ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Eviplera 200 mg/25 mg/245 mg film-coated tablets

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 of dimensions 19 mm x 8.5 mm, debossed on one side with “GSI” and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Eviplera is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve adult patients with a viral load ≤ 100,000 HIV-1 RNA copies/ml.

The demonstration of the benefit of the combination emtricitabine, rilpivirine hydrochloride and tenofovir disoproxil fumarate in antiretroviral therapy is based on week 48 safety and efficacy analyses from two randomised, double-blind, controlled Phase III studies in treatment-naïve patients (see section 5.1).

As with other antiretroviral medicinal products, genotypic resistance testing should guide the use of Eviplera (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Therapy 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 a meal** (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 fumarate 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 a meal 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 a meal. 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.

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 50-80 ml/min). However, long-term safety data for the emtricitabine and tenofovir disoproxil fumarate 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 (creatinine clearance < 50 ml/min). Patients with moderate or severe renal impairment require a dose interval adjustment of emtricitabine and tenofovir disoproxil fumarate 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.

Method of administration
Eviplera must be taken orally, once daily with a meal (see section 5.2). It is recommended that Eviplera be swallowed whole with water. The film-coated tablet should not be chewed or crushed 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 CYP3A enzyme induction or gastric pH increase), which may result in loss of therapeutic effect of Eviplera:

- the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- the antimycobacterials rifabutin, 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

Patients should be advised that current antiretroviral therapy does not cure HIV, and there is still a risk of passing HIV to others through sexual contact or contamination with blood when taking Eviplera. Appropriate precautions to prevent the transmission of HIV should continue to be employed.

Virologic failure and development of resistance
Eviplera has not been evaluated in patients with previous virologic failure to any other antiretroviral therapy. Eviplera should be avoided in patients with HIV-1 harbouring the K65R mutation. The list of rilpivirine-associated mutations presented in section 5.1 should only guide the use of Eviplera in the treatment-naïve population.

In the pooled analysis from the two Phase III clinical studies (C209 and C215), patients treated with emtricitabine/tenofovir disoproxil fumarate + rilpivirine with a baseline viral load > 100,000 HIV-1 RNA copies/ml had a greater risk of virologic failure (15.3% with rilpivirine versus 5.9% with efavirenz) compared to patients with a baseline viral load ≤ 100,000 HIV-1 RNA copies/ml (4.2% with rilpivirine versus 2.3% with efavirenz). 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 non-nucleoside reverse transcriptase inhibitor (NNRTI) class. More patients who failed virologically on rilpivirine than who failed virologically on efavirenz developed lamivudine/emtricitabine associated resistance (see section 5.1).

As with other antiretroviral medicinal products, resistance testing should guide the use of Eviplera (see section 5.1).

Cardiovascular
At supra-therapeutic 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, 4.8, and 5.2). 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, rilpivirine hydrochloride, tenofovir disoproxil fumarate or other cytidine analogues, such as lamivudine (see section 4.5). Eviplera should not be administered concomitantly with adefovir dipivoxil.

Co-administration of Eviplera and didanosine: is not recommended since exposure to didanosine is significantly increased following co-administration with tenofovir disoproxil fumarate that may increase the risk of didanosine-related adverse reactions (see section 4.5). Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported.

Renal impairment
Eviplera is not recommended for patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min). Patients with moderate or severe renal impairment require a dose interval adjustment of emtricitabine and tenofovir disoproxil fumarate 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 section 4.5).

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

It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy with Eviplera and renal function (creatinine clearance and serum phosphate) is also monitored every four

weeks during the first year and then every three months. In patients at risk for renal impairment, including patients who have previously experienced renal events while receiving adefovir dipivoxil, consideration should be given to more frequent monitoring of renal function.

If serum phosphate is < 1.5 mg/dl (0.48 mmol/l) or creatinine clearance 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 creatinine clearance decreased to < 50 ml/min or decreases in serum phosphate to < 1.0 mg/dl (0.32 mmol/l). 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 fumarate are available.

Bone effects

A dual energy x-ray absorptiometry (DEXA) 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. DEXA 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 fumarate.

In a 144-week controlled clinical study that compared tenofovir disoproxil fumarate with stavudine in combination with lamivudine and efavirenz in antiretroviral-naïve patients, small decreases in BMD of the hip and spine were observed in both treatment groups. Decreases in BMD of spine and changes in bone biomarkers from baseline were significantly greater in the tenofovir disoproxil fumarate treatment group at 144 weeks. Decreases in BMD of hip were significantly greater in this group until 96 weeks. However, there was no increased risk of fractures or evidence for clinically relevant bone abnormalities over 144 weeks.

Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy (see section 4.8). If bone abnormalities are suspected 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 have 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 have 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 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.

Lactic acidosis
Lactic acidosis, usually associated with hepatic steatosis, has been reported with the use of nucleoside analogues. Early symptoms (symptomatic hyperlactataemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness). Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure or renal failure. Lactic acidosis generally occurred after a few or several months of treatment.

Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactataemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.

Caution should be exercised when administering nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.

Patients at increased risk should be followed closely.

Lipodystrophy
Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors and lipoatrophy and nucleoside reverse transcriptase inhibitors has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

Mitochondrial dysfunction
Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or postnatally to nucleoside analogues. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactataemia, hyperlipasaemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological

disorders are transient or permanent is currently unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. 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 combination antiretroviral therapy (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.

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).

Excipients
Eviplera contains lactose monohydrate. Consequently, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

Eviplera contains a colourant called sunset yellow aluminium lake (E110), this may cause allergic reactions in some people.

4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been conducted using Eviplera. As Eviplera contains emtricitabine, rilpivirine hydrochloride and tenofovir disoproxil fumarate, any interactions that have been identified with these agents individually may occur with Eviplera. Interaction studies with these agents have only been performed in adults.

Rilpivirine is primarily metabolised by cytochrome P450 (CYP)3A. 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
As a fixed combination, Eviplera should not be administered concomitantly with other medicinal products containing any of the components emtricitabine, rilpivirine hydrochloride or tenofovir disoproxil fumarate.

