1.3.1.1 PROPOSED CLEAN PROFESSIONAL INFORMATION

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).

TERESTIME IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF TERESTIME 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 TERESTIME.

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).

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TERESTIME (film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Tenofovir disoproxil fumarate 300 mg (which is equivalent to 245 mg of tenofovir disoproxil)

Emtricitabine 200 mg

Rilpivirine hydrochloride 27,5 mg (equivalent to 25 mg rilpivirine)

Contains sugar: 243,025 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

A purple film-coated, capsule shaped, biconvex, bevelled edge tablet debossed with M on one side of the tablet and TER on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TERESTIME, is indicated for the use as a complete regimen for the treatment of HIV-1 infection in adult patients weighing at least 35 kg as initial therapy in those with no antiretroviral treatment history and with HIV-1 RNA less than or equal to 100 000 copies/mL at the start of therapy, or to replace a stable antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen for at least 6 months with no treatment failure and no known substitutions associated with resistance to the individual components of TERESTIME.

4.2 Posology and method of administration

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

Testing prior to or when initiating TERESTIME, test for hepatitis B virus infection. Prior to initiation and during treatment with TERESTIME, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus.

Recommended dosage in adult patients weighing at least 35 kg: One tablet taken orally once daily with food (see section 5.2).

If a patient misses a dose of TERESTIME within 12 hours of the time it is usually taken, the patient should take TERESTIME with food as soon as possible and resume the normal dosing schedule. If a patient misses a dose of TERESTIME by more than 12 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.

If a patient vomits within 4 hours of taking TERESTIME another TERESTIME tablet should be taken with food. If a patient vomits more than 4 hours after taking TERESTIME they do not need to take another dose of TERESTIME until the next regularly scheduled dose.

Special Population

Elderly:

TERESTIME has not been studied in patients over the age of 65 years. TERESTIME should be administered with caution to elderly patients.

Paediatric use:

The safety and effectiveness of TERESTIME in children under the age of 18 years have not been established.

TERESTIME should only be administered to adult patients with a body weight greater than or equal to 35 kg. Because TERESTIME is a fixed-dose combination tablet, the dose of TERESTIME cannot be adjusted for patients of a lower weight.

Dosage for HIV-1 infected adult patients with creatinine clearance ≥ 50 (mL/min)

	Creatinine Clearance (mL/min)[1]
Recommended dosing interval	≥ 50 Every 24 hours

[1.] Calculated using ideal (lean) body weight

Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in all individuals (see section 4.3 and 4.4 - *Renal impairment*)

Renal impairment:

Because TERESTIME is a fixed-dose combination, and cannot be dose adjusted, it is not for use in patients with moderate, severe, or end-stage renal impairment (estimated creatinine clearance below 50 mL per minute) or that require dialysis (see section 4.3).

Hepatic impairment:

No dose-adjustment of TERESTIME is required in patients with mild or moderate hepatic impairment (Child-Pugh score A or B). TERESTIME has not been studied in patients with severe hepatic impairment (Child-Pugh score C). Therefore, TERESTIME is not recommended in patients with severe hepatic impairment (see section 4.3).

If TERESTIME is discontinued in patients co-infected with HIV and hepatitis B virus (HBV), these patients should be closely monitored for evidence of exacerbation of hepatitis (see section 4.4).

Method of administration

TERESTIME must be taken orally, once daily with food. It is recommended that TERESTIME be swallowed whole with water. The film-coated tablet should not be chewed, crushed or split as it may impact the absorption of TERESTIME.

4.3 Contraindications

TERESTIME is contraindicated in patients with previously demonstrated hypersensitivity to tenofovir, emtricitabine or rilpivirine.

It is not recommended that TERESTIME be co-administered with other Non-Nucleoside Reverse Transcriptase inhibitors (NNRTIs) e.g. delavirdine, efavirenz, etravirine, nevirapine (see section 4.5).

TERESTIME should not be used in combination with carbamazepine, oxcarbazepine, phenobarbitone, phenytoin and dexamethasone (except as a single-dose treatment) as co-administration may cause significant decreases in rilpivirine plasma concentrations due to the induction of CYP3A enzymes. This may result in loss of therapeutic effect of TERESTIME.

Rifabutin, rifampicin and rifapentine are potent inducers of CYP3A enzymes. TERESTIME should not be used in combination with these medicines as co-administration may cause significant decreases in rilpivirine plasma concentrations. This may result in loss of therapeutic effect of TERESTIME.

TERESTIME should not be used concomitantly with products containing St. John's Wort because co-administration may cause significant decreases in rilpivirine plasma concentrations. This may result in loss of therapeutic effect of TERESTIME.

The proton-pump inhibitors (PPIs) lansoprazole, omeprazole, rabeprazole, pantoprazole and esomeprazole should not be administered concurrently with TERESTIME as this may result in significant decreases in rilpivirine plasma concentration due to gastric pH increase. This may result in loss of therapeutic effect of TERESTIME.

- TERESTIME should not be co-administered with other tenofovir-containing medicines, or with other emtricitabine, or rilpivirine-containing medicines.
- TERESTIME should not be administered with lamivudine-containing medicines due to similarities between emtricitabine and lamivudine.
- TERESTIME should not be administered to patients with moderate, severe, or end-stage renal impairment (estimated creatinine clearance below 50 mL per minute) or that require dialysis.
- TERESTIME is not for patients with severe hepatic impairment. (Child-Pugh score C).
- Pregnancy and lactation (see section 4.6).

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 the transmission of HIV should continue to be employed.

- There are no study results demonstrating the effect of TERESTIME on clinical progression of HIV-1.
- It is not recommended that TERESTIME be used as a component of a triple nucleoside regimen.
- Individuals should be warned that full compliance with treatment is essential to the efficacy in preventing HIV-1 transmission and should be fully informed about the use of other preventative measures including barrier contraception (condoms).

Lactic acidosis/severe hepatomegaly with steatosis:

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues such as TERESTIME alone or in combination with other antiretrovirals. This is caused by mitochondrial dysfunction. The majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogues such as TERESTIME to any patient with known risk factors for liver disease. However, cases have also been reported in patients with no known risk factors. Treatment with TERESTIME should be suspended in any patient 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 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 < 2 mmol/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 TERESTIME and change treatment option. Once lactate has settled, use medicines that are less likely to cause lactic acidosis. Exclude other causes (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis and hyperthyroidism).
- Lactate > 10 mmol/L: Stop all therapy (80 % mortality).

The above lactate values may not be applicable to paediatric patients. Caution should be exercised when administering TERESTIME to patients with known risk factors for liver disease. Treatment with TERESTIME should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Pancreatitis:

Pancreatitis has been observed in some patients receiving TERESTIME. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers (serum lipase). Discontinue use of TERESTIME until diagnosis of pancreatitis is excluded.

Liver disease:

Use of TERESTIME can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis).

The safety and efficacy of TERESTIME has not been established in patients with significant underlying liver disorders/diseases. 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.

Mitochondrial dysfunction:

Nucleoside and nucleotide analogues such as TERESTIME have been demonstrated *in vitro* and *in vivo* to cause variable degrees of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or post-natally to nucleoside analogues. Apart from lactic acidosis / hyperlactatemia (see above), other manifestations of mitochondrial dysfunction include haematological disorders (anaemia, neutropenia) and peripheral neuropathy. Some late-onset neurological disorders have been reported (hypertonia, convulsions, abnormal behaviour). It is not known whether the neurological disorders are transient or permanent. Any foetus exposed *in utero* to nucleoside and nucleotide analogues, including HIV-negative infants/children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs and symptoms.

