenamide

Tabulated summary of adverse reactions

The adverse reactions in Table 4 are listed by system organ class and highest frequency observed. Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) or not known (cannot be estimated from the available data).

Emtricitabine and tenofovir alafenamide

Table 4: Tabulated list of adverse reactions

Frequency	Adverse reaction
Blood and lymphatic system disorders	
Uncommon:	Anaemia.
Psychiatric disorders	
Common:	Abnormal dreams.
Nervous system disorders	
Very common:	Headache, dizziness.
Gastrointestinal disorders	
Very common:	Nausea, diarrhoea, vomiting, flatulence, upper abdominal pain.
Uncommon:	Dyspepsia.
Skin and subcutaneous tissue disorders	
Common:	Rash.
Musculoskeletal and connective tissue disorders	
Uncommon:	Arthralgia.
General disorders and administration site conditions	
Common:	Fatigue.

Rilpivirine

Table 4: Tabulated list of adverse reactions

Frequency	Adverse reaction

Blood and lymphatic system disorders	
Common:	Increased AST, increased pancreatic amylase.
Uncommon:	Decreased haemoglobin, decreased platelet count, decreased white blood cell count, increased ALT, increased bilirubin, increased lipase, increased total cholesterol (fasted), increased LDL cholesterol (fasted), increased triglycerides (fasted).
Not known:	Increased creatinine.
Metabolism and nutrition disorders	
Uncommon:	Decreased appetite.
Psychiatric Disorders	
Common:	Depression, insomnia.
Uncommon:	Abnormal dreams, sleep disorders, depressed mood.
Nervous system disorders	
Common:	Headache.
Uncommon:	Dizziness, somnolence.
Gastrointestinal disorders	
Uncommon:	Abdominal pain, nausea, vomiting, abdominal discomfort.
Skin and subcutaneous tissue disorders	
Common:	Rash.
General disorders and *administration site conditions*	
Uncommon:	Fatigue.
Investigations	
Common:	Transaminases increased.

c) Description of selected adverse reactions

Emtricitabine and tenofovir alafenamide

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 emtricitabine/tenofovir alafenamide fumarate while maintaining the third antiretroviral agent, increases from baseline were observed in the fasting lipid parameters total cholesterol, direct LDL-cholesterol and triglycerides.

Metabolic parameters

Weight and levels of blood lipids and glucose may increase.

Rilpivirine

There may be changes from baseline in total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides. The impact of such findings has not been demonstrated.

Lipodystrophy

Combination antiretroviral therapy (cART) has been associated with redistribution of body fat (lipodystrophy) in HIV-infected patients, including loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump) (see section 4.4).

Immune reconstitution syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (cART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (immune reconstitution syndrome) (see section 4.4).

d) Other special populations

Emtricitabine and tenofovir alafenamide

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-naive 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.

Rilpivirine

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

In patients co-infected with hepatitis B or C virus receiving rilpivirine, the incidence of hepatic enzyme elevation was higher than in patients receiving rilpivirine who were not co-infected. The pharmacokinetic exposure of rilpivirine in co-infected patients was comparable to that in patients without co-infection.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care 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 or to Cipla Medpro (Pty) Ltd by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9. Overdose

In overdose, side effects can be precipitated and/or be of increased severity. There is no specific treatment for an overdose of TAVIRANT. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary such as monitoring of vital signs and ECG (QT interval) as well as observation of the clinical status of the patient. Rilpivirine is highly bound to plasma proteins, it is unlikely that it will significantly be removed by dialysis. If indicated, elimination of unabsorbed rilpivirine may be achieved by gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed rilpivirine.

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

Pharmacological classification: A 20.2.8 Antiviral agents.

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

Mechanism of Action

Emtricitabine and tenofovir alafenamide

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 (NRTI) and phosphonamidite 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 (EC_{50} values ranged from 0,007 to 0,075 µm) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0,007 to 1,5 µm). The antiviral activity of tenofovir alafenamide against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells and CD4+-T lymphocytes. The 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).

Rilpivirine

Rilpivirine is a diarylpyrimidine NNRTI of HIV. Rilpivirine activity is mediated by non-competitive inhibition of HIV-1 reverse transcriptase (RT). Rilpivirine does not inhibit the human cellular DNA polymerases α, β and γ.