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: Eviplera should be administered with caution when co-administered with medicinal products that are substrates for P-glycoprotein (e.g. digoxin and dabigatran). Rilpivirine inhibits P-glycoprotein *in vitro*. The clinical relevance of this inhibition is unknown. Rilpivirine may inhibit intestinal P-glycoprotein and affect medicinal products that are transported by P-glycoprotein in the intestine, such as dabigatran. This may lead to increased plasma concentrations of such medicinal products.

Rilpivirine inhibits the active renal tubular secretion of creatinine. Via the same mechanism exposure to metformin may be increased. Patients should be carefully monitored when initiating or stopping the concomitant administration of rilpivirine and metformin.

Other interactions
Interactions between the components of Eviplera 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 the individual components of Eviplera and other medicinal products

Medicinal product by therapeutic areas	Effects on drug 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).
Didanosine (400 mg once daily) /Rilpivirine[1]	Didanosine: AUC: ↑ 12% C_{min}: NA C_{max}: ↔ Rilpivirine: AUC: ↔ C_{min}: ↔ C_{max}: ↔	
Didanosine/Tenofovir disoproxil fumarate	Co-administration of tenofovir disoproxil fumarate and didanosine results in a 40-60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co-administration of tenofovir disoproxil fumarate 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 fumarate therapy has been associated with reports of high rates of virological failure within several tested combinations for the treatment of HIV-1 infection.	
Protease Inhibitors (PI) - 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 fumarate (300 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.	

Medicinal product by therapeutic areas	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with Eviplera
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 fumarate (300 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 fumarate(300 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 fumarate (300 mg once daily)	AUC: ↔ C_{max}: ↔ Tenofovir concentrations not measured, no effect is expected	

Medicinal product by therapeutic areas	Effects on drug 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	Interaction not studied	
Raltegravir (400 mg twice daily)/ Tenofovir disoproxil fumarate	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		
Ribavirin	Interaction not studied with any components of Eviplera	No clinically relevant drug-drug interaction is expected. 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 fumarate	Interaction not studied.	
Antimycobacterials		
Rifabutin/Emtricitabine	Interaction not studied.	Eviplera must not be used in combination with rifabutin 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.
Rifabutin (300 mg once daily)/ Rilpivirine[1]	Rifabutin: AUC: ↔ C_{min}: ↔ C_{max}: ↔ 25-*O*-desacetyl-rifabutin: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Rilpivirine: AUC: ↓ 46% C_{min}: ↓ 49% C_{max}: ↓ 35%	
Rifabutin/Tenofovir disoproxil fumarate	Interaction not studied.	
Rifampicin/Emtricitabine	Interaction not studied.	Eviplera must not be used in

Medicinal product by therapeutic areas	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with Eviplera
Rifampicin (600 mg once daily)/ Rilpivirine[1] Rifapentine[2]	Rifampicin: AUC: ↔ C_{min}: NA C_{max}: ↔ 25-desacetyl-rifampicin: AUC: ↓ 9% C_{min}: NA C_{max}: ↔ Rilpivirine: AUC: ↓ 80% C_{min}: ↓ 89% C_{max}: ↓ 69%	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.
Rifampicin (600 mg once daily)/ Tenofovir disoproxil fumarate (300 mg once daily)	Rifampicin: AUC: ↔ C_{max}: ↔ Tenofovir: AUC: ↔ C_{max}: ↔	
Macrolide antibiotics		
Clarithromycin Erythromycin Troleandomycin	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.
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. Alternatives should be considered, particularly for long-term use.

Medicinal product by therapeutic areas	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with Eviplera
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.
Omeprazole (20 mg once daily)/ Rilpivirine[1] Lansoprazole[2] Rabeprazole[2] Pantoprazole[2] Esomeprazole[2]	Omeprazole: AUC: ↓ 14% C_{min}: NA C_{max}: ↓ 14% Rilpivirine: AUC: ↓ 40% C_{min}: ↓ 33% C_{max}: ↓ 40%	
Omeprazole/Tenofovir disoproxil fumarate	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}: NA C_{max}: ↔	
Famotidine (40 mg single dose taken 2 hours before rilpivirine)/ Rilpivirine[1]	Rilpivirine: AUC: ↓ 76% C_{min}: NA C_{max}: ↓ 85%	
Famotidine (40 mg single dose taken 4 hours after rilpivirine)/ Rilpivirine[1]	Rilpivirine: AUC: ↑ 13% C_{min}: NA C_{max}: ↑ 21%	
Famotidine/Tenofovir disoproxil fumarate	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.
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	

Medicinal product by therapeutic areas	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with Eviplera
Methadone/Tenofovir disoproxil fumarate	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}: NA C_{max}: ↔ Rilpivirine: AUC: ↔ C_{min}: ↑ 26% C_{max}: ↔	
Paracetamol/Tenofovir disoproxil fumarate	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 fumarate	Ethinylestradiol: AUC: ↔ C_{max}: ↔ Tenofovir: AUC: ↔ C_{max}: ↔	
ANTIARRHYTHMICS		
Digoxin	Interaction not studied with any of the components of Eviplera.	Increases in digoxin plasma concentrations may occur (inhibition of intestinal P-glycoprotein) It is recommended that digoxin levels be monitored when digoxin is combined with Eviplera.

Medicinal product by therapeutic areas	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with Eviplera
ANTICOAGULANTS		
Dabigatran	Interaction not studied with any of the components of Eviplera.	The combination of Eviplera and dabigatran should be used with caution as increases in dabigatran plasma concentrations are expected (inhibition of intestinal P-glycoprotein).
ANTIDIABETICS		
Metformin	Interaction not studied with any of the components of Eviplera.	The combination of Eviplera with metformin may cause an increase in the plasma concentrations of metformin (inhibition of the active renal secretion of metformin). It is recommended that patients are carefully monitored when starting or ending concomitant metformin treatment.
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.
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 fumarate	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}: NA C_{max}: ↔ Rilpivirine: AUC: ↔ C_{min}: ↔ C_{max}: ↔	
Sildenafil/Tenofovir disoproxil fumarate	Interaction not studied.	

[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 drugs within class where similar interactions could be predicted.

