1. NAME OF THE MEDICINAL PRODUCT

Eviplera®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg of emtricitabine, 25 mg of rilpivirine (as hydrochloride) and 245 mg of tenofovir disoproxil (as fumarate).

Excipients with known effect

Each film-coated tablet contains 277 mg lactose monohydrate and 4 micrograms sunset yellow aluminium lake (E110).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Purplish-pink, capsule-shaped, film-coated tablet debossed on one side with "GSI" and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EVIPLERA, a combination of two nucleoside analog HIV 1 reverse transcriptase inhibitors (emtricitabine and tenofovir disoproxil) and one non-nucleoside reverse transcriptase inhibitor (rilpivirine), is indicated for use as a complete regimen for the treatment of HIV-1 infection in adult patients with no antiretroviral treatment history and with HIV-1 RNA less than or equal to 100,000 copies/mL at the start of therapy, and in certain virologically-suppressed (HIV-1 RNA <50 copies/mL) adult patients on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen (see below).
The following points should be considered when initiating therapy with EVIPLERA in adult patients with no antiretroviral treatment history:

- More rilpivirine-treated subjects with HIV-1 RNA greater than 100,000 copies/mL at the start of therapy experienced virologic failure (HIV-1 RNA ≥50 copies/mL) compared to rilpivirine-treated subjects with HIV-1 RNA less than or equal to 100,000 copies/mL *[See Pharmacodynamic properties (5.1)]*.

- Regardless of HIV-1 RNA level at the start of therapy, more rilpivirine-treated subjects with CD4+ cell count less than 200 cells/mm^3 experienced virologic failure compared to rilpivirine-treated subjects with CD4+ cell count greater than or equal to 200 cells/mm^3 *[See Pharmacodynamic properties (5.1)]*.

- The observed virologic failure rate in rilpivirine-treated subjects conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz *[See Pharmacodynamic properties (5.1)]*.

- More subjects treated with rilpivirine developed tenofovir and lamivudine/emtricitabine associated resistance compared to efavirenz *[See Pharmacodynamic properties (5.1)]*.

4.2 Posology and method of administration

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

Posology

Adults
The recommended dose of Eviplera is one tablet, taken orally, once daily. Eviplera **must be taken with food** (see section 5.2).

Where discontinuation of therapy with one of the components of Eviplera 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 Eviplera within 12 hours of the time it is usually taken, the patient should take Eviplera with food as soon as possible and resume the normal dosing schedule. If a patient misses a dose of Eviplera 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 Eviplera another Eviplera tablet should be taken with food. If a patient vomits more than 4 hours after taking Eviplera they do not need to take another dose of Eviplera until the next regularly scheduled dose.

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

Special populations

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

Renal impairment
Treatment with Eviplera resulted in an early small increase of mean serum creatinine levels which remained stable over time and is not considered clinically relevant (see section 4.8).

Limited data from clinical studies support once daily dosing of Eviplera in patients with mild renal impairment (creatinine clearance (CrCl) 50-80 mL/min). However, long-term safety data for the emtricitabine and tenofovir disoproxil components of Eviplera have not been evaluated in patients with mild renal impairment. Therefore, in patients with mild renal impairment Eviplera should only be used if the potential benefits of treatment outweigh the potential risks (see sections 4.4 and 5.2).

Eviplera 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 Eviplera in patients with mild or moderate hepatic impairment (Child-Pugh-Turcotte (CPT) Score A or B). No dose adjustment of Eviplera is required in

patients with mild or moderate hepatic impairment. Eviplera should be used with caution in patients with moderate hepatic impairment. Eviplera has not been studied in patients with severe hepatic impairment (CPT Score C). Therefore, Eviplera is not recommended in patients with severe hepatic impairment (see sections 4.4 and 5.2).

If Eviplera 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 Eviplera 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
Lower exposures of rilpivirine (one of the components of Eviplera) were observed during pregnancy; therefore viral load should be monitored closely. Alternatively, switching to another antiretroviral regimen could be considered (see sections 4.4, 4.6, 5.1 and 5.2).

Method of administration

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

4.3 Contraindications

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

Eviplera 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 Eviplera:
- 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

Eviplera 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 Eviplera (see section 5.1).

In the pooled efficacy analysis from the two Phase III clinical studies (C209 [ECHO] and C215 [THRIVE]) through 96 weeks, patients treated with emtricitabine/tenofovir disoproxil + rilpivirine with a baseline viral load > 100,000 HIV-1 RNA copies/mL had a greater risk of virologic failure (17.6% with rilpivirine *versus* 7.6% with efavirenz) compared to patients with a baseline viral load ≤ 100,000 HIV-1 RNA copies/mL (5.9% with rilpivirine *versus* 2.4% with efavirenz). The virologic failure rate in patients treated with emtricitabine/tenofovir disoproxil + rilpivirine at week 48 and week 96 was 9.5% and 11.5% respectively, and 4.2% and 5.1% in the emtricitabine/tenofovir disoproxil + efavirenz arm. The difference in the rate of new virologic failures from the week 48 to week 96 analysis between rilpivirine and efavirenz arms was not statistically significant. 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. More patients who failed

virologically on rilpivirine than who failed virologically on efavirenz developed lamivudine/emtricitabine associated resistance (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. Eviplera 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

Eviplera 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). Eviplera should not be administered concomitantly with rilpivirine hydrochloride unless needed for dose adjustment with rifabutin (see sections 4.2 and 4.5). Eviplera should not be administered concomitantly with adefovir dipivoxil (see section 4.5).

Co-administration of Eviplera and didanosine is not recommended (see section 4.5).

Renal impairment

Eviplera 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 Eviplera should be avoided with concurrent or recent use of a nephrotoxic medicinal product (see section 4.5). If concomitant use of Eviplera 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 Eviplera 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 Eviplera 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 Eviplera, 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 Eviplera is a combination product and the dosing interval of the individual components cannot be altered, treatment with Eviplera 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 Eviplera 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 Eviplera is indicated or where dose modification is necessary, separate preparations of emtricitabine, rilpivirine hydrochloride and tenofovir disoproxil are available.

Bone effects

A dual energy X ray absorptiometry (DXA) substudy for both the Phase III studies (C209 and C215) investigated the effect of rilpivirine as compared with control, overall and by background regimen on changes in whole body bone mineral density (BMD) and bone mineral content (BMC) at week 48 and week 96. DXA substudies showed that small but statistically significant decreases from baseline in whole body BMD and BMC were similar for rilpivirine and control at week 48 and week 96. There was no difference in the change from baseline in whole body BMD or BMC for rilpivirine compared with control, in the overall population or in those patients treated with a backbone regimen including tenofovir disoproxil.

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).