Antiviral activity in vitro

Rilpivirine exhibited activity against laboratory strains of wild type HIV-1 in an acutely infected T-cell line with a median EC_{50} value for HIV-M1/IIIB of 0,73 nM (0,27 ng/mL). Although rilpivirine demonstrated limited *in vitro* activity against HIV-2 with EC_{50} values ranging from 2 510 to 5 220 nM (920 to 1 910 ng/mL), treatment of HIV-2 infection with rilpivirine is not recommended in the absence of clinical data.

Rilpivirine also demonstrated antiviral activity against a broad panel of HIV-1 group M (subtype A, B,C, D, F, G, H) primary isolates with EC_{50} values ranging from 0,07 to 1,01 nM

(0,03 to 0,37 ng/mL) and group O primary isolates with EC_{50} values ranging from 2,88 to 8,45 nM (1,06 to 3,10 ng/mL).

Rilpivirine showed additive antiviral activity in combination with the N (t)RTIs abacavir, didanosine, emtricitabine, stavudine and tenofovir; the PIs amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and tipranavir; the NNRTIs efavirenz, etravirine and nevirapine; the fusion inhibitor enfuvirtide. Rilpivirine also shows additive to synergistic antiviral activity in combination with the NRTIs lamivudine and zidovudine, and the integrase inhibitor raltegravir.

Mechanism of resistance

Emtricitabine and tenofovir alafenamide

Resistance in vitro

Reduced susceptibility to emtricitabine is associated with M1B4VII 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-naive patients

In a pooled analysis of antiretroviral-naive patients receiving emtricitabine and tenofovir alafenamide (1 0 mg) given with elvitegravir and cobicistat as a fixed-dose combination tablet in Phase 3 studies GS-US-292-0104 and GS-US-292-0111, genotyping was performed on plasma HIV-1 isolates from all patients with HIV-1 RNA≥ 400 copies/mL at confirmed virological failure, at week 144, or at the time of early study drug discontinuation. Through week 144, the development of one or more primary emtricitabine, tenofovir alafenamide, or elvitegravir resistance-associated mutations was observed in HIV-1 isolates from 12 of 22 patients with evaluable genotypic data from paired baseline and E/C/F/TAF treatment-failure isolates (12 of 866 patients [1,4 %]) compared with 12 of 20 treatment-failure isolates

from patients with evaluable genotypic data in the E/C/FITDF 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/N (n = 2), E920 (n = 4), 01480/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 184V/I (n = 9), K65R/N (n = 4), and L210W (n = 1) in RT and E920N (n = 4) and 0148R (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 (EIC/FIT AF), 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-naive or virologically suppressed patient

Emtricitabine-resistant viruses with the M184VII 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 Q151 M mutation complex including K65R showed reduced susceptibility to tenofovir alafenamide.

Rilpivirine

In cell culture

Rilpivirine resistant strains were selected in cell culture starting from wild type HIV-1 of different origins and subtypes as well as NNRTI resistant HIV-1. The most commonly observed amino acid substitutions that emerged included: L100I, K101E, V108I, E138K, V179F, Y181C, H221Y, F227C and M230I.

A biological cut off (BCO) for rilpivirine was determined at the fold change In EC_{50} value (FC) of 3, 7 on the basis of the analysis of the susceptibility of a large panel of HIV-1 wild type recombinant clinical isolates.

In treatment-naive subjects

In the pooled resistance analysis from the phase III trials, 62 (of a total of 72) virologic failures in the rilpivirine arm had resistance data at baseline and time of failure. The amino acid substitutions associated with NNRTI resistance that developed most commonly in these subjects were: V90I, K101E, E138K, E138Q, Y181C, V189I and H221Y. However, in the trials, the presence of the substitutions V90I and V189I, at baseline, did not affect response. Considering all of the available *in vitro* and *in vivo* data, the following amino acid substitutions when present at baseline, are likely to affect the activity of rilpivirine: K101E, K101P, E138G, E138K, E138R, E138Q, Y181C, Y181I, Y181V and H221Y.

