SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Emtricitabine/Rilpivirine/Tenofovir disoproxil fumarate 200 mg/25 mg/300 mg film-coated tablets

Erestz

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg of emtricitabine, 25 mg of rilpivirine (as hydrochloride) and 300 mg of tenofovir disoproxil fumarate.

Excipients with known effect

Each film-coated tablet contains 237.25 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Emtricitabine/rilpivirine/tenofovir disoproxil fumarate is indicated for the treatment of adults infected with human immunodeficiency virus type 1 (HIV-1) without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or emtricitabine, and with a viral load ≤ 100,000 HIV-1 RNA copies/mL (see sections 4.2, 4.4 and 5.1).

Genotypic resistance testing and/or historical resistance data should guide the use of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Emtricitabine/rilpivirine/tenofovir disoproxil fumarate should be initiated by a physician experienced in the management of HIV infection.

Posology

Adults

The recommended dose of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate is one tablet, taken orally, once daily. Emtricitabine/rilpivirine/tenofovir disoproxil fumarate **must be taken with food** (see section 5.2).

Where discontinuation of therapy with one of the components of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate is indicated or where dose modification is necessary, separate preparations of emtricitabine, rilpivirine hydrochloride and tenofovir disoproxil are available. Please refer to the Summary of Product Characteristics for these medicinal products.

If a patient misses a dose of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate within 12 hours of the time it is usually taken, the patient should take Emtricitabine/rilpivirine/tenofovir disoproxil fumarate with food as soon as possible and resume the normal dosing schedule. If a patient misses a dose of

Emtricitabine/rilpivirine/tenofovir disoproxil fumarate 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 Emtricitabine/rilpivirine/tenofovir disoproxil fumarate another Emtricitabine/rilpivirine/tenofovir disoproxil fumarate tablet should be taken with food. If a patient vomits more than 4 hours after taking Emtricitabine/rilpivirine/tenofovir disoproxil fumarate they do not need to take another dose of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate until the next regularly scheduled dose.

Dose adjustment
If Emtricitabine/rilpivirine/tenofovir disoproxil fumarate is co-administered with rifabutin, an additional 25 mg tablet of rilpivirine per day is recommended to be taken concomitantly with Emtricitabine/rilpivirine/tenofovir disoproxil fumarate, for the duration of the rifabutin co- administration (see section 4.5).

Special populations

Elderly
Emtricitabine/rilpivirine/tenofovir disoproxil fumarate has not been studied in patients over the age of 65 years. Emtricitabine/rilpivirine/tenofovir disoproxil fumarate should be administered with caution to elderly patients (see sections 4.4 and 5.2).

Renal impairment
In patients with mild renal impairment Emtricitabine/rilpivirine/tenofovir disoproxil fumarate should only be used if the potential benefits of treatment outweigh the potential risks (see sections 4.4 and 5.2).

Emtricitabine/rilpivirine/tenofovir disoproxil fumarate is not recommended for patients with moderate or severe renal impairment (CrCl< 50 mL/min). Patients with moderate or severe renal impairment require a dose interval adjustment of emtricitabine and tenofovir disoproxil that cannot be achieved with the combination tablet (see sections 4.4 and 5.2).

Hepatic impairment
There is limited information regarding the use of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate in patients with mild or moderate hepatic impairment (Child-Pugh-Turcotte (CPT) Score A or B). No dose adjustment of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate is required in patients with mild or moderate hepatic impairment. Emtricitabine/rilpivirine/tenofovir disoproxil fumarate should be used with caution in patients with moderate hepatic impairment. Emtricitabine/rilpivirine/tenofovir disoproxil fumarate has not been studied in patients with severe hepatic impairment (CPT Score C). Therefore, Emtricitabine/rilpivirine/tenofovir disoproxil fumarate is not recommended in patients with severe hepatic impairment (see sections 4.4 and 5.2).

If Emtricitabine/rilpivirine/tenofovir disoproxil fumarate 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).

Paediatric population
The safety and efficacy of emtricitabine/rilpivirine/tenofovir disoproxil fumarate in children under the age of 18 years have not been established. Currently available data are described in section 5.2, but no recommendation on a posology can be made.

Pregnancy
See sections 4.4, 4.6, 5.1 and 5.2.

Method of administration
Emtricitabine/rilpivirine/tenofovir disoproxil fumarate must be taken orally, once daily with food (see section 5.2). It is recommended that emtricitabine/rilpivirine/tenofovir disoproxil fumarate be swallowed whole with water. The film-coated tablet should not be chewed, crushed or split as it may impact the absorption of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate.

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

Emtricitabine/rilpivirine/tenofovir disoproxil fumarate should not be co-administered with the following medicinal products as significant decreases in rilpivirine plasma concentrations may occur (due to cytochrome P450 [CYP]3A enzyme induction or gastric pH increase), which may result in loss of therapeutic effect of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate:

- the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- the antimycobacterials rifampicin, rifapentine
- proton pump inhibitors, such as omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole
- the systemic glucocorticoid dexamethasone, except as a single dose treatment
- St. John's wort (*Hypericum perforatum*)

4.4 Special warnings and precautions for use
Virologic failure and development of resistance

Emtricitabine/rilpivirine/tenofovir disoproxil fumarate has not been evaluated in patients with previous virologic failure to any other antiretroviral therapy. There is not sufficient data to justify the use in patients with prior NNRTI failure. Resistance testing and/or historical resistance data should guide the use of emtricitabine/rilpivirine/tenofovir disoproxil fumarate (see section 5.1).
Cardiovascular

At supratherapeutic doses (75 mg and 300 mg once daily), rilpivirine has been associated with prolongation of the QTc interval of the electrocardiogram (ECG) (see sections 4.5 and 5.1).
Rilpivirine at the recommended dose of 25 mg once daily is not associated with a clinically relevant effect on QTc. Emtricitabine/rilpivirine/tenofovir disoproxil fumarate should be used with caution when co-administered with medicinal products with a known risk of Torsade de Pointes.

Co-administration of other medicinal products

Emtricitabine/rilpivirine/tenofovir disoproxil fumarate should not be administered concomitantly with other medicinal products containing emtricitabine, tenofovir disoproxil, tenofovir alafenamide, or other cytidine analogues, such as lamivudine (see section 4.5). Emtricitabine/rilpivirine/tenofovir disoproxil fumarate should not be administered concomitantly with rilpivirine hydrochloride unless needed for dose adjustment with rifabutin (see sections 4.2 and 4.5). Emtricitabine/rilpivirine/tenofovir disoproxil fumarate should not be administered concomitantly with adefovir dipivoxil (see section 4.5).

