DATA SHEET

1. EVIPLERA® (TENOFOVIR DISOPROXIL FUMARATE, EMTRICITABINE AND RILPIVIRINE) TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

300 mg tenofovir disoproxil fumarate/200 mg emtricitabine/25 mg rilpivirine

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

EVIPLERA tablets are capsule shaped, film-coated and purplish-pink in colour. Each tablet is debossed with 'GSI' on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

EVIPLERA is indicated for the treatment of HIV infection in treatment-naïve adult patients with plasma HIV-1 RNA ≤ 100,000 copies/mL at the start of therapy.

EVIPLERA is also indicated in certain virologically-suppressed (HIV-1 RNA <50 copies/mL) adult patients on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen (see section 5.1 Pharmacodynamic properties, Clinical trials). Patients must not have a history of resistance to any of the components of EVIPLERA (tenofovir DF, emtricitabine or rilpivirine).

4.2 Dose and method of administration

Adults: The recommended dose of EVIPLERA is one tablet once daily taken orally with food.

When discontinuation of EVIPLERA is necessary due to one of the components, or where dose modification is necessary, separate preparations of tenofovir DF, emtricitabine and rilpivirine should be used. Please refer to the product information for these products (see section 4.5 Interactions with other medicines and other forms of interactions).

Paediatric population: EVIPLERA is not recommended for use in children below 18 years of age due to insufficient data on safety and efficacy.

Special populations

Renal impairment: EVIPLERA is not recommended for use in patients with moderate or severe renal impairment (Creatinine Clearance (CrCl) < 50 mL/min). Patients with moderate or severe renal impairment require dose interval adjustments of tenofovir DF and emtricitabine that cannot

be achieved with the combination tablet (see section 4.4 Special warnings and precautions for use).

Elderly*:* Clinical studies of tenofovir DF, emtricitabine and rilpivirine did not contain sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. Caution should be exercised when prescribing EVIPLERA to the elderly, keeping in mind the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Pregnancy and postpartum: Lower exposures of rilpivirine were observed during pregnancy; therefore, viral load should be monitored closely. Alternatively, switching to another ART regimen could be considered (see sections 5.2 Pharmacokinetic Properties and 4.6 Fertility, Pregnancy and Lactation, Use in Pregnancy).

4.3 Contraindications

EVIPLERA is contraindicated in patients with known hypersensitivity to any of the active substances or any other component of the tablets.

EVIPLERA must not be administered to children or adolescents under the age of 18 years.

EVIPLERA is a fixed-dose combination of tenofovir DF, emtricitabine and rilpivirine.

EVIPLERA should not be administered concurrently with other medicinal products containing any of the same active components: tenofovir DF, emtricitabine, or with medicinal products containing lamivudine, tenofovir alafenamide or adefovir dipivoxil. EVIPLERA should not be coadministered with rilpivirine unless required for dose adjustment (e.g, with rifabutin, see Drug Interactions).

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

4.4 Special warnings and precautions for use

Patients receiving EVIPLERA or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV-1 infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.

Patients should be advised that antiretroviral therapies, including EVIPLERA, have not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions must continue to be used. Patients should also be informed that EVIPLERA is not a cure for HIV-1 infection.

Virologic Failure and Development of Resistance
Regardless of HIV-1 RNA level at the start of therapy, more rilpivirine-treated patients with CD4+ cell count less than 200 cells/mm^3 at the start of therapy experienced virologic failure compared to patients with CD4+ cell count greater than or equal to 200 cells/mm^3. More rilpivirine-treated patients with HIV-1 RNA greater than 100,000 copies/mL at the start of therapy experienced virologic failure compared to patients with HIV-1 RNA less than 100,000 copies/mL at the start of therapy.

The observed virologic failure rate in rilpivirine-treated patients conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz. More patients treated with rilpivirine developed lamivudine/emtricitabine associated resistance compared to efavirenz (see section 5.1 Pharmacodynamic properties and 5.2 Pharmacokinetic properties).

Resistance testing and/or historical resistance data should guide the use of EVIPLERA.

Lactic Acidosis/Severe Hepatomegaly with Steatosis:
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported with the use of antiretroviral nucleoside analogues including the tenofovir DF component of EVIPLERA, alone or in combination with other antiretrovirals, in the treatment of HIV infection. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogues to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with EVIPLERA should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Renal Impairment:
The emtricitabine and tenofovir DF components of EVIPLERA are primarily excreted by the kidneys; however, rilpivirine is not. Renal failure, renal impairment, elevated creatinine, hypophosphataemia and Fanconi syndrome have been reported with the use of tenofovir DF in clinical practice.

It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy and, as clinically appropriate, during EVIPLERA therapy. Patients at risk for, or with a history of, renal dysfunction, including patients who have previously experienced renal events while receiving adefovir dipivoxil, should be routinely monitored for changes in serum creatinine and phosphorus.

EVIPLERA is not recommended for patients with moderate or severe renal impairment (CrCl <50 mL/min, including patients who require haemodialysis). Patients with moderate or severe

renal impairment require a dose adjustment of emtricitabine and tenofovir DF that cannot be achieved with the combination tablet.

EVIPLERA should be avoided with concurrent or recent use of a nephrotoxic agent.

Hepatic Impairment:
There is limited information regarding the use of rilpivirine in patients with mild or moderate hepatic impairment, resulting in unexpected variability in the available data. Rilpivirine has not been studied in patients with severe hepatic impairment (see section 5.2 Pharmacokinetic properties). EVIPLERA should be used with caution in patients with moderate to severe hepatic impairment (see section Pharmacokinetic properties).

Bone Effects:
Bone toxicity including a reduction in bone mineral density have been observed in tenofovir DF studies in three animal species. Clinically relevant bone abnormalities have not been seen in long term clinical studies (>3 years) with VIREAD. However, bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy (see section 4.8 Undesirable effects). If bone abnormalities are suspected during therapy then appropriate consultation should be obtained.

HIV and Hepatitis B Virus (HBV) Co-infection:
Discontinuation of EVIPLERA therapy in patients co-infected with HIV-1 and HBV may be associated with severe acute exacerbations of hepatitis due to the emtricitabine and tenofovir DF components of EVIPLERA. Patients co-infected with HIV-1 and HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping EVIPLERA treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, discontinuation of anti-hepatitis B therapy is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Immune Reconstitution Syndrome:
Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including tenofovir DF, emtricitabine and rilpivirine. In HIV-1 infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy, 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 antiretroviral therapy. Relevant examples include cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

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

4.5 Interaction with other medicines and other forms of interaction

As EVIPLERA–contains tenofovir DF, emtricitabine and rilpivirine, any interactions that have been identified with these agents individually may occur with EVIPLERA.

Tenofovir and emtricitabine are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No drug-drug interactions due to competition for renal excretion have been observed; however, co-administration of TRUVADA with drugs that are eliminated by active tubular secretion may increase serum concentrations of tenofovir, emtricitabine, and/or the co-administered drug. Drugs that decrease renal function may increase serum concentrations of tenofovir and/or emtricitabine.

Drugs Inducing or Inhibiting CYP3A Enzymes:
Rilpivirine is primarily metabolized by cytochrome P450 (CYP) 3A, and drugs that induce or inhibit CYP3A may thus affect the clearance of rilpivirine.

Coadministration of rilpivirine and drugs that induce CYP3A resulted in decreased plasma concentrations of rilpivirine which could potentially reduce the therapeutic effect of EVIPLERA (see Table 5 for drugs studied). Other drugs inducing CYP3A enzymes include carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifapentine, dexamethasone, and St. John's wort (*Hypericum perforatum)* (see section 4.3 Contraindications).

Coadministration of rilpivirine and drugs that inhibit CYP3A resulted in increased plasma concentrations of rilpivirine (see Table 2 for drugs studied).

Drugs Increasing Gastric pH:
Coadministration of rilpivirine with drugs that increase gastric pH (such as proton pump inhibitors, H_2-receptor antagonists, and antacids) may decrease plasma concentrations of rilpivirine which could potentially reduce the therapeutic effect of EVIPLERA (see Table 2 for drugs studied) (see section 4.3 Contraindications).

Didanosine:
Concomitant dosing of tenofovir DF with didanosine buffered tablets or enteric-coated capsules significantly increase the C_{max} and AUC of didanosine. When didanosine 250 mg enteric-coated capsules were administered with tenofovir DF, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions. The mechanism of this interaction is unknown. Table 1 below, summarises the effects of tenofovir DF on the pharmacokinetics of didanosine.