Cross resistance

Site-directed NNRTI mutant virus

In a panel of 67 HIV-1 recombinant laboratory strains with one amino acid substitution at RT positions associated with NNRTI resistance, including the most commonly found K103N and Y181C, rilpivirine showed antiviral activity against 64 (96 %) of these strains. The single amino acid substitutions associated with a loss of susceptibility to rilpivirine were: K101P,

Y181I andY181V.

Recombinant clinical isolates

Rilpivirine retained sensitivity (FC ≤ BCO) against 62 % of 4 786 HIV-1 recombinant clinical isolates resistant to efavirenz and/or nevirapine.

Treatment-naïve HIV-1 infected patients

In the pooled analysis of the phase Ill trials ECHO and THRIVE, 31 of the 62 subjects with virologic failure on rilpivirine with phenotypic resistance data lost susceptibility to rilpivirine. Of these, 28 were resistant to etravirine, 27 to efavirenz, and 14 to nevirapine.

Effects on QTc Interval

The effect of rilpivirine at the recommended dose of 25 mg daily on the QTcF interval was evaluated in a randomised, placebo and active (moxifloxacin 400 mg once daily) controlled crossover study in 60 healthy adults, with 13 measurements over 24 hours at steady-state. Rilpivirine, at the recommended dose of 25 mg daily, is not associated with a clinically relevant effect on QTc interval.

When supratherapeutic doses of 75 mg daily and 300 mg daily of rilpivirine were studied in healthy adults there was a dose related QTcF prolongation. The maximum mean time-matched (95 %upper confidence bound) differences in QTcF interval from placebo after baseline correction were 10,7 (15,3) and 23,3 (28,4) ms, respectively. Steady-state administration of rilpivirine 75 mg daily and 300 mg daily resulted in a mean Cmax approximately 2,6-fold and 6,7 -fold, respectively, higher than the mean steady-state Cmax observed with the recommended 25 mg daily dose of rilpivirine.

5.2. Pharmacokinetic properties

Rilpivirine

The pharmacokinetic properties of rilpivirine have been evaluated in healthy adult subjects and in adult antiretroviral treatment-naive HIV-1 infected patients. Exposure to rilpivirine was generally lower in HIV-1 infected patients than in healthy subjects.

Absorption

Emtricitabine and tenofovir alafenamide

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 ± SO) steady state plasma emtricitabine peak concentrations (C_{max}) were 1,8 ± 0, 7 µl/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 AUC_{last}, (mean ± SD) under fed conditions following a single 25 mg dose of tenofovir alafenamide administered, a component of TAVIRANT were 0,21 ± 0,13 µL/mL and 0,25 ± 0,11 µL/mL, respectively. The mean C_{max} and AUC_{last} following a single 10 mg dose of tenofovir alafenamide administered in E/C/F/TAF were 0,21 ± 0,10 µg/mL and 0,25 ± 0,08 µg•h/mL, respectively.

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

Rilpivirine

After oral administration, the maximum plasma concentration of rilpivirine is generally achieved within four to five hours. The absolute bioavailability of rilpivirine is unknown.

Effect of food on absorption

The exposure to rilpivirine was approximately 40 % lower when rilpivirine was taken in a fasted condition as compared to a normal caloric meal (533 kcal) or high fat high caloric meal (928 kcal). When rilpivirine was taken with only a protein rich nutritional drink, exposures were 50 % lower than when taken with a meal.

Distribution

Emtricitabine and tenofovir alafenamide

In vitro binding of emtricitabine to human plasma proteins was < 4% and independent of concentration over the range of 0,02 to 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 to 25 µg/mL. *Ex* vivo binding of tenofovir alafenamide to human plasma proteins in samples collected during clinical studies was approximately 80 %.

Rilpivirine

Rilpivirine is approximately 99,7 % bound to plasma proteins *in vitro* primarily to albumin. The distribution of rilpivirine into compartments other than plasma (e.g., cerebrospinal fluid, genital tract secretions) has not been evaluated in humans.