Co-administration of emtricitabine/rilpivirine/tenofovir disoproxil fumarate and didanosine is not recommended (see section 4.5).

Renal impairment

Emtricitabine/rilpivirine/tenofovir disoproxil fumarate is not recommended for patients with moderate or severe renal impairment (CrCl< 50 mL/min). Patients with moderate or severe renal impairment require a dose interval adjustment of emtricitabine and tenofovir disoproxil that cannot be achieved with the combination tablet (see sections 4.2 and 5.2). Use of emtricitabine/rilpivirine/tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic medicinal product (see section 4.5). If concomitant use of emtricitabine/rilpivirine/tenofovir disoproxil fumarate and nephrotoxic agents is unavoidable, renal function must be monitored weekly (see sections 4.5 and 4.8).

Cases of acute renal failure after initiation of high dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) have been reported in patients treated with tenofovir disoproxil and with risk factors for renal dysfunction. If Emtricitabine/rilpivirine/tenofovir disoproxil fumarate is co-administered with an NSAID, renal function should be monitored adequately.

Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil in clinical practice (see section 4.8).

It is recommended that CrCl is calculated in all patients prior to initiating therapy with emtricitabine/rilpivirine/tenofovir disoproxil fumarate and renal function (CrCl and serum phosphate) is also monitored after two to four weeks of treatment, after three months of treatment and every three to six months thereafter in patients without renal risk factors. In patients at risk for renal impairment, a more frequent monitoring of renal function is required.

If serum phosphate is < 1.5 mg/dL (0.48 mmol/L) or CrCl is decreased to < 50 mL/min in any patient receiving emtricitabine/rilpivirine/tenofovir disoproxil fumarate, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). Since emtricitabine/rilpivirine/tenofovir disoproxil fumarate is a combination product and the dosing interval of the individual components cannot be altered, treatment with emtricitabine/rilpivirine/tenofovir disoproxil fumarate must be interrupted in patients with confirmed CrCl decreased to < 50 mL/min or decreases in serum phosphate to < 1.0 mg/dL (0.32 mmol/L).
Interrupting treatment with emtricitabine/rilpivirine/tenofovir disoproxil fumarate should also be considered in case of progressive decline of renal function when no other cause has been identified. Where discontinuation of therapy with one of the components of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate is indicated or where dose modification is necessary, separate preparations of emtricitabine, rilpivirine hydrochloride and tenofovir disoproxil are available.

Bone effects

Bone abnormalities such as osteomalacia which can manifest as persistent or worsening bone pain and, which can infrequently contribute to fractures may be associated with tenofovir disoproxil- induced proximal renal tubulopathy (see section 4.8).

Tenofovir disoproxil may also cause a reduction in BMD. If bone abnormalities are suspected or detected then appropriate consultation should be obtained.

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

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

Physicians should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with HBV.

In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant Summary of Product Characteristics for these medicinal products.

The safety and efficacy of emtricitabine/rilpivirine/tenofovir disoproxil fumarate have not been established for the treatment of chronic HBV infection. Emtricitabine and tenofovir individually and in combination have shown activity against HBV in pharmacodynamic studies (see section 5.1).

Discontinuation of emtricitabine/rilpivirine/tenofovir disoproxil fumarate therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis. Patients co-infected with HIV and HBV who discontinue emtricitabine/rilpivirine/tenofovir disoproxil fumarate should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of hepatitis B therapy may be warranted. 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

The safety and efficacy of emtricitabine/rilpivirine/tenofovir disoproxil fumarate have not been established in patients with significant underlying liver disorders. The pharmacokinetics of emtricitabine has not been studied in patients with hepatic impairment. Emtricitabine is not significantly metabolised by liver enzymes, so the impact of liver impairment should be limited. No dose adjustment is required for rilpivirine hydrochloride in patients with mild or moderate hepatic impairment (CPT Score A or B). Rilpivirine hydrochloride has not been studied in patients with severe hepatic impairment (CPT Score C). The pharmacokinetics of tenofovir has been studied in patients with hepatic impairment and no dose adjustment is required in these patients.

It is unlikely that a dose adjustment would be required for emtricitabine/rilpivirine/tenofovir disoproxil fumarate in patients with mild or moderate hepatic impairment (see sections 4.2 and 5.2). Emtricitabine/rilpivirine/tenofovir disoproxil fumarate should be used with caution in patients with moderate hepatic impairment (CPT Score B) and is not recommended in patients with severe hepatic impairment (CPT Score C).

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Severe skin reactions

Cases of severe skin reactions with systemic symptoms have been reported during post-marketing experience with emtricitabine/rilpivirine/tenofovir disoproxil fumarate, including but not limited to rashes accompanied by fever, blisters, conjunctivitis, angioedema, elevated liver function tests, and/or eosinophilia. These symptoms resolved

after emtricitabine/rilpivirine/tenofovir disoproxil fumarate was discontinued. As soon as serious skin and/or mucosal reactions are observed, emtricitabine/rilpivirine/tenofovir disoproxil fumarate must be discontinued and appropriate therapy should be initiated.

Weight and metabolic parameters

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

Mitochondrial dysfunction following exposure *in utero*

Nucleos(t)ide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or postnatally to nucleoside analogues; these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactatemia, hyperlipasemia). These events have often been transitory. Late onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed *in utero* to nucleos(t)ide analogues, who present with severe clinical findings of unknown etiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Immune Reactivation Syndrome

In HIV infected patients with severe immune deficiency at the time of institution of CART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia.

Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

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

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.

Elderly

Emtricitabine/rilpivirine/tenofovir disoproxil fumarate 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 Emtricitabine/rilpivirine/tenofovir disoproxil fumarate (see sections 4.2 and 5.2).

Pregnancy
Lower exposures of rilpivirine were observed when rilpivirine 25 mg once daily was taken during pregnancy. Lower rilpivirine exposure, similar to that seen during pregnancy, has been associated with an increased risk of virological failure, therefore viral load should be monitored closely (see sections 4.6, 5.1 and 5.2). Alternatively, switching to another antiretroviral regimen could be considered.

Excipients
Emtricitabine/rilpivirine/tenofovir disoproxil fumarate contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

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

Rilpivirine is primarily metabolised by 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 Emtricitabine/rilpivirine/tenofovir disoproxil fumarate and medicinal products that induce CYP3A has been observed to decrease the plasma concentrations of rilpivirine which could potentially lead to loss of therapeutic effect of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate (see section 4.3).

Co-administration of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate 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 Emtricitabine/rilpivirine/tenofovir disoproxil fumarate (see section 4.3).