As a result of this increased exposure, patients receiving EVIPLERA and didanosine should be carefully monitored for didanosine-associated adverse events, including pancreatitis, lactic acidosis and neuropathy. Suppression of CD4 cell counts has been observed in patients receiving tenofovir DF with didanosine at a dose of 400 mg daily. In adults weighing ≥60kg, the didanosine dose should be reduced to 250 mg daily when it is coadministered with EVIPLERA. Data are not available to recommend a dose adjustment of didanosine for patients weighing <60 kg. Didanosine should be discontinued in patients who develop didanosine-associated adverse events.

Table 1. Drug Interactions: Changes in Pharmacokinetic Parameters for Didanosine and Atazanavir in the Presence of Tenofovir DF

Co-administered Drug	Dose of Co-administered Drug (mg)	N	% Change of Co-administered Drug Pharmacokinetic Parameters[1] (90% CI)		
			C_{max}	AUC	C_{min}
Didanosine[3] enteric-coated capsules	400 once / with or without food[2]	26	↑ 48–64% (↑ 25–↑ 89)	↑ 48–60% (↑ 31–↑ 79)	NC
	250 once / Simultaneously with tenofovir DF, fasted[3]	28	⇔	↑ 14 (0–↑ 31)	NC
	250 once / Simultaneously with tenofovir DF, fed[2,3]	28	↓ 29 (↓ 39–↓ 18)	↓ 11 (↓ 23–↑ 2)	NC
Atazanavir sulfate[5]	400 once daily x 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
	Atazanavir/Ritonavir[5] 300/100 once daily x 42 days	10	↓ 28 (↓ 50 to ↑ 5) [5]	↓ 25 (↓ 42 to ↓ 3) [5]	↓ 23 (↓ 46 to ↑ 10) [5]

1. Increase = ↑; Decrease = ↓; No Effect = ⇔; NC = Not Calculated
2. Administration with food was with a light meal (~373 kcal, 20% fat).
3. Relative to 400 mg alone, fasted.
4. Reyataz Prescribing Information (Bristol-Myers Squibb)
5. In HIV-1 infected patients, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2.3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone (Reyataz March 2004 United States Package Insert)

Atazanavir:

Tenofovir DF decreases exposure to atazanavir and should only be administered with boosted atazanavir (atazanavir 300 mg/ritonavir 100 mg). No data are available to support dosing recommendations for atazanavir or atazanavir/ritonavir in combination with EVIPLERA. Table 4 summarises the effects of tenofovir DF on the pharmacokinetics of atazanavir.

QT Prolonging Drugs:

There is limited information available on the potential for a pharmacodynamic interaction between rilpivirine and drugs that prolong the QTc interval of the electrocardiogram. In a study of healthy patients, supratherapeutic doses of rilpivirine (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval of the electrocardiogram. EVIPLERA should be used with caution when coadministered with a drug with a known risk of QTc prolongation.

Table 2. Established Significant [a] Drug Interactions

Concomitant Drug Class: Drug Name	Effect[b]	Clinical Comment
Antiretroviral Agents:		
didanosine[c]	↑ didanosine	**In patients weighing > 60 kg, the didanosine dose should be reduced to 250 mg if used concomitantly with EVIPLERA. Data are not adequate to support a specific recommendation for dosing in patients weighing < 60 kg. Patients receiving EVIPLERA and didanosine should be monitored closely for didanosine-associated adverse reactions e.g., pancreatitis, lactic acidosis.** Didanosine should be administered on an empty stomach at least two hours before or four hours after EVIPLERA (which should be administered with food). For additional information, please consult the Videx/Videx EC (didanosine) product information.
atazanavir/ritonavir atazanavir	↑ tenofovir[c] ↓ atazanavir[c]	Tenofovir DF decreases exposure to atazanavir and should only be administered with boosted atazanavir (atazanavir 300 mg/ritonavir 100 mg). No data are available to support dosing recommendations for atazanavir or atazanavir/ritonavir in combination with EVIPLERA.
darunavir/ritonavir[c]	↑ rilpivirine	Concomitant use of EVIPLERA with darunavir/ritonavir may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). No dose adjustment is required when EVIPLERA is coadministered with darunavir/ritonavir.
lopinavir/ritonavir[c]	↑ rilpivirine	No dose adjustment is required when EVIPLERA is coadministered with lopinavir/ritonavir.
Hepatitis C Virus Antiviral Agents: ledipasvir/sofosbuvir sofosbuvir/velpatasvir sofosbuvir/velpatasvir/ voxilaprevir	↑ tenofovir	Patients receiving EVIPLERA concomitantly with HARVONI (ledipasvir/sofosbuvir), EPCLUSA (sofosbuvir/velpatasvir) or VOSEVI (sofosbuvir/velpatasvir/voxilaprevir) should be monitored for adverse reactions associated with tenofovir disoproxil fumarate.
Other Agents:		
Azole Antifungal Agents: ketoconazole[c]	↑ rilpivirine ↓ ketoconazole	Concomitant use of EVIPLERA with azole antifungal agents may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). No dose adjustment is required when EVIPLERA is coadministered with azole antifungal agents.

Concomitant Drug Class: Drug Name	Effect[b]	Clinical Comment
Antimycobacterials: rifabutin[c] rifampin[c]	↓ rilpivirine	Concomitant use of EVIPLERA with rifabutin may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of EVIPLERA. If EVIPLERA is coadministered with rifabutin, an additional 25 mg tablet of rilpivirine per day is recommended to be taken concomitantly with EVIPLERA, for the duration of rifabutin coadministration. EVIPLERA should not be used in combination with rifampin as coadministration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of EVIPLERA.
Proton Pump Inhibitors: omeprazole[c]	↓ rilpivirine ↓ omeprazole	EVIPLERA should not be used in combination with proton pump inhibitors as coadministration may cause significant decreases in rilpivirine plasma concentrations (increase in gastric pH). This may result in loss of therapeutic effect of EVIPLERA.
H_2-Receptor Antagonists: famotidine[c]	↔ rilpivirine (famotidine taken 12 hours before rilpivirine) ↓ rilpivirine (famotidine taken 2 hours before rilpivirine) ↔ rilpivirine (famotidine taken 4 hours after rilpivirine)	The combination of EVIPLERA and H_2-receptor antagonists should be used with caution as coadministration may cause significant decreases in rilpivirine plasma concentrations (increase in gastric pH). H_2-receptor antagonists should only be administered at least 12 hours before or at least 4 hours after EVIPLERA.
Narcotic Analgesics: methadone	↓ R (–) methadone ↓ S (+) methadone	No dose adjustments are required when initiating coadministration of methadone with EVIPLERA. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.

a. This table is not all inclusive.
b. ↑ = increase, ↓ = decrease, ↔ = no effect
c. This interaction study has been performed with a dose (150 mg of rilpivirine) higher than the recommended dose for rilpivirine assessing the maximal effect on the coadministered drug. The dosing recommendation is applicable to the recommended dose of rilpivirine 25 mg once daily.

Interactions with Other Medicinal Products:

Caution should be given to prescribing rilpivirine with medicinal products that may reduce the exposure to rilpivirine. For information on interactions with other medicinal products (see Table 2 above).

Drugs Without Clinically Significant Interactions:
The drug interactions described are based on studies conducted with the individual components of EVIPLERA (emtricitabine, rilpivirine, or tenofovir disoproxil fumarate) or EVIPLERA as a combination product.

Tenofovir disoproxil fumarate: No clinically significant drug interactions have been observed between tenofovir DF and abacavir, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, ribavirin, saquinavir/ritonavir or sofosbuvir.

Emtricitabine: No clinically significant drug interactions have been observed between emtricitabine and indinavir, zidovudine, stavudine, famciclovir, ledipasvir/sofosbuvir, sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, or tenofovir DF.

Rilpivirine: No clinically significant drug interactions have been observed between rilpivirine and acetaminophen, atorvastatin, didanosine, digoxin, ethinyl estradiol, ledipasvir/sofosbuvir, metformin, norethindrone, raltegravir, sildenafil, sofosbuvir, sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, or tenofovir DF.

Paediatric population:
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy Category B3

There are no well controlled clinical studies of EVIPLERA in pregnant women. No embryofoetal development studies have been conducted with tenofovir DF, emtricitabine and rilpivirine in combination. Because animal reproductive studies are not always predictive of human response, EVIPLERA should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Women of childbearing potential should undergo pregnancy testing before initiation of EVIPLERA. Women of childbearing potential who are taking EVIPLERA should use effective contraception throughout treatment.