Studies conducted with other medicinal products
Emtricitabine: In vitro, emtricitabine did not inhibit metabolism mediated by any of the following human CYP450 isoforms: 1A2, 2A6, 2B6, 2C9, 2C19, 2D6 and 3A4. Emtricitabine did not inhibit the enzyme responsible for glucuronidation.

There are no clinically significant pharmacokinetic interactions when emtricitabine is co-administered with indinavir, zidovudine, stavudine or famciclovir.

Tenofovir disoproxil fumarate: Co-administration of lamivudine, indinavir, efavirenz, nelfinavir or saquinavir (ritonavir boosted), ribavirin or adefovir dipivoxil with tenofovir disoproxil fumarate did not result in any clinically significant pharmacokinetic interaction.

Emtricitabine/tenofovir disoproxil fumarate fixed dose combination: Co-administration of tacrolimus with emtricitabine/tenofovir disoproxil fumarate did not result in any clinically significant pharmacokinetic interaction.

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 (see section 4.5).

Pregnancy
There are no clinical data with Eviplera in pregnant women. However, a moderate amount of data in pregnant women (between 300-1,000 pregnancy outcomes) indicate no malformations or foetal/neonatal toxicity associated with emtricitabine and tenofovir disoproxil fumarate.

Studies in animals have shown no reproductive toxicity (see section 5.3) with the components of Eviplera. 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.

Eviplera should not be used during pregnancy unless clearly needed.

Breast-feeding
Emtricitabine and tenofovir have been shown to be excreted in human milk. It is not known whether rilpivirine is excreted in human milk. There is insufficient information on the effects of all of the components of Eviplera in newborns/infants. Therefore Eviplera should not be used during breast-feeding.

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

Fertility
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 fumarate 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. No studies on the effects on the ability to drive and use machines have been performed. 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 most frequently reported adverse reactions considered possibly or probably related to rilpivirine hydrochloride and emtricitabine/tenofovir disoproxil fumarate were nausea (9%), dizziness (8%), abnormal dreams (7%), headache (6%), diarrhoea (5%) and insomnia (5%) (pooled data from the Phase III clinical studies C209 [ECHO] and C215 [THRIVE], see section 5.1). The safety profile of emtricitabine and tenofovir disoproxil fumarate 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 fumarate, rare events of renal impairment, renal failure and proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have been reported. Monitoring of renal function is recommended for patients receiving Eviplera (see section 4.4).

Lactic acidosis, severe hepatomegaly with steatosis and lipodystrophy are associated with tenofovir disoproxil fumarate and emtricitabine (see sections 4.4 and 4.8 *Description of selected adverse reactions*).

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 associated with the individual components of Eviplera based on clinical study and post-marketing experience

Frequency	Emtricitabine	Rilpivirine hydrochloride	Tenofovir disoproxil fumarate
Blood and lymphatic system disorders:			
Common:	neutropenia	decreased white blood cell count, decreased haemoglobin, decreased platelet count	
Uncommon:	anaemia[3]		
Immune system disorders:			
Common:	allergic reaction		
Uncommon:		immune reactivation syndrome	
Metabolism and nutrition disorders:			
Very common:		increased total cholesterol (fasted), increased LDL cholesterol (fasted)	hypophosphataemia[1]
Common:	hyperglycaemia, hypertriglyceridaemia	decreased appetite, increased triglycerides (fasted)	
Uncommon:			hypokalaemia[1]
Rare:			lactic acidosis[2]

Frequency	Emtricitabine	Rilpivirine hydrochloride	Tenofovir disoproxil fumarate
Psychiatric disorders:			
Common:	insomnia, abnormal dreams	depression, insomnia, abnormal dreams, sleep disorders, depressed mood	
Nervous system disorders:			
Very common:	headache	headache	dizziness
Common:	dizziness	dizziness, somnolence	headache
Gastrointestinal disorders:			
Very common:	diarrhoea, nausea	nausea, increased pancreatic amylase	diarrhoea, vomiting, nausea
Common:	elevated amylase including elevated pancreatic amylase, elevated serum lipase, vomiting, abdominal pain, dyspepsia	abdominal pain, vomiting, increased lipase, abdominal discomfort, dry mouth	abdominal pain, abdominal distension, flatulence
Uncommon:			pancreatitis[2]
Hepatobiliary disorders:			
Very common:		increased transaminases (AST and/or ALT)	
Common:	elevated serum aspartate aminotransferase (AST) and/or elevated serum alanine aminotransferase (ALT), hyperbilirubinaemia	increased bilirubin	increased transaminases (AST and/or ALT)
Rare:			hepatic steatosis[2], hepatitis
Skin and subcutaneous tissue disorders:			
Very common:			rash
Common:	vesiculobullous rash, pustular rash, maculopapular rash, rash, pruritus, urticaria, skin discolouration (increased pigmentation)[3]	rash	
Uncommon:	angioedema[4]		
Rare:			angioedema[4]
Musculoskeletal and connective tissue disorders:			
Very common:	elevated creatine kinase		
Uncommon:			rhabdomyolysis[1], muscular weakness[1]
Rare:			osteomalacia (manifested as bone pain and infrequently contributing to fractures)[1,4], myopathy[1]

Frequency	Emtricitabine	Rilpivirine hydrochloride	Tenofovir disoproxil fumarate
Renal and urinary disorders:			
Uncommon:			increased creatinine, proteinuria
Rare:			renal failure (acute and chronic), acute tubular necrosis, proximal renal tubulopathy including Fanconi syndrome, nephritis (including acute interstitial nephritis)[4], nephrogenic diabetes insipidus
General disorders and administration site conditions:			
Very common:			asthenia
Common:	pain, asthenia	fatigue	

[1] This adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil fumarate in the absence of this condition.
[2] See section 4.8. Description of selected adverse reactions for more details.
[3] Anaemia was common and skin discolouration (increased pigmentation) was very common when emtricitabine was administered to paediatric patients.
[4] This adverse reaction was identified through post-marketing surveillance but not observed in randomised controlled clinical studies in adults or paediatric HIV clinical studies for emtricitabine or in randomised controlled clinical studies or the tenofovir disoproxil fumarate expanded access program for tenofovir disoproxil fumarate. The frequency category was estimated from a statistical calculation based on the total number of patients exposed to emtricitabine in randomised controlled clinical studies (n = 1,563) or tenofovir disoproxil fumarate in randomised controlled clinical studies and the expanded access program (n = 7,319).