Reductions of BMD have been observed with tenofovir disoproxil in randomized 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 (PI). 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.

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 Eviplera 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 Eviplera 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 Eviplera 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 Eviplera 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 Eviplera in patients with mild or moderate hepatic impairment (see sections 4.2 and 5.2). Eviplera 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 Eviplera, including but not limited to rashes accompanied by fever, blisters, conjunctivitis, angioedema, elevated liver function tests, and/or eosinophilia. These symptoms resolved after Eviplera was discontinued. As soon as serious skin and/or mucosal reactions are observed, Eviplera 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

Eviplera 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 Eviplera (see sections 4.2 and 5.2).

Pregnancy

Lower exposures of rilpivirine were observed when rilpivirine 25 mg once daily was taken during pregnancy. In the Phase III studies (C209 and C215), 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

Eviplera contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Eviplera contains a colourant called sunset yellow aluminium lake (E110), which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

As Eviplera contains emtricitabine, rilpivirine hydrochloride and tenofovir disoproxil, any interactions that have been identified with these active substances individually may occur with Eviplera. 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 Eviplera 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 Eviplera (see section 4.3).

Co-administration of Eviplera 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 Eviplera (see section 4.3).

Concomitant use not recommended

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

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

Didanosine
The co-administration of Eviplera 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 Eviplera 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 Eviplera 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 Eviplera with other NNRTIs.

Concomitant use where caution is recommended

Cytochrome P450 enzyme inhibitors
Co-administration of Eviplera with medicinal products that inhibit CYP3A enzyme activity has been observed to increase rilpivirine plasma concentrations.

QT prolonging medicinal products
Eviplera 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). In a clinical study rilpivirine did not significantly affect the pharmacokinetics of digoxin. However, it may not be completely excluded that rilpivirine can increase the exposure to other medicinal products transported by P-gp that are more sensitive to intestinal P-gp inhibition (e.g. dabigatran etexilate).

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 Eviplera 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 Eviplera or its individual component(s) and other medicinal products

Medicinal product by therapeutic areas	Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with Eviplera
ANTI-INFECTIVES		
Antiretrovirals		
Nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs/N[t]RTIs)		
Didanosine/Emtricitabine	Interaction not studied.	Co-administration of Eviplera 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 (400 mg once daily)/ Rilpivirine[1]	Didanosine: AUC: ↑ 12% C_{min}: N/A C_{max}: ↔ Rilpivirine: AUC: ↔ C_{min}: ↔ C_{max}: ↔	
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, C_{max}, C_{min}	Recommendation concerning co-administration with Eviplera
Protease inhibitors (PIs) - boosted (with co-administration of low-dose ritonavir)		
Atazanavir/Ritonavir/Emtricitabine	Interaction not studied.	Concomitant use of Eviplera 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	Interaction not studied.	
Atazanavir (300 mg once daily)/ Ritonavir (100 mg once daily)/ Tenofovir disoproxil (245 mg once daily)	Atazanavir: AUC: ↓ 25% C_{max}: ↓ 28% C_{min}: ↓ 26% Tenofovir: AUC: ↑ 37% C_{max}: ↑ 34% C_{min}: ↑ 29%	
Darunavir/Ritonavir/Emtricitabine	Interaction not studied.	
Darunavir (800 mg once daily)/ Ritonavir (100 mg once daily)/ Rilpivirine[1]	Darunavir: AUC: ↔ C_{min}: ↓ 11% C_{max}: ↔ 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: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 22% C_{min}: ↑ 37%	
Lopinavir/Ritonavir/Emtricitabine	Interaction not studied.	
Lopinavir (400 mg twice daily)/ Ritonavir (100 mg twice daily)/ Rilpivirine[1] (soft capsule)	Lopinavir: AUC: ↔ C_{min}: ↓ 11% C_{max}: ↔ 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: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 32% C_{max}: ↔ C_{min}: ↑ 51%	
CCR5 antagonists		
Maraviroc/Emtricitabine	Interaction not studied.	No clinically relevant drug-drug interaction is expected. No dose adjustment is required.
Maraviroc/Rilpivirine	Interaction not studied.	
Maraviroc (300 mg twice daily)/ Tenofovir disoproxil (245 mg once daily)	AUC: ↔ C_{max}: ↔ Tenofovir concentrations not measured, no effect is expected.	

Medicinal product by therapeutic areas	Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with Eviplera
Integrase strand transfer inhibitors		
Raltegravir/Emtricitabine	Interaction not studied.	No clinically relevant drug-drug interaction is expected. No dose adjustment is required.
Raltegravir/Rilpivirine	Raltegravir: AUC: ↑ 9% C_{min}: ↑ 27% C_{max}: ↑ 10% Rilpivirine: AUC: ↔ C_{min}: ↔ C_{max}: ↔	
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, C_{max}, C_{min}	Recommendation concerning co-administration with Eviplera
Sofosbuvir/Velpatasvir (400 mg/100 mg once daily)/ Emtricitabine/Rilpivirine/Tenofovir disoproxil (200 mg/25 mg/245 mg once daily)	Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[4]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Rilpivirine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ 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, C_{max}, C_{min}	Recommendation concerning co-administration with Eviplera
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 Eviplera. *Expected:* Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[4]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Voxilaprevir AUC: ↔ C_{max}: ↔ C_{min}: ↔ Rilpivirine: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ C_{max}: ↑ 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 required.
Sofosbuvir (400 mg once daily)/ Rilpivirine (25 mg once daily)	Sofosbuvir: AUC: ↔ C_{max}: ↑ 21% GS-331007[4]: AUC: ↔ C_{max}: ↔ Rilpivirine: AUC: ↔ C_{max}: ↔ C_{min}: ↔	
Sofosbuvir/Tenofovir disoproxil	Interaction not studied.	
Ribavirin/Tenofovir disoproxil	Ribavirin: AUC: ↔ C_{max}: ↔ C_{min}: N/A	No dose adjustment is required.