Concomitant use not recommended
Emtricitabine/rilpivirine/tenofovir disoproxil fumarate should not be administered concomitantly with other medicinal products containing emtricitabine, tenofovir disoproxil or tenofovir alafenamide. Emtricitabine/rilpivirine/tenofovir disoproxil fumarate should not be administered concomitantly with rilpivirine hydrochloride unless needed for dose adjustment with rifabutin (see section 4.2).

Due to similarities with emtricitabine, Emtricitabine/rilpivirine/tenofovir disoproxil fumarate should not be administered concomitantly with other cytidine analogues, such as lamivudine (see section 4.4). Emtricitabine/rilpivirine/tenofovir disoproxil fumarate should not be administered concomitantly with adefovir dipivoxil.

Didanosine
The co-administration of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate and didanosine is not recommended (see section 4.4 and Table 1).

Renally eliminated medicinal products
Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate with medicinal products 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 medicinal products.

Use of emtricitabine/rilpivirine/tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic medicinal product. 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 emtricitabine/rilpivirine/tenofovir disoproxil fumarate with NNRTIs.

Concomitant use where caution is recommended
Cytochrome P450 enzyme inhibitors
Co-administration of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate with medicinal products that inhibit CYP3A enzyme activity has been observed to increase rilpivirine plasma concentrations.

QT prolonging medicinal products
Emtricitabine/rilpivirine/tenofovir disoproxil fumarate should be used with caution when co-administered with a medicinal product with a known risk of Torsade de Pointes. There is limited information available on the potential for a pharmacodynamic interaction between rilpivirine and medicinal products 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).

P-glycoprotein substrates
Rilpivirine inhibits P-glycoprotein (P-gp) *in vitro* (IC_{50} is 9.2 µM).

Rilpivirine is an *in vitro* inhibitor of the transporter MATE-2K with an IC_{50} of < 2.7 nM. The clinical implications of this finding are currently unknown.

Other interactions

Interactions between Emtricitabine/rilpivirine/tenofovir disoproxil fumarate or its individual component(s) and co-administered medicinal products are listed in Table 1 below (increase is indicated as "↑", decrease as "↓" and no change as "↔").

Table 1: Interactions between Emtricitabine/rilpivirine/tenofovir disoproxil fumarate or its individual component(s) and other medicinal products

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean percent change in AUC, Cmax, Cmin**	**Recommendation concerning co-administration with Emtricitabine/rilpivirine/tenofovir disoproxil fumarate**
ANTI-INFECTIVES		
Antiretrovirals		
Nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs/N[t]RTIs)		
Didanosine/Emtricitabine	Interaction not studied.	Co-administration of

Didanosine (400 mg once daily)/ Rilpivirine[1]	Didanosine: AUC: ↑ 12% C_{min}: N/A Cmax: ↔ Rilpivirine: AUC: ↔ Cmin: ↔ C_{max}: ↔	Emtricitabine/rilpivirine/tenofovir disoproxil fumarate and didanosine is not recommended (see section 4.4). Increased systemic exposure to didanosine may increase didanosine related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported.
Didanosine/Tenofovir disoproxil	Co-administration of tenofovir disoproxil and didanosine results in a 40-60% increase in systemic exposure to didanosine.	Co-administration of tenofovir disoproxil and didanosine at a dose of 400 mg daily has been associated with a significant decrease in CD4+ cell count, possibly due to an intracellular interaction increasing phosphorylated (i.e. active) didanosine. A decreased dosage of 250 mg didanosine co-administered with tenofovir disoproxil therapy has been associated with reports of high rates of virological failure within several tested combinations for the treatment of HIV-1 infection.

Medicinal product by therapeutic areas	**Effects on medicinal product levels.** **Mean percent change in AUC,** **Cmax, Cmin**	**Recommendation concerning co-administration with Emtricitabine/rilpivirine/tenofovir disoproxil fumarate**
Protease inhibitors (PIs) - boosted (with co-administration of low-dose ritonavir)		
Atazanavir/Ritonavir/Emtricitabine	Interaction not studied.	Concomitant use of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate with ritonavir-boosted PIs causes an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). No dose adjustment is required.
Atazanavir/Ritonavir/Rilpivirine Atazanavir (300 mg once daily)/ Ritonavir (100 mg once daily)/ Tenofovir disoproxil (245 mg once daily)	Interaction not studied. Atazanavir: AUC: ↓ 25% C_{max}: ↓ 28% C_{min}: ↓ 26% Tenofovir: AUC: ↑ 37% C_{max}: ↑ 34% C_{min}: ↑ 29%	
Darunavir/Ritonavir/Emtricitabine Darunavir (800 mg once daily)/ Ritonavir (100 mg once daily)/ Rilpivirine[1]	Interaction not studied. Darunavir: AUC: ↔ C_{min}: ↓ 11% Cmax: ↔ Rilpivirine: AUC: ↑ 130% C_{min}: ↑ 178% C_{max}: ↑ 79%	
Darunavir (300 mg once daily)/ Ritonavir (100 mg once daily)/ Tenofovir disoproxil (245 mg once daily)	Darunavir: AUC: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 22% C_{min}: ↑ 37%	
Lopinavir/Ritonavir/Emtricitabine Lopinavir (400 mg twice daily)/ Ritonavir (100 mg twice daily)/ Rilpivirine[1] (soft capsule)	Interaction not studied. Lopinavir: AUC: ↔ C_{min}: ↓ 11% Cmax: ↔ Rilpivirine: AUC: ↑ 52% C_{min}: ↑ 74% C_{max}: ↑ 29%	

Lopinavir (400 mg twice daily)/ Ritonavir (100 mg twice daily)/ Tenofovir disoproxil (245 mg once daily)	Lopinavir/Ritonavir: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 32% Cmax: ↔ C_{min}: ↑ 51%	
CCR5 antagonists		
Maraviroc/Emtricitabine Maraviroc/Rilpivirine Maraviroc (300 mg twice daily)/ Tenofovir disoproxil (245 mg once daily)	Interaction not studied. Interaction not studied. AUC: ↔ C_{max}: ↔ Tenofovir concentrations not measured, no effect is expected.	No clinically relevant drug-drug interaction is expected. No dose adjustment is required.