Tenofovir disoproxil fumarate: Reproductive toxicity studies performed in rats and rabbits did not reveal any evidence of harm to the foetus due to tenofovir at respective exposures (AUC) of 4-13 and 66-fold the human exposure. Subcutaneous treatment of pregnant rhesus monkeys with a dose of 30 mg/kg/day of the tenofovir base during the last half of pregnancy resulted in reduced foetal serum phosphorus concentrations.

Emtricitabine: No evidence of embryofoetal toxicity or teratogenicity was observed in mice or rabbits at respective emtricitabine exposures (AUC) of 50 and 130 fold the clinical exposure. Impaired weight gain observed in pregnant rabbits at doses resulting in emtricitabine exposures (AUC) at least 33 times the clinical exposure was not associated with any adverse foetal effects.

Rilpivirine: Lower exposures of rilpivirine were observed during pregnancy; therefore, viral load should be monitored closely.

Rilpivirine in combination with a background regimen was evaluated in a clinical trial of 19 pregnant women during the second and third trimesters, and postpartum. The pharmacokinetic data demonstrate that total exposure (AUC) to rilpivirine as a part of an antiretroviral regimen was approximately 30% lower during pregnancy compared with postpartum (6−12 weeks). Virologic response was preserved throughout the trial period. No mother to child transmission occurred in all 10 infants born to the mothers who completed the trial and for whom the HIV status was available. Rilpivirine was well tolerated during pregnancy and postpartum. There were no new safety findings compared with the known safety profile of rilpivirine in HIV-1 infected adults (see section 5.2 Pharmacological properties).

Placental transfer of rilpivirine or its metabolites from dam to foetus was demonstrated in rats. Studies in animals have shown no evidence of relevant embryonic or foetal toxicity or an effect on reproductive function. There was no clinically relevant teratogenicity with rilpivirine in rats and rabbits. The exposures at the embryofoetal No Observed Adverse Effect Levels (NOAELs) in rats and rabbits were respectively 15 and 70 times higher than the exposure in humans at the recommended dose of 25 mg rilpivirine once daily.

Breastfeeding
Studies in rats have demonstrated that tenofovir and rilpivirine is excreted into milk.

It is not known whether rilpivirine is secreted in human milk. Because of the potential for both HIV-1 transmission and for serious adverse events in nursing infants, mothers should be instructed not to breast feed if they are receiving EVIPLERA.

Tenofovir disoproxil fumarate: In humans, samples of breast milk obtained from five HIV-1 infected mothers show that tenofovir is secreted in human milk at low concentrations (estimated neonatal concentrations 128 to 266 times lower than the tenofovir IC_{50}) (50% maximal inhibitory concentration). Tenofovir associated risks, including the risk of developing viral resistance to tenofovir, in infants breastfed by mothers being treated with tenofovir disoproxil fumarate are unknown.

Emtricitabine: Samples of breast milk obtained from five HIV-1 infected mothers show that emtricitabine is secreted in human milk at estimated neonatal concentrations 3 to 12 times higher than the emtricitabine IC_{50} but 3 to 12 times lower than the C_{min} (minimal expected trough concentrations in adults) achieved from oral administration of emtricitabine. Breastfeeding infants whose mothers are being treated with emtricitabine may be at risk for developing viral resistance to emtricitabine. Other emtricitabine-associated risks in infants breastfed by mothers being treated with emtricitabine are unknown.

Fertility

No reproductive toxicity studies have been conducted with tenofovir DF, emtricitabine and rilpivirine in combination.

Tenofovir disoproxil fumarate: Male and female rat fertility and mating performance or early embryonic development were unaffected by an oral tenofovir DF dose (600 mg/kg/day) that achieved systemic drug exposures that were in excess of the expected value in humans receiving the therapeutic dose (5-fold based on plasma AUC). There was, however, an alteration of the oestrous cycle in female rats.

Emtricitabine: Emtricitabine did not affect fertility in male rats or in female and male mice at respective approximate exposures (AUC) of 130 and 50 to 80 times the exposure in humans. The fertility of offspring was unaffected by treatment of mice from early gestation to the end of lactation (50 times the human exposure).

Rilpivirine: In a study conducted in rats, there were no effects on mating or fertility with rilpivirine up to 400 mg/kg/day, a dose of rilpivirine that showed maternal toxicity. This dose is associated with an exposure that is approximately 40 times higher than the exposure in humans at the recommended dose of 25 mg once daily.

4.7 Effects on ability to drive and use machines

No studies on the effects of EVIPLERA on the ability to drive and use machines have been performed. However, patients should be informed that dizziness has been reported during treatment with tenofovir DF, emtricitabine, and rilpivirine.

4.8 Undesirable effects

Clinical Trials

As EVIPLERA contains tenofovir DF, emtricitabine and rilpivirine, adverse events associated with these individual antiretroviral agents may be expected to occur with the fixed combination tablet.

For additional safety information about tenofovir DF, emtricitabine or rilpivirine in combination with other antiretroviral agents, consult the Product Information for these products.

4.8.1 In Treatment –Naïve HIV-1 Infected Adults

Studies C209 and C215

Tenofovir disoproxil fumarate + Emtricitabine + Rilpivirine:

Treatment Emergent Adverse Reactions: Studies C209 and C215 were randomised, double-blind, active-controlled studies in which 80% of antiretroviral-naive patients received tenofovir DF + emtricitabine administered in combination either with rilpivirine (N=550) or with efavirenz (N=546) (see section 5.1 Pharmacodynamic properties). The median duration of exposure for patients in either treatment arm was 104 weeks. No new adverse reaction terms were identified between 48 weeks and 96 weeks. Adverse reactions observed in these studies were generally consistent with those seen in previous studies of the individual components (Table 3).

The most common adverse reactions (incidence ≥3%, Grades 2-4) that occurred in patients receiving tenofovir DF, emtricitabine, and rilpivirine in clinical trials C209 and C215 were depression, insomnia and headache and diarrhoea.

Table 3. Selected Treatment-Emergent Adverse Reactions[a] (Grades 2–4) Reported in >2% of Patients Receiving Rilpivirine or Efavirenz in Combination with Tenofovir DF/Emtricitabine in Studies C209 and C215 (Week 96 Analysis)

	TDF/FTC + Rilpivirine	TDF/FTC + Efavirenz
	N=550	N=546
Gastrointestinal Disorder		
Diarrhoea[b]	5%	3%
Nausea	1%	3%
Nervous System Disorders		
Dizziness	1%	7%
Headache	4%	4%
Psychiatric Disorders		
Abnormal dreams	2%	5%
Depression	5%	3%
Insomnia	3%	3%
General Disorders and Administration site disorders		
Fatigue	2%	3%
Skin and Subcutaneous Tissue Disorders		
Rash	3%	10%

a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.
b. Adverse reactions not associated with rilpivirine.

Laboratory Abnormalities: Laboratory abnormalities observed in studies C209 and C215 were generally consistent with those seen in other studies of the individual components (Table 4).

Table 4. Significant Laboratory Abnormalities (Grades 3-4) Reported in ≥1% of Patients Who Received Rilpivirine or Efavirenz in Combination with Tenofovir DF/Emtricitabine in Studies C209 and C215 (Week 96 Analysis)

	TDF/FTC + Rilpivirine	TDF/FTC + Efavirenz
Hypophosphatemia	1.3% (7/549)	1.9% (10/535)
Pancreatic Amylase (>2 ULN[a])	4.2% (23/549)	4.9% (26/536)
Lipase (>3 ULN)	<1% (5/549)	1.5% (8/536)
AST (>5 ULN)	2.6% (14/549)	3.6% (19/535)
ALT (>5 ULN)	1.6% (9/549)	3.5% (19/536)
Total Cholesterol (fasted) (>300 mg/dL)	<1% (1/549)	2.2% (12/535)
LDL-Cholesterol (fasted) (>191 mg/dL)	<1% (5/549)	3.9% (21/534)
Triglycerides (fasted) (>751 mg/dL)	<1% (3/549)	2.6% 14/535)

a. ULN=Upper limit of normal value.

Rilpivirine was associated with fewer neurological and psychiatric adverse reactions than efavirenz in patients who received emtricitabine/tenofovir DF in Studies C209 and C215. In addition to the adverse events in Studies C209 and C215 (Table 3), the following adverse events were observed in clinical studies of tenofovir DF, emtricitabine and rilpivirine in combination with other antiretroviral agents.