Medicinal product by therapeutic areas	Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with Eviplera
Herpesvirus antiviral agents		
Famciclovir/Emtricitabine	Famciclovir: AUC: ↔ C_{max}: ↔ C_{min}: N/A Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: N/A	No dose adjustment is required.
Antifungals		
Ketoconazole/Emtricitabine	Interaction not studied.	Concomitant use of Eviplera 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 (400 mg once daily)/ Rilpivirine[1] Fluconazole[2] Itraconazole[2] Posaconazole[2] Voriconazole[2]	Ketoconazole: AUC: ↓ 24% C_{min}: ↓ 66% C_{max}: ↔ Rilpivirine: AUC: ↑ 49% C_{min}: ↑ 76% C_{max}: ↑ 30%	
Ketoconazole/Tenofovir disoproxil	Interaction not studied.	
Antimycobacterials		
Rifabutin/Emtricitabine	Interaction not studied.	Co-administration is likely to cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). When Eviplera is co-administered with rifabutin, an additional 25 mg tablet of rilpivirine per day is recommended to be taken concomitantly with Eviplera, for the duration of the rifabutin co-administration.
Rifabutin (300 mg once daily)/ Rilpivirine[3]	Rifabutin: AUC: ↔ C_{min}: ↔ C_{max}: ↔ 25-O-desacetyl-rifabutin: AUC: ↔ C_{min}: ↔ C_{max}: ↔	
Rifabutin (300 mg once daily)/ Rilpivirine (25 mg once daily)	Rilpivirine: AUC: ↓ 42% C_{min}: ↓ 48% C_{max}: ↓ 31%	
Rifabutin (300 mg once daily)/ Rilpivirine (50 mg once daily)	Rilpivirine: AUC: ↑ 16%* C_{min}: ↔* C_{max}: ↑ 43%* *compared to 25 mg once daily rilpivirine alone	
Rifabutin/Tenofovir disoproxil	Interaction not studied.	

Medicinal product by therapeutic areas	Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with Eviplera
Rifampicin/Emtricitabine	Interaction not studied.	Eviplera 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 Eviplera (see section 4.3).
Rifampicin (600 mg once daily)/ Rilpivirine[1]	Rifampicin: AUC: ↔ C_{min}: N/A C_{max}: ↔ 25-desacetyl-rifampicin: AUC: ↓ 9% C_{min}: N/A C_{max}: ↔ Rilpivirine: AUC: ↓ 80% C_{min}: ↓ 89% C_{max}: ↓ 69%	
Rifampicin (600 mg once daily)/ Tenofovir disoproxil (245 mg once daily)	Rifampicin: AUC: ↔ C_{max}: ↔ Tenofovir: AUC: ↔ C_{max}: ↔	
Rifapentine[2]	Interaction not studied with any components of Eviplera.	Eviplera 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 Eviplera (see section 4.3).
Macrolide antibiotics		
Clarithromycin Erythromycin	Interaction not studied with any components of Eviplera.	The combination of Eviplera 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 Eviplera.	Eviplera 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 Eviplera (see section 4.3).

Medicinal product by therapeutic areas	Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with Eviplera
GLUCOCORTICOIDS		
Dexamethasone (systemic, except for single dose use)	Interaction not studied with any components of Eviplera.	Eviplera 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 Eviplera (see section 4.3). Alternatives should be considered, particularly for long-term use.
PROTON PUMP INHIBITORS		
Omeprazole/Emtricitabine	Interaction not studied.	Eviplera 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 Eviplera (see section 4.3).
Omeprazole (20 mg once daily)/ Rilpivirine[1] Lansoprazole[2] Rabeprazole[2] Pantoprazole[2] Esomeprazole[2]	Omeprazole: AUC: ↓ 14% C_{min}: N/A C_{max}: ↓ 14% Rilpivirine: AUC: ↓ 40% C_{min}: ↓ 33% C_{max}: ↓ 40%	
Omeprazole/Tenofovir disoproxil	Interaction not studied.	
H_2-RECEPTOR ANTAGONISTS		
Famotidine/Emtricitabine	Interaction not studied.	The combination of Eviplera 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 Eviplera should be used.
Famotidine (40 mg single dose taken 12 hours before rilpivirine)/ Rilpivirine[1] Cimetidine[2] Nizatidine[2] Ranitidine[2]	Rilpivirine: AUC: ↓ 9% C_{min}: N/A C_{max}: ↔	
Famotidine (40 mg single dose taken 2 hours before rilpivirine)/ Rilpivirine[1]	Rilpivirine: AUC: ↓ 76% C_{min}: N/A C_{max}: ↓ 85%	
Famotidine (40 mg single dose taken 4 hours after rilpivirine)/ Rilpivirine[1]	Rilpivirine: AUC: ↑ 13% C_{min}: N/A C_{max}: ↑ 21%	
Famotidine/Tenofovir disoproxil	Interaction not studied.	
ANTACIDS		
Antacids (e.g. aluminium or magnesium hydroxide, calcium carbonate)	Interaction not studied with any of the components of Eviplera.	The combination of Eviplera 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 Eviplera.

Medicinal product by therapeutic areas	Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with Eviplera
NARCOTIC ANALGESICS		
Methadone/Emtricitabine	Interaction not studied.	No dose adjustments are required when initiating co-administration of methadone with Eviplera. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.
Methadone (60-100 mg once daily, individualised dose)/Rilpivirine	R(-) methadone: AUC: ↓ 16% C_{min}: ↓ 22% C_{max}: ↓ 14% Rilpivirine: AUC: ↔* C_{min}: ↔* C_{max}: ↔* *based on historic controls	
Methadone/Tenofovir disoproxil	Methadone: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Tenofovir: AUC: ↔ C_{min}: ↔ C_{max}: ↔	
ANALGESICS		
Paracetamol/Emtricitabine	Interaction not studied.	No dose adjustment is required.
Paracetamol (500 mg single dose)/ Rilpivirine[1]	Paracetamol: AUC: ↔ C_{min}: N/A C_{max}: ↔ Rilpivirine: AUC: ↔ 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: ↔ C_{min}: ↔ C_{max}: ↑ 17% Norethindrone: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Rilpivirine: AUC: ↔* C_{min}: ↔* C_{max}: ↔* *based on historic controls	
Ethinylestradiol/Norethindrone/ Tenofovir disoproxil	Ethinylestradiol: AUC: ↔ C_{max}: ↔ Tenofovir: AUC: ↔ C_{max}: ↔	

Medicinal product by therapeutic areas	Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with Eviplera
Norgestimate/Ethinylestradiol/ Tenofovir disoproxil	Norgestimate: AUC: ↔ C_{max}: ↔ C_{min}: N/A Ethinylestradiol: AUC: ↔ C_{max}: ↔ C_{min}: ↔	No dose adjustment is required.
ANTIARRHYTHMICS		
Digoxin/Emtricitabine	Interaction not studied.	No dose adjustment is required.
Digoxin/Rilpivirine	Digoxin: AUC: ↔ C_{min}: N/A C_{max}: ↔	
Digoxin/Tenofovir disoproxil	Interaction not studied.	
ANTICOAGULANTS		
Dabigatran etexilate	Interaction not studied with any of the components of Eviplera.	A risk for increases in dabigatran plasma concentrations cannot be excluded (inhibition of intestinal P-gp. The combination of Eviplera and dabigatran etexilate should be used with caution.
IMMUNOSUPPRESSANTS		
Tacrolimus/Tenofovir disoproxil/ Emtricitabine	Tacrolimus: AUC: ↔ C_{max}: ↔ C_{min}: N/A Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: N/A Tenofovir: AUC: ↔ C_{max}: ↔ C_{min}: N/A	No dose adjustment is required.
ANTIDIABETICS		
Metformin/Emtricitabine	Interaction not studied.	No dose adjustment is required.
Metformin (850 mg single dose)/ Rilpivirine	Metformin: AUC: ↔ C_{min}: N/A C_{max}: ↔	
Metformin/Tenofovir disoproxil	Interaction not studied.	
HERBAL PRODUCTS		
St. John's wort (*Hypericum perforatum*)	Interaction not studied with any of the components of Eviplera.	Eviplera 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 Eviplera (see section 4.3).