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean percent change in AUC, Cmax, Cmin**	**Recommendation concerning co-administration with Emtricitabine/rilpivirine/tenofovir disoproxil fumarate**
Integrase strand transfer inhibitors		
Raltegravir/Emtricitabine Raltegravir/Rilpivirine	Interaction not studied. Raltegravir: AUC: ↑ 9% C_{min}: ↑ 27% C_{max}: ↑ 10% Rilpivirine: AUC: ↔ Cmin: ↔ C_{max}: ↔	No clinically relevant drug-drug interaction is expected. No dose adjustment is required.
~~Raltegravir (400 mg twice~~ daily)/ Tenofovir disoproxil	~~Raltegravir:~~ AUC: ↑ 49% C_{12h}: ↑ 3% C_{max}: ↑ 64% (mechanism of interaction unknown) Tenofovir: AUC: ↓ 10% C_{12h}: ↓ 13% C_{max}: ↓ 23%	
Other antiviral agents		

Ledipasvir/Sofosbuvir (90 mg/400 mg once daily)/ Emtricitabine/Rilpivirine/ Tenofovir disoproxil (200 mg/25 mg/245 mg once daily)	Ledipasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[4]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Rilpivirine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 40% C_{max}: ↔ C_{min}: ↑ 91%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).

Medicinal product by therapeutic areas	**Effects on medicinal product levels.** **Mean percent change in AUC,** **Cmax, Cmin**	**Recommendation concerning co-administration with Emtricitabine/rilpivirine/tenofovir disoproxil fumarate**
Sofosbuvir/Velpatasvir (400 mg/100 mg once daily)/ Emtricitabine/Rilpivirine/Tenofovir disoproxil (200 mg/25 mg/245 mg once daily)	Sofosbuvir: AUC: ↔ Cmax: ↔ GS-331007[4]: AUC: ↔ Cmax: ↔ Cmin: ↔ Velpatasvir: AUC: ↔ Cmax: ↔ Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Rilpivirine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 40% C_{max}: ↑ 44% C_{min}: ↑ 84%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).

Medicinal product by therapeutic areas	**Effects on medicinal product levels.** **Mean percent change in AUC,** **Cmax, Cmin**	**Recommendation concerning co-administration with Emtricitabine/rilpivirine/tenofovir disoproxil fumarate**
Sofosbuvir/Velpatasvir/ Voxilaprevir (400 mg/100 mg/ 100 mg + 100 mg once daily)[5]/ Rilpivirine/Emtricitabine (25 mg/200 mg once daily)[6]	Interaction not studied with Emtricitabine/rilpiviri ne/tenofovir disoproxil fumarate. *Expected :* Sofosbuv ir: AUC: ↔ Cmax: ↔ GS-331007[4]: AUC: ↔ Cmax: ↔ Cmin: ↔ Velpatasvir: AUC: ↔ Cmax: ↔ Cmin: ↔ Voxilaprevir AUC: ↔ Cmax: ↔ Cmin: ↔ Rilpivirine: AUC: ↔ Cmin: ↔ Cmax: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↑ Cmax: ↑ C_{min}: ↑	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).
Sofosbuvir/Emtricitabine	Interaction not studied.	No dose adjustment is

Sofosbuvir (400 mg once daily)/ Rilpivirine (25 mg once daily) Sofosbuvir/Tenofovir disoproxil	Sofosbuvir: AUC: ↔ C_{max}: ↑ 21% GS-331007[4]: AUC: ↔ Cmax: ↔ Rilpivirine: AUC: ↔ Cmax: ↔ C_{min}: ↔ Interaction not studied.	required.
Ribavirin/Tenofovir disoproxil	Ribavirin: AUC: ↔ Cmax: ↔ C_{min}: N/A	No dose adjustment is required.

Medicinal product by therapeutic areas	**Effects on medicinal product levels.** **Mean percent change in AUC,** **Cmax, Cmin**	**Recommendation concerning co-administration with Emtricitabine/rilpivirine/tenofovir disoproxil fumarate**
Herpesvirus antiviral agents		
Famciclovir/Emtricitabine	Famciclovir: AUC: ↔ Cmax: ↔ C_{min}: N/A Emtricitabine: AUC: ↔ Cmax: ↔ C_{min}: N/A	No dose adjustment is required.
Antifungals		
Ketoconazole/Emtricitabine Ketoconazole (400 mg once daily)/ Rilpivirine[1] Fluconazole[2] Itraconazole[2] Posaconazole[2] Voriconazole[2]	Interaction not studied. Ketoconazole: AUC: ↓ 24% C_{min}: ↓ 66% Cmax: ↔ Rilpivirine: AUC: ↑ 49% C_{min}: ↑ 76% C_{max}: ↑ 30%	Concomitant use of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate with azole antifungal agents may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). At a dose of 25 mg of rilpivirine, no dose adjustment is required.

Ketoconazole/Tenofovir disoproxil	Interaction not studied.	
Antimycobacterials		
Rifabutin/Emtricitabine Rifabutin (300 mg once daily)/ Rilpivirine[3]	Interaction not studied. Rifabutin: AUC: ↔ Cmin: ↔ Cmax: ↔ 25-O-desacetyl-rifabutin: AUC: ↔ Cmin: ↔ Cmax: ↔ Rilpivirine: AUC: ↓ 42% C_{min}: ↓ 48% C_{max}: ↓ 31%	Co-administration is likely to cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). When Emtricitabine/rilpivirine/tenofovir disoproxil fumarate is co-administered with rifabutin, an additional 25 mg tablet of rilpivirine per day is recommended to be taken concomitantly with Emtricitabine/rilpivirine/tenofovir disoproxil fumarate, for the duration of the rifabutin co- administration.
Rifabutin (300 mg once daily)/ Rilpivirine (25 mg once daily) Rifabutin (300 mg once daily)/ Rilpivirine (50 mg once daily)		
Rifabutin/Tenofovir disoproxil	Interaction not studied.	

Medicinal product by therapeutic areas	**Effects on medicinal product levels.** **Mean percent change in AUC,** **Cmax, Cmin**	**Recommendation concerning co-administration with Emtricitabine/rilpivirine/tenofovir disoproxil fumarate**
Rifampicin/Emtricitabine Rifampicin (600 mg once daily)/ Rilpivirine[1]	Interaction not studied. Rifampicin: AUC: ↔ C_{min}: N/A Cmax: ↔ 25-desacetyl-rifampicin: AUC: ↓ 9% C_{min}: N/A Cmax: ↔ Rilpivirine: AUC: ↓ 80% C_{min}: ↓ 89%	Emtricitabine/rilpivirine/tenofovir disoproxil fumarate must not be used in combination with rifampicin as co-administration is likely to cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate (see section 4.3).