***Tenofovir disoproxil fumarate*:** More than 12,000 patients have been treated with VIREAD alone or in combination with other antiretroviral medicinal products for periods of 28 days to 215 weeks in Phase I-III clinical trials and expanded access studies. A total of 1,544 patients have received VIREAD 300 mg once daily in Phase I-III clinical trials; over 11,000 patients have received VIREAD in expanded access studies.

The most common adverse events that occurred in patients receiving VIREAD with other antiretroviral agents in clinical trials were mild to moderate gastrointestinal events, such as nausea, diarrhoea, vomiting and flatulence.

Emtricitabine: More than 2000 adult patients with HIV-1 infection have been treated with EMTRIVA alone or in combination with other antiretroviral agents for periods of 10 days to 200 weeks in Phase I-III clinical trials.

Assessment of adverse reactions is based on data from studies 301A and 303 in which 571 treatment naïve (301A) and 440 treatment experienced (303) patients received EMTRIVA 200 mg (n=580) or comparator drug (n=431) for 48 weeks.

The most common adverse events that occurred in patients receiving EMTRIVA with other antiretroviral agents in clinical trials were headache, diarrhoea, nausea, and rash, which were generally of mild to moderate severity. Approximately 1% of patients discontinued participation in the clinical studies due to these events. All adverse events were reported with similar frequency in EMTRIVA and control treatment groups with the exception of skin discolouration which was reported with higher frequency in the EMTRIVA treated group.

Skin discolouration, manifested by hyperpigmentation on the palms and/or soles was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

In addition to the adverse reactions reported in adults, anaemia has been reported commonly and hyperpigmentation very commonly, in paediatric patients.

Rilpivirine: Adverse reactions that occurred in up to 2% of patients receiving rilpivirine with other antiretroviral agents in clinical trials include decreased appetite, sleep disorders, abnormal dreams, depressed mood, somnolence, abdominal pain, vomiting, abdominal discomfort and dizziness.

Adrenal Function: In the pooled Phase 3 trials of C209 and C215, in patients treated with rilpivirine plus any of the allowed background regimen (N=686), at Week 96, there was an overall mean change from baseline in basal cortisol of -19.1 nmol/L in the rilpivirine group, and an increase of +.06 nmol/L in the efavirenz group. At Week 96, the mean change from baseline in ACTH-stimulated cortisol levels was lower in the rilpivirine group (+18.4 ± 8.36 nmol/L) than in the efavirenz group (+54.1 ± 7.24 nmol/L). Mean values for both basal and ACTH-stimulated cortisol values at Week 96 were within the normal range. Overall, there were no serious adverse events, deaths, or treatment discontinuations that could clearly be attributed to adrenal insufficiency. Effects on adrenal function were comparable by background N(t)RTIs.

Serum Creatinine: In the pooled Phase 3 trials of C209 and C215 trials in patients treated with rilpivirine plus any of the allowed background regimen (N=686), there was a small increase in serum creatinine over 96 weeks of treatment with rilpivirine. Most of this increase occurred within the first four weeks of treatment, a mean change of 9 µmol/L (range: -26 µmol/L to 53 µmol/L) was observed through week 96. In patients who entered the trial with mild or moderate renal impairment, the serum creatinine increase observed was similar to that seen in patients with normal renal function. These changes are not considered to be clinically relevant and no subject discontinued treatment due to increases in serum creatinine. Creatinine increases were comparable by background N(t)RTIs.

Serum Lipids: Changes from baseline in total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides are presented in Table 5. The mean changes from baseline were smaller in the rilpivirine arm versus the efavirenz arm. The impact of such findings has not been demonstrated.

Table 5. Lipid Values Reported in Subjects Patients Receiving Rilpivirine or Efavirenz in Combination with Tenofovir DF/Emtricitabine in Studies C209 and C215[a]

		Pooled Data from the Week 96 Analysis of C209 and C215 Trials			
		TDF/FTC + Rilpivirine N=550		TDF/FTC + Efavirenz N=546	
	N	Baseline	Week 96	Baseline	Week 96
		Mean (nmol/L)	Mean Change[b] (nmol/L)	Mean (nmol/L)	Mean Change[b] (nmol/L)
Total Cholesterol (fasted)	430	4	<1	4	<1
HDL-cholesterol (fasted)	429	1	<1	1	<1
LDL-cholesterol (fasted)	427	2	<1	2	<1
Triglycerides (fasted)	430	3	<1	3	<1

a. Excludes patients who received lipid lowering agents during the treatment period
b. The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 96 values.

Patients coinfected with hepatitis B and/or hepatitis C virus:
In patients coinfected with hepatitis B or C virus receiving rilpivirine in studies C209 and C215, the incidence of hepatic enzyme elevation was higher than in patients receiving rilpivirine who were not coinfected. The same increase was also observed in the efavirenz arm. The pharmacokinetic exposure of rilpivirine in coinfected patients was comparable to that in patients without coinfection.

4.8.2 In Virologically Supressed HIV-1 Infected Patients

Studies GS-US-264-0106 and GS-US-264-0111
No new adverse reactions to EVIPLERA were identified in clinical trials of virologically suppressed patients who switched from a regimen containing a ritonavir-boosted protease inhibitor (GS-US-264-0106, N=469) or from ATRIPLA (GS-US-264-0111, N=49) to EVIPLERA.

Post Marketing Experience

In addition to adverse events reported from clinical trials, the following events have been reported in post marketing surveillance. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Tenofovir disoproxil fumarate
IMMUNE SYSTEM DISORDERS
Allergic reaction (including angioedema), immune reconstitution syndrome

METABOLISM AND NUTRITION DISORDERS
Hypokaleamia, hypophosphataemia, lactic acidosis

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS
Dyspnoea

GASTROINTESTINAL DISORDERS
Increased amylase, abdominal pain, pancreatitis

HEPATOBILIARY DISORDERS
Hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT, gamma GT)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS
Rash

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS
Rhabdomyolysis, muscular weakness, myopathy, osteomalacia (manifested as bone pain and infrequently contributing to fractures)

RENAL AND URINARY DISORDERS
Increased creatinine, renal insufficiency, renal failure, acute renal failure, Fanconi syndrome, proximal renal tubulopathy, nephrogenic diabetes insipidus, proteinuria, acute tubular necrosis, polyuria, interstitial nephritis (including acute cases).

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS
Asthaenia

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), hypokalaemia, muscular weakness, myopathy, hypophosphataemia. These events are not considered to be causally associated with tenofovir DF therapy in the absence of proximal renal tubulopathy.

Exacerbations of Hepatitis after Discontinuation of Treatment
In HIV-1 infected patients co-infected with HBV, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of treatment (see section 4.4 Special warnings and precautions for use).

Emtricitabine
IMMUNE SYSTEM DISORDERS
Immune reconstitution syndrome

EVIPLERA
SKIN AND SUBCUTANEOUS TISSUE DISORDERS
Severe skin reactions with systemic symptoms have been reported during postmarketing experience, including rashes accompanied by fever, blisters, conjunctivitis, angioedema, elevated liver function tests, and/or eosinophilia.

METABOLISM AND NUTRITION DISORDERS
Weight increased.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions: https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with EVIPLERA consists of general supportive measures including monitoring of vital signs and ECG (QT interval) as well as observation of the clinical status of the patient.

Tenofovir disoproxil fumarate: Clinical experience of doses higher than the therapeutic dose of VIREAD 300 mg is available from two studies. In one study, intravenous tenofovir, equivalent to 16.7 mg/kg/day of tenofovir DF, was administered daily for 7 days. In the second study, 600 mg of tenofovir DF was administered to patients orally for 28 days. No unexpected or severe adverse reactions were reported in either study. The effects of higher doses are not known.

Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of VIREAD, a four-hour haemodialysis session removed approximately 10% of the administered tenofovir dose.

Emtricitabine: Limited clinical experience is available at doses higher than the therapeutic dose of EMTRIVA. In one clinical pharmacology study single doses of emtricitabine 1200 mg were administered to 11 patients. No severe adverse reactions were reported. The effects of higher doses are not known.

Haemodialysis treatment removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

Rilpivirine: There is no specific antidote for overdose with rilpivirine. Human experience of overdose with rilpivirine is limited. Since rilpivirine is highly bound to plasma protein, dialysis is unlikely to result in significant removal of the active substance.