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

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 Eviplera must be accompanied by the use of effective contraception.

Pregnancy

There are no adequate and well-controlled studies of Eviplera or its components in pregnant women. A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicate no malformative or foetal/neonatal toxicity of rilpivirine (see sections 4.4, 5.1 and 5.2). Lower exposures of rilpivirine were observed during pregnancy; therefore viral load should be monitored closely. A large amount of data on pregnant women (more than 1,000 pregnancy outcomes) indicate no malformative nor foetal/neonatal toxicity associated with emtricitabine and tenofovir disoproxil.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3) with the components of Eviplera.

The use of Eviplera 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 Eviplera 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 Eviplera.

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 Eviplera 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

Eviplera 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 Eviplera (see section 4.8). This should be considered when assessing a patient's ability to drive or operate machinery.

4.8 Undesirable effects

Summary of the safety profile

The combination of emtricitabine, rilpivirine and tenofovir disoproxil has been studied as the component products in treatment-naïve patients (Phase III studies C209 and C215). The single-tablet regimen (STR), Eviplera, has been studied in virologically suppressed patients who switched from a regimen containing a ritonavir-boosted PI (Phase III study GS-US-264-0106) or from efavirenz/emtricitabine/tenofovir disoproxil (Phase IIb study GS-US-264-0111). In treatment-naïve patients, the most frequently reported adverse reactions considered possibly or probably related to rilpivirine hydrochloride and emtricitabine/tenofovir disoproxil were nausea (9%), dizziness (8%), abnormal dreams (8%), headache (6%), diarrhoea (5%) and insomnia (5%) (pooled data from the Phase III clinical studies C209 and C215, see section 5.1). In virologically suppressed patients switching to Eviplera, the most frequently reported adverse reactions considered possibly or probably related to Eviplera were fatigue (3%), diarrhoea (3%), nausea (2%) and insomnia (2%) (48 week data from the Phase III study GS-US-264-0106). The safety profile of emtricitabine and tenofovir disoproxil in these studies was consistent with the previous experience with these agents when each was administered with other antiretroviral agents.

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 Eviplera (see section 4.4).

Discontinuation of Eviplera 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 Eviplera 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 Eviplera based on clinical study and post-marketing experience with Eviplera 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]
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, 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]

Frequency	Adverse reaction
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. 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 a statistical calculation based on the total number of patients exposed to emtricitabine in these clinical studies (n = 1,563).
7 This adverse reaction was identified through post-marketing surveillance for Eviplera (fixed-dose combination) but not observed in randomised controlled clinical studies for Eviplera. The frequency category was estimated from a statistical calculation based on the total number of patients exposed to Eviplera or all of its components in randomised controlled clinical studies (n = 1,261). See section 4.8, *Description of selected adverse reactions.*
8 This adverse reaction was identified through post-marketing surveillance for tenofovir disoproxil but not observed in randomised controlled clinical studies or the expanded access program for tenofovir disoproxil. The frequency category was estimated from a statistical calculation based on the total number of patients exposed to tenofovir disoproxil in randomised controlled clinical studies and the expanded access program (n = 7,319).

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 high-density lipoprotein (HDL)-cholesterol (fasted) 4 mg/dL, in low density lipoprotein (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 Eviplera from a regimen containing a ritonavir-boosted PI, 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 Eviplera 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 Eviplera, 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. Eviplera is not recommended in this population (see section 4.2).

When emtricitabine (one of the components of Eviplera) 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*).

Other special populations

Elderly
Eviplera 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 Eviplera (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 Eviplera (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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form : https://sideeffects.health.gov.il/

4.9 Overdose

An increased risk of adverse reactions associated with Eviplera 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 Eviplera. 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

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

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.

The antiviral activity of emtricitabine against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The 50% effective concentration (EC_{50}) values for emtricitabine were in the range of 0.0013 to 0.64 μM.

Emtricitabine displayed antiviral activity in cell culture against HIV-1 subtype A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007 to 0.075 μM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.007 to 1.5 μM).

In combination studies of emtricitabine with NRTIs (abacavir, didanosine, lamivudine, stavudine, tenofovir, and zidovudine), NNRTIs (delavirdine, efavirenz, nevirapine, and rilpivirine), and PIs (amprenavir, nelfinavir, ritonavir, and saquinavir), additive to synergistic effects were observed.

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 10,830 nM (920 to 3,970 ng/mL), treatment of HIV-2 infection with rilpivirine hydrochloride is not recommended in the absence of clinical data.

Rilpivirine also demonstrated antiviral activity against a broad panel of HIV-1 group M (subtype A, B, C, D, F, G, H) primary isolates with EC_{50} values ranging from 0.07 to 1.01 nM (0.03 to 0.37 ng/mL) and group O primary isolates with EC_{50} values ranging from 2.88 to 8.45 nM (1.06 to 3.10 ng/mL).

The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC_{50} values for tenofovir were in the range of 0.04 to 8.5 μM.

Tenofovir displayed antiviral activity in cell culture against HIV-1 subtype A, B, C, D, E, F, G, and O (EC_{50} values ranged from 0.5 to 2.2 μM) and strain specific activity against HIV-2 (EC_{50} values ranged from 1.6 to 5.5 μM).

In combination studies of tenofovir with NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, and zidovudine), NNRTIs (delavirdine, efavirenz, nevirapine, and rilpivirine), and PIs (amprenavir, indinavir, nelfinavir, ritonavir, and saquinavir), additive to synergistic effects were observed.

Resistance

Considering all of the available *in vitro* data and data generated in previously untreated patients, the following resistance-associated mutations in HIV-1 RT, when present at baseline, may affect the activity of Eviplera: K65R, K70E, K101E, K101P, E138A, E138G, E138K, E138Q, E138R, V179L, Y181C, Y181I, Y181V, M184I, M184V, Y188L, H221Y, F227C, M230I, M230L and the combination of L100I and K103N.

A negative impact by NNRTI mutations other than those listed above (e.g. mutations K103N or L100I as single mutations) cannot be excluded, since this was not studied *in vivo* in a sufficient number of patients.