	C_{max}: ↓ 69%	
Rifampicin (600 mg once daily)/ Tenofovir disoproxil (245 mg once daily)	Rifampicin: AUC: ↔ Cmax: ↔ Tenofovir: AUC: ↔ C_{max}: ↔	
Rifapentine[2]	Interaction not studied with any components of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate.	Emtricitabine/rilpivirine/tenofovir disoproxil fumarate must not be used in combination with rifapentine as co-administration is likely to cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate (see section 4.3).
Macrolide antibiotics		
Clarithromycin Erythromycin	Interaction not studied with any components of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate.	The combination of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate with these macrolide antibiotics may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). Where possible, alternatives such as azithromycin should be considered.
ANTICONVULSANTS		

Carbamazepine ~~Oxcarbazepine~~ Phenobarbital Phenytoin	Interaction not studied with any components of ~~Emtricitabine/rilpivirine/t~~enofovir disoproxil fumarate.	Emtricitabine/rilpivirine/tenofovir disoproxil fumarate must 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 Emtricitabine/rilpivirine/tenofovir disoproxil fumarate (see section 4.3).

Medicinal product by therapeutic areas	**Effects on medicinal product levels.** **Mean percent change in AUC,** **Cmax, Cmin**	**Recommendation concerning co-administration with Emtricitabine/rilpivirine/tenofovir disoproxil fumarate**
GLUCOCORTICOIDS		
Dexamethasone (systemic, except for single dose use)	Interaction not studied with any components of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate.	Emtricitabine/rilpivirine/tenofovir disoproxil fumarate should not be used in combination with systemic dexamethasone (except as a single dose) as co-administration may cause significant dose dependent decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate (see section 4.3). Alternatives should be considered, particularly for long-term use.
PROTON PUMP INHIBITORS		
Omeprazole/Emtricitabine	Interaction not studied.	Emtricitabine/rilpivirine/ten

Omeprazole (20 mg once daily)/ Rilpivirine[1] Lansoprazole[2] Rabeprazole[2] Pantoprazole[2] Esomeprazole[2] Omeprazole/Tenofovir disoproxil	Omeprazole: AUC: ↓ 14% C_{min}: N/A C_{max}: ↓ 14% Rilpivirine: AUC: ↓ 40% C_{min}: ↓ 33% C_{max}: ↓ 40% Interaction not studied.	ofovir disoproxil fumarate must not be used in combination with proton pump inhibitors as co-administration is likely to cause significant decreases in rilpivirine plasma concentrations (reduced absorption, increase in gastric pH). This may result in loss of therapeutic effect of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate (see section 4.3).
H2-RECEPTOR ANTAGONISTS		
Famotidine/Emtricitabine Famotidine (40 mg single dose taken 12 hours before rilpivirine)/ Rilpivirine[1] Cimetidin[2] Nizatidin[2] Ranitidine[2] Famotidine (40 mg single dose taken 2 hours before rilpivirine)/ Rilpivirine[1] Famotidine (40 mg single dose taken 4 hours after rilpivirine)/ Rilpivirine[1] Famotidine/Tenofovir disoproxil	Interaction not studied. Rilpivirine: AUC: ↓ 9% C_{min}: N/A Cmax: ↔ Rilpivirine: AUC: ↓ 76% C_{min}: N/A C_{max}: ↓ 85% Rilpivirine: AUC: ↑ 13% C_{min}: N/A C_{max}: ↑ 21% Interaction not studied.	The combination of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate and H_2-receptor antagonists should be used with particular caution as co-administration may cause significant decreases in rilpivirine plasma concentrations (reduced absorption, increase in gastric pH). Only H_2-receptor antagonists that can be dosed once daily should be used. A strict dosing schedule with intake of the H_2-receptor antagonists at least 12 hours before or at least 4 hours after Emtricitabine/rilpivirine/tenofovir disoproxil fumarate should be used.
ANTACIDS		
Antacids (e.g. aluminium or magnesium hydroxide, calcium carbonate)	Interaction not studied with any of the components of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate.	The combination of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate and antacids should be used with caution as co-administration may cause significant decreases in rilpivirine plasma concentrations (reduced absorption, gastric pH increase). Antacids

		should only be administered either at least 2 hours before or at least 4 hours after Emtricitabine/rilpivirine/tenofovir disoproxil fumarate.

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean percent change in AUC, Cmax, Cmin**	**Recommendation concerning co-administration with Emtricitabine/rilpivirine/tenofovir disoproxil fumarate**
NARCOTIC ANALGESICS		
Methadone/Emtricitabine Methadone (60-100 mg once daily, individualised dose)/Rilpivirine	Interaction not studied. R(-) methadone: AUC: ↓ 16% C_{min}: ↓ 22% C_{max}: ↓ 14% Rilpivirine: AUC: ↔* C_{min}: ↔* C_{max}: ↔* *based on historic controls	No dose adjustments are required when initiating co-administration of methadone with Emtricitabine/rilpivirine/tenofovir disoproxil fumarate. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.
Methadone/Tenofovir disoproxil	Methadone: AUC: ↔ Cmin: ↔ Cmax: ↔ Tenofovir: AUC: ↔ Cmin: ↔ C_{max}: ↔	
ANALGESICS		
Paracetamol/Emtricitabine Paracetamol (500 mg single dose)/ Rilpivirine[1]	Interaction not studied. Paracetamol: AUC: ↔ C_{min}: N/A Cmax: ↔ Rilpivirine: AUC: ↔	No dose adjustment is required.

	C_{min}: ↑ 26% C_{max}: ↔	
Paracetamol/Tenofovir disoproxil	Interaction not studied.	
ORAL CONTRACEPTIVES		
Ethinylestradiol/Norethindrone/ Emtricitabine	Interaction not studied.	No dose adjustment is required.
Ethinylestradiol (0.035 mg once daily)/Rilpivirine Norethindrone (1 mg once daily)/ Rilpivirine	Ethinylestradiol: AUC: ↔ Cmin: ↔ C_{max}: ↑ 17% Norethindrone: AUC: ↔ Cmin: ↔ Cmax: ↔ Rilpivirine: AUC: ↔* C_{min}: ↔* C_{max}: ↔* *based on historic controls	
Ethinylestradiol/Norethindrone/ Tenofovir disoproxil	Ethinylestradiol: AUC: ↔ Cmax: ↔ Tenofovir: AUC: ↔ C_{max}: ↔	

Medicinal product by therapeutic areas	**Effects on medicinal product levels.** **Mean percent change in AUC, Cmax, Cmin**	**Recommendation concerning co-administration with Emtricitabine/rilpivirine/tenofovir disoproxil fumarate**

Norgestimate/Ethinylestradiol/ Tenofovir disoproxil	Norgestimate: AUC: ↔ Cmax: ↔ C_{min}: N/A Ethinylestradiol: AUC: ↔ Cmax: ↔ C_{min}: ↔	No dose adjustment is required.
ANTIARRHYTHMICS		
Digoxin/Emtricitabine Digoxin/Rilpivirine Digoxin/Tenofovir disoproxil	Interaction not studied. Digoxin: AUC: ↔ C_{min}: N/A C_{max}: ↔ Interaction not studied.	No dose adjustment is required.
ANTICOAGULANTS		
Dabigatran etexilate	Interaction not studied with any of the components of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate.	A risk for increases in dabigatran plasma concentrations cannot be excluded (inhibition of intestinal P-gp. The combination of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate and dabigatran etexilate should be used with caution.
IMMUNOSUPPRESSANTS		
Tacrolimus/Tenofovir disoproxil/ Emtricitabine	Tacrolimus: AUC: ↔ Cmax: ↔ C_{min}: N/A Emtricitabine: AUC: ↔ Cmax: ↔ C_{min}: N/A Tenofovir: AUC: ↔ Cmax: ↔ C_{min}: N/A	No dose adjustment is required.
ANTIDIABETICS		
Metformin/Emtricitabine Metformin (850 mg single dose)/ Rilpivirine	Interaction not studied. Metformin: AUC: ↔ C_{min}: N/A C_{max}: ↔	No dose adjustment is required.