For information on the management of overdose, contact the National Poisons Centre on 0800 764 766.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic effects

Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations, ATC code: J05AR06.

Mechanism of Action

Tenofovir disoproxil fumarate: is an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate. Tenofovir DF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of human immunodeficiency virus-type 1 (HIV-1) reverse transciptase (RT) by competing with the natural substrate deoxyadenosine 5′-triphosphate and, after incorporation into deoxyribonucleic acid (DNA), by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

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

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

Antiviral Activity *In Vitro*

Tenofovir disoproxil fumarate, emtricitabine and rilpivirine: The triple combination of tenofovir, emtricitabine and rilpivirine demonstrated synergistic antiviral activity in cell culture.

Tenofovir disoproxil fumarate: The *in vitro* 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 IC_{50} (50% inhibitory concentration) values for tenofovir were in the range of 0.04 to 8.5 μM. In drug combination studies of tenofovir with nucleoside analogue reverse transcriptase inhibitors (NRTIs) (abacavir, didanosine, lamivudine (3TC), stavudine (d4T), zalcitabine, zidovudine (AZT)), NNRTIs (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Tenofovir displayed antiviral activity *in vitro* against HIV-1 clades A, B, C, D, E, F, G and O (IC_{50} values ranged from 0.5 to 2.2 μM). In addition, tenofovir has also been shown to be active *in vitro* against HIV-2, with similar potency as observed against HIV-1.

Emtricitabine: The *in vitro* antiviral activity of emtricitabine against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The IC_{50} value for emtricitabine was in the range of 0.0013 to 0.64 μM (0.0003 to 0.158 μg/mL). In drug combination studies of emtricitabine with NRTIs (abacavir, 3TC, d4T, zalcitabine, AZT), NNRTIs (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Emtricitabine displayed antiviral activity *in vitro* against HIV-1 clades A, C, D,

E, F, and G (IC_{50} values ranged from 0.007 to 0.075 μM) and showed strain specific activity against HIV-2 (IC_{50} values ranged from 0.007 to 1.5 μM).

Rilpivirine: Rilpivirine exhibited activity against laboratory strains of wild-type HIV-1 in an acutely infected T-cell line with a median EC_{50} value for HIV-1/IIIB of 0.73 nM. Although rilpivirine demonstrated limited *in vitro* activity against HIV-2 with EC_{50} values ranging from 2510 to 10830 nM, treatment of HIV-2 infection with rilpivirine is not recommended in the absence of clinical data. Rilpivirine 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 and group O primary isolates with EC_{50} values ranging from 2.88 to 8.45 nM. Rilpivirine showed additive to synergistic antiviral activity in combination with the N(t)RTIs abacavir, didanosine, emtricitabine, 3TC, d4T, tenofovir, and AZT; the PIs amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and tipranavir; the NNRTIs efavirenz, etravirine and nevirapine; the fusion inhibitor enfuvirtide; the entry inhibitor maraviroc; and the integrase inhibitor raltegravir.

Drug Resistance

In Cell Culture:

Tenofovir disoproxil fumarate: HIV-1 isolates with reduced susceptibility to tenofovir have been selected *in vitro*. These viruses expressed a K65R mutation in reverse transcriptase and showed a 2 to 4 fold reduction in susceptibility to tenofovir. In addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in low-level reduced susceptibility to abacavir, emtricitabine, tenofovir and lamivudine.

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

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 amino acid substitutions that emerged included: L100I, K101E, V108I, E138K, V179F, Y181C, H221Y, F227C and M230I.

In Clinical Studies: Treatment-Naïve Patients

Studies C209 and C215

Tenofovir disoproxil fumarate, emtricitabine, and rilpivirine: In the cumulative Week 96 pooled resistance analysis for patients receiving rilpivirine in combination with emtricitabine/tenofovir disoproxil fumarate, in clinical trials C209 and C215 (see section 5.1 Pharmacodynamic properties, Clinical trials; N=550), resistance information was available for 71 of 78 patients who qualified for resistance analysis; 43 of these patients had an amino acid substitution associated with NNRTI (N=39) or NRTI (N=41) resistance. Among patients receiving efavirenz in combination with emtricitabine/tenofovir disoproxil fumarate, resistance information was available for 30 of 37 patients who qualified for resistance analysis; 17 of these

patients had an amino acid substitution associated with NNRTI (N=15) or NRTI (N=8) resistance.

The NNRTI resistance that developed most commonly in these patients were: V90I, K101E, E138K/Q, V179I, Y181C, V189I, H221Y and H221Y and F227C. The most common mutations were the same in the Week 48 and Week 96 analyses. In the trials, the presence of the substitutions V90I and V189I at baseline did not affect the viral response. The E138K substitution emerged most frequently during rilpivirine treatment, commonly in combination with the M184I substitution. The amino acid substitutions associated with NRTI resistance that developed in 3 or more patients were: K65R, K70E, M184V/I, and K219E during the treatment period.

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

Considering all of the available *in vitro* and *in vivo* data in treatment naïve patients the following resistance-associated substitutions, when present at baseline, may affect the activity of EVIPLERA: K65R, K70E, K101E, K101P, E138A, E138G, E138K, E138Q, E138R, V179L, Y181C, Y181I, Y181V, M184I, M184V, Y188L, H221Y, F227C, M230I, M230L and the combination of L1001+K103N.

In Clinical Studies: Virologically Suppressed Patients

Study GS-US-264-0106

Of the 469 EVIPLERA-treated patients (317 patients who switched to EVIPLERA at baseline and 152 patients who switched at Week 24), a total of 7 patients were analysed for resistance development and all had genotypic and phenotypic data available. Through Week 24, two patients who switched to EVIPLERA at baseline (2 of 317 patients, 0.6%) developed genotypic and/or phenotypic resistance to study drugs. After Week 24, 2 additional patients in the EVIPLERA arm developed resistance by Week 48 (total of 4 of 469 patients, 0.9%). The most common emergent resistance mutations in EVIPLERA-treated patients were M184V/I and E138K in reverse transcriptase. All patients remained susceptible to tenofovir.

Of the 24 patients treated with EVIPLERA that had the NNRTI-associated K103N substitution pre-existing at baseline, 17 of 18 patients in the EVIPLERA arm and 5 of 6 patients in the SBR arm maintained virologic suppression after switching to EVIPLERA through 48 weeks and 24 weeks of treatment, respectively.

Study GS-US-264-0111

Through Week 48, no emergent resistance developed among patients that switched to EVIPLERA from ATRIPLA (0 of 49 patients).

Cross-resistance

Tenofovir disoproxil fumarate, emtricitabine and rilpivirine:
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 Clinical Studies: Treatment-Naïve Patients

In the 96-week pooled resistance analysis of the HIV-1 from patients receiving rilpivirine in combination with tenofovir DF/emtricitabine in clinical trials C209 and C215 (see section 5.1 Pharmacodynamic properties, Clinical trials), 66 patients had available HIV-1 phenotypic resistance data at virologic failure, 40 had reduced susceptibility to emtricitabine, 31 had reduced susceptibility to rilpivirine, and 2 had reduced susceptibility to tenofovir DF. Among these patients, 39 had HIV-1 with reduced susceptibility to 3TC, 31 with reduced susceptibility to etravirine, 28 with reduced susceptibility to efavirenz, and 13 with reduced susceptibility to nevirapine. In the rilpivirine group, 6 patients had HIV-1 with reduced susceptibility to abacavir, 9 with reduced susceptibility to didanosine, 3 with reduced susceptibility to stavudine and 2 with reduced susceptibility to zidovudine.

In Clinical Studies: Virologically Suppressed Patients

In Study GS-US-264-0106, 4 of the 469 patients that switched from a protease inhibitor-based regimen to EVIPLERA had reduced susceptibility to at least one component of EVIPLERA through Week 48. Among these patients, all 4 had reduced susceptibility to emtricitabine and 2 had reduced susceptibility to rilpivirine. Patients with reduced susceptibility to emtricitabine also had reduced susceptibility to lamivudine. These patients with reduced susceptibility to rilpivirine developed phenotypic cross-resistance to the other NNRTIs delavirdine, efavirenz, and nevirapine, but remained susceptible to etravirine in 1 of 2 cases.