As with other antiretroviral medicinal products, resistance testing and/or historical resistance data should guide the use of Eviplera (see section 4.4).

In cell culture
Resistance to emtricitabine or tenofovir has been seen *in vitro* and in some HIV-1 infected patients due to the development of the M184V or M184I substitution in RT with emtricitabine, or the K65R substitution in RT with tenofovir. In addition, a K70E substitution in HIV-1 RT has been selected by tenofovir and results in low-level reduced susceptibility to abacavir, emtricitabine, tenofovir and lamivudine. No other pathways of resistance to emtricitabine or tenofovir have been identified. Emtricitabine-resistant viruses with the M184V/I mutation were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir, zalcitabine and zidovudine. The K65R mutation can also be selected by abacavir or didanosine and results in reduced susceptibility to these agents plus to lamivudine, emtricitabine, and tenofovir. Tenofovir disoproxil should be avoided in patients with HIV-1 harbouring the K65R mutation. The K65R, M184V, and K65R+M184V mutants of HIV-1 remain fully susceptible to rilpivirine.

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 resistance-associated mutations that emerged included L100I, K101E, V108I, E138K, V179F, Y181C, H221Y, F227C and M230I.

In treatment-naïve HIV-1 infected patients
For the resistance analyses, a broader definition of virologic failure was used than in the primary efficacy analysis. In the cumulative week 96 pooled resistance analysis for patients receiving

rilpivirine in combination with emtricitabine/tenofovir disoproxil, a greater risk of virologic failure for patients in the rilpivirine arm was observed within the first 48 weeks of these studies (11.5% in the rilpivirine arm and 4.2% in the efavirenz arm) while low rates of virologic failure, similar between the treatment arms, were observed from the week 48 to week 96 analysis (15 patients or 2.7% in the rilpivirine arm and 14 patients or 2.6% in the efavirenz arm). Of these virologic failures 5/15 (rilpivirine) and 5/14 (efavirenz) were in patients with a baseline viral load of ≤ 100,000 copies/mL.

In the week 96 pooled resistance analysis for patients receiving emtricitabine/tenofovir disoproxil + rilpivirine hydrochloride in the Phase III clinical studies C209 and C215, there were 78 virologic failure patients with genotypic resistance information available for 71 of those patients. In this analysis, the NNRTI resistance-associated mutations that developed most commonly in these patients were: V90I, K101E, E138K/Q, V179I, Y181C, V189I, H221Y and F227C. The most common mutations were the same in the week 48 and week 96 analyses. In the studies, the presence of the mutations V90I and V189I at baseline did not affect the response. The E138K substitution emerged most frequently during rilpivirine treatment, commonly in combination with the M184I substitution. 52% of patients with virologic failure in the rilpivirine arm developed concomitant NNRTI and NRTI mutations. The mutations associated with NRTI resistance that developed in 3 or more patients were: K65R, K70E, M184V/I and K219E during the treatment period.

Through week 96, fewer patients in the rilpivirine arm with baseline viral load ≤ 100,000 copies/mL had emerging resistance-associated substitutions and/or phenotypic resistance to rilpivirine (7/288) than patients with baseline viral load > 100,000 copies/mL (30/262). Among those patients who developed resistance to rilpivirine, 4/7 patients with baseline viral load ≤ 100,000 copies/mL and 28/30 patients with baseline viral load > 100,000 copies/mL had cross-resistance to other NNRTIs.

In virologically suppressed HIV-1 infected patients
Study GS-US-264-0106
Of the 469 Eviplera-treated patients [317 patients who switched to Eviplera at baseline (Eviplera arm) and 152 patients who switched at week 24 (Delayed Switch arm)], a total of 7 patients were analysed for resistance development and all had genotypic and phenotypic data available. Through week 24, two patients who switched to Eviplera at baseline (2 of 317 patients, 0.6%) and one patient who maintained their ritonavir-boosted PI-based regimen [Stayed on Baseline Regimen (SBR) arm] (1 of 159 patients, 0.6%) developed genotypic and/or phenotypic resistance to study drugs. After week 24, the HIV-1 from 2 additional patients in the Eviplera arm developed resistance by week 48 (total of 4 of 469 patients, 0.9%). The remaining 3 Eviplera-treated patients did not have emergent resistance.

The most common emergent resistance mutations in Eviplera-treated patients were M184V/I and E138K in RT. All patients remained susceptible to tenofovir. Of the 24 patients treated with Eviplera who had the NNRTI-associated K103N substitution pre-existing at baseline in their HIV-1, 17 of 18 patients in the Eviplera arm and 5 of 6 patients in the SBR arm maintained virologic suppression after switching to Eviplera through 48 weeks and 24 weeks of treatment, respectively. One patient with pre-existing K103N at baseline had virologic failure with additional emergent resistance by week 48.

Study GS-US-264-0111
Through week 48, no emergent resistance developed in the 2 patients who failed virologically among patients who switched to Eviplera from efavirenz/emtricitabine/tenofovir disoproxil (0 of 49 patients).

Cross-resistance

No significant cross-resistance has been demonstrated between rilpivirine-resistant HIV-1 variants and emtricitabine or tenofovir, or between emtricitabine- or tenofovir-resistant variants and rilpivirine.

In cell culture
Emtricitabine
Emtricitabine-resistant viruses with the M184V/I substitution were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir, and zidovudine.

Viruses harbouring substitutions conferring reduced susceptibility to stavudine and zidovudine-thymidine analogue-associated mutations-TAMs (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E), or didanosine (L74V) remained sensitive to emtricitabine. HIV-1 containing the K103N substitution or other substitutions associated with resistance to rilpivirine and other NNRTIs was susceptible to emtricitabine.

Rilpivirine hydrochloride
In a panel of 67 HIV-1 recombinant laboratory strains with one resistance-associated mutation 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 resistance-associated mutations associated with a loss of susceptibility to rilpivirine were: K101P and Y181V/I. The K103N substitution alone did not result in reduced susceptibility to rilpivirine, but the combination of K103N and L100I resulted in a 7-fold reduced susceptibility to rilpivirine. In another study, the Y188L substitution resulted in a reduced susceptibility to rilpivirine of 9-fold for clinical isolates and 6-fold for site-directed mutants.

Tenofovir disoproxil
The K65R and also the K70E substitution result in reduced susceptibility to abacavir, didanosine, lamivudine, emtricitabine, and tenofovir, but retain sensitivity to zidovudine.

Patients with HIV-1 expressing three or more TAMs that included either the M41L or L210W RT substitution showed reduced response to tenofovir disoproxil.

Virologic response to tenofovir disoproxil was not reduced in patients with HIV-1 that expressed the abacavir/emtricitabine/lamivudine resistance-associated M184V substitution.