Metformin/Tenofovir disoproxil	Interaction not studied.	
HERBAL PRODUCTS		
St. John's wort (*Hypericum perforatum*)	Interaction not studied with any of the components of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate.	Emtricitabine/rilpivirine/tenofovir disoproxil fumarate must not be used in combination with products containing St. John's wort as co- administration may cause significant decreases in rilpivirine plasma concentrations. This may result in loss of therapeutic effect of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate (see section 4.3).

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean percent change in AUC, Cmax, Cmin**	**Recommendation concerning co-administration with Emtricitabine/rilpivirine/tenofovir disoproxil fumarate**
HMG CO-A REDUCTASE INHIBITORS		
Atorvastatin/Emtricitabine Atorvastatin (40 mg once daily)/ Rilpivirine[1]	Interaction not studied. Atorvastatin: AUC: ↔ C_{min}: ↓ 15% C_{max}: ↑ 35% Rilpivirine: AUC: ↔ Cmin: ↔ C_{max}: ↓ 9%	No dose adjustment is required.
Atorvastatin/Tenofovir disoproxil	Interaction not studied.	
PHOSPHODIESTERASE TYPE 5 (PDE-5) INHIBITORS		
Sildenafil/Emtricitabine Sildenafil (50 mg single dose)/ Rilpivirine[1] Vardenafil[2] Tadalafil[2] Sildenafil/Tenofovir	Interaction not studied. Sildenafil: AUC: ↔ C_{min}: N/A Cmax: ↔ Rilpivirine: AUC: ↔ Cmin: ↔ C_{max}: ↔ Interaction not studied.	No dose adjustment is required.

disoproxil		

N/A = not applicable

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

2 These are medicinal products within class where similar interactions could be predicted.

3 This interaction study has been performed with a dose higher than the recommended dose for rilpivirine hydrochloride assessing the maximal effect on the co-administered medicinal product.

4 The predominant circulating metabolite of sofosbuvir.

5 Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in hepatitis C virus (HCV) infected patients.

6 Study conducted with emtricitabine/rilpivirine/tenofovir alafenamide fixed-dose combination tablet.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / contraception in males and females

The use of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate must be accompanied by the use of effective contraception.

Pregnancy

The use of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate may be considered during pregnancy, if necessary.

Breast-feeding

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.

There is insufficient information on the effects of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate in newborns/infants.

Because of the potential for adverse reactions in breastfed infants, women should be instructed not to breast-feed if they are receiving Emtricitabine/rilpivirine/tenofovir disoproxil fumarate.

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

Fertility

No human data on the effect of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate 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

Emtricitabine/rilpivirine/tenofovir disoproxil fumarate has no or negligible influence on the ability to drive and use machines. However, patients should be informed that fatigue, dizziness and somnolence have been reported during treatment with the components of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate (see section 4.8). This should be considered when assessing a patient's ability to drive or operate machinery.

4.8 Undesirable effects

In patients receiving tenofovir disoproxil, rare events of renal impairment, renal failure and

uncommon events of 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 Emtricitabine/rilpivirine/tenofovir disoproxil fumarate (see section 4.4).

Discontinuation of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis (see section 4.4).

Tabulated summary of adverse reactions

The adverse reactions considered at least possibly related to treatment with the components of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate from clinical study and post-marketing experience are listed in Table 2, below, by body system organ class and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) or rare (≥ 1/10,000 to < 1/1,000).

Table 2: Tabulated summary of adverse reactions to Emtricitabine/rilpivirine/tenofovir disoproxil fumarate based on clinical study and post-marketing experience with Emtricitabine/rilpivirine/tenofovir disoproxil fumarate and its individual components

Frequency	**Adverse reaction**
Blood and lymphatic system disorders	
Common:	neutropenia[1], decreased white blood cell count[2], decreased haemoglobin[2], decreased platelet count[2]
Uncommon:	anaemia[1, 4]
Immune system disorders	
Common:	allergic reaction[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, 6], severe skin reactions with systemic symptoms[7]
Musculoskeletal and connective tissue disorders	
Very common:	elevated creatine kinase[1]
Uncommon:	rhabdomyolysis[3, 5], muscular weakness[3, 5]
Rare:	osteomalacia (manifested as bone pain and infrequently contributing to fractures)[3, 5, 8], 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, 8], 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.
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 in the absence of this condition.
6 This was a rare adverse reaction for tenofovir disoproxil.
7 See section 4.8, *Description of selected adverse reactions.*
8 The frequency category was estimated from a statistical calculation

Description of selected adverse reactions

Renal impairment
As emtricitabine/rilpivirine/tenofovir disoproxil fumarate may cause renal damage, monitoring of renal function is recommended (see sections 4.4 and 4.8, *Summary of the*

safety profile). Proximal renal tubulopathy generally resolved or improved after tenofovir disoproxil discontinuation. However, in some patients, declines in CrCl did not completely resolve despite tenofovir disoproxil 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 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 medications 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).

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

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

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

<u>Paediatric population</u>

Insufficient safety data are available for children under the age of 18 years. Emtricitabine/rilpivirine/tenofovir disoproxil fumarate is not recommended in this population (see section 4.2).

When emtricitabine (one of the components of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate) was administered to paediatric patients, the following adverse reactions were observed more frequently in addition to the adverse reactions reported in adults: anaemia was common (9.5%) and skin discolouration (increased pigmentation) was very common (31.8%) in paediatric patients (see section 4.8, *Tabulated summary of adverse reactions*).

<u>Other special populations</u>

Elderly
Emtricitabine/rilpivirine/tenofovir disoproxil fumarate 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 Emtricitabine/rilpivirine/tenofovir disoproxil fumarate (see section 4.4).