Tenofovir disoproxil fumarate: The K65R and K70E mutations selected by tenofovir are also selected in some HIV-1 infected patients treated with abacavir, didanosine, or zalcitabine. HIV isolates with this mutation result in reduced susceptibility to abacavir, didanosine, emtricitabine and 3TC. Therefore, cross-resistance among these drugs may occur in patients whose virus harbours the K65R mutation. Patients with HIV-1 expressing three or more thymidine analogue associated mutations (TAMs) that included either the M41L or L210W reverse transcriptase mutation showed reduced susceptibility to tenofovir DF. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the reverse transcriptase showed reduced susceptibility to tenofovir. HIV-1 containing the substitutions associated with NNRTI resistance K103N and Y181C, or rilpivirine-associated substitutions were susceptible to tenofovir.

Emtricitabine: Emtricitabine-resistant isolates (M184V/I) were cross-resistant to 3TC and zalcitabine but retained sensitivity to abacavir, didanosine, d4T, tenofovir, AZT, and NNRTIs (delavirdine, efavirenz, and nevirapine). HIV-1 isolates containing the K65R mutation, selected *in vivo* by abacavir, didanosine, tenofovir, and zalcitabine, demonstrated reduced susceptibility to inhibition by emtricitabine. Viruses harbouring mutations conferring reduced susceptibility to d4T and AZT (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V)

remained sensitive to emtricitabine. HIV-1 containing the substitutions associated with NNRTI resistance K103N or rilpivirine-associated substitutions were susceptible to emtricitabine.

Rilpivirine: In a panel of 67 HIV-1 recombinant laboratory strains with one amino acid substitution at RT positions associated with NNRTI resistance, including the most commonly found K103N and Y181C, rilpivirine showed antiviral activity against 64 (96%) of these strains. The single amino acid substitutions associated with a loss of susceptibility to rilpivirine were: K101P, Y181I and Y181V. The K103N substitution did not result in reduced susceptibility to rilpivirine by itself, but the combination of K103N with L100I resulted in a 7-fold reduced susceptibility to rilpivirine. In another study, the Y188L substitution resulted in a reduced susceptibility to rilpivirine of 9-fold for clinical isolates and 6-fold for site-directed mutants.

Effects on Electrocardiogram

The effect of rilpivirine 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 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 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 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.

Clinical Efficacy

In Treatment-Naïve HIV-1 Infected Adults

Studies C209 and C215

The data available to support the efficacy of EVIPLERA tablets include the available data for each individual agent, the data from clinical studies C209 and C215 where the three agents were used concurrently, and the demonstration of bioequivalence between EVIPLERA tablets and the three individual agents co-administered under fed conditions. No new clinical efficacy or safety studies have been conducted with the EVIPLERA tablet.

The efficacy of EVIPLERA is analysed at Week 48 and Week 96 from two randomised, double-blind, controlled studies C209 and C215 in treatment naïve, HIV-1 infected patients (N = 1368). 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 25 mg (N = 686) once daily or efavirenz 600 mg (N = 682) once daily in addition to a BR. In C209 (N = 690), the BR was tenofovir DF/emtricitabine. In C215 (N = 678), the BR consisted of 2 NRTIs: tenofovir DF/emtricitabine (60%, N = 406) or lamivudine/zidovudine (30%, N = 204) or abacavir plus lamivudine (10%, N = 68).

For patients who received tenofovir DF/emtricitabine (N = 1096) in C209 and C215, the mean age was 37 years (range 18 to 78), 78% were male, 62% were White, 24% were Black, and 11% were Asian. The mean baseline CD4 cell count was 265 cells/mm^3 (range 1 to 888) and 31% had CD4+ cell counts <200 cells/mm^3. The median baseline plasma HIV-1 RNA was 5 log_{10} copies/mL (range 2 to 7).

At Week 48, rilpivirine administered in combination with tenofovir DF /emtricitabine has been shown to be non-inferior (with 12% noninferiority margin) in achieving the primary efficacy outcome of HIV-1 RNA <50 copies/mL when compared to efavirenz administered in combination with tenofovir DF /emtricitabine. The response rate (HIV-1 RNA <50 copies/mL) at Week 96 was comparable between the rilpivirine arm and the efavirenz arm. The incidence of virologic failure was higher in the rilpivirine arm than the efavirenz arm at Week 96; however, most of the virologic failures occurred within the first 48 weeks of treatment. The virological failure rate in the rilpivirine arm at Week 48 and at Week 96 was 9% and 11%, respectively, and 4% and 5% in the efavirenz arm. Low rates of new virologic failure, similar between the treatment arms, were observed between the Week 48 and the Week 96 analysis (see Table 2). Discontinuations due to adverse events were higher in the efavirenz arm at Week 96 than the rilpivirine arm.

Patients were stratified by baseline HIV-1 RNA. Fifty percent of patients had baseline viral loads ≤ 100,000 copies/mL, 39% of patients had baseline viral load between 100,000 copies/mL to 500,000 copies/mL and 11% of patients had baseline viral load >500,000 copies/mL. A subgroup analysis of the virologic response (<50 HIV-1 RNA copies/mL) at Week 48 and Week 96 and virologic failure by baseline viral load (pooled data from the two Phase 3 clinical studies C209 and C215, for patients receiving the tenofovir DF/emtricitabine background regimen) is presented in Table 6.

Table 6. Virologic Outcome of Randomised Treatment of Studies C209 and C215 (Pooled Data for Patients Receiving Rilpivirine or Efavirenz in Combination with Tenofovir DF/Emtricitabine) through Week 48 and Week 96

	Outcome at Week 48		Outcome at Week 96	
	TDF/FTC + Rilpivirine N = 550	**TDF/FTC + Efavirenz N = 546**	**TDF/FTC + Rilpivirine N = 550**	**TDF/FTC + Efavirenz N = 546**
Overall Response (HIV-1 RNA <50 copies/mL [a] (TLOVR[b]))	83% (459/550)	82% (450/546)	77% (423/550)	77% (422/546)
By baseline viral load (copies/mL)				
≤ 100,000	**90% (258/288)**	**85% (217/256)**	**84% (241/288)**	**81% (206/255)**
> 100,000	77% (201/262)	80% (233/290)	69% (182/262)	74% (216/291)
By CD4 count (cells/mm^2)				
< 200	76% (138/181)	80% (132/164)	67% (122/181)	73% (119/164)
≥ 200	87% (321/368)	83% (318/382)	82% (301/368)	79% (303/382)
Non-response				
Virological Failure[c] (all patients)	9% (52/550)	4% (23/546)	11% (63/550)	5% (28/546)
By baseline viral load (copies/mL)				
≤ 100,000	**4% (12/288)**	**2% (6/256)**	**6% (17/288)**	**2% (6/255)**
> 100,000	15% (40/262)	6% (17/290)	18% (46/262)	8% (22/291)
By CD4 count (cells/mm^2)				
< 200	15% (28/181)	7% (12/164)	20% (36/181)	9% (14/164)
≥ 200	7% (24/368)	3% (11/382)	7% (27/368)	4% (14/382)
Death	0	0.2% (1/546)	0	1% (4/546)
Discontinued due to adverse event (AE)	2% (12/550)	7% (39/546)	4% (20/550)	8% (44/546)
Discontinued for non-AE reason[d]	5% (27/550)	6% (33/546)	8% (44/550)	9% (48/546)

N=total number of patients per treatment arm.

a. Patients achieved virologic response (two consecutive viral loads < 50 copies/mL) and maintained it through week 48 or 96.

b. ITT TLOVR = Intention to Treat Time to loss of virologic response.

c. Includes patients who were rebounder (confirmed viral load ≥ 50 copies/mL after being responder) or who were never suppressed (no confirmed viral load < 50 copies/mL, either ongoing or discontinued due to lack or loss of efficacy).

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

Virologic outcomes were comparable in males and females in studies C209 and C215.

Based on the pooled data from the C209 and C215 trials at 48 weeks of treatment, the mean CD4 cell count increase from baseline at Week 96 was 226 cells/mm^3 for rilpivirine plus tenofovir DF/emtricitabine-treated patients and 222 cells/mm^3 for efavirenz plus tenofovir DF/emtricitabine-treated patients.