HIV-1 containing the K103N, Y181C, or rilpivirine-associated substitutions with resistance to NNRTIs were susceptible to tenofovir.

In treatment-naïve patients
Resistance outcomes, including cross-resistance to other NNRTIs, in patients receiving rilpivirine hydrochloride in combination with emtricitabine/tenofovir disoproxil in Phase III studies (C209 and C215 pooled data) and experiencing virological failure, are shown in Table 3 below.

Table 3: Phenotypic resistance and cross-resistance outcomes from studies C209 and C215 (pooled data) for patients receiving rilpivirine hydrochloride in combination with emtricitabine/tenofovir disoproxil at week 96 (based on resistance analysis)

	In patients with phenotypic data (n = 66)	**In patients with BL VL[1] ≤ 100,000 copies/mL (n = 22)**	**In patients with BL VL[1] > 100,000 copies/mL (n = 44)**
Resistance to rilpivirine[2]	31/66	4/22	27/44
Cross-resistance[3] to			
etravirine	28/31	3/4	25/27
efavirenz	27/31	3/4	24/27
nevirapine	13/31	1/4	12/27
Resistance to emtricitabine/lamivudine (M184I/V)	40/66	9/22	31/44
Resistance to tenofovir (K65R)	2/66	0/22	2/44

1 BL VL = Baseline viral load.
2 Phenotypic resistance to rilpivirine (> 3.7-fold change compared to control).
3 Phenotypic resistance (Antivirogram).

In virologically suppressed HIV-1 infected patients
In study GS-US-264-0106, 4 of the 469 patients who switched from a ritonavir-boosted protease inhibitor (PI)-based regimen to Eviplera had HIV-1 with reduced susceptibility to at least one

component of Eviplera through week 48. *De novo* resistance to emtricitabine/lamivudine was seen in 4 cases, and also to rilpivirine in 2 cases, with a consequent cross-resistance to efavirenz (2/2), nevirapine (2/2) and etravirine (1/2).

Effects on electrocardiogram

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

When supratherapeutic doses of 75 mg once daily and 300 mg once daily of rilpivirine hydrochloride were studied in healthy adults, the maximum mean time-matched (95% upper confidence bound) differences in QTcF interval from placebo after baseline correction were 10.7 (15.3) and 23.3 (28.4) ms, respectively. Steady-state administration of rilpivirine hydrochloride 75 mg once daily and 300 mg once 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 once daily dose of rilpivirine hydrochloride.

Clinical experience

Treatment-naïve HIV-1 infected patients
The efficacy of Eviplera is based on the analyses of 96 week data from two randomised, double-blind, controlled studies C209 and C215. Antiretroviral treatment-naïve HIV-1 infected patients were enrolled (n = 1,368) who had a plasma HIV-1 RNA ≥ 5,000 copies/mL and were screened for susceptibility to N(t)RTI and for absence of specific NNRTI resistance-associated mutations. The studies are identical in design with the exception of the background regimen (BR). Patients were randomised in a 1:1 ratio to receive either rilpivirine hydrochloride 25 mg (n = 686) once daily or efavirenz 600 mg (n = 682) once daily in addition to a BR. In study C209 (n = 690), the BR was emtricitabine/tenofovir disoproxil. In study C215 (n = 678), the BR consisted of 2 investigator selected N(t)RTIs: emtricitabine/tenofovir disoproxil (60%, n = 406) or lamivudine/zidovudine (30%, n = 204) or abacavir plus lamivudine (10%, n = 68).

In the pooled analysis for C209 and C215 of patients who received a background regimen of emtricitabine/tenofovir disoproxil, demographic and baseline characteristics were balanced between the rilpivirine and efavirenz arm. Table 4 displays selected demographic and baseline disease characteristics. Median plasma HIV-1 RNA was 5.0 and 5.0 $\log_{10}$ copies/mL and median CD4+ count was 247 x 10^6 cells/L and 261 x 10^6 cells/L for patients randomised to rilpivirine and efavirenz arm, respectively.

Table 4: Demographic and baseline characteristics of antiretroviral treatment-naïve HIV-1 infected adult patients in studies C209 and C215 (pooled data for patients receiving rilpivirine hydrochloride or efavirenz in combination with emtricitabine/tenofovir disoproxil) at week 96

	Rilpivirine + Emtricitabine/Tenofovir disoproxil n = 550	**Efavirenz + Emtricitabine/Tenofovir disoproxil n = 546**
Demographic Characteristics		
Median age (range), years	36.0 (18-78)	36.0 (19-69)
Sex		
Male	78%	79%
Female	22%	21%
Ethnicity		
White	64%	61%
Black/African American	25%	23%
Asian	10%	13%
Other	1%	1%
Not allowed to ask per local regulations	1%	1%
Baseline disease characteristics		
Median baseline plasma HIV-1 RNA (range), $\log_{10}$ copies/mL	5.0 (2-7)	5.0 (3-7)
Median baseline CD4+ cell count (range), x 10^6 cells/L	247 (1-888)	261 (1-857)
Percentage of patients with HBV/HCV co-infection	7.7%	8.1%

A subgroup analysis of the virologic response (< 50 HIV-1 RNA copies/mL) at both 48 weeks and 96 weeks, and virologic failure by baseline viral load (pooled data from the two Phase III clinical studies, C209 and C215, for patients receiving the emtricitabine/tenofovir disoproxil background regimen) is presented in Table 5. The response rate (confirmed undetectable viral load < 50 HIV-1 RNA copies/mL) at week 96 was comparable between the rilpivirine arm and the efavirenz arm. The incidence of virologic failure was higher in the rilpivirine arm than in the efavirenz arm at week 96; however, most of the virologic failures occurred within the first 48 weeks of treatment. Discontinuations due to adverse events were higher in the efavirenz arm at week 96 than in the rilpivirine arm.