Mean change from baseline in total cholesterol (fasted) was 2 mg/dl, in HDL cholesterol (fasted) 4 mg/dl, in LDL cholesterol (fasted) -1 mg/dl, and in triglycerides (fasted) -7 mg/dl in two Phase III clinical studies (C209 and C215).

Increases in serum creatinine in the Phase III clinical studies C209 and C215 occurred within the first four weeks of treatment with rilpivirine and remained stable through 48 weeks. A mean change of 0.09 mg/dl (range: -0.20 mg/dl to 0.62 mg/dl) was observed after 48 weeks of treatment. In subjects who entered the studies with mild or moderate renal impairment, the serum creatinine increase observed was similar to that seen in subjects with normal renal function. These changes are not considered to be clinically relevant since they do not reflect a change in actual glomerular filtration rate and no subject discontinued treatment due to increases in serum creatinine.

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*).

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

Lipids, lipodystrophy and metabolic abnormalities: CART has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

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

Immune 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 (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).

Lactic acidosis and severe hepatomegaly with steatosis: Lactic acidosis, usually associated with hepatic steatosis, has been reported with the use of nucleoside analogues. Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactataemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels (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).

Other special population(s)
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 fumarate 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 fumarate in patients co-infected with HIV/HBV or HIV/HCV was similar to that observed in patients infected with HIV without co-infection. However, as would be expected in this patient population, elevations in AST and ALT occurred more frequently than in the general HIV infected population.

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

4.9 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.

Administration of activated charcoal may also be used to aid in removal of unabsorbed rilpivirine hydrochloride.

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 fumarate is converted *in vivo* to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate. Both emtricitabine and tenofovir have activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2) and hepatitis B virus.

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 drug 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 µM to 5.5 µM).

In drug 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

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. 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 fumarate 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

In a pooled analysis for patients receiving emtricitabine/tenofovir disoproxil fumarate + rilpivirine hydrochloride in the Phase III clinical studies C209 and C215, there were 62 virologic failure patients with resistance information available for 54 of those patients. The NNRTI resistance-associated mutations that developed most commonly in these patients were: V90I, K101E, E138K/Q, Y181C, V189I, and H221Y. However, in the studies, the presence of the mutations V90I and V189I at baseline did not affect the response. The mutations associated with NRTI resistance that developed in 3 or more patients were: K65R, K70E, M184V/I and K219E during the treatment period.

Considering all of the available *in vitro* and *in vivo* data in treatment naïve subjects, the following resistance-associated mutations, when present at baseline, may affect the activity of Eviplera: K65R, K101E, K101P, E138A, E138G, E138K, E138Q, E138R, V179L, Y181C, Y181I, Y181V, M184I, M184V, H221Y, F227C, M230I and M230L. These resistance-associated mutations should only guide the use of Eviplera in the treatment-naïve population.

These resistance-associated mutations were derived from *in vivo* data involving treatment-naïve subjects only and therefore cannot be used to predict the activity of Eviplera in subjects who have virologically failed an antiretroviral-containing regimen.

As with other antiretroviral medicinal products resistance testing should guide the use of Eviplera (see section 4.4).

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.

In the pooled analysis of all subjects in the Phase III clinical studies C209 and C215, 31 of the 62 patients with virologic failure on rilpivirine hydrochloride with phenotypic resistance data lost susceptibility to rilpivirine. Of these, 28 were resistant to etravirine, 27 to efavirenz, and 14 to nevirapine.

Tenofovir disoproxil fumarate: The K65R substitution can also be selected by abacavir or didanosine and results in reduced susceptibility to these agents plus lamivudine, emtricitabine, and tenofovir, but retains sensitivity to zidovudine.

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

Virologic response to tenofovir disoproxil fumarate 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
In a pooled analysis for patients receiving emtricitabine/tenofovir disoproxil fumarate + rilpivirine hydrochloride in the Phase III clinical studies C209 and C215, 54 patients with virologic failure had available phenotypic resistance data at virologic failure, 37 lost susceptibility to emtricitabine, 29 lost susceptibility to rilpivirine hydrochloride, and 2 lost susceptibility to tenofovir disoproxil fumarate. Among these subjects, 37 were resistant to lamivudine, 28 to etravirine, 26 to efavirenz, and 12 to nevirapine. Reduced susceptibility was observed to abacavir and/or didanosine in some cases.

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 48 week data from two ongoing, 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 $\geq$ 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 fumarate. In study C215 (n = 678), the BR consisted of 2 investigator selected N(t)RTIs: emtricitabine/tenofovir disoproxil fumarate (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 fumarate, demographic and baseline characteristics were balanced between the rilpivirine and efavirenz arm. Table 3 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 3: Demographic and baseline characteristics of antiretroviral treatment-naïve HIV-1 infected adult subjects in studies C209 and C215 (pooled data for patients receiving rilpivirine hydrochloride or efavirenz in combination with emtricitabine/tenofovir disoproxil fumarate) at week 48

	Rilpivirine + Emtricitabine/Tenofovir disoproxil fumarate n = 550	**Efavirenz + Emtricitabine/Tenofovir disoproxil fumarate n = 546**
Demographic Characteristics		
Median age, years (min-max)	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 subjects with hepatitis B/C virus co-infection	7.7%	8.1%

A subgroup analysis of the virologic response (< 50 HIV-1 RNA copies/ml) at 48 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 fumarate background regimen) is presented in Table 4.