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

HIV/HBV or HCV co-infected patients
The adverse reaction profile of emtricitabine, rilpivirine hydrochloride and tenofovir disoproxil 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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the e-PV desktop applications (https://drive.google.com/file/d/16hwTz0587ZWtSWadbBAMwQPOD_KSExZP/view) or search for e-PV Mobile applications on the Google Play or Apple App Store.

4.9 Overdose
An increased risk of adverse reactions associated with Emtricitabine/rilpivirine/tenofovir disoproxil fumarate and its individual components may be seen in the event of an overdose.

If overdose occurs the patient must be monitored for evidence of toxicity (see section 4.8), and standard supportive treatment applied as necessary including observation of the clinical status of the patient and monitoring of vital signs and ECG (QT interval).

There is no specific antidote for overdose with Emtricitabine/rilpivirine/tenofovir disoproxil fumarate. Up to 30% of the emtricitabine dose and approximately 10% of the tenofovir dose can be removed by haemodialysis. It is not known whether emtricitabine or tenofovir can be removed by peritoneal dialysis. Since rilpivirine is highly protein bound, dialysis is unlikely to result in significant removal of the active substance. Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacological classification: 7.13 Antivirals

Mechanism of action and pharmacodynamic effects

Emtricitabine is a nucleoside analogue of cytidine. Tenofovir disoproxil is converted *in vivo* to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate. Both emtricitabine and tenofovir have activity that is specific to HIV-1, HIV-2 and, HBV.

Rilpivirine is a diarylpyrimidine NNRTI of HIV-1. Rilpivirine activity is mediated by non-competitive inhibition of HIV-1 reverse transcriptase (RT).

Emtricitabine and tenofovir are phosphorylated by cellular enzymes to form emtricitabine triphosphate and tenofovir diphosphate, respectively. *In vitro* studies have shown that both emtricitabine and tenofovir can be fully phosphorylated when combined together in cells. Emtricitabine triphosphate and tenofovir diphosphate competitively inhibit HIV-1 RT, resulting in DNA chain termination.

Both emtricitabine triphosphate and tenofovir diphosphate are weak inhibitors of mammalian DNA polymerases and there was no evidence of toxicity to mitochondria *in vitro* and *in vivo.* Rilpivirine does not inhibit the human cellular DNA polymerases α, β and mitochondrial DNA polymerase γ.

Antiviral activity *in vitro*
The triple combination of emtricitabine, rilpivirine, and tenofovir demonstrated synergistic antiviral activity in cell culture.

Paediatrics
See section 4.2 for information on paediatric use.

Pregnancy
See sections 4.2, 4.4 and 5.2.

5.2 Pharmacokinetic properties

Absorption of emtricitabine/rilpivirine/tenofovir disoproxil fumarate
The adsorption characteristics of emtricitabine/rilpivirine/tenofovir disoproxil fumarate have been demonstrated after administration of 1 tablet of emtricitabine/rilpivirine/tenofovir disoproxil fumarate 200mg/25mg/300mg tablets in healthy subjects in the fed state as follows:

Pharmacokinetic variable	**Mean value***		
	Emtricitabine	**Rilpivirine**	**Tenofovir disoproxil fumarate**
Maximum concentration (C_{max}) (ng/mL)	1953.855	144.873	309.542
Area under curve ($AUC_{0-\infty}$), a measure of the extent of absorption (ng/mL*hour)	12286.480	N/A	2928.694
Time to attain maximum concentration (T_{max})[#] (hour)	1.92	4.01	1.91
*geometric mean [#] upper T_{max}			

Distribution

Following intravenous administration the volume of distribution of the single components emtricitabine and tenofovir was approximately 1,400 mL/kg and 800 mL/kg, respectively. After oral administration of the single components emtricitabine and tenofovir disoproxil, emtricitabine and tenofovir are widely distributed throughout the body. *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.
In vitro binding of rilpivirine to human plasma proteins is approximately 99.7%, primarily to albumin. *In vitro* binding of tenofovir to plasma or serum protein was less than 0.7% and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 µg/mL.

Biotransformation
There is limited metabolism of emtricitabine. The biotransformation of emtricitabine includes oxidation of the thiol moiety to form the 3'-sulphoxide diastereomers (approximately 9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (approximately 4% of dose). *In vitro* experiments indicate that rilpivirine hydrochloride primarily undergoes oxidative metabolism mediated by the CYP3A system. *In vitro* studies have determined that neither tenofovir disoproxil nor tenofovir are substrates for the CYP450 enzymes. Neither emtricitabine nor tenofovir inhibited
in vitro drug metabolism mediated by any of the major human CYP450 isoforms involved in drug biotransformation. Also, emtricitabine did not inhibit uridine-5'-diphosphoglucuronyl transferase, the enzyme responsible for glucuronidation.

Elimination
Emtricitabine is primarily excreted by the kidneys with complete recovery of the dose achieved in urine (approximately 86%) and faeces (approximately 14%). Thirteen percent of the emtricitabine dose was recovered in urine as three metabolites. The systemic clearance of emtricitabine averaged 307 mL/min. Following oral administration, the elimination half-life of emtricitabine is approximately 10 hours.

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 urine.

Tenofovir is primarily excreted by the kidney by both filtration and an active tubular transport system (human organic anion transporter 1 [hOAT1]) with approximately 70-80% of the dose excreted unchanged in urine following intravenous administration. The apparent clearance of tenofovir averaged approximately 307 mL/min. Renal clearance has been estimated to be approximately
210 mL/min, which is in excess of the glomerular filtration rate. This indicates that active tubular secretion is an important part of the elimination of tenofovir. Following oral administration, the elimination half-life of tenofovir is approximately 12 to 18 hours.

Pharmacokinetics in special populations
Elderly
Population pharmacokinetic analysis in HIV infected patients showed that rilpivirine pharmacokinetics is not different across the age range (18 to 78 years) evaluated, with only 2

patients aged 65 years of age or older.

Gender
Emtricitabine and tenofovir pharmacokinetics are similar in male and female patients. No clinically relevant differences in pharmacokinetics of rilpivirine have been observed between men and women.

Ethnicity
No clinically important pharmacokinetic differences due to ethnicity have been identified.

Paediatric population
In general, the pharmacokinetics of emtricitabine in infants, children and adolescents (aged 4 months up to 18 years) is similar to those seen in adults. The pharmacokinetics of rilpivirine and tenofovir disoproxil in children and adolescents are under investigation. Dosing recommendations for paediatric patients cannot be made due to insufficient data (see section 4.2).