Table 5: Virologic outcomes of randomised treatment of studies C209 and C215 (pooled data for patients receiving rilpivirine hydrochloride or efavirenz in combination with emtricitabine/tenofovir disoproxil) at week 48 (primary) and week 96

	Rilpivirine + Emtricitabine/ Tenofovir disoproxil n = 550	**Efavirenz + Emtricitabine/ Tenofovir disoproxil n = 546**	**Rilpivirine + Emtricitabine/ Tenofovir disoproxil n = 550**	**Efavirenz + Emtricitabine/ Tenofovir disoproxil n = 546**
	Week 48		**Week 96**	
Overall response (HIV-1 RNA < 50 copies/mL (TLOVR[a]))[b]	83.5% (459/550) (80.4, 86.6)	82.4% (450/546) (79.2, 85.6)	76.9% (423/550)	77.3% (422/546)
By baseline viral load (copies/mL)				
≤ 100,000	**89.6% (258/288) (86.1, 93.1)**	**84.8% (217/256) (80.4, 89.2)**	**83.7% (241/288)**	**80.8% (206/255)**
> 100,000	76.7% (201/262) (71.6, 81.8)	80.3% (233/290) (75.8, 84.9)	69.5% (182/262)	74.2% (216/291)
By baseline CD4+ cell count (x 10^6 cells/L)				
< 50	51.7% (15/29) (33.5, 69.9)	79.3% (23/29) (64.6, 94.1)	48.3% (28.9, 67.6)	72.4% (55.1, 89.7)
≥ 50-200	80.9% (123/152) (74.7, 87.2)	80.7% (109/135) (74.1, 87.4)	71.1% (63.8, 78.3)	72.6% (65.0, 80.2)
≥ 200-350	86.3% (215/249) (82.1, 90.6)	82.3% (205/249) (77.6, 87.1)	80.7% (75.8, 85.7)	78.7% (73.6, 83.8)
≥ 350	89.1% (106/119) (83.5, 94.7)	85.0% (113/133) (78.9, 91.0)	84.0% (77.4, 90.7)	80.5% (73.6, 87.3)
Non-response				
Virologic failure (all patients)	9.5% (52/550)	4.2% (23/546)	11.5% (63/550)[c]	5.1% (28/546)[d]
By baseline viral load (copies/mL)				
≤ 100,000	**4.2% (12/288)**	**2.3% (6/256)**	**5.9% (17/288)**	**2.4% (6/255)**
> 100,000	15.3% (40/262)	5.9% (17/290)	17.6% (46/262)	7.6% (22/291)
Death	0	0.2% (1/546)	0	0.7% (4/546)
Discontinued due to adverse event (AE)	2.2% (12/550)	7.1% (39/546)	3.6% (20/550)	8.1% (44/546)
Discontinued for non-AE reason[e]	4.9% (27/550)	6.0% (33/546)	8% (44/550)	8.8% (48/546)

n = total number of patients per treatment group

a ITT TLOVR = Intention to treat time to loss of virologic response

b The difference of response rate is 1% (95% confidence interval -3% to 6%) using normal approximation.

c There were 17 new virologic failures between the week 48 primary analysis and week 96 (6 patients with baseline viral load ≤ 100,000 copies/mL and 11 patients with baseline viral load > 100,000 copies/mL). There were also reclassifications in the week 48 primary analysis with the most common being reclassification from virologic failure to discontinued for non-AE reasons.

d There were 10 new virologic failures between the week 48 primary analysis and week 96 (3 patients with baseline viral load ≤ 100,000 copies/mL and 7 patients with baseline viral load > 100,000 copies/mL). There were also reclassifications in the week 48 primary analysis with the most common being reclassification from virologic failure to discontinued for non-AE reasons.

e e.g. lost to follow up, non-compliance, withdrew consent.

Emtricitabine/tenofovir disoproxil + rilpivirine hydrochloride has been shown to be non-inferior in achieving HIV-1 RNA < 50 copies/mL compared to emtricitabine/tenofovir disoproxil + efavirenz.

At week 96 the mean changes in CD4+ cell count from baseline were +226 x 10^6 cells/L and +222 x 10^6 cells/L for the rilpivirine and efavirenz treatment arms, respectively, of patients receiving the emtricitabine/tenofovir disoproxil background regimen.

There were no new cross-resistance patterns at week 96 compared to week 48. The resistance outcome for patients with protocol defined virological failure and phenotypic resistance at week 96 are shown in Table 6:

Table 6: Phenotypic resistance outcomes from studies C209 and C215 (pooled data for patients receiving rilpivirine hydrochloride or efavirenz in combination with emtricitabine/tenofovir disoproxil) at week 96 (based on resistance analysis)

	Rilpivirine + Emtricitabine/Tenofovir disoproxil n = 550	**Efavirenz + Emtricitabine/Tenofovir disoproxil n = 546**
Resistance to emtricitabine/lamivudine	7.3% (40/550)	0.9% (5/546)
Resistance to rilpivirine	5.6% (31/550)	0
Resistance to efavirenz	5.1% (28/550)	2.2% (12/546)

For those patients failing therapy with Eviplera and who developed resistance to Eviplera cross-resistance to other approved NNRTIs (etravirine, efavirenz, nevirapine) was generally seen.

Virologically suppressed HIV-1 infected patients
Study GS-US-264-0106
The efficacy and safety of switching from a ritonavir-boosted PI in combination with two NRTIs to Eviplera STR was evaluated in a randomised, open-label study in virologically suppressed HIV-1 infected adults. Patients had to be on either their first or second antiretroviral regimen with no history of virologic failure, have no current or past history of resistance to any of the three components of Eviplera, and must have been stably suppressed (HIV-1 RNA < 50 copies/mL) for at least 6 months prior to screening. Patients were randomised in a 2:1 ratio to either switch to Eviplera at baseline (Eviplera arm, n = 317), or stay on their baseline antiretroviral regimen for 24 weeks (SBR arm, n = 159) before switching to Eviplera for an additional 24 weeks (Delayed Switch arm, n = 152). Patients had a mean age of 42 years (range 19-73), 88% were male, 77% were White, 17% were Black, and 17% were Hispanic/Latino. The mean baseline CD4 cell count was 584 x 10^6 cells/L (range 42-1,484). Randomisation was stratified by use of tenofovir disoproxil and/or lopinavir/ritonavir in the baseline regimen.

Treatment outcomes through 24 weeks are presented in Table 7.

Table 7: Outcomes of randomised treatment in study GS-US-264-0106 at week 24[a]

	Eviplera arm n = 317	**Stayed on Baseline Regimen (SBR) arm n = 159**
Virologic success after 24 weeks of treatment[b] HIV-1 RNA < 50 copies/mL	94% (297/317)	90% (143/159)
Virologic failure[c]	1% (3/317)	5% (8/159)
No virologic data in week 24 window		
Discontinued study drug due to AE or death[d]	2% (6/317)	0%
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[e]	3% (11/317)	3% (5/159)
Missing data during window but on study drug	0%	2% (3/159)

	Eviplera arm n = 317	Stayed on Baseline Regimen (SBR) arm n = 159
CD4+ median increase from baseline (x 10^6 cells/L)	+10	+22

a Week 24 window is between day 127 and 210 (inclusive).
b Snapshot analysis.
c Includes patients who had HIV-1 RNA ≥ 50 copies/mL in the week 24 window, patients who discontinued early due to lack or loss of efficacy, patients who discontinued for reasons other than an adverse event (AE) or death, and at the time of discontinuation had a viral value of ≥ 50 copies/mL.
d Includes patients who discontinued due to AE or death at any time point from day 1 through the week 24 window resulting in no virologic data on treatment during the specified window.
e Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

Switching to Eviplera was non-inferior in maintaining HIV-1 RNA < 50 copies/mL when compared to patients who stayed on a ritonavir-boosted PI in combination with two NRTIs [treatment difference (95% CI): + 3.8% (-1.6% to 9.1%)].