Patients with HIV and Hepatitis B or C Virus co-infection:

Patients with chronic hepatitis B or C and treated with antiretroviral therapy such as TERESTIME, are at an increased risk for severe and potentially fatal hepatic adverse reactions. Patients co-infected with HBV to discontinue TERESTIME should be closely monitored, with both clinical and laboratory follow-up, after stopping treatment. Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV). TERESTIME is not indicated for the treatment of chronic HBV infection. The safety and efficacy of TERESTIME have not been established in patients co-infected with HBV and HIV.

In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant professional information for these medicines. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended, since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Discontinuation of TERESTIME therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis which may lead to liver decompensation and liver failure.

All patients with HIV should be tested for the presence of chronic hepatitis B virus (HBV) before initiating TERESTIME therapy. Hepatic function should be closely monitored with both clinical and laboratory follow-up for at least several months, in patients who are co-infected with HIV and HBV and who discontinue TERESTIME. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Renal impairment:

TERESTIME is principally eliminated by the kidney.

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphataemia), has been reported in association with the use of tenofovir disoproxil fumarate (see section 4.3). It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with TERESTIME. Routine monitoring or calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment (see section 4.3).

TERESTIME should be avoided with concurrent or recent use of a nephrotoxic medicine.

TERESTIME should not be administered to patients with creatinine clearance below 50 mL/min or to patients requiring haemodialysis or for pre-exposure prophylaxis in patients with creatinine clearance below 60 mL/min (see section 4.3).

If a decrease in creatinine clearance develops in uninfected individuals, TERESTIME should be discontinued (see section 4.3).

Depressive Disorders

The adverse reaction depressive disorders (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) has been reported with RPV. Patients with severe depressive symptoms should seek immediate medical evaluation to assess the possibility that the symptoms are related to TERESTIME.

Co-administration of other medicines:

TERESTIME is a fixed-dose combination of emtricitabine, tenofovir disoproxil fumarate and rilpivirine. TERESTIME should not be co-administered with other medicines containing emtricitabine, tenofovir or rilpivirine (see section 4.3).

Due to similarities between emtricitabine and lamivudine, TERESTIME should not be co-administered with other medicines containing lamivudine, including lamivudine and zidovudine co-formulation, lamivudine for HIV, lamivudine for HBV, abacavir sulfate and lamivudine co-formulation or abacavir sulfate, lamivudine and zidovudine co-formulation (see section 4.3).

Co-administration of didanosine buffered tablet formulation with TERESTIME should be under fasting conditions (see section 4.5).

Co-administration of TERESTIME and didanosine should be undertaken with caution, and patients receiving this combination should be monitored closely for didanosine-associated adverse events.

Didanosine should be discontinued in patients who develop didanosine-associated adverse events (see section 4.8).

Patients receiving atazanavir and lopinavir/ritonavir and TERESTIME should be monitored for TERESTIME -associated adverse events.
TERESTIME should be discontinued in patients who develop TERESTIME -associated adverse events (see section 4.8).

Tenofovir decreases the AUC and C_{min} of atazanavir (see section 4.5). When co-administered with TERESTIME, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Atazanavir without ritonavir should not be co-administered with TERESTIME.

Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of TERESTIME with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of emtricitabine, tenofovir, and/or other renally eliminated medicines (see section 4.5). Some examples include, but are not limited to adefovir dipivoxil, cidfovir, acyclovir, valaciclovir, ganciclovir and valganciclovir.

Caution should be given to prescribing TERESTIME 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 sections

4.5 and 5.1). TERESTIME should be used with caution when co-administered with medicines with a known risk of Torsade de Pointes.

Important drug interaction information for TERESTIME is summarised in the table below.

Significant[a] Drug Interactions

Concomitant Drug Class: Drug Name	**Effect on Concentration[b]**	**Clinical Comment**
Antacids: Antacids (e.g., aluminium, magnesium hydroxide, or calcium carbonate)	↔ RPV (antacids taken at least 2 hours before or at least 4 hours after RPV) ↓ RPV (concomitant intake)	Administer antacids at least 2 hours before or at least 4 hours after TERESTIME.
Anticonvulsants: Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	↓ RPV	Co-administration is contraindicated due to potential for loss of virologic response and development of resistance.
Antimycobacterials: Rifampin Rifapentine	↓ RPV	Co-administration is contraindicated due to potential for loss of virologic response and development of resistance.

Rifabutin	↓ RPV[c]	If TERESTIME is co-administered with rifabutin, an additional 25 mg tablet of RPV (Edurant) once per day is recommended to be taken concomitantly with TERESTIME and with a meal for the duration of rifabutin coadministration.
Azole Antifungal Agents: Fluconazole Itraconazole Ketoconazole Posaconazole Voriconazole	↑ RPV[c,d] ↓ ketoconazole[c,d]	No dose adjustment is required when TERESTIME is co-administered with azole antifungal agents. Clinically monitor for breakthrough fungal infections when azole antifungals are co-administered with TERESTIME.
Glucocorticoid (systemic): Dexamethasone (more than a single-dose treatment)	↓ RPV	Co-administration is contraindicated due to potential for loss of virologic response and

		development of resistance.
Hepatitis C Antiviral Agents: Ledipasvir/sofosbuvir Sofosbuvir/velpatasvir Sofosbuvir/velpatasvir/ voxilaprevir	↑ tenofovir[c]	Patients receiving TERESTIME concomitantly with HARVONI® (ledipasvir/ sofosbuvir), EPCLUSA® (sofosbuvir/velpatasvir) or VOSEVI® (sovosbuvir/ velpatasvir/ voxilaprevir) should be monitored for adverse reactions associated with TDF.
H_2-Receptor Antagonists: Cimetidine Famotidine Nizatidine Ranitidine	↔ RPV[c,d] (famotidine taken 12 hours before RPV or 4 hours after RPV) ↓ RPV[c,d] (famotidine taken 2 hours before RPV)	Administer H_2-receptor antagonists at least 12 hours before or at least 4 hours after TERESTIME.
Herbal Products: St John's wort (*Hypericum perforatum*)	↓ RPV	Co-administration is contraindicated due to potential for loss of virologic response and development of resistance.

Macrolides or Ketolide Antibiotics: Clarithromycin Erythromycin Telithromycin	↑ RPV ↔ clarithromycin ↔ erythromycin ↔ telithromycin	Where possible, alternatives such as azithromycin should be considered.
Narcotic Analgesics: Methadone	↓ R(-) methadone[c] ↓ S(+) methadone[c] ↔ RPV[c] ↔ methadone[c] (when used with tenofovir)	No dose adjustments are required when initiating co-administration of methadone with TERESTIME. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.
Proton Pump Inhibitors: e.g., dexlansoprazole esomeprazole lansoprazole omeprazole pantoprazole rabeprazole	↓ RPV	Co-administration is contraindicated due to potential for loss of virologic response and development for resistance.

a. This table is not all inclusive.

b. Increase = ↑; Decrease = ↓; No effect = ↔

c. The interaction was evaluated in a clinical study. All other drug-drug interactions shown are predicted.

d. This interaction study has been performed with a dose higher than the recommended dose of RPV assessing the maximal effect on the co-administered drug. The dosing recommendation is applicable to the recommended dose of RPV 25 mg once daily.