Table 4: 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 fumarate) at week 48

	Rilpivirine + Emtricitabine/Tenofovir disoproxil fumarate n = 550	**Efavirenz + Emtricitabine/Tenofovir disoproxil fumarate n = 546**
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)
By baseline viral load (copies/ml)		
≤ 100,000	**89.6% (258/288) (86.1, 93.1)**	**84.8% (217/256) (80.4, 89.2)**
> 100,000	76.7% (201/262) (71.6, 81.8)	80.3% (233/290) (75.8, 84.9)
By baseline CD4 count (cells/µl)		
< 50	51.7% (15/29) (33.5, 69.9)	79.3% (23/29) (64.6, 94.1)
≥ 50-200	80.9% (123/152) (74.7, 87.2)	80.7% (109/135) (74.1, 87.4)
≥ 200-350	86.3% (215/249) (82.1, 90.6)	82.3% (205/249) (77.6, 87.1)
≥ 350	89.1% (106/119) (83.5, 94.7)	85.0% (113/133) (78.9, 91.0)
Non-response		
Virologic Failure (all subjects)	9.5% (52/550)	4.2% (23/546)
By baseline viral load (copies/ml)		
≤ 100,000	**4.2% (12/288)**	**2.3% (6/256)**
> 100,000	15.3% (40/262)	5.9% (17/290)
Death	0	0.2% (1/546)
Discontinued due to adverse event (AE)	2.2% (12/550)	7.1% (39/546)
Discontinued for non-AE reason [c]	4.9% (27/550)	6.0% (33/546)

n = total number of subjects 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 e.g. lost to follow up, non-compliance, withdrew consent.

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

The mean changes in CD4 cell count from baseline were +193 x 10^6 cells/l and + 182 x 10^6 cells/l for the rilpivirine and efavirenz treatment arms, respectively, of patients receiving the emtricitabine/tenofovir disoproxil fumarate background regimen.

The resistance outcome for patients with protocol defined virological failure and phenotypic resistance are shown in Table 5:

Table 5: Resistance outcomes from studies C209 and C215 (pooled data for patients receiving rilpivirine hydrochloride or efavirenz in combination with emtricitabine/tenofovir disoproxil fumarate) at week 48

	Rilpivirine + Emtricitabine/Tenofovir disoproxil fumarate n = 550	**Efavirenz + Emtricitabine/Tenofovir disoproxil fumarate n = 546**
Resistance to emtricitabine/lamivudine	6.7% (37/550)	0.7% (4/546)
Resistance to rilpivirine	5.3% (29/550)	0
Resistance to efavirenz	4.7% (26/550)	1.8% (10/546)

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.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Eviplera in one or more subsets of the paediatric population in the treatment of HIV-1 (see section 4.2 for information on paediatric use).

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 (as fumarate) 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 fumarate to HIV infected patients, tenofovir disoproxil fumarate is rapidly absorbed and converted to tenofovir. The absolute bioavailability of emtricitabine from 200 mg hard capsules was estimated to be 93%. Administration of emtricitabine 200 mg hard capsules with a high-fat meal did not affect systemic exposure (AUC) of emtricitabine. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate tablets in fasted patients was approximately 25%. Administration of tenofovir disoproxil fumarate with a high-fat meal enhanced the oral bioavailability, with an increase in tenofovir AUC by approximately 40% and C_{max} by approximately 14%. The absolute bioavailability of rilpivirine is unknown. The exposure to rilpivirine was approximately 40% lower when rilpivirine hydrochloride was taken in a fasted condition as compared to a normal caloric meal (533 kcal) or high-fat high-caloric meal (928 kcal). When rilpivirine hydrochloride was taken with only a protein-rich nutritional drink, exposures were 50% lower than when taken with a meal. Taking rilpivirine hydrochloride in a fasted condition or with only a nutritional drink may result in decreased plasma concentrations of rilpivirine, which could potentially reduce the therapeutic effect of Eviplera. Eviplera must be administered with a meal 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 fumarate, 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 cytochrome P450 (CYP)3A system. *In vitro* studies have determined that neither tenofovir disoproxil fumarate 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.

Elderly
Population pharmacokinetic analysis in HIV infected patients showed that rilpivirine pharmacokinetics are not different across the age range (18 to 78 years) evaluated, with only 2 subjects 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) are similar to those seen in adults. The pharmacokinetics of rilpivirine and tenofovir disoproxil fumarate 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 (creatinine clearance 50-80 ml/min). However, long-term safety data for the emtricitabine and tenofovir disoproxil fumarate 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 (creatinine clearance < 50 ml/min). Patients with moderate or severe renal impairment require a dose interval adjustment of emtricitabine and tenofovir disoproxil fumarate 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 creatinine clearance (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 subjects 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 fumarate in combination with emtricitabine in HIV infected patients with renal impairment. A subgroup of patients with baseline creatinine clearance between 50 and 60 ml/min, receiving once daily dosing, had a 2-4-fold increase in tenofovir exposure and worsening renal function.

The pharmacokinetics of rilpivirine have 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 have not been studied in subjects 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 patients with varying degrees of hepatic impairment defined according to CPT classification. Tenofovir

pharmacokinetics were 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 subjects were similar to those in healthy subjects and in HIV infected subjects.

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

5.3 Preclinical safety data

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

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

Carcinogenicity studies with rilpivirine in mice and rats revealed tumorigenic potential specific for these species, but are regarded as of no relevance for humans.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Croscarmellose sodium
Lactose monohydrate
Magnesium stearate (E407b)
Microcrystalline cellulose (E460(i))
Polysorbate 20 (E432)
Povidone (E1201)
Pregelatinised maize starch

Film-coating
Hypromellose (E464)
Indigo carmine aluminium lake (E132)
Lactose monohydrate
Polyethylene glycol
Red iron oxide (E172)
Sunset yellow aluminium lake (E110)
Titanium dioxide (E171)
Triacetin (E1518)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

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

The following pack sizes are available: outer cartons containing 1 bottle of 30 film-coated tablets and outer cartons containing 90 (3 bottles of 30) film-coated tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Gilead Sciences International Limited
Cambridge
CB21 6GT
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000
EU/0/00/000/000

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Gilead Sciences Limited
IDA Business & Technology Park
Carrigtohill
County Cork
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)
The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan presented in Module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

BOTTLE AND CARTON LABELLING

1. NAME OF THE MEDICINAL PRODUCT

Eviplera 200 mg/25 mg/245 mg film-coated tablets
emtricitabine/rilpivirine/tenofovir disoproxil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose monohydrate and sunset yellow aluminium lake (E110), see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets.
90 (3 bottles of 30) film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Intl Ltd
Cambridge
CB21 6GT
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000 30 film-coated tablets.
EU/0/00/000/000 90 (3 bottles of 30) film-coated tablets.