Among patients in the SBR arm who maintained their baseline regimen for 24 weeks and then switched to Eviplera, 92% (140/152) of patients had HIV-1 RNA < 50 copies/mL after 24 weeks of Eviplera, consistent with the week 24 results for patients who switched to Eviplera at baseline.

At week 48, 89% (283/317) of patients randomised to switch to Eviplera at baseline (Eviplera) had HIV-1 RNA < 50 copies/mL, 3% (8/317) were considered virologic failures (HIV RNA ≥ 50 copies/mL), and 8% (26/317) did not have data available in the week 48 window. Of the 26 patients without data available in the week 48 window, 7 patients discontinued due to adverse event (AE) or death, 16 patients discontinued for other reasons, and 3 patients were missing data but remained on study drug. The median change in CD4+ cell count at week 48 was +17 x 10^6 cells/L, in the on-treatment analysis.

There were 7/317 patients (2%) in the Eviplera arm and 6/152 patients (4%) in the Delayed Switch arm who permanently discontinued study drug due to a treatment-emergent adverse event (TEAE). No patients discontinued from the study due to a TEAE in the SBR arm.

Study GS-US-264-0111
The efficacy, safety, and pharmacokinetics of switching from efavirenz/emtricitabine/tenofovir disoproxil STR to Eviplera STR were evaluated in an open-label study in virologically suppressed HIV-1 infected adults. Patients had to have previously only received efavirenz/emtricitabine/tenofovir disoproxil as their first antiretroviral regimen for at least three months, and wished to switch regimens due to efavirenz intolerance. Patients had to be stably suppressed for at least 8 weeks prior to study entry, have no current or past history of resistance to any of the three components of Eviplera, and have HIV-1 RNA < 50 copies/mL at screening. Patients were switched from efavirenz/emtricitabine/tenofovir disoproxil to Eviplera without a washout period. Among 49 patients who received at least one dose of Eviplera, 100% of patients remained suppressed (HIV-1 RNA < 50 copies/mL) at week 12 and week 24. At week 48, 94% (46/49) of patients remained suppressed, and 4% (2/49) were considered virologic failures (HIV-1 RNA ≥ 50 copies/mL). One patient (2%) did not have data available in the week 48 window; study drug was discontinued due to a protocol violation (i.e. reason other than AE or death) and the last available HIV-1 RNA was < 50 copies/mL.

Pregnancy

Rilpivirine (taken as Eviplera in 16 of 19 patients and another background regimen in 3 of 19 patients) was evaluated in study TMC114HIV3015 in pregnant women during the 2nd and 3rd trimesters, and postpartum. The pharmacokinetic data demonstrate that total exposure (AUC) to rilpivirine as a part of an antiretroviral regimen was approximately 30% lower during pregnancy compared with postpartum (6-12 weeks). The virologic response was generally preserved throughout the study: of the

12 patients that completed the study, 10 patients were suppressed at the end of the study; in the other 2 patients an increase in viral load was observed only postpartum, for at least 1 patient due to suspected suboptimal adherence. No mother to child transmission occurred in all 10 infants born to the mothers who completed the study and for whom the HIV status was available. Rilpivirine was well tolerated during pregnancy and postpartum. There were no new safety findings compared with the known safety profile of rilpivirine in HIV-1 infected adults (see sections 4.2, 4.4 and 5.2).

5.2 Pharmacokinetic properties

Absorption

The bioequivalence of one Eviplera film-coated tablet with one emtricitabine 200 mg hard capsule, one rilpivirine (as hydrochloride) 25 mg film-coated tablet and one tenofovir disoproxil 245 mg film-coated tablet was established following single dose administration to fed, healthy subjects. Following oral administration of Eviplera with food emtricitabine is rapidly and extensively absorbed with maximum plasma concentrations occurring within 2.5 hours post-dose. Maximum tenofovir concentrations are observed in plasma within 2 hours and maximum plasma concentrations of rilpivirine are generally achieved within 4-5 hours. Following oral administration of tenofovir disoproxil to HIV infected patients, tenofovir disoproxil is rapidly absorbed and converted to tenofovir. The absolute bioavailability of emtricitabine from 200 mg hard capsules was estimated to be 93%. The oral bioavailability of tenofovir from tenofovir disoproxil tablets in fasted patients was approximately 25%. The absolute bioavailability of rilpivirine is unknown. The administration of Eviplera to healthy adult subjects with either a light meal (390 kcal) or a standard meal (540 kcal) resulted in increased exposures of rilpivirine and tenofovir relative to fasting conditions. The C_{max} and AUC of rilpivirine increased by 34% and 9% (light meal) and 26% and 16% (standard meal), respectively. The C_{max} and AUC for tenofovir increased by 12% and 28% (light meal) and 32% and 38% (standard meal), respectively. Emtricitabine exposures were not affected by food. Eviplera must be administered with food to ensure optimal absorption (see section 4.2).

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

Eviplera 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 Eviplera is suggested but caution is advised in patients with moderate hepatic impairment. Eviplera has not been studied in patients with severe hepatic impairment (CPT Score C). Therefore, Eviplera 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 Eviplera. 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: Lactose Monohydrate, Microcrystalline Cellulose, Croscarmellose Sodium, Pregelatinized Starch, Magnesium Stearate, Povidone, Polysorbate 20.

Film-coating: Hypromellose, Titanium Dioxide (E171), Lactose Monohydrate, Polyethylene Glycol, Triacetin, Red Iron Oxide (E172), Indigo Carmine (E132) Aluminum Lake, Sunset Yellow (E110) Aluminum Lake.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 25^0C. Store in the original package in order to protect from moisture. Keep the bottle tightly closed.
After first opening the package, Eviplera should be used within 30 days, but no later than the expiry date.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with a polypropylene child-resistant closure containing 30 film-coated tablets and a silica gel desiccant.

The following pack size is available: outer cartons containing 1 bottle of 30 film-coated tablets.

6.6 Special precautions for disposal

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

7. MANUFACTURER

Janssen Cilag S.P.A., Via C. Janssen 04100, Borgo S.Michele , Latina, , Italy.

8. MARKETING AUTHORISATION HOLDER

J-C Health Care Ltd, Kibbutz Shefayim 6099000, Israel.

Revised in 06.2024.

Based on EUPI from 06.2024