Renal impairment
Limited data from clinical studies support once daily dosing of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate in patients with mild renal impairment (CrCl 50-80 mL/min). However, long-term safety data for the emtricitabine and tenofovir disoproxil components of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate have not been evaluated in patients with mild renal impairment.
Therefore, in patients with mild renal impairment Emtricitabine/rilpivirine/tenofovir disoproxil fumarate should only be used if the potential benefits of treatment are considered to outweigh the potential risks (see sections 4.2 and 4.4).

Emtricitabine/rilpivirine/tenofovir disoproxil fumarate is not recommended for patients with moderate or severe renal impairment (CrCl< 50 mL/min). Patients with moderate or severe renal impairment require a dose interval adjustment of emtricitabine and tenofovir disoproxil that cannot be achieved with the combination tablet (see sections 4.2 and 4.4).

Pharmacokinetic parameters were mainly determined following administration of single doses of emtricitabine 200 mg or tenofovir disoproxil 245 mg to non-HIV infected patients with varying degrees of renal impairment. The degree of renal impairment was defined according to baseline CrCl (normal renal function when CrCl > 80 mL/min; mild impairment with CrCl = 50-79 mL/min; moderate impairment with CrCl = 30-49 mL/min and severe impairment with CrCl = 10-29 mL/min).

The mean (%CV) emtricitabine drug exposure increased from 12 (25%) µg•h/mL in patients with normal renal function, to 20 (6%) µg•h/mL, 25 (23%) µg•h/mL and 34 (6%) µg•h/mL, in patients with mild, moderate and severe renal impairment, respectively.

The mean (%CV) tenofovir drug exposure increased from 2,185 (12%) ng•h/mL in patients with normal renal function, to 3,064 (30%) ng•h/mL, 6,009 (42%) ng•h/mL and 15,985 (45%) ng•h/mL, in patients with mild, moderate and severe renal impairment, respectively.

In patients with end-stage renal disease (ESRD) requiring haemodialysis, between dialysis drug exposures substantially increased over 72 hours to 53 µg•h/mL (19%) of emtricitabine, and over 48 hours to 42,857 ng•h/mL (29%) of tenofovir.

A small clinical study was conducted to evaluate the safety, antiviral activity and pharmacokinetics of tenofovir disoproxil in combination with emtricitabine in HIV infected patients with renal impairment. A subgroup of patients with baseline CrCl between 50 and 60 mL/min, receiving once daily dosing, had a 2- to 4-fold increase in tenofovir exposure and worsening renal function.

The pharmacokinetics of rilpivirine has not been studied in patients with renal insufficiency. Renal elimination of rilpivirine is negligible. In patients with severe renal impairment or ESRD, plasma concentrations may be increased due to alteration of drug absorption, distribution and/or metabolism secondary to renal dysfunction. As rilpivirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis (see section 4.9).

Hepatic impairment
No dose adjustment of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate is suggested but caution is advised in patients with moderate hepatic impairment. Emtricitabine/rilpivirine/tenofovir disoproxil fumarate has not been studied in patients with severe hepatic impairment (CPT Score C).

Therefore, Emtricitabine/rilpivirine/tenofovir disoproxil fumarate is not recommended in patients with severe hepatic impairment (see sections 4.2 and 4.4).

The pharmacokinetics of emtricitabine has not been studied in patients with varying degrees of hepatic insufficiency.

Rilpivirine hydrochloride is primarily metabolised and eliminated by the liver. In a study comparing 8 patients with mild hepatic impairment (CPT Score A) to 8 matched controls and 8 patients with moderate hepatic impairment (CPT Score B) to 8 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. Rilpivirine has not been studied in patients with severe hepatic impairment (CPT Score C) (see section 4.2). However, it may not be excluded that the pharmacologically active, unbound, rilpivirine exposure is significantly increased in moderate impairment.

A single 245 mg dose of tenofovir disoproxil was administered to non-HIV infected subjects with varying degrees of hepatic impairment defined according to CPT classification. Tenofovir pharmacokinetics was not substantially altered in subjects with hepatic impairment suggesting that no dose adjustment is required in these subjects. The mean (%CV) tenofovir C_{max} and $AUC_{0-\infty}$ values were 223 (34.8%) ng/mL and 2,050 (50.8%) ng•h/mL, respectively, in normal subjects compared with 289 (46.0%) ng/mL and 2,310 (43.5%) ng•h/mL in subjects with moderate hepatic impairment, and 305 (24.8%) ng/mL and 2,740 (44.0%) ng•h/mL in subjects with severe hepatic impairment.

Hepatitis B and/or hepatitis C virus co-infection
In general, emtricitabine pharmacokinetics in HBV infected patients was similar to those in healthy subjects and in HIV infected patients.

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

Switching from an efavirenz-based regimen

The efficacy data from study GS-US-264-0111 (see section 5.1) indicates that the brief period of lower rilpivirine exposure does not impact antiviral efficacy of Emtricitabine/rilpivirine/tenofovir disoproxil fumarate. Due to the decline in efavirenz plasma levels, the inductive effect decreased and rilpivirine concentrations started to normalise. During the time period of declining efavirenz plasma levels and increasing rilpivirine plasma levels after switching, none of the patients had efavirenz or rilpivirine levels below their respective IC_{90} levels at the same time. No dose adjustment is required following the switch from an efavirenz-containing regimen.

Pregnancy and postpartum
After taking rilpivirine 25 mg once daily as part of an antiretroviral regimen, the total exposure of rilpivirine was lower during pregnancy (similar for the 2nd and 3rd trimester) compared with postpartum. The decrease in the unbound free fraction of rilpivirine exposure (i.e. active) during pregnancy compared to postpartum was less pronounced than for total exposure of rilpivirine.

In women receiving rilpivirine 25 mg once daily during the 2nd trimester of pregnancy, mean intra- individual values for total rilpivirine C_{max}, AUC_{24h} and C_{min} values were 21%, 29% and 35% lower, respectively, as compared to postpartum; during the 3rd trimester of pregnancy, C_{max}, AUC_{24h} and C_{min} values were 20%, 31% and 42% lower, respectively, as compared to postpartum.

5.3 Preclinical safety data

Non-clinical data on emtricitabine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, 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 reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential, and toxicity to reproduction and development. Findings in repeated 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 BMD (rats and dogs).

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline
cellulose
Lactose monohydrate
Corn starch
Croscarmellose sodium
Povidone
Polysorbate
Magnesium stearate

Film-coating
Opadry II purple

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with a polypropylene screw cap with aluminium induction sealing liner wad with/without a desiccant. Pack size: 30 tablets

6.6 Special precautions for disposal

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

7. APPLICANT

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9. REGISTRATION DETAILS

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Zimbabwe category for distribution: Prescription Preparations (P.P.)

10. DATE OF REVISION OF THE TEXT

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