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Eviplera [outer packaging only]

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Eviplera 200 mg/25 mg/245 mg film-coated tablets
emtricitabine/rilpivirine/tenofovir disoproxil

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any of the side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Eviplera is and what it is used for

Eviplera contains three active substances that are used to treat Human Immunodeficiency Virus (HIV) infection:

- Emtricitabine, a nucleoside reverse transcriptase inhibitor (NRTI).
- Rilpivirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI).
- Tenofovir, a nucleotide reverse transcriptase inhibitor (NtRTI).

Each of these active substances, also known as antiretroviral medicines, works by interfering with an enzyme (a protein called 'reverse transcriptase') that is essential for the virus to multiply.

Eviplera reduces the amount of HIV in your body. This, will improve your immune system and reduces the risk of developing illnesses linked to HIV infection.

Eviplera is a treatment for Human Immunodeficiency Virus (HIV) infection in adults aged 18 years and over who have never been treated before with HIV medicines.

This medicine is not a cure for HIV infection. While taking Eviplera you may still develop infections or other illnesses associated with HIV infection. You can also pass on the virus to others, so it is important to take precautions to avoid infecting other people.

2. What you need to know before you take Eviplera

Do not take Eviplera

- **If you are allergic** to emtricitabine, rilpivirine, tenofovir disoproxil, or any of the other ingredients of this medicine (listed in section 6 of this leaflet).

  →If this applies to you, tell your doctor immediately.

- **If you are currently taking any of the following medicines**
  - **carbamazepine, oxcarbazepine, phenobarbital and phenytoin** (medicines to treat epilepsy and prevent seizures)
  - **rifabutin, rifampicin and rifapentine** (used to treat some bacterial infections such as tuberculosis)
  - **omeprazole, lansoprazole, rabeprazole, pantoprazole and esomeprazole** (proton pump inhibitors that are medicines used to prevent and treat stomach ulcers, heartburn, acid reflux disease)
  - **dexamethasone** (a corticosteroid used to treat inflammation and suppress the immune system) when taken by mouth or injected (except as a single dose treatment)
  - **products that contain St. John's wort** (*Hypericum perforatum*) (a herbal remedy used for depression and anxiety)

Warnings and precautions

You must remain under the care of your doctor while taking Eviplera.

- **You can still pass on HIV** when taking this medicine, so it is important to take precautions to avoid infecting other people through sexual contact or blood transfer. This medicine is not a cure for HIV infection. While taking Eviplera you may still develop infections or other illnesses associated with HIV infection.

- **Tell your doctor if you have kidney problems,** or have had kidney problems, or if tests have shown problems with your kidneys. Eviplera is not recommended if you have moderate to severe kidney disease.

  Eviplera may affect your kidneys. Before starting treatment, your doctor may order blood tests to assess kidney function. Your doctor may also order blood tests during treatment to monitor your kidneys.

  Eviplera is not usually taken with other medicines that can damage your kidneys (*see Other medicines and Eviplera*). If this is unavoidable, your doctor will monitor your kidney function once a week.

- **Tell your doctor if you have liver problems** or a history of liver disease, including chronic active hepatitis. Patients with liver disease including chronic hepatitis B or C, who are treated with combination antiretroviral medicines like Eviplera have a higher risk of severe and potentially life-threatening liver problems. Your doctor will monitor your liver while you take this medicine.

  If you have hepatitis B infection, these liver problems may become worse after you stop taking Eviplera. It's important not to stop taking Eviplera without talking to your doctor: *see section 3, Don't stop taking Eviplera*.

- **Tell your doctor if you have diabetes, are overweight or have high cholesterol.** Combination antiretroviral medicines, including Eviplera, may raise blood sugar levels, increase blood fats (*hyperlipaemia*), cause changes to body fat, and resistance to insulin (insulin becomes less effective at controlling the sugar levels in your body, which can lead to diabetes). *See section 4, Possible side effects*.

- **Talk to your doctor if you are over 65 years of age.** Not enough patients over the age of 65 have been studied. If you are over 65 years of age and are prescribed Eviplera, your doctor will monitor you carefully.

While you take Eviplera
Once you start taking Eviplera, look out for important signs and symptoms.

Signs of lactic acidosis (excess lactic acid in your blood) including:
- deep, rapid breathing
- tiredness or drowsiness
- feeling sick (*nausea*), being sick (*vomiting*)
- stomach pain

You also need to look out for:
- any signs of inflammation or infection
- bone problems

→ **If you notice any of these symptoms, tell your doctor immediately**, as lactic acidosis can be potentially life threatening**.** For more information, *see section 4, Possible side effects*.

Children and adolescents

Do not give this medicine to children and adolescents under 18 years of age. The use of Eviplera in children and adolescents has not yet been studied.

Other medicines and Eviplera

Tell your doctor or pharmacist if you are taking any other medicines or have recently taken any. This includes medicines and herbal products obtained without a prescription.

Tell your doctor if you are taking any of the following:

- **Any other medicines containing**:
  - emtricitabine
  - rilpivirine
  - tenofovir
  - any other antiviral medicines that contain lamivudine or adefovir dipivoxil

Eviplera may interact with other medicines. As a result, the amounts of Eviplera or other medicines in your blood may be affected. This may stop your medicines from working properly, or may make any side effects worse. In some cases, your doctor may need to adjust your dose or check your blood levels.

- **Medicines that may damage your kidneys,** examples include:
  - aminoglycosides (such as streptomycin, neomycin and gentamicin), vancomycin (for bacterial infections)
  - foscarnet, ganciclovir, cidofovir (for viral infections)
  - amphotericin B, pentamidine (for fungal infections)
  - interleukin-2, also called aldesleukin (to treat cancer)

- **Medicines containing didanosine (for HIV infection):** Taking Eviplera with other antiviral medicines that contain didanosine can raise the levels of didanosine in your blood and may reduce CD4 cell counts. Inflammation of the pancreas and lactic acidosis (excess lactic acid in the blood), which sometimes caused death, have been reported rarely when medicines containing tenofovir disoproxil fumarate and didanosine were taken together. Your doctor will carefully consider whether to treat you with other medicines used for treating HIV infection (*see Other medicines used for HIV infection).*

- **Other medicines used for HIV infection:** Non-nucleoside reverse transcriptase inhibitors (NNRTIs). Eviplera contains an NNRTI (rilpivirine) and so Eviplera is not to be combined with

other medicines of this type (such as efavirenz, nevirapine, delavirdine, etravirine). Your doctor will discuss a different medicine if required.