Metabolism

Emtricitabine and tenofovir alafenamide

Biotransformation

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

Metabolism is a major elimination pathway for tenofovir alafenamide in humans, accounting for > 80% of an oral dose. In vitro studies have shown that tenofovir alafenamide is metabolised to tenofovir (major metabolite) by cathepsin A in PBMCs (including lymphocytes and other HIV target cells) and macrophages; and by carboxylesterase-1 in hepatocytes. I*n vivo*, tenofovir alafenamide is hydrolysed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite tenofovir diphosphate. In human clinical studies, a 10 mg oral dose of tenofovir alafenamide (given with emtricitabine and elvitegravir and cobicistat) resulted in tenofovir diphosphate concentrations > 4-fold higher in PBMCs and > 90 % lower concentrations of tenofovir in plasma as compared to a 245 mg oral dose of tenofovir disoproxil (as fumarate) (given with emtricitabine and elvitegravir and cobicistat).

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

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

Rilpivirine

In vitro experiments indicate that rilpivirine primarily undergoes oxidative metabolism mediated by the cytochrome P450 (CYP3A) system.

Elimination

Emtricitabine and tenofovir alafenamide

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.

Rilpivirine

The terminal elimination hail-life of rilpivirine is approximately 45 hours. After single-dose oral administration of ^{14}C rilpivirine, on average 85 % and 6,1 % of the radioactivity could be retrieved in faeces and urine, respectively. In faeces, unchanged rilpivirine accounted for on average 25 % of the administered dose. Only trace amounts of unchanged rilpivirine (< 1 % of dose) were detected in urine.

Special Populations

Emtricitabine and tenofovir alafenamide

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

Emtricitabine and tenofovir alafenamide

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]
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 (511)	15,2 (26,1)
Ctau (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-292-01 06 population PK analysis)

c n = 539 (TAF) or 841 (TFV) adults (GS-US-292-0111 and GS-US-292·01 04, population PK analysis)

Rilpivirine

Dosing recommendations for paediatric patients cannot be made due to insufficient data.

Elderly

Rilpivirine

Population pharmacokinetic analysis in HIV infected patients showed that rilpivirine pharmacokinetics is not different across the age range (18 to 78 years) evaluated. No dose adjustment is required in elderly patients.

Renal Impairment

Emtricitabine and tenofovir alafenamide

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 atone 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.

Rilpivirine

The pharmacokinetics of rilpivirine has not been studied in patients with renal insufficiency. Renal elimination of rilpivirine is negligible. Therefore, the impact of renal impairment on rilpivirine elimination is expected to be minimal. As rilpivirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis.

Hepatic Impairment

Emtricitabine and tenofovir alafenamide

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.

Rilpivirine

Rilpivirine is primarily metabolised and eliminated by the liver. In a study comparing eight patients with mild hepatic impairment (Child-Pugh score A) to eight matched controls, and eight patients with moderate hepatic impairment (Child-Pugh score B) to eight matched controls, the multiple dose exposure of rilpivirine was 47 % higher in patients with mild hepatic impairment and 5 % higher in patients with moderate hepatic impairment. No dose adjustment is required in patients with mild or moderate hepatic impairment. Rilpivirine has not been studied in patients with severe hepatic impairment (Child-Pugh score C).

Hepatitis B and/or hepatitis C virus co-infection

Emtricitabine and tenofovir alafenamide

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

- Anhydrous lactose
- Crospovidone

- Ferric oxide red
- Lactose monohydrate
- Magnesium Stearate
- Povidone
- Polysorbate
- Sodium starch glycolate

Film-coating

Opadry AMB pink 80W54485

- Iron oxide red
- Iron oxide yellow
- Lecithin (Soya)
- Polyvinyl alcohol – part hydrolyzed
- Talc
- Titanium dioxide
- Xanthan gum.

6.2. Incompatibilities

Not applicable.

6.3. Shelf Life

24 months.

6.4. Special precautions for storage

Store at or below 30 °C.

6.5. Nature and contents of container

TAVIRANT is packed in a 60 cc white round HDPE bottle consisting of a silica gel bag 3 gm Stripax (Multisorb) R/F. The bottle consists of a 33 mm white child resistant cap. The HDPE bottles may be packed with or without a printed cardboard carton. Pack sizes are 28 and 30 tablets.

6.6. Special precautions for disposal and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

56/20.2.8/0020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 September 2023

10. DATE OF REVISION OF THE TEXT

Not applicable.

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