In Virologically Suppressed HIV-1 Infected Patients

Study GS-US-264-0106

The efficacy and safety of switching from a ritonavir-boosted protease inhibitor in combination with two NRTIs to EVIPLERA was evaluated in a randomised, open-label study in virologically suppressed HIV-1 infected adults. Patients had to be on either their first or second antiretroviral regimen with no history of virologic failure, have no current or past history of resistance to any of the three components of EVIPLERA, and must have been stably suppressed (HIV-1 RNA < 50 copies/mL) for at least 6 months prior to screening. Patients were randomised in a 2:1 ratio to either switch to EVIPLERA at baseline (EVIPLERA, N = 317), or stay on their baseline antiretroviral regimen for 24 weeks (SBR, N = 159) before switching to EVIPLERA for an additional 24 weeks (N =152). Patients had a mean age of 42 years (range 19-73), 88% were male, 77% were White, 17% were Black, and 17% were Hispanic/Latino. The mean baseline CD4 cell count was 584 cells/mm^3 (range 42–1484). Randomisation was stratified by use of tenofovir DF and/or lopinavir/ritonavir in the baseline regimen.

Treatment outcomes through 24 weeks are presented in Table 7. Switching to EVIPLERA was non-inferior in maintaining HIV-1 RNA < 50 copies/mL when compared to patients who stayed on a ritonavir-boosted protease inhibitor in combination with two NRTIs [Treatment difference (95% CI): + 3.8% (-1.6% to 9.1%)].

Table 7. Virologic Outcomes of Randomised Treatment in Study GS-US-264-0106 at Week 24[a]

	EVIPLERA	**Stayed on Baseline Regimen (SBR)**
	N =317	**N=159**
Virologic Success after 24 Weeks of Treatment HIV-1 RNA < 50 copies/mL[b]	94% (297/317)	90% (143/159)
Virologic Failure[c]	1% (3/317)	5% (8/159)
No Virologic Data at Week 24 Window		
Discontinued Study Drug Due to AE or Death[d]	2% (6/317)	0%
Discontinued Study Drug Due to Other Reasons And Last Available HIV-1 RNA < 50 copies/mL[e]	3% (11/317)	3% (5/159)
Missing Data During Window but on Study Drug	0%	2% (3/159)

a. Week 24 window is between Day 127 and 210 (inclusive).
b Snapshot analysis
c. Includes patients who had HIV-1 RNA ≥ 50 copies/mL in the Week 48 window, patients who discontinued early due to lack or loss of efficacy, patients who discontinued for reasons other than an adverse event or death, and at the time of discontinuation had a viral value of ≥ 50 copies/mL.
d. Includes patients who discontinued due to adverse event or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
e. Includes patients who discontinued for reasons other than an adverse event, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

The mean CD4+ cell count increase from baseline to Week 24 was 10 cells/mm^3 for the EVIPLERA arm and 22 cells/mm^3 for the SBR arm. The difference in median CD4+ cell count change between the EVIPLERA arm and the SBR arm was not statistically significant at Week 24 ($p = 0.28$).

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

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

Study GS-US-264-0111

The efficacy, safety, and pharmacokinetics of switching from ATRIPLA to EVIPLERA was evaluated in an open-label study in virologically suppressed HIV-1 infected adults. Patients had to have previously only received ATRIPLA as their first antiretroviral regimen for at least three months, and wished to switch regimens due to efavirenz intolerance. Patients had to be stably suppressed for at least 8 weeks prior to study entry, have no current or past history of resistance to any of the three components of EVIPLERA, and have HIV-1 RNA < 50 copies/mL at screening. The majority of subjects were male (92%), with an overall mean age of 38 years (range 24-57 years); most were white (82%) or black (12%) and non-Hispanic/Latino (80%). The mean baseline CD4 cell count was 656 cells/mm^3(range 188 to 1528 cells/mm^3).

Patients were switched from ATRIPLA to EVIPLERA without a washout period. Among 49 patients who received at least one dose of EVIPLERA, 100% of patients remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 12 and Week 24. At Week 48, 94% (46/49) of patients remained suppressed, and 4% (2/49) were considered virologic failures (HIV-1 RNA ≥ 50 copies/mL). One patient (2%) did not have data available in the Week 48 window; study drug was discontinued due to a protocol violation (ie, reason other than AE or death) and the last available HIV-1 RNA was < 50 copies/mL.

5.2 Pharmacokinetic properties

One EVIPLERA tablet is bioequivalent to one tenofovir DF tablet (300 mg) plus one emtricitabine capsule (200 mg) plus one rilpivirine tablet (25 mg) following single-dose administration to fed healthy patients (N=34).

The separate pharmaceutical forms of tenofovir DF, emtricitabine and rilpivirine were used to determine the pharmacokinetics of tenofovir DF, emtricitabine and rilpivirine in HIV infected patients.

Solubility

Tenofovir DF is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in water at 25 °C. The partition coefficient (*log p*) for tenofovir disoproxil is 1.25 and the pKa is 3.75.

Emtricitabine is a white to off-white crystalline powder with a solubility of approximately 112 mg/mL in water at 25 ºC. The partition coefficient (*log p*) for emtricitabine is -0.43 and the pKa is 2.65

Rilpivirine hydrochloride is a white to almost white powder. Rilpivirine hydrochloride is practically insoluble in water and over a wide pH range.

Absorption, Distribution, Metabolism and Elimination

Tenofovir disoproxil fumarate: The pharmacokinetic properties of tenofovir DF are summarized in Table 8. Following oral administration of tenofovir DF, maximum tenofovir serum concentrations are achieved in 1.0 ± 0.4 hour. *In vitro* binding of tenofovir to human plasma proteins is <0.7% and is independent of concentration over the range of 0.01 to 25 µg/mL. Approximately 70 to 80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of tenofovir DF, the terminal elimination half-life of tenofovir is approximately 17 hours.

Emtricitabine: The pharmacokinetic properties of emtricitabine are summarized in Table 8. Following oral administration of emtricitabine 200 mg capsules, emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1 to 2 hours post-dose. *In vitro* binding of emtricitabine to human plasma proteins is <4% and is independent of concentration over the range of 0.02 to 200 µg/mL. Following administration of radiolabelled emtricitabine approximately 86% is recovered in the urine and 13% is recovered as metabolites. The metabolites of emtricitabine include 3′-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of emtricitabine 200 mg capsules, the plasma emtricitabine half-life is approximately 10 hours.

Table 8. Single Dose Pharmacokinetic Parameters for Tenofovir and Emtricitabine in Adults[1]

	Tenofovir	Emtricitabine
Fasted Oral Bioavailability (%)	25	93
Plasma Terminal Elimination Half-Life (hr)	17	10
C_{max} (µg/mL)	0.30 ± 0.09	1.8 ± 0.7[2]
AUC (µg*hr/mL)	2.29 ± 0.69	10.0 ± 3.1[2]
CL/F (mL/min)	1043 ± 115	302 ± 94
CL_{renal} (mL/min)	243 ± 33	213 ± 89

1. Data presented as mean values.
2. Data presented as steady state values.

Rilpivirine: The pharmacokinetic properties of rilpivirine have been evaluated in adult healthy patients and in adult antiretroviral treatment-naïve HIV-1 infected patients. Exposure to

rilpivirine was generally lower in HIV-1 infected patients than in healthy patients. After oral administration, the maximum plasma concentration of rilpivirine is generally achieved within 4 to 5 hours. The mean C_{0h} and AUC_{24h} values in HIV-1 infected patients were 0.080 ± 0.037 µg/mL and 2.40 ± 1.03 µg•hr/mL, respectively. The absolute bioavailability of RPV is unknown. Rilpivirine is approximately 99.7% bound to plasma proteins in vitro, primarily to albumin. In vitro experiments indicate that rilpivirine primarily undergoes oxidative metabolism mediated by the cytochrome CYP3A system. 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.

Effect of Food on Oral Absorption

The administration of Eviplera to healthy adult subjects with either a light meal or a standard meal resulted in increased exposures of rilpivirine and tenofovir relative to fasting conditions. The C_{max} and AUC of rilpivirine increased by 34% and 9% (light meal) and 26% and 16% (standard meal), respectively. The C_{max} and AUC for tenofovir increased by 12% and 28% (light meal) and 32% and 38% (standard meal), respectively. Emtricitabine exposures were not affected by food. Eviplera must be administered with food to ensure optimal absorption.

Special Populations:

Age, Gender and Ethnicity
Pharmacokinetic studies with EVIPLERA have not been fully evaluated in children (<18 years) or in the elderly (over 65 years) (see section 4.4 Special warnings and precautions for use).

Population pharmacokinetic analysis in HIV-1 infected patients showed that rilpivirine pharmacokinetics are not different across the age range (18 to 78 years) evaluated.

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

Renal inpairment:
EVIPLERA is not recommended for patients with moderate or severe renal impairment (creatinine clearance (CrCl) < 50 ml/min).

Tenofovir disoproxil fumarate and emtricitabine: Patients with moderate or severe renal impairment require dose interval adjustment of emtricitabine and tenofovir DF that cannot be achieved with the combination tablet (see section 4.4 Special warnings and precautions for use).

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

Hepatic impairment:
The pharmacokinetics of EVIPLERA-have not been studied in patients with hepatic impairment.
Tenofovir disoproxil fumarate and emtricitabine: The pharmacokinetics of tenofovir following a 300 mg dose of tenofovir DF have been studied in non-HIV infected patients with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. The pharmacokinetics of emtricitabine have not been studied in patients with moderate to severe hepatic impairment; however, emtricitabine is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.

Rilpivirine: Rilpivirine is primarily metabolized and eliminated by the liver. In a study comparing 8 patients with mild hepatic impairment (Child Pugh score A) to 8 matched controls, and 8 patients with moderate hepatic impairment (Child Pugh 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. No rilpivirine dose adjustment is required in patients with mild or moderate hepatic impairment. Rilpivirine has not been studied in patients with severe hepatic impairment (Child Pugh score C).

Hepatitis B and/or hepatitis C virus co-infection:
Pharmacokinetics of tenofovir DF and emtricitabine have not been fully evaluated in hepatitis B and/or C co-infected patients. Population pharmacokinetic analysis indicated that hepatitis B and/or C virus coinfection had no clinically relevant effect on the exposure to rilpivirine.

Switching From an Efavirenz-Containing Regimen:
The pharmacokinetics of rilpivirine and efavirenz were evaluated in 49 virologically suppressed, HIV-1 infected patients following the switch from an efavirenz-containing regimen to EVIPLERA (Study GS-US-264-0111). Consistent with the established half-life for efavirenz, efavirenz concentrations remained above its protein-binding adjusted IC90 (10 ng/mL) for 4 weeks post-switch. Despite the expected CYP3A induction by efavirenz, rilpivirine mean trough concentrations achieved levels that were in the range of historical data starting 2 weeks post-switch. The efficacy data from Study GS-US-264-0111 (see section 5.1 Pharmacodynamic properties, Clinical trials) indicates that the brief period of lower rilpivirine exposure following the switch from an efavirenz-containing regimen does not impact antiviral efficacy. No dose adjustment is required following the switch from an efavirenz-containing regimen.

Pregnancy and Postpartum

The exposure to total rilpivirine after intake of rilpivirine 25 mg once daily as part of an antiretroviral regimen was lower during pregnancy (similar for the 2nd and 3rd trimesters) compared with postpartum (see Table 9). The decrease in unbound (i.e., active) rilpivirine pharmacokinetic parameters during pregnancy compared to postpartum was less pronounced than for total rilpivirine. In women receiving rilpivirine 25 mg once daily during the 2nd trimester of pregnancy, mean intra-individual values for total rilpivirine C_{max}, AUC_{24h}, and C_{min} values were, respectively, 21%, 29%, and 35% lower as compared to postpartum; during the 3rd trimester of pregnancy, C_{max}, AUC_{24h}, and C_{min} values were, respectively, 20%, 31%, and 42% lower as compared to postpartum.

Table 9 Pharmacokinetic Results of Total Rilpivirine after Administration of Rilpivirine 25 mg Once Daily as Part of an Antiretroviral Regimen, During the 2nd Trimester of Pregnancy, the 3rd Trimester of Pregnancy, and Postpartum

Pharmacokinetics of Total Rilpivirine (mean ± SD, t_{max}:median [range])	Postpartum (6-12 Weeks) (n=11)	2nd Trimester of Pregnancy (n=15)	3rd Trimester of Pregnancy (n=13)
C_{min}, ng/mL	84.0 ± 58.8	54.3 ± 25.8	52.9 ± 24.4
C_{max}, ng/mL	167 ± 101	121 ± 45.9	123 ± 47.5
T_{max}, h	4.00 (2.03-25.08)	4.00 (1.00-9.00)	4.00 (2.00-24.93)
AUC $_{24h}$, ng.h/mL	2714 ± 1535	1792 ± 711	1762 ± 662

5.3 Preclinical safety data

Tenofovir disoproxil fumarate: Tenofovir and tenofovir DF administered in toxicology studies to rats, dogs and monkeys at exposures (based on AUCs) greater than or equal to 6-fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

Evidence of renal toxicity was noted in 4 animal species. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2 to 20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

Genotoxicity

No genotoxicity studies have been conducted with tenofovir DF, emtricitabine and rilpivirine in combination.

Tenofovir disoproxil fumarate was mutagenic in an in vitro mouse L5178Y lymphoma cell assay (tk locus) and in an *ex vivo* assay for unscheduled DNA synthesis in rat hepatocytes, but it was negative in *in vitro* bacterial assays for gene mutation and an *in vivo* mouse micronucleus test for chromosomal damage.
Emtricitabine was not mutagenic in bacteria or mouse lymphoma cell assays *in vitro* nor clastogenic in the mouse micronucleus test *in vivo*.

Rilpivirine has tested negative in the in vitro Ames reverse mutation assay, in vitro chromosomal aberration assay in human lymphocyte and in vitro clastogenicity mouse lymphoma assay, tested in the absence and presence of a metabolic activation system. Rilpivirine did not induce chromosomal damage in the in vivo micronucleus test in mice.

Mutagenicity

No carcinogenicity studies have been conducted with tenofovir DF, emtricitabine and rilpivirine in combination.

Tenofovir disoproxil fumarate: In a long-term carcinogenicity study conducted in mice with tenofovir DF there was a low incidence of duodenal tumours with the highest dose of 600 mg/kg/day. These were associated with a high incidence of duodenal mucosal hyperplasia, which was also observed with a dose of 300 mg/kg/day. These findings may be related to high local drug concentrations in the gastro-intestinal tract, likely to result in much higher exposure margins than that based on the AUC. At therapeutic doses the risk of these duodenal effects occurring in humans is likely to be low. The systemic drug exposure (AUC) with the 600 mg/kg/day dose was approximately 15 times the human exposure at the therapeutic dose of 300 mg/day. No tumourigenic response was observed in rats treated with doses of up to 300 mg/kg/day (5 times the human systemic exposure at the therapeutic dose based on AUC).

Emtricitabine: In long-term oral carcinogenicity studies conducted with emtricitabine, no drug-related increases in tumour incidence were found in mice at doses up to 750 mg/kg/day (32 times the human systemic exposure (AUC) at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (38 times the human systemic exposure at the therapeutic dose).

Rilpivirine: Rilpivirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 20, 60 and 160 mg/kg/day were administered to mice and doses of 40, 200, 500 and 1,500 mg/kg/day were administered to rats. An increase in the incidences of hepatocellular adenomas and carcinomas was observed in mice and rats. An increase in the incidences of follicular cell adenomas and/or carcinomas in the thyroid gland was observed in rats. Administration of rilpivirine did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. The observed hepatocellular findings in mice and rats are considered to be rodent specific, associated with liver enzyme induction. A similar mechanism does not exist in humans; hence, these tumors are not relevant for humans. The follicular cell findings are considered to be rat specific, associated with increased clearance of thyroxine and are not considered to be relevant for humans. At the lowest tested doses in the carcinogenicity studies, the systemic exposures (based on AUC) to rilpivirine were 21 fold (mice) and 3 fold (rats), relative to those observed in humans at the recommended dose (25 mg once daily).

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablet core:

Pregelatinized starch
Lactose
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate
Povidone
Polysorbate 20

Coating:

Macrogol 3350
Hypromellose
Lactose
Glycerol triacetate
Titanium dioxide
Iron oxide red
Indigo carmine aluminium lake
Sunset yellow FCF aluminium lake

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

EVIPLERA should be stored below 25 °C.

6.5 Nature and Contents of Container

EVIPLERA is supplied in high density polyethylene (HDPE) bottles containing 30 tablets and a desiccant (silica gel canister or sachet), polyester coil and is closed with a child resistant closure.

6.6 Special precautions for disposal

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Grant Thornton New Zealand Limited,
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Tel: 0800 443 933

9. DATE OF FIRST APPROVAL

5 July 2012

10. DATE OF REVISION OF THE TEXT

06 November 2020

Summary table of changes

Section changed	Summary of new information
4.4	Removal of class warning for lipodystrophy