- **Antibiotics used to treat bacterial infections** including tuberculosis containing:
  - clarithromycin
  - erythromycin
  - troleandomycin

  These medicines can increase the amount of rilpivirine (a component of Eviplera) in your blood. Your doctor may need to change the dose of the antibiotic or give you a different antibiotic.

- **Medicines for stomach ulcers, heartburn or acid reflux** such as:
  - antacids (aluminium/magnesium hydroxide or calcium carbonate)
  - H_2-antagonists (famotidine, cimetidine, nizatidine or ranitidine)

  These medicines can decrease the amount of rilpivirine (a component of Eviplera) in your blood. If you are taking one of these medicines your doctor will either give you a different medicine for stomach ulcers, heartburn or acid reflux, or recommend how and when you take that medicine.

- **If you are taking an antacid,** take it at least 2 hours before or at least 4 hours after Eviplera.

- **If you are taking an H_2-antagonist,** take it at least 12 hours before or at least 4 hours after Eviplera. H_2-antagonists can only be taken once a day if you take Eviplera. H_2-antagonists should not be taken in a twice a day regimen. Talk to your doctor about an alternative regimen (*see How to take Eviplera).*

- **Methadone,** a medicine used to treat opiate addiction, as your doctor may need to change your methadone dose.

- **Digoxin or dabigatran,** medicines used to treat heart conditions, as your doctor may need to monitor the levels of these medicines in your blood.

- **Metformin**, a medicine used to treat diabetes, as your doctor may need to monitor the levels of this medicine in your blood.

→ **Tell your doctor if you are taking any of these medicines.** Do not stop your treatment without contacting your doctor.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

- **Women must not get pregnant** while taking Eviplera.
- **Use effective contraception** while taking Eviplera.
- **Tell your doctor immediately if you become pregnant.** Pregnant women should not take Eviplera unless you and your doctor decide it is clearly needed. Your doctor will discuss the potential benefits and risks of taking Eviplera to you and your child.

Do not breast-feed during treatment with Eviplera:
- This is because the active substances in this medicine pass into human breast milk.
- If you are a woman with HIV it is recommended that you do not breast-feed, to avoid passing the virus to the baby in breast milk.

Driving and using machines

Do not drive or operate machines if you feel tired, sleepy or dizzy after taking your medicine.

Eviplera contains lactose and sunset yellow aluminium lake /E110

- **Tell your doctor if you are lactose intolerant or intolerant to other sugars.** Eviplera contains lactose monohydrate. If you are lactose-intolerant, or if you have been told that you have an intolerance to other sugars, talk to your doctor before taking this medicine.
- **Tell your doctor if you have an allergy to sunset yellow aluminium lake (E110).** Eviplera contains sunset yellow aluminium lake also called "E110" that may cause allergic reactions.

3. How to take Eviplera

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The usual dose is one tablet taken each day by mouth. The tablet must be taken with a meal. A meal is important to get the right levels of active substance in your body. A nutritional drink (e.g. protein-rich) alone does not replace a meal.

Swallow the tablet whole with water.

Do not chew, crush or split the tablet – if you do it may affect the way the medicine is released into your body.

If your doctor decides to stop one of the components of Eviplera or change the dose of Eviplera, you may be given emtricitabine, rilpivirine and/or tenofovir disoproxil separately or with other medicines for the treatment of HIV infection.

If you are taking an antacid such as aluminium/magnesium hydroxide, or calcium carbonate. Take it at least 2 hours before or at least 4 hours after Eviplera.

If you are taking an H_2-antagonist such as famotidine, cimetidine, nizatidine or ranitidine. Take it at least 12 hours before or at least 4 hours after Eviplera. H_2-antagonists can only be taken once a day if you take Eviplera. H_2-antagonists should not be taken twice a day. Talk to your doctor about an alternative regimen.

If you take more Eviplera than you should

If you accidentally take more than the recommended dose of Eviplera you may be at increased risk of experiencing possible side effects with this medicine (*see section 4 Possible side effects*)

Contact your doctor or nearest emergency department immediately for advice. Keep the tablet bottle with you so that you can easily describe what you have taken.

If you forget to take Eviplera

It is important not to miss a dose of Eviplera.

If you do miss a dose:
- **If you notice within 12 hours** of the time you usually take Eviplera, you must take the tablet as soon as possible. Always take the tablet with a meal. Then take the next dose as usual.
- **If you notice after 12 hours or more** of the time you usually take Eviplera, then do not take the missed dose. Wait and take the next dose, with a meal, at your usual time.

If you vomit less than 4 hours after taking Eviplera, take another tablet with a meal. **If you vomit more than 4 hours after taking Eviplera** you do not need to take another tablet until your next regularly scheduled tablet.

Do not stop taking Eviplera

Do not stop taking Eviplera without talking to your doctor. Stopping Eviplera can seriously affect your response to future treatment. If Eviplera for any reason is stopped, speak to your doctor before you restart taking Eviplera tablets. Your doctor may consider giving you the components of Eviplera separately if you are having problems or need your dose adjusted.

When your supply of Eviplera starts to run low, get more from your doctor or pharmacist. This is very important because the amount of virus may start to increase if the medicine is stopped for even a short time. The virus may then become harder to treat.

If you have both HIV infection and hepatitis B, it is especially important not to stop your Eviplera treatment without talking to your doctor first. Some patients have had blood tests or symptoms indicating that their hepatitis has got worse after stopping emtricitabine or tenofovir disoproxil fumarate (two of the three components of Eviplera). If Eviplera is stopped your doctor may recommend that you resume hepatitis B treatment. You may need blood tests to check how your liver is working for 4 months after stopping treatment. In some patients with advanced liver disease or cirrhosis, stopping treatment is not recommended as this may lead to worsening of your hepatitis, which may be life-threatening.