Fat redistribution:

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

Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Immune reconstitution inflammatory syndrome:

Immune reconstitution inflammatory syndrome (IRIS) 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 Anti-Retroviral Therapy (cART). Typically, such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are pulmonary tuberculosis, cytomegalovirus retinitis, *Pneumocystis jirovecii* pneumonia (PJP), cryptococcal meningitis and other forms of tuberculosis and atypical myco-bacterial infections. Appropriate treatment of the opportunistic disease 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 IRIS.

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

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 combination antiretroviral therapy (cART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Bone effects:

Tenofovir combination therapy as in TERESTIME is associated with decreased bone mineral density. During therapy with TERESTIME bone mineral density (BMD) monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or other risk factors for osteopenia, osteoporosis or bone loss. The effect of supplementation with calcium and vitamin D was not studied. If bone abnormalities are suspected, appropriate consultation should be obtained. Bone mineral density monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk for osteopenia.

Reductions of bone mineral density (BMD) have been observed with tenofovir disoproxil in randomised controlled clinical trials of duration up to 144 weeks in HIV or HBV-infected patients. These BMD decreases generally improved after treatment discontinuation.

In other studies (prospective and cross sectional), the most pronounced decreases in BMD were seen in patients treated with tenofovir disoproxil as part of a regimen containing a boosted protease inhibitor. Overall in view of the bone abnormalities associated with tenofovir disoproxil and the limitations of long-term data on the impact of tenofovir disoproxil on bone health and fracture risk, alternative treatment regimens should be considered for patients with osteoporosis or with a history of bone fractures.

Cases of osteomalacia, which can manifest as persistent or worsening bone pain and, which can infrequently contribute to fractures, have been reported in association with tenofovir disoproxil-induced proximal renal tubulopathy (see section 4.8).

Opportunistic infections:

Patients receiving TERESTIME 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.

The risk of HIV transmission to others:

Patients should be advised that current antiretroviral therapy, including TERESTIME, does not prevent the risk of transmission of HIV-1 to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Early virologic failure and development of resistance:

Clinical trials in HIV-1 infected patients have demonstrated that certain regimens that only contain three nucleoside reverse transcriptase inhibitors (NRTIs) are generally less effective than regimens containing two NRTIs in combination with either a non-nucleoside reverse transcriptase inhibitor or a HIV-1 protease inhibitor. Early virological failure and high rates of resistance substitutions have been reported.

Triple nucleoside-only regime should be carefully monitored and considered for treatment modification.

In the pooled analysis from the phase III trials, patients treated with TERESTIME with a baseline viral load > 100 000 HIV-1 RNA copies/mL had a greater risk of virologic failure compared to patients with a baseline viral load ≤ 100 000 HIV-1 RNA copies/mL. Patients with a baseline viral load > 100 000 HIV-1 RNA copies/mL who experienced virologic failure exhibited a higher rate of treatment-emergent resistance to the NNRTI class. Patients who failed virologically on TERESTIME developed lamivudine/ emtricitabine-associated resistance. This information should be taken into consideration when initiating therapy with TERESTIME.

Paediatric use:

Safety and effectiveness of TERESTIME in paediatric patients have not been established.

Geriatric use:

Clinical studies of emtricitabine (200 mg) or tenofovir disoproxil fumarate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patients should

be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other medicinal therapy.

Lactose:

TERESTIME contains lactose monohydrate.

Patients with rare hereditary problems of galactose intolerance, e.g. galactosaemia, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take TERESTIME.

Lactose may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

As TERESTIME contains emtricitabine, rilpivirine hydrochloride and tenofovir fumarate, any interactions that have been identified with these active substances individually may occur with TERESTIME. Interaction studies with these active substances have only been performed in adults.

Rilpivirine is primarily metabolised by cytochrome P450 (CYP3A). Medicinal products that induce or inhibit CYP3A may thus affect the clearance of rilpivirine (see section 5.2).

Concomitant use contraindicated

Co-administration of TERESTIME and medicines that induce CYP3A have been observed to decrease the plasma concentrations of rilpivirine which could potentially lead to loss of therapeutic effect of TERESTIME (see section 4.3).

Co-administration of TERESTIME with proton pump inhibitors has been observed to decrease the plasma concentrations of rilpivirine (due to an increase in gastric pH) which could potentially lead to loss of therapeutic effect of TERESTIME (see section 4.3).

Concomitant use not recommended

TERESTIME should not be administered concomitantly with other medicines containing emtricitabine, tenofovir disoproxil fumarate or tenofovir alafenamide. TERESTIME should not be administered concomitantly with rilpivirine hydrochloride unless needed for dose adjustment with rifabutin (see section 4.2)

Due to similarities with emtricitabine, TERESTIME should not be administered concomitantly with other cytidine analogues, such as lamivudine (see section 4.4). TERESTIME should not be administered concomitantly with adefovir dipivoxil.

Didanosine

The co-administration of TERESTIME and didanosine is not recommended (see section 4.4 and Table 1).

Renally eliminated medicines

Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of TERESTIME with medicines that reduce renal function or compete for active tubular secretion (e.g. cidofovir) may increase serum concentrations of emtricitabine, tenofovir and/or the co-administered medicines.

Use of TERESTIME should be avoided with concurrent or recent use of nephrotoxic medicines. Some examples include, but are not limited to, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2 (also called aldesleukin).

Other NNRTIs

It is not recommended to co-administer TERESTIME with other NNRTIs.

Concomitant use where caution is recommended

Cytochrome P450 enzyme inhibitors

Co-administration of TERESTIME with medicines that inhibit CYP3A enzyme activity have been observed to increase rilpivirine plasma concentrations.

QT prolonging medicines

TERESTIME should be used with caution when co-administered with medicines with a known risk of Torsade de Pointes. 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 once daily and 300 mg once daily) have been shown to prolong the QTc interval of the ECG (see section 5.1).

Other interactions

Interactions between TERESTIME or its individual component(s) and co-administered medicines are listed in Table 1 below

Interactions between rilpivirine and co-administered medicines are listed in Table 1 and Table 2 below

Table 1:

Table 1: Medicine Interactions – Rilpivirine co-administered with antiretroviral and antiviral medicines					
Co-administered medicine	**Dose of co-administered medicines**	**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 rilpivirine 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 or 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 concentration 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 concentration 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 rilpivirine is co-administered with ribavirin.	
* The interaction between rilpivirine and the medicine was evaluated in clinical study. All other medicine interactions shown are predicted. # This interaction study has been performed with a dose higher than the recommended dose of rilpivirine assessing the maximal effect on the co-administered medicine. The dosing recommendation is applicable to the recommended dose of rilpivirine 25 mg daily.		

Table 2:

Table 2: 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 anti-convulsants 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 (see section 4.3).				
AZOLE ANTIFUNGAL MEDICINES					
Ketoconazole*#	400 mg daily	ketoconazole	↔	↓ 24 %	↓ 66 %
		rilpivirine	↑ 30 %	↑ 49 %	↑ 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-descacetyl-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 DYP3A enzymes). This may result in loss of therapeutic effect of rilpivirine.			
Rifampicin*#	600 mg daily	rifampicin	↔	↔	NA
		25-desacetyl-rifmapicin	↔	↓ 9 %	NA

		rilpivirine	↓ 69 %	↓ 80 %	↓ 89 %
Rifapentine	Rilpivirine should not be used in combination with rifampicin or rifapentine 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 (see section).				
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. Alternative should be considered, particularly for long-term use (see section 4.3).				
PROTON PUMP INHIBITORS					
Omeprazole *#	20 mg daily	omeprazole	↓14 %	↓14 %	NA
		rilpivirine	↓40 %	↓40 %	↓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 rilpivirine (see section 4.3).				
H_2-RECEPTOR ANTAGONISTS					
Famotidine *#	40 mg single dose taken 12 hours before rilpivirine	rilpivirine	↔	↓9 %	NA

	40 mg single dose taken two hours before rilpivirine	rilpivirine	↓85 %	↓76 %	NA
	40 mg single dose taken four 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 at least 12 hours before or at least four hours after rilpivirine.				
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 rilpivirine.				
NARCOTIC ANALGESICS					
Methadone*	60 – 100 mg daily, individualised dose	R(-) methadone S(+) methadone	↓4 % ↓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 rilpivirine (see section 4.3).				
ANALGESICS					
Acetaminophen *# (paracetamol)	500 mg single dose	acetaminophen	↔	↔	NA
		rilpivirine	↔	↔	↑26 %

		No dose-adjustment is required when rilpivirine is co-administered with acetaminophen (paracetamol).			
OESTROGEN-BASED CONTRACEPTIVES					
Ethinyloestradiol* Norethinidrone*	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	↑35 %	↔	↓15 %
		rilpivirine	↓9 %	↔	↔
Fluvastatin 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	↔	↔	NA
		rilpivirine	↔	↔	↔
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 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 rilpivirine 25 mg daily.					

Table 3:

Interactions: Changes in pharmacokinetic parameters for co-administered medicine in the presence of emtricitabine[1]

Co-administered medicine	Dose of co-administered medicine (mg)	Emtricitabine Dose (mg)	N	% change of emtricitabine pharmacokinetic parameters[2] (90 % CI)		
				C_{max}	AUC	C_{min}
Tenofovir disoproxil fumarate	300 once daily x 7 days	200 once daily x 7 days	17	↔	↔	↑20 (↑12 - ↑29)
Zidovudine	300 twice daily x 7 days	200 once daily x 7 days	27	↑17 (↑0 - ↑38)	↑13 (↑5 - ↑20)	↔
Indinavir	800 x 1	200 x 1	12	↔	↔	NA
Famciclovir	500 x 1	200 x 1	12	↔	↔	NA
Stavudine	40 x 1	200 x 1	6	↔	↔	NA

1. All interaction studies conducted in healthy volunteers.

2. ↑ = Increase; ↓ = Decrease; ↔ = No effect; NA = Not Applicable

Table 4:

Interactions: Changes in pharmacokinetic parameters for tenofovir[1] in the presence of the co-administered medicine

Co-administered medicine	Dose of co-administered medicine (mg)	N	% change of co-administered medicine pharmacokinetic parameters[2] (90 % CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	↔	↔	NC
Adefovir dipivoxil	10 once	22	↔	↔	NC
Atazanavir[3]	400 once daily x 14 days	33	↑14 (↑8 - ↑20)	↑24 (↑21 - ↑28)	↑22 (↑15 - ↑30)
Didanosine (enteric-coated)	400 once	25	↔	↔	↔

Didanosine (buffered)	250 or 400 once daily x 7 days	14	↔	↔	↔
Efavirenz	600 once daily x 14 days	29	↔	↔	↔
Emtricitabine	200 once daily x 7 days	17	↔	↔	↔
Indinavir	800 three times daily x 7 days	13	↑14 (↓3 - ↑33)	↔	↔
Lamivudine	150 twice daily x 7 days	15	↔	↔	↔
Lopinavir/ Ritonavir	400/100 twice daily x 14 days	24	↔	↑32 (↑25 - ↑38)	↑51 (↑37 - ↑66)
Nelfinavir	1 250 twice daily x 14 days	29	↔	↔	↔
Saquinavir/ Ritonavir	1 000/ 100 twice daily x 14 days	35	↔	↔	↑23 (↑16 - ↑30)

1. Patients received tenofovir disoproxil fumarate 300 mg once daily.

2. Increase = ↑; Decrease = ↓; No Effect = ↔; NC = Not Calculated

3. Reyataz South African Prescribing Information (Bristol-Myers Squibb)

Table 5:

Interactions: Changes in pharmacokinetic parameters for co-administered medicine in the presence of tenofovir

Co-administered medicine	**Dose of co-administered medicine (mg)**	**N**	**% change of co-administered medicine pharmacokinetic parameters[1] (90 % CI)**		
			C_{max}	**AUC**	**C_{min}**
Abacavir	300 once	8	↑ 12 (↓ 1 - ↑ 26)	↔	NA
Adefovir dipivoxil	10 once	22	↔	↔	NA
Atazanavir[2]	400 once daily x 14 days	34	↓ 21 (↓ 27 - ↓ 14)	↓ 25 (↓ 30 - ↓ 19)	↓ 40 (↓ 48 - ↓ 32)

Atazanavir[2]	Atazanavir/ Ritonavir 300/ 100 once daily x 42 days	10	↓ 28 (↓ 50 - ↑ 5)	↓ 25[3] (↓ 42 - ↓ 3)	↓ 23[3] (↓ 46 - ↑ 10)
Efavirenz	600 once daily x 14 days	30	↔	↔	↔
Emtricitabine	200 once daily x 7 days	17	↔	↔	↑ 20 (↑ 12 - ↑ 29)
Indinavir	800 three times daily x 7 days	12	↓ 11 (↓ 30 - ↑ 12)	↔	↔
Lamivudine	150 twice daily x 7 days	15	↓ 24 (↓ 34 - ↓ 12)	↔	↔
Lopinavir Ritonavir	Lopinavir/ Ritonavir 400/ 100 twice daily x 14 days	24	↔	↔	↔
Methadone[4]	40 to 110 once daily x 14 days[5]	13	↔	↔	↔
Nelfinavir M8 metabolite	1 250 twice daily x 14 days	29	↔	↔	↔
Oral Contraceptives[6]	Ethinyl Estradiol 0,035 mg/ Norgestimate 0,25 mg once daily x 7 days	20	↔	↔	↔
Ribavirin	600 once	22	↔	↔	NA
Saquinavir Ritonavir	Saquinavir/ Ritonavir 1 000/100 twice daily x 14 days	32	↑ 22 (↑ 6 - ↑ 14) ↔	↑ 29[7] (↑ 12 - ↑ 48) ↔	↑ 17[7] (↑ 23 - ↑ 76) ↑ 23 (↑ 3 - ↑ 46)

1. Increase = ↑; Decrease = ↓; No Effect = ↔; NA = Not Applicable

2. REYATAZ South African Prescribing Information (Bristol-Myers Squibb).

3. In HIV-infected patients, addition of tenofovir disoproxil fumarate to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2, 3 and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.
4. R-(active), S- and total methadone exposure were equivalent when dosed alone or with tenofovir disoproxil fumarate.
5. Individual subjects were maintained on their stable methadone dose. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported.
6. Ethinyl estradiol 0,035 mg and 17-deacetyl norgestimate 0,25 mg (pharmacologically active metabolite) exposures were equivalent when dosed alone or with tenofovir disoproxil fumarate.
7. Increases in AUC and C_{min} are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir disoproxil fumarate and ritonavir-boosted saquinavir are co-administered.

Following multiple dosing to HIV negative subjects receiving either chronic methadone maintenance therapy or oral contraceptives or single doses of ribavirin, steady state tenofovir pharmacokinetics were similar to those observed in previous studies, indicating lack of clinically significant interactions between these medicines and tenofovir disoproxil fumarate. Co-administration of tenofovir disoproxil fumarate with didanosine results in changes in the pharmacokinetics of didanosine that may be of clinical significance. Table 6 summarises the effects of tenofovir disoproxil fumarate on the pharmacokinetics of didanosine. Concomitant dosing of tenofovir disoproxil fumarate with didanosine buffered tablets or enteric coated capsules significantly increases the C_{max} and AUC of didanosine. When didanosine 250 mg enteric-coated capsules were administered with tenofovir disoproxil fumarate, systemic exposures of didanosine were similar to those seen with the

400 mg enteric-coated capsules alone under fasting conditions. The mechanism of this interaction is unknown.

Table 6:

Interactions: Pharmacokinetic parameters for didanosine in the presence of tenofovir

Didanosine[1] dose (mg) / Method of administration[2]	Tenofovir method of administration[2]	N	% Difference (90 % CI) vs. didanosine 400 mg alone, fasted[3]	
			C_{max}	AUC
Buffered tablets				
400 once daily[4] x 7 days	Fasted 1 hour after didanosine	14	↑28 (↑11 - ↑48)	↑44 (↑31 - ↑59)
Enteric-coated capsules				
400 once, fasted	With food, 2 hr after didanosine	26	↑48 (↑25 - ↑76)	↑48 (↑31 - ↑67)
400 once, with food	Simultaneously with didanosine	26	↑64 (↑41 - ↑89)	↑60 (↑44 - ↑79)
250 once, fasted	With food, 2 hrs after didanosine	28	↓10 (↓22 - ↑3)	↔
250 once, fasted	Simultaneously with didanosine	28	↔	↑14 (0 - ↑31)
250 once, with food	Simultaneously with didanosine	28	↓29 (↓39 - ↓18)	↓11 (↓23 - ↑2)

1. See Special warnings and precautions for use regarding use of didanosine with tenofovir.

2. Administration with food was with a light meal (~ 373 kcal, 20 % fat).

3. Increase = ↑; Decrease = ↓; No Difference = ↔

4. Includes 4 subjects weighing < 60 kg receiving ddI 250 mg.

4.6 Fertility, pregnancy and lactation

TERESTIME should not be used in pregnancy and lactation as safety and efficacy has not been established (see section 4.3). A reliable method of contraception should be used to avoid pregnancy while taking TERESTIME.

Contraception in females

The effect of TERESTIME when co-administered with oral contraceptives demonstrated that TERESTIME is unlikely to decrease the effectiveness of oral contraceptives. TERESTIME and oestrogen and/or progesterone-based contraceptives can be used without dose adjustments.

Pregnancy:

Safe use in pregnancy has not been proven.

TERESTIME should not be used in pregnancy (see section 4.3).

Lactation:

Nursing Mothers: HIV -infected mothers should not breastfeed their infants, to avoid risk of postnatal transmission of HIV. Because of the potential for HIV transmission and serious adverse reactions in nursing infants, mother should be instructed not to breastfeed if they are receiving TERESTIME.

Emtricitabine and tenofovir disoproxil are excreted in human milk.

It is not known whether rilpivirine is excreted in human milk. Rilpivirine is excreted in the milk of rats. Because of both the potential for HIV transmission and the potential for adverse events in nursing infants, mothers should be instructed not to breastfeed if they are receiving TERESTIME.

Fertility:

No human data on the effect of TERESTIME on fertility are available. Animal studies do not indicate harmful effects of emtricitabine, rilpivirine hydrochloride or tenofovir disoproxil on fertility.

4.7 Effects on ability to drive and use machines

Patients should be informed that fatigue, dizziness and somnolence have been reported during treatment with components of TERESTIME. This should be considered when assessing a patient's ability to drive or operate machinery.

4.8 Undesirable effects

Side effects have been reported.

The combination of emtricitabine, rilpivirine and tenofovir disoproxil fumarate have been studied as the component products in treatment-naïve patients. The single-tablet regimen, TERESTIME, has been studied in virologically suppressed patients who switched from a regiment containing a ritonavir-boosted protease inhibitor or from efavirenz/emtricitabine/tenofovir disoproxil fumarate. In treatment naïve patients, the most frequently reported adverse reactions considered possibly or probably related to rilpivirine hydrochloride and emtricitabine/tenofovir disoproxil fumarate were nausea (9 %), dizziness (8 %), abnormal dreams (8 %), headache (6 %), diarrhoea (5 %) and insomnia (5 %). In virologically suppressed patients switching to TERESTIME, the most frequently reported adverse reactions considered possibly or probably related to TERESTIME were fatigue (3 %), diarrhoea (3 %), nausea (2 %) and insomnia (2 %). The safety profile of emtricitabine and tenofovir disoproxil fumarate in these studies were consistent with the previous experience with agents when each was administered with other antiretroviral agents.

In patients receiving tenofovir disoproxil fumarate, rare events of renal impairment, renal failure and proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to

bone abnormalities (infrequently contributing to fractures) have been reported. Monitoring of renal function is recommended for patients receiving TERESTIME (see section 4.4).

Discontinuation of TERESTIME therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis (see section 4.4).

The following frequency classes apply to the Table below:
Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000); very rare (< 1/10 000); Not known (cannot be estimated from the available data).

These frequencies are from clinical trials.

Tabulated summary of adverse reactions

Tabulated summary of adverse reactions to TERESTIME and its individual components	
Frequency	**Adverse reaction**
Blood and lymphatic system disorders	
Common:	Neuropenia[1], decreased white cell count[2], decreased haemoglobin[2], decreased platelet count[2]
Uncommon:	Anaemia[1, 4]
Immune system disorders	
Common:	Allergic reactions[1]
Uncommon:	Immune reactivation syndrome
Metabolism and nutrition disorders	
Very common:	Increased total cholesterol (fasted)[2], increased LDL-cholesterol (fasted)[2], hypophosphataemia [3,5]

Common:	Hypertriglyceridaemia[1,2], hyperglycaemia[1], decreased appetite[2]
Uncommon:	Hypokalaemia[3,5]
Rare:	Lactic acidosis[3]
Psychiatric disorders	
Very common:	Insomnia[1, 2]
Common:	Depression[2], depressed mood[2], sleep disorders[2], abnormal dreams[1,2]
Nervous system disorders	
Very common:	Headache[1,2,3], dizziness[1,2,3]
Common:	Somnolence[2]
Gastrointestinal disorders	
Very common:	Increased pancreatic amylase[2], vomiting[1,2,3], diarrhoea[1,3], nausea[1,2,3]
Common:	Elevated amylase including elevated pancreatic amylase[1], elevated serum lipase[1,2], abdominal pain[1,2,3], abdominal discomfort[2], abdominal distension[3], dyspepsia[1], flatulence[3], dry mouth[2]
Uncommon:	Pancreatitis[3]
Hepatobiliary disorders	
Very common:	Increased transaminases (AST and/or ALT)[1,2,3]
Common:	Increased bilirubin[1,2]
Rare:	Hepatitis[3], hepatic steatosis[3]
Skin and subcutaneous tissue disorders	
Very common:	Rash[1,2,3]

Common:	Vesiculobullous rash[1], pustular rash[1], urticaria[1], skin discolouration (increased pigmentation)[1,4], maculopapular rash[1], pruritus[1]
Uncommon:	Angioedema[1,3]
Musculoskeletal and connective tissue disorders	
Very common:	Elevated creatine kinase[1]
Common	Bone mineral density decreased[3]
Uncommon:	Rhabdomyolysis[3,5], muscular weakness[3,5]
Rare:	Osteomalacia manifested as bone pain and infrequently contributing to fractures)[3,5], myopathy[3,5]
Renal and urinary disorders	
Uncommon:	Proximal renal tubulopathy including Fanconi syndrome[3], increased creatinine[3], proteinuria[3]
Rare:	Renal failure (acute and chronic)[3], acute tubular necrosis[3], nephritis (including acute interstitial nephritis)[3], nephrogenic diabetes insipidus[3]
General disorders and administration site conditions	
Very common:	Asthenia[1,3]
Common:	Pain[1], fatigue[2]

[1] Adverse reaction identified for emtricitabine

[2] Adverse reaction identified for rilpivirine hydrochloride.

[3] Adverse reaction identified for tenofovir disoproxil fumarate.

[4] Anaemia was common and skin discolouration (increased pigmentation) was very common when emtricitabine was administered to paediatric patients (see section 4.8 Paediatric population).

[5] This adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil fumarate in the absence of this condition.

[6] This was a rare adverse reaction for tenofovir disoproxil fumarate. It was also identified as an adverse reaction for emtricitabine through post-marketing surveillance but was not observed in randomised controlled clinical studies in adults or paediatric HIV clinical studies of emtricitabine. The frequency category of uncommon was estimated from statistical calculation based on the total number of patients exposed to emtricitabine in these clinical studies (n = 1 563).

Tabulated summary of adverse reactions reported post-marketing.

Tabulated summary of post-marketing adverse reactions to TERESTIME and its individual components

Adverse reaction:	
Skin and subcutaneous tissue disorders:	Angioedema[6], severe skin reactions with systemic symptoms[7]
Musculoskeletal and connective tissue disorders:	Osteomalacia manifested as bone pain and infrequently contributing to fractures)[8]
Renal and urinary disorders:	Nephritis (including acute interstitial nephritis)[8]

[7] This adverse reaction was identified through post-marketing surveillance for TERESTIME (fixed-dose combination) but not observed in randomised controlled clinical studies for TERESTIME. The frequency could not be determined. See section 4.8 Description of selected adverse reactions.

[8] This adverse reaction was identified through post-marketing surveillance for tenofovir disoproxil fumarate but not observed in randomised controlled clinical studies or the

expanded access program for tenofovir disoproxil fumarate. The frequency could not be determined.

Laboratory abnormalities

Lipids

At 96 weeks in the pooled Phase III C209 and C215 studies of treatment-naïve patients, in the rilpivirine arm the mean change from baseline in total cholesterol (fasted) was 5 mg/dL, in HDL cholesterol (fasted) 4 mg/dL, in LDL cholesterol (fasted) 1 mg/dL, and in triglycerides (fasted) -7 mg/dL. At 48 weeks in Phase III study GS-US-264-0106 of virologically suppressed patients switching to TERESTIME from a regimen containing a ritonavir-boosted protease inhibitor, the mean change from baseline in total cholesterol (fasted) was -24 mg/dL, in HDL cholesterol (fasted) -2 mg/dL, in LDL cholesterol (fasted) -16 mg/dL, and in triglycerides (fasted) -64 mg/dL.

Description of selected adverse reactions

Renal impairment

As TERESTIME may cause renal damage, monitoring of renal function is recommended (see section 4.4 and 4.8 Summary of the safety profile). Proximal renal tubulopathy generally resolved or improved after tenofovir disoproxil fumarate discontinuation. However, in some patients, declines in creatinine clearance did not completely resolve despite tenofovir disoproxil fumarate discontinuation. Patients at risk of renal impairment (such as patients with baseline renal risk factors, advanced HIV disease, or patients receiving concomitant nephrotoxic medications) are at increased risk of experiencing incomplete recovery of renal function despite tenofovir disoproxil fumarate discontinuation (see section 4.4).

Lactic acidosis

Cases of lactic acidosis have been reported with tenofovir disoproxil alone or in combination with other antiretrovirals. Patients with predisposing factors such as patients with decompensated liver disease, or patients receiving concomitant medicines known to induce lactic acidosis are at increased risk of experiencing severe lactic acidosis during tenofovir disoproxil treatment, including fatal outcomes.

Metabolic parameters

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

Interaction with didanosine

Co-administration of TERESTIME and didanosine is not recommended as it results in a 40 – 60 % increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions (see section 4.5). Rarely, pancreatitis and lactic acidosis, sometimes fatal have been reported.

Immune Reactivation Syndrome

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

Osteonecrosis

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

Severe skin reactions

Severe skin reactions with systemic symptoms have been reported during post-marketing experience with TERESTIME, including rashes accompanied by fever, blisters, conjunctivitis, angioedema, elevated liver function tests, and/or eosinophilia (see section 4.4).

Paediatric population

Insufficient safety data are available for children under the age of 18 years. TERESTIME is not recommended in this population (see section 4.2).

Other special population(s)

Elderly

TERESTIME has not been studied in patients over the age of 65 years. Elderly patients are more likely to have decreased renal function; therefore, caution should be exercised when treating elderly patients with TERESTIME (see section 4.4)

Patients with renal impairment

Since tenofovir disoproxil fumarate can cause renal toxicity, close monitoring of renal function is recommended in any patient with renal impairment treated with TERESTIME (see section 4.2, 4.4 and 5.2).

HIV/HBV of HCV co-infected patients

The adverse reaction profile of emtricitabine, rilpivirine hydrochloride and tenofovir disoproxil fumarate in patients co-infected with HIV/HBV or HIV/HCV was similar to that observed in patients infected with HIV without co-infection. However, as would be expected in this patient population, elevations in AST and ALT occurred more frequently than in the general HIV infected population.

Exacerbations of hepatitis after discontinuation of treatment

In HIV infected patients co-infected with HBV, clinical and laboratory evidence of hepatitis have occurred after discontinuation of treatment (see section 4.4).

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 requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

If overdose occurs the side effects listed will be exacerbated and exaggerated (see section 4.8). The patient must be monitored for evidence of toxicity and standard supportive treatment provided as necessary.

Emtricitabine:

Haemodialysis treatment removed approximately 30 % of the emtricitabine dose over a 3-hour dialysis period, starting within 1,5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

Tenofovir disoproxil fumarate:

Tenofovir is poorly removed by haemodialysis. Following a single 300 mg dose of tenofovir disoproxil fumarate, a four-hour haemodialysis session removed only approximately 10 % of the administered tenofovir dose.

Rilpivirine:

Human experience of overdose with TERESTIME is limited. Treatment of overdose with TERESTIME consists of general supportive measures including monitoring of vital signs and ECG (QT interval) as well as observation of clinical status of the patient. If indicated, elimination of unabsorbed active substance may be achieved by gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since rilpivirine is highly bound to plasma protein, dialysis is unlikely to result in significant removal of the active substance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

A 20.2.8 Antiviral agents

Pharmacotherapeutic group: Antiviral for systemic use; antivirals for treatment of HIV infections, combinations. ATC code: J05AR08.

Emtricitabine:

Emtricitabine, a synthetic nucleoside analogue of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase (RT) by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5'-triphosphate is a weak inhibitor of mammalian DNA polymerases α, β, ε and mitochondrial DNA polymerase γ.

Tenofovir disoproxil fumarate:

Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis

for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 RT by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β and mitochondrial DNA polymerase γ.

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.

Resistance:

Emtricitabine and tenofovir disoproxil fumarate:

HIV-1 isolates with reduced susceptibility to the combination of emtricitabine and tenofovir were selected in cell culture. Genotypic analysis of these isolates identified the M184I/V and/or K65R amino acid substitutions in the viral RT.

In a clinical study of treatment-naïve patients (emtricitabine + tenofovir + efavirenz versus zidovudine + lamivudine + efavirenz), resistance analysis was performed on HIV isolates from all virologic failure patients with > 400 copies/mL of HIV-1 RNA at week 144 or early discontinuations. Development of efavirenz resistance-associated mutations occurred most frequently and was similar between the treatment arms.

The M184V amino acid substitution, associated with resistance to emtricitabine and lamivudine, was observed in 2/19 analysed subject isolates in the emtricitabine + tenofovir disoproxil fumarate group and in 10/29 analysed subject isolates in the

zidovudine/lamivudine group. Through 144 weeks of this study, no subjects developed a detectable K65R substitution in their HIV-1 as analysed through standard genotypic analysis.

The M184V amino acid substitution, associated with resistance to emtricitabine and lamivudine, was observed in 2/12 (17 %) analysed patient isolates in the emtricitabine + tenofovir disoproxil fumarate group and in 7/22 (32 %) analysed patient isolates in the zidovudine/lamivudine group.

Emtricitabine:

Emtricitabine-resistant isolates of HIV have been selected in cell culture and *in vivo*. Genotypic analysis of these isolates showed that the reduced susceptibility to emtricitabine was associated with a mutation in the HIV RT gene at codon 184, which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I).

Emtricitabine-resistant isolates of HIV have been recovered from some patients treated with emtricitabine alone or in combination with other antiretroviral medicines. In a clinical study, viral isolates from 6/16 (37,5 %) treatment-naïve patients with virological failure showed > 20-fold reduced susceptibility to emtricitabine. Genotypic analysis of these isolates showed that the resistance was due to M184V/I mutations in the HIV RT gene.

Tenofovir disoproxil fumarate:

HIV-1 isolates with reduced susceptibility to tenofovir were selected in cell culture. These viruses expressed a K65R mutation in RT and showed a 2 to 4-fold reduction in susceptibility to tenofovir.

Tenofovir-resistant isolates of HIV-1 were also recovered from some patients treated with tenofovir in combination with certain antiretroviral medicines. In treatment-naïve patients,

8/47 (17 %) isolates from patients on tenofovir + lamivudine + efavirenz through week 144 showed > 1,4-fold (median 3,7) reduced susceptibility in cell culture to tenofovir. In treatment-experienced patients, 14/304 (5 %, Studies 902 and 907) isolates from patients failing tenofovir through week 96 showed > 1,4-fold (median 2,7) reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a mutation in the HIV-1 RT gene resulting in the K65R amino acid substitution.

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-naïve 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:

Emtricitabine and tenofovir disoproxil fumarate:

Cross-resistance among certain nucleoside reverse transcriptase inhibitors (NRTIs) has been recognised. The M184V/I and/or K65R substitutions selected in cell culture by the combination of emtricitabine and tenofovir are also observed in some HIV-1 isolates from subjects failing treatment with tenofovir in combination with either lamivudine or emtricitabine, and either abacavir or didanosine. Therefore, cross-resistance among these medicines may occur in patients whose virus harbours either or both of these amino acid substitutions.

Emtricitabine:

Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine and zalcitabine but retained susceptibility *in vitro* to didanosine, stavudine, tenofovir, zidovudine and NNRTIs (delavirdine, efavirenz, and nevirapine). Isolates from heavily treatment experienced patients containing the M184V/I amino acid substitution in the context of other NRTI resistance-associated substitutions may retain susceptibility to tenofovir. HIV-1 isolates containing the K65R substitution, selected *in vivo* by abacavir, didanosine, tenofovir and zalcitabine, demonstrated reduced susceptibility to inhibition by emtricitabine. Viruses harbouring mutations conferring reduced susceptibility to stavudine and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to emtricitabine. HIV-1 containing the K103N substitution associated with resistance to NNRTIs was susceptible to emtricitabine.

Tenofovir disoproxil fumarate:

HIV-1 isolates from patients (N = 20) whose HIV-1 expressed a mean of 3’ zidovudine-associated RT amino acid substitutions (M41L, D67N, K70R, L210W, T215Y/F or

K219Q/E/N) showed a 3,1-fold decreased susceptibility to tenofovir. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the RT showed reduced susceptibility to tenofovir.

Rilpivirine:

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 and Y181V.

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 analyses of the phase III 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.

Switching patients at Low HIV-1 RNA Into Fixed dose combination:

A total of 424 patients were enrolled in the SALIF phase 3b, randomized, open-label, non-inferiority study in virologically suppressed adults on NNRTI-based first line antiretroviral treatment. The study evaluated the efficacy and safety/tolerability of switching to Single Table Regimen (STR) of tenofovir disoproxil fumarate/ emtricitabine/ rilpivirine versus tenofovir disoproxil fumarate/ emtricitabine/ efavirenz in suppressed (HIV-1 RNA < 50

copies/mL) patients on an NNRTI-based ART. The primary endpoint was the proportion of subjects with virologic suppression (HIV-1 RNA < 400 copies/mL) at week 48 (intent-to-treat [ITT], FDA snapshot, 10 % non-inferiority margin). The overall analysis of SALIF demonstrated non-inferiority (10 % margin) of tenofovir disoproxil fumarate/ emtricitabine/ rilpivirine versus tenofovir disoproxil fumarate/ emtricitabine/ efavirenz in maintaining HIV-1 RNA suppression defined as HIV-1 RNA < 400 copies/mL (93,9 % vs. 96,2 %; different -2,3 %; 95 % CI: -6,4 %, 1,8 %) at week 48. In conclusion, the single tablet regimen of tenofovir disoproxil fumarate/ emtricitabine/ rilpivirine was an effective, well-tolerated once-daily treatment option for virologically suppressed patients compared to generic tenofovir disoproxil fumarate/ emtricitabine / efavirenz. The results for < 50 copies/mL were also non-inferior between the two treatment arms.

Effects on QTc interval

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) difference 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 C_{max} approximately 2,6-fold and 6,7-fold, respectively, higher than the mean steady-state C_{max} observed with the recommended 25 mg daily dose of rilpivirine.

Antiviral Activity:

Emtricitabine and tenofovir disoproxil fumarate:

In combination studies evaluating, the in-cell culture antiviral activity of emtricitabine and tenofovir together, synergistic antiviral effects were observed.

Rilpivirine:

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-1/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.

5.2 Pharmacokinetic properties

Emtricitabine:

The pharmacokinetic properties of emtricitabine are summarised in Table 1. Following oral administration, emtricitabine (200 mg), is rapidly absorbed, with peak plasma concentrations occurring at 1 to 2 hours post-dose. *In vitro* binding of emtricitabine to human plasma proteins is < 4 % and is independent of concentration over the range of 0,02 to 200 μg/mL. Approximately 86 % is recovered in the urine and 13 % is recovered as metabolites. The metabolites of emtricitabine include 3'-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by glomerular filtration and active tubular secretion. The plasma emtricitabine half-life is approximately 10 hours.

Tenofovir disoproxil fumarate:

The pharmacokinetic properties of tenofovir disoproxil fumarate are summarised in Table 1. Following oral administration, the maximum tenofovir serum concentrations are achieved in 1,0 ± 0,4 hours. In cell culture 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.

Approximately 70 to 80 % of the intravenous dose of tenofovir is recovered as unchanged medicine in the urine.

Tenofovir is eliminated by glomerular filtration and active tubular secretion. Terminal elimination half-life is approximately 17 hours.

Table 1:

Single Dose Pharmacokinetic Parameters for Emtricitabine and Tenofovir in Adults[1]

	Emtricitabine	**Tenofovir**
Fasted Oral Bioavailability[2] (%)	92 (83,1 – 106,4)	25 (NC – 45,0)
Plasma Terminal Elimination Half-life[2] (hr)	10 (7,4 – 18,0)	17 (12,0 – 25,7)
C_{max}[3] (μg/mL)	1,8 ± 0,72[4]	0,30 ± 0,09
AUC[3] (μg·hr/mL)	10,0 ± 3,12[4]	2,29 ± 0,69
CL/F[3] (min/mL)	302 ± 94	1043 ± 115
CLrenal[3] (mL/min)	213 ± 8	243 ± 33

1. NC = Not calculated
2. Median (range)
3. Mean (± SD)
4. Data presented as steady state values

Rilpivirine:

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

Absorption:

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.

Effects of food on oral absorption

Emtricitabine and Tenofovir:

The combination tablet may be administered with or without food. Administration of the combination tablet following a high fat meal (784 kcal; 49 grams of fat) or a light meal (373 kal; 8 grams of fat) delayed the time of tenofovir C_{max} by approximately 0,75 hours. The mean increases in tenofovir AUC and C_{max} were approximately 35 % and 15 %, respectively, when administered with high fat or light meal, compared to administration in the fasted state. In previous safety and efficacy studies, tenofovir was taken under fed conditions. Emtricitabine systemic exposures (AUC and C_{max}) were unaffected when the combination tablet was administered with either a high fat or a light meal.

Rilpivirine:

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

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

Rilpivirine:

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

Elimination

Rilpivirine:

The terminal elimination half-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 the urine.

Special populations

Race:

Emtricitabine:

No pharmacokinetic differences due to race have been identified following the administration of emtricitabine (200 mg).

Tenofovir disoproxil fumarate:

There were insufficient numbers from racial and ethnic groups other than Caucasian, to adequately determine potential pharmacokinetic differences among these populations following the administration of tenofovir disoproxil fumarate.

Paediatric patients:

Emtricitabine and tenofovir:

Pharmacokinetics of emtricitabine and tenofovir have not been fully evaluated in children (< 12 years of age, weighing less than 35 kg) (see section 4.4).

Rilpivirine:

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

Elderly

Emtricitabine and tenofovir:

Pharmacokinetics of emtricitabine and tenofovir have not been evaluated in the elderly (> 65 years of age) (see section 4.4).

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.

Patients with impaired renal function:

Emtricitabine and tenofovir:

The pharmacokinetics of emtricitabine and tenofovir are altered in patients with renal impairment (see sections 4.3 and 4.4). In patients with creatinine clearance < 50 mL/min, C_{max}, $AUC_{0-\infty}$ of emtricitabine and tenofovir were significantly increased. TERESTIME should not be used in patients with creatinine clearance < 50 mL/min or in patients with end-stage renal disease requiring dialysis (see sections 4.3 and 4.4).

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 rilpivirne is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis.

Patients with hepatic impairment:

Emtricitabine and tenofovir:

The pharmacokinetics of tenofovir following a 300-mg dose of tenofovir disoproxil fumarate have been studied in non-HIV infected patients with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. The pharmacokinetics of TERESTIME or emtricitabine has not been studied in patients with hepatic impairment. However, emtricitabine is not significantly metabolised by liver enzymes, so that the impact of liver impairment should be limited.

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

Population pharmacokinetic analysis indicated that hepatitis B and/or C virus co-infection had no clinically relevant effect on the exposure to rilpivirine.

5.3 Preclinical safety data

Non-clinical data on emtricitabine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction and development.

Non-clinical data on rilpivirine hydrochloride reveal no special hazard for humans based on studies of safety pharmacology, drug disposition, genotoxicity, carcinogenic potential, and toxicity to reproduction and development. Liver toxicity associated with liver enzyme induction was observed in rodents. In dogs cholestasis-like effects were noted.

Carcinogenicity studies with rilpivirine in mice and rats revealed tumorigenic potential specific for these species but are regarded as of no relevance for humans. Studies in animals have shown limited placenta passage of rilpivirine. It is not known whether placental transfer of rilpivirine occurs in pregnant women. There was no teratogenicity with rilpivirine in rats and rabbits.

Non-clinical data on tenofovir disoproxil fumarate reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential, and toxicity to reproduction and development. Findings in repeat-dose toxicity studies in rats, dogs and monkeys at exposure levels greater than or equal to clinical exposure levels and with possible relevance to clinical use included kidney and bone changes and a decrease in serum phosphate concentration. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone marrow density (BMD) (rats and dogs).

Genotoxicity and repeat-dose toxicity studies of one month or less with the combination of emtricitabine and tenofovir disoproxil fumarate found no exacerbation of toxicological effects compared to studies with the separate components.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Croscarmellose sodium;

lactose monohydrate;

magnesium stearate;

microcrystalline cellulose;

polysorbate 20;

povidone;

corn starch.

Tablet coating: hypromellose; iron oxide black; iron oxide red; lactose monohydrate; polyethylene glycol; titanium dioxide; triacetin.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 30 ºC. Store in the original container. Do not remove from the carton until required for use. Keep the bottle tightly closed.

6.5 Nature and contents of container

TERESTIME tablets are packed in the following:

HDPE bottle pack with desiccant: HDPE bottle pack (marketable pack) comprises of round wide mouth white high-density polyethylene (HDPE) bottle white opaque polypropylene screw cap with aluminium induction sealing liner wad with desiccant. The HDPE bottle pack with desiccant may be placed in an outer cardboard carton based on commercial requirement.

HDPE bottle pack without desiccant: HDPE bottle pack (marketable pack) comprises of round wide mouth white high-density polyethylene (HDPE) bottle with white opaque polypropylene screw cap with aluminium induction sealing liner wad without desiccant. The HDPE bottle pack without desiccant may be placed in an outer cardboard carton based on commercial requirement.

Pack sizes: 28's, 30's.

* Not all packs and pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

4 Brewery Street,

Isando

Johannesburg, 1609

8. REGISTRATION NUMBER(S)

55/20.2.8/0342.341

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 July 2022

10 DATE OF REVISION OF THE TEXT

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