Tell your doctor immediately about new or unusual symptoms after you stop treatment, particularly symptoms you associate with hepatitis B infection.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. When treating HIV infection, it is not always possible to tell whether some of the unwanted effects are caused by Eviplera or by other medicines that you are taking at the same time, or by the HIV disease itself.

Possible side effects: tell a doctor immediately

- **Lactic acidosis** (excess lactic acid in the blood) is a rare but potentially life-threatening side effect of some HIV medicines. Lactic acidosis occurs more often in women – particularly if they are overweight, and in people with liver disease. The following may be signs of lactic acidosis:
  - Deep, rapid breathing
  - Tiredness or drowsiness
  - Feeling sick (*nausea*), being sick (*vomiting*)
  - Stomach pain

  →If you think you may have lactic acidosis, tell your doctor immediately.

Any signs of inflammation or infection. In some patients with advanced HIV infection (AIDS) and a history of opportunistic infections (infections that occur in people with a weak immune system), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is thought that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms.
→If you notice any symptoms of inflammation or infection, tell your doctor immediately.

Very common side effects
(*may affect more than 1 in every 10 people treated*)

- Diarrhoea, being sick (*vomiting*), feeling sick (*nausea*)
- Dizziness, headache
- Rash

- Feeling weak.

Tests may also show:
- Decreases in phosphate levels in the blood
- Increased levels of creatine kinase in the blood that may result in muscle pain and weakness

→ If any of the side effects get serious tell your doctor.

Common side effects
(*may affect up to 1 in every 10 people treated*)
- Decreased appetite
- Depression and depressed mood
- Tiredness, feeling sleepy (somnolence)
- Drowsiness
- Pain, stomach pain or discomfort, feeling bloated, dry mouth
- Difficulty sleeping (*insomnia*), abnormal dreams, sleep disorders
- Problems with digestion resulting in discomfort after meals, wind (*flatulence*)
- Rashes (including red spots or blotches sometimes with blistering and swelling of the skin), which may be allergic reactions, itching, changes in skin colour including darkening of the skin in patches
- Other allergic reactions, such as wheezing, swelling or feeling light-headed

Tests may also show:
- Low white blood cell count (a reduced white blood cell count can make you more prone to infection)
- Increased fatty acids (*triglycerides*), bilirubin or sugar in the blood
- Liver and pancreas problems

→If any of the side effects get serious tell your doctor.

Uncommon side effects
(*may affect up to 1 in every 100 people treated*)
- Anaemia (low red blood cell count)
- Pain in the abdomen (tummy) caused by inflammation of the pancreas
- Breakdown of muscle, muscle pain or weakness
- Swelling of the face, lips, tongue or throat
- Signs or symptoms of inflammation or infection

Tests may also show:
- Decreases in potassium in the blood
- Increases in creatinine in your blood
- Changes to your urine
- Low platelet count (a type of blood cell involved in clotting blood)
- Increased cholesterol.

→If any of the side effects get serious tell your doctor.

Rare side effects
(*may affect up to 1 in every 1,000 people treated*)
- Lactic acidosis (see *Possible side effects: tell a doctor immediately*)
- Back pain caused by kidney problems, including kidney failure. Your doctor may do blood tests to see if your kidneys are working properly
- Fatty liver
- Yellow skin or eyes, itching or pain in the abdomen (tummy) caused by inflammation of the liver
- Inflammation of the kidney, passing a lot of urine and feeling thirsty
- Softening of the bones (with bone pain and sometimes resulting in fractures)

Tests may also show:
- Damage to kidney tubule cells may cause breakdown of muscle, bone softening (with bone pain and sometimes resulting in fractures), muscle pain, muscle weakness and decreases in potassium or phosphate in the blood.

→If any of the side effects get serious tell your doctor.

Other possible side effects

The frequency of the following side effects is not known (frequency cannot be estimated from the available data).

- **Bone problems.** Some patients taking combination antiretroviral medicines such as Eviplera may develop a bone disease called *osteonecrosis* (death of bone tissue caused by loss of blood supply to the bone). Taking this type of medicine for a long time, taking corticosteroids, drinking alcohol, having a very weak immune system, and being overweight, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are:
  - Joint stiffness
  - Joint aches and pains (especially of the hip, knee and shoulder)
  - Difficulty with movement

  →If you notice any of these symptoms tell your doctor.

- **Changes to your body shape.** Some patients taking combination antiretroviral medicines such as Eviplera may notice changes to the way body fat is distributed. You may lose fat from your legs, arms and face. You may gain fat around the tummy (*abdomen*) and internal organs, get larger breasts or fatty lumps on the back of the neck ('buffalo hump'). The cause and the long-term effects of these changes are not yet known.
  →If you notice any of these symptoms tell your doctor.

- **Increased fat levels in the blood** (*hyperlipaemia*) and resistance to insulin (insulin becomes less effective at controlling the sugar levels in your body which can lead to diabetes). Your doctor will test for these changes.

→ If you get side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. How to store Eviplera

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle and carton after {EXP}. The expiry date refers to the last day of that month.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Eviplera contains

- **The active substances are** *emtricitabine, rilpivirine* and *tenofovir disoproxil*. Each Eviplera film-coated tablet contains 200 mg of emtricitabine, 25 mg of rilpivirine (as hydrochloride) and 245 mg of tenofovir disoproxil (as fumarate).

- **The other ingredients are:**
  Tablet core:
  Microcrystalline cellulose (E460(i)), lactose monohydrate, povidone (E1201), pregelatinised maize starch, polysorbate 20 (E432), croscarmellose sodium, and magnesium stearate (E470b).

  Film-coating:
  Hypromellose (E464), indigo carmine aluminium lake (E132), lactose monohydrate, polyethylene glycol, red iron oxide (E172), sunset yellow aluminium lake (E110), titanium dioxide (E171), and triacetin (E1518).

What Eviplera looks like and contents of the pack

Eviplera is a purplish-pink, capsule-shaped, film-coated tablet debossed on one side with "GSI" and plain on the other side. Eviplera comes in bottles of 30 tablets and in packs made up of 3 bottles, each containing 30 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
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Manufacturer:
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu