PRODUCT NAME

COMPLERA™

DOSAGE FORMS AND STRENGTHS

Dosage Form	Purplish-pink, capsule-shaped, film-coated tablets, debossed with "GSI" on one side of the tablet and plain-faced on the other side of the tablet.
Strength	Each tablet contains 200 mg of emtricitabine, 25 mg of rilpivirine (equivalent to 27.5 mg of rilpivirine hydrochloride), and 300 mg of tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil).

For excipients, see *List of Excipients*.

CLINICAL INFORMATION

Indications

COMPLERA™ is indicated for use as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve adult patients and pediatric patients 12 to less than 18 years of age with a viral load ≤ 100,000 HIV-1 RNA copies/mL at the start of therapy, and in certain virologically-suppressed (HIV-1 RNA <50 copies/mL) patients on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen.

The efficacy of COMPLERA™ was established in patients who were virologically-suppressed (HIV-1 RNA <50 copies/mL) on stable ritonavir-boosted protease inhibitor-containing regimen. The following points should be met when considering replacing the current regimen with COMPLERA™ in virologically-suppressed (HIV-1 RNA <50 copies/mL) patients:

- Patients should have no history of virologic failure.
- Patients should have been suppressed (HIV-1 RNA <50 copies/mL) for at least 6 months prior to switching therapy.
- Patients should currently be on their first or second antiretroviral regimen prior to switching therapy.
- Patients should have no current or past history of resistance to any of the three components of COMPLERA™.

Additional monitoring of HIV-1 RNA and regimen tolerability is recommended after replacing therapy to assess for potential virologic failure or rebound. (see *Pharmacological Properties – Clinical Studies*).

Dosage and Administration

Adults and pediatric patients 12 to less than 18 years of age and weighing ≥ 35kg

The recommended dose of COMPLERA™ is one tablet once daily taken orally with a meal

(see *Pharmacological Properties - Pharmacokinetic Properties*).

Where discontinuation of therapy with one of the components of COMPLERA™ is indicated or when dose modification is necessary, separate formulations of rilpivirine, emtricitabine, and tenofovir disoproxil fumarate should be used (see *Interactions*).

Dose adjustment: If COMPLERA™ is co-administered with rifabutin, an additional 25mg tablet of rilpivirine once per day is recommended to be taken concomitantly with COMPLERA™ and with a meal for the duration of the rifabutin coadministration (see *Interactions*).

Missed dose(s)

If the patient misses a dose of COMPLERA™ within 12 hours of the time it is usually taken instruct the patient to take COMPLERA™ with a meal as soon as possible and then take the next dose of COMPLERA™ at the regularly scheduled time. If a patient misses a dose of COMPLERA™ by more than 12 hours, instruct the patient not to take the missed dose, but resume the usual dosing schedule.

Special populations

Pediatrics (less than 12 years of age)

The safety and efficacy of COMPLERA™ have not been established in pediatric patients less than 12 years of age or weighing < 35kg.

Elderly (over 65 years of age)

Clinical studies of emtricitabine, rilpivirine, or tenofovir DF did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patients should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Renal impairment

Treatment with COMPLERA™ resulted in an early small increase of mean serum creatinine levels which remained stable over time and is not considered clinically relevant (see *Adverse Reactions*).

COMPLERA™ is not recommended for use in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min). Patients with moderate or severe renal impairment require dose interval adjustment of emtricitabine and tenofovir disoproxil fumarate that cannot be achieved with the combination tablet (see *Warnings and Precautions – Renal Impairment*).

Hepatic impairment

There is limited information regarding the use of COMPLERA™ in patients with mild or moderate hepatic impairment (Child-Pugh score A or B). No dose adjustment of COMPLERA™ is required in patients with mild or moderate hepatic impairment. COMPLERA™ should be used with caution in patients with moderate hepatic impairment. COMPLERA™ has not been studied in patients with severe hepatic impairment (Child-Pugh score C). Therefore, COMPLERA™ is

not recommended in patients with severe hepatic impairment (see *Pharmacokinetic Properties*).

If COMPLERA™ 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 *Warnings and Precautions*).

Contraindications

Hypersensitivity to emtricitabine, rilpivirine, tenofovir disoproxil fumarate, or to any of the excipients.

COMPLERA™ must not be coadministered 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 COMPLERA™ (see *Interactions*):

- 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*)

Warnings and Precautions

Patients should be advised that current antiretroviral therapy does not cure HIV and has not been proven to prevent the transmission of HIV to others through blood or sexual contact. Appropriate precautions to prevent the transmission of HIV should continue to be employed.

Virologic failure and development of resistance

COMPLERA™ has not been evaluated in patients with previous virologic failure to any other antiretroviral therapy. Resistance testing and/or historical resistance data should guide the use of COMPLERA™.

In the pooled analysis from the phase 3 trials in adults through 96 weeks, patients treated with emtricitabine/tenofovir disoproxil fumarate + rilpivirine with a baseline viral load > 100000 HIV 1 RNA copies/mL had a greater risk of virologic failure (17.6% with rilpivirine versus 7.6% with efavirenz) compared to patients with a baseline viral load ≤ 100000 HIV 1 RNA copies/mL (5.9% with rilpivirine versus 2.4% with efavirenz). Patients with a baseline viral load > 100000 HIV 1 RNA copies/mL who experienced virologic failure exhibited a higher rate of treatment emergent resistance to the NNRTI class than patients with a baseline viral load ≤ 100000 HIV-1 RNA copies/mL. More patients who failed virologically on rilpivirine than who failed virologically on efavirenz developed lamivudine/emtricitabine associated resistance (see *Pharmacological Properties - Resistance*). At Week 48, the virologic failure rate in the

rilpivirine arm was 9%, versus 4% in the efavirenz arm. At Week 96, the virologic failure rate in the rilpivirine arm was 11%, versus 5% in the efavirenz arm.

No new information was identified in pediatric patients ≥ 12 years of age in trial C213.

This information is to be taken into consideration when initiating therapy with COMPLERA™.

Cardiovascular

At supra-therapeutic doses (75 and 300 mg once daily), rilpivirine has been associated with prolongation of the QTc interval of the electrocardiogram (ECG).

Rilpivirine at the recommended dose of 25 mg once daily is not associated with a clinically relevant effect on QTc. COMPLERA™ should be used with caution when coadministered with medicinal products with a known risk of QTc prolongation.

Depressive Disorders

The adverse reaction depressive disorders (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) has been reported with rilpivirine. During the Phase 3 trials (N = 1368) through 96 weeks, the incidence of depressive disorders (regardless of causality, severity) reported among rilpivirine (n = 686) or efavirenz (n = 682) was 9% and 8%, respectively. Most events were mild or moderate in severity. The incidence of Grade 3 and 4 depressive disorders (regardless of causality) was 1% for both rilpivirine and efavirenz. The incidence of discontinuation due to depressive disorders among rilpivirine or efavirenz was 1% in each arm. Suicide ideation was reported in 4 subjects in each arm while suicide attempt was reported in 2 subjects in the rilpivirine arm. Patients with severe depressive symptoms should seek immediate medical evaluation to assess the possibility that the symptoms are related to COMPLERA™, and if so, to determine whether the risks of continued therapy outweigh the benefits.

Renal impairment

The emtricitabine and tenofovir disoproxil fumarate components of COMPLERA™ are primarily excreted by the kidney. Renal failure, renal impairment, elevated creatinine, hypophosphatemia, and Fanconi syndrome have been reported with the use of tenofovir disoproxil fumarate in clinical practice.

COMPLERA™ is not recommended for patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min, including patients who require hemodialysis). Patients with moderate or severe renal impairment require dose interval adjustment of emtricitabine and tenofovir disoproxil fumarate that cannot be achieved with the combination tablet.

It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy and, as clinically appropriate, during COMPLERA™ therapy.

Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment, including patients who have previously

experienced renal events while receiving adefovir dipivoxil.

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

HIV and hepatitis B virus (HBV) co-infection

It is recommended that all patients with HIV be tested for the presence of HBV before initiating antiretroviral therapy. COMPLERA™ is not approved for the treatment of chronic HBV infection and the safety and efficacy of COMPLERA™ have not been established in patients co-infected with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued emtricitabine or tenofovir DF, two of the components of COMPLERA™. In some patients infected with HBV and treated with emtricitabine, the exacerbations of hepatitis B were associated with liver decompensation and liver failure. Closely monitor patients co-infected with HIV and HBV who discontinue COMPLERA™ with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, initiation 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.

Coadministration with other drugs

COMPLERA™ must not be administered concurrently with other medicinal products containing the same active components, emtricitabine or tenofovir disoproxil fumarate, or with medicinal products containing tenofovir alafenamide or lamivudine, or with adefovir dipivoxil.

COMPLERA™ should not be coadministered with rilpivirine unless required for dose adjustment (i.e., with rifabutin). Use caution when prescribing COMPLERA™ with medicinal products that may reduce the exposure of rilpivirine (see *Contraindications* and *Interactions*).

Co-administration of COMPLERA™ 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 *Interactions*). Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported.

Bone effects

Bone toxicity, including a reduction in bone mineral density (BMD), was seen in animals following treatment with tenofovir or tenofovir disoproxil. In clinical trials in HIV-1 infected adults, tenofovir DF was associated with slightly greater decreases in BMD and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators. Serum parathyroid hormone levels and 1,25 vitamin D levels were also higher in subjects receiving tenofovir DF. The effects of tenofovir DF associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Assessment

of BMD should be considered for patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and Vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected, obtain appropriate consultation.

There is limited clinical experience with tenofovir disoproxil fumarate in pediatric patients. In clinical studies of HIV-1 infected patients aged 12 to < 18 years, small decreases in median BMD Z-scores were observed following treatment with tenofovir disoproxil fumarate. The long-term clinical relevance of these observations is unknown.

Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy (see *Adverse Reactions*). If bone abnormalities are suspected, then appropriate consultation should be obtained. Cases of osteomalacia (associated with proximal renal tubulopathy and which may contribute to fractures) have been reported in association with the use of tenofovir DF. Arthralgia and muscle pain or weakness have been reported in cases of proximal renal tubulopathy. Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving tenofovir DF-containing products.

Fat redistribution

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

Immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome has been reported in patients treated with combination antiretroviral therapy, including emtricitabine, rilpivirine, and tenofovir disoproxil fumarate. In HIV 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 are cytomegalovirus retinitis, generalized and/or focal mycobacterial infections and Pneumocystis jiroveci pneumonia. Any inflammatory symptoms are to be evaluated and treatment instituted when necessary. Autoimmune disorders such as Graves' disease have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and these events can occur many months after initiation of treatment.

Hepatotoxicity

Hepatic adverse events have been reported in patients receiving a rilpivirine containing regimen. Patients with underlying hepatitis B or C, or marked elevations in liver-associated tests prior to

treatment may be at increased risk for worsening or development of liver-associated test elevations with use of COMPLERA™. A few cases of hepatic toxicity have been reported in patients receiving a rilpivirine containing regimen who had no pre-existing hepatic disease or other identifiable risk factors. Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with COMPLERA™ is recommended in patients with underlying hepatic disease such as hepatitis B or C, or in patients with marked elevations in liver-associated tests prior to treatment initiation. Liver-associated test monitoring should also be considered for patients without pre-existing hepatic dysfunction or other risk factors.

Interactions

COMPLERA™ is a complete regimen for the treatment of HIV-1 infection; therefore, COMPLERA™ should not be administered with other antiretroviral medications. Information regarding potential drug-drug interactions with other antiretroviral medications is not provided. As COMPLERA™ contains emtricitabine, rilpivirine, and tenofovir disoproxil fumarate, any interactions that have been identified with these agents individually or COMPLERA™ as a combination product may occur with COMPLERA™. Please refer to the prescribing information for emtricitabine, rilpivirine, and tenofovir disoproxil fumarate respectively, as needed.

There were no drug-drug interaction trials conducted with the fixed-dose combination tablet. Drug interaction studies were conducted with emtricitabine, rilpivirine, or tenofovir DF, the components of COMPLERA™.

Theoretical and studied interactions of rilpivirine with selected medicinal products are listed in Table 1.

Table 1: Theoretical and Studied Drug Interactions of Rilpivirine with Selected Medicinal Products

Co-administered medicinal product	Dose of co-administered medicinal product	Medicinal product assessed	C_{max}[a]	AUC[a]	C_{min}[a]
ANTIARRHYTHMICS					
Digoxin[b]	0.5 mg single dose	digoxin	↔	↔	NA
	No dose adjustment is required when COMPLERA™ is co-administered with digoxin.				
ANTIDIABETIC					
Metformin[b]	850 mg single dose	metformin	↔	↔	NA
	No dose adjustment is required when COMPLERA™ is co-administered with metformin.				
ANTICOAGULANTS					
Dabigatran	A risk for increases in dabigatran plasma concentrations cannot be excluded (inhibition of intestinal P-gp). The combination of COMPLERA™ and dabigatran etexilate should be used with caution.				
ANTICONVULSANTS					
Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	COMPLERA™ should 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 COMPLERA™.				
AZOLE ANTIFUNGAL AGENTS					

Table 1: Theoretical and Studied Drug Interactions of Rilpivirine with Selected Medicinal Products

Co-administered medicinal product	Dose of co-administered medicinal product	Medicinal product assessed	C_{max}[a]	AUC[a]	C_{min}[a]
Ketoconazole[b,c]	400 mg once daily	ketoconazole	↔	↓ 24%	↓ 66%
		rilpivirine	↑ 30%	↑ 49%	↑ 76%
Fluconazole Itraconazole Posaconazole Voriconazole	Concomitant use of COMPLERA™ with azole antifungal agents may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). No dose adjustment is required when COMPLERA™ is co-administered with azole antifungal agents. Clinically monitor for breakthrough fungal infections when azole antifungals are co-administered with COMPLERA™.				
ANTIMYCOBACTERIALS					
Rifabutin[b,c]	300 mg once daily[d]	rifabutin	↔	↔	↔
		25-*O*-desacetyl-rifabutin	↔	↔	↔
	300 mg once daily	rilpivirine (25mg once daily)	↓ 31%	↓ 42%	↓ 48%
	300 mg once daily	rilpivirine (50mg once daily)	↑ 43% (as compared to 25mg q.d. rilpivirine alone)	↑ 16%	↔
	Concomitant use of COMPLERA™ with rifabutin may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of COMPLERA™. If COMPLERA™ is coadministered with rifabutin, an additional 25mg tablet of rilpivirine per day is recommended to be taken concomitantly with COMPLERA™, for the duration of rifabutin coadministration. When rifabutin co-administration is stopped, the additional 25mg dose of rilpivirine should be discontinued.				
Rifampicin[b,c]	600 mg once daily	rifampicin	↔	↔	NA
		25-desacetyl-rifampicin	↔	↓ 9%	NA
		rilpivirine	↓ 69%	↓ 80%	↓ 89%
Rifapentine	COMPLERA™ should not be used in combination with rifampicin or rifapentine as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of COMPLERA™.				
MACROLIDE ANTIBIOTICS					
Clarithromycin Erythromycin	Concomitant use of COMPLERA™ with clarithromycin or erythromycin may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). Where possible, alternatives such as azithromycin should be considered.				
GLUCOCORTICOIDS					
Dexamethasone (systemic)	COMPLERA™ should not be used in combination with systemic dexamethasone as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of COMPLERA™. Alternatives should be considered, particularly for long-term use.				
PROTON PUMP INHIBITORS					
Omeprazole[b,c]	20 mg once daily	omeprazole	↓ 14%	↓ 14%	NA
		rilpivirine	↓ 40%	↓ 40%	↓ 33%
Lansoprazole Rabeprazole Pantoprazole Esomeprazole	COMPLERA™ should not be used in combination with proton pump inhibitors as co-administration may cause significant decreases in rilpivirine plasma concentrations (gastric pH increase). This may result in loss of therapeutic effect of COMPLERA™.				
H_2-RECEPTOR ANTAGONISTS					
Famotidine[b,c]	40 mg single dose taken 12 hours before rilpivirine	rilpivirine	↔	↓9%	NA

Table 1: Theoretical and Studied Drug Interactions of Rilpivirine with Selected Medicinal Products

Co-administered medicinal product	Dose of co-administered medicinal product	Medicinal product assessed	C_{max}[a]	AUC[a]	C_{min}[a]
	40 mg single dose taken 2 hours before rilpivirine	rilpivirine	↓ 85%	↓ 76%	NA
	40 mg single dose taken 4 hours after rilpivirine	rilpivirine	↑ 21%	↑ 13%	NA
Cimetidine Nizatidine Ranitidine	The combination of COMPLERA™ and H_2-receptor antagonists should be used with caution as co-administration may cause significant decreases in rilpivirine plasma concentrations (gastric pH increase). H_2-receptor antagonists should only be administered at least 12 hours before or at least 4 hours after COMPLERA™.				
ANTACIDS					
Antacids (e.g., aluminium or magnesium hydroxide, calcium carbonate)	The combination of COMPLERA™ and antacids should be used with caution as co-administration may cause significant decreases in rilpivirine plasma concentrations (gastric pH increase). Antacids should only be administered either at least 2 hours before or at least 4 hours after COMPLERA™.				
NARCOTIC ANALGESICS					
Methadone[b]	60–100 mg once daily, individualised dose	R(–) methadone	↓ 14%	↓ 16%	↓ 22%
		S(+) methadone	↓ 13%	↓ 16%	↓ 21%
	No dose adjustments are required when initiating co-administration of methadone with COMPLERA™. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.				
HERBAL PRODUCTS					
St John's wort (*Hypericum perforatum*)	COMPLERA™ should not be used in combination with products containing St John's wort as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of COMPLERA™.				
ANALGESICS					
Acetaminophen[b,c] (paracetamol)	500 mg single dose	acetaminophen	↔	↔	NA
		rilpivirine	↔	↔	↑ 26%
	No dose adjustment is required when COMPLERA™ is co-administered with acetaminophen (paracetamol).				
ESTROGEN-BASED CONTRACEPTIVES					
Ethinylestradiol[b]	0.035 mg once daily	ethinylestradiol	↑ 17%	↔	↔
Norethindrone[c]	1 mg once daily	norethindrone	↔	↔	↔
	No dose adjustment is required for the concomitant use of COMPLERA™ and estrogen and/or progesterone based contraceptives.				
HMG CO A REDUCTASE INHIBITORS					
Atorvastatin[b,c]	40 mg once daily	atorvastatin	↑ 35%	↔	↓ 15%
		rilpivirine	↓ 9%	↔	↔
Fluvastatin Lovastatin Pitavastatin Pravastatin Rosuvastatin Simvastatin	No dose adjustment is required when COMPLERA™ is co-administered with an HMG Co-A reductase inhibitor.				
PHOSPHODIESTERASE TYPE 5 (PDE-5) INHIBITORS					
Sildenafil[b,c]	50 mg single dose	sildenafil	↔	↔	NA
		rilpivirine	↔	↔	↔
Vardenafil Tadalafil	No dose adjustment is required when COMPLERA™ is co-administered with a PDE-5 inhibitor.				
OTHER ANTIVIRAL AGENTS					

Table 1: Theoretical and Studied Drug Interactions of Rilpivirine with Selected Medicinal Products

Co-administered medicinal product	Dose of co-administered medicinal product	Medicinal product assessed	C_{max}[a]	AUC[a]	C_{min}[a]
Ledipasvir/Sofosbuvir Sofosbuvir/velpatasvir Sofosbuvir/velpatasvir/voxilaprevir	Concentrations of tenofovir have been shown to increase when coadministered with HARVONI (ledipasvir/sofosbuvir), EPCLUSA (sofosbuvir/velpatasvir), or VOSEVI (sofosbuvir/velpatasvir/voxilaprevir). Patients receiving COMPLERA™ concomitantly with HARVONI (ledipasvir/sofosbuvir), EPCLUSA (sofosbuvir/velpatasvir), or VOSEVI (sofosbuvir/velpatasvir/voxilaprevir) should be monitored for adverse reactions associated with tenofovir disoproxil fumarate.				
Ribavirin	No clinically relevant drug-drug interaction is expected when COMPLERA™ is co-administered with ribavirin.				
Simeprevir	150 mg once daily	simeprevir	↑ 10%	↔	↔
		rilpivirine	↔	↔	↑ 25%
	No clinically relevant drug drug interaction is expected when COMPLERA™ is co administered with simeprevir.				

[a] ↑ = increase; ↓ = decrease; ↔ = no changes; NA = not applicable

[b] The interaction between rilpivirine and the drug was evaluated in a clinical study. All other drug-drug interactions shown are predicted.

[c] This interaction study has been performed with a dose higher than the recommended dose for rilpivirine assessing the maximal effect on the co-administered drug. The dosing recommendation is applicable to the recommended dose of rilpivirine 25 mg q.d.

[d] This interaction study has been performed with a dose higher than the recommended dose for rilpivirine.

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 subjects, supratherapeutic doses of rilpivirine (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval of the electrocardiogram. COMPLERA™ should be used with caution when coadministered with a drug with a known risk of Torsade de Pointes.

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 may result in decreased plasma concentrations of rilpivirine and loss of virologic response and possible resistance to rilpivirine or to the class of NNRTIs. Coadministration of rilpivirine and drugs that inhibit CYP3A may result in increased plasma concentrations of rilpivirine.

Rilpivirine at a dose of 25 mg once daily is not likely to have a clinically relevant effect on the exposure of drugs metabolized by CYP enzymes.

Drugs Increasing Gastric pH

Coadministration of rilpivirine with drugs that increase gastric pH may decrease plasma concentrations of rilpivirine and loss of virologic response and possible resistance to rilpivirine or to the class of NNRTIs.

Drugs Affecting Renal Function

Because emtricitabine and tenofovir are primarily eliminated by the kidneys through a combination of glomerular filtration and active tubular secretion, coadministration of COMPLERA™ with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of emtricitabine, tenofovir, and/or other renally eliminated drugs. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs (see *Warnings and Precautions*).

Drugs without clinically significant interactions

Please refer to the prescribing information for emtricitabine, rilpivirine, and tenofovir disoproxil fumarate, respectively, as needed.

Pregnancy, Breast-feeding and Fertility

Pregnancy and fertility

There are no adequate and well-controlled studies of COMPLERA™ or its components in pregnant women. COMPLERA™ is only to be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

Emtricitabine

The incidence of fetal variations and malformations was not increased in embryofetal toxicity studies performed with emtricitabine in mice at exposures (AUC) approximately 60-fold higher and in rabbits at approximately 120-fold higher than human exposures at the recommended daily dose.

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 *Pharmacological Properties*).

Studies in animals have shown no evidence of relevant embryonic or fetal toxicity or an effect on reproductive function. There was no teratogenicity with rilpivirine in rats and rabbits. The exposures at the embryo fetal 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 (see *Non-clinical Information*).

No human data on the effect of rilpivirine on fertility are available. 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 (see *Non-clinical Information*). 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 rilpivirine once daily.

Tenofovir disoproxil fumarate

Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir.

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 COMPLERA™ in newborns/infants. Because of the potential for adverse events in nursing infants, COMPLERA™ 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.

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} achieved from oral administration of emtricitabine. Breast-feeding infants whose mothers are being treated with emtricitabine may be at risk for developing viral resistance to emtricitabine. Other emtricitabine-associated risks in infants breast-fed by mothers being treated with emtricitabine are unknown.

Rilpivirine

It is not known whether rilpivirine is secreted in human milk.

Tenofovir disoproxil fumarate

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

Effects on Ability to Drive and Use Machines

No studies on the effects of COMPLERA™ 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 emtricitabine, rilpivirine, and tenofovir disoproxil fumarate. This should be considered when assessing a patient's ability to drive or operate machinery.

Adverse Reactions

Adverse Reactions from Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In HIV-1-Infected Subjects with No Antiretroviral Treatment History

Studies C209 and C215 – Treatment-Emergent Adverse Drug Reactions: The safety assessment of rilpivirine, used in combination with other antiretroviral drugs, is based on the Week 96 pooled data from 1368 subjects in the Phase 3 trials TMC278-C209 (ECHO) and TMC278-C215 (THRIVE) in antiretroviral treatment-naïve HIV-1-infected adult subjects. A total of 686 subjects received rilpivirine in combination with other antiretroviral drugs as background regimen; most (N=550) received emtricitabine/tenofovir DF as background regimen. The number of subjects randomized to the control arm efavirenz was 682, of which 546 received emtricitabine/tenofovir DF as background regimen (see *Clinical Experience*). The median duration of exposure for subjects in either treatment arm was 104 weeks.

Adverse drug reactions (ADR) observed at Week 96 in subjects who received rilpivirine or efavirenz plus emtricitabine/tenofovir DF as background regimen are shown in Table 2. No new types of adverse reactions were identified between Week 48 and Week 96. The adverse drug reactions observed in this subset of subjects were generally consistent with those seen for the overall patient population participating in these studies (refer to the prescribing information for Edurant).

The proportion of subjects who discontinued treatment with rilpivirine or efavirenz + emtricitabine/tenofovir DF due to ADR, regardless of severity, was 2% and 5%, respectively. The most common ADRs leading to discontinuation were psychiatric disorders: 9 (1.6%) subjects in the rilpivirine + emtricitabine/tenofovir DF arm and 12 (2.2%) subjects in the efavirenz + emtricitabine/tenofovir DF arm. Rash led to discontinuation in 1 (0.2%) subject in the rilpivirine + emtricitabine/tenofovir DF arm and 10 (1.8%) subjects in the efavirenz + emtricitabine/tenofovir DF arm.

Common Adverse Drug Reactions

Clinical ADRs to rilpivirine or efavirenz of at least moderate intensity (≥ Grade 2) reported in at least 2% of adult subjects are shown in Table 2.

Table 2: Selected Treatment-Emergent Adverse Drug Reactions[a] (Grades 2-4) Reported in ≥2% of Subjects Receiving Rilpivirine or Efavirenz in Combination with Emtricitabine/Tenofovir DF in Studies C209 and C215 (Week 96 analysis)

	Rilpivirine + FTC/TDF	**Efavirenz + FTC/TDF**
	N=550	**N=546**
Gastrointestinal Disorder		
Nausea	1%	2%
Nervous System Disorders		
Headache	2%	2%
Dizziness	1%	7%
Psychiatric Disorders	2%	2%
Depressive disorders[b]	2%	2%
Insomnia	1%	3%

Abnormal dreams		
Skin and Subcutaneous Tissue Disorders Rash	1%	5%

[a] Frequencies of adverse reactions are based on all Grades 2-4 treatment-emergent adverse events assessed to be related to study drug.

[b] Includes adverse drug reactions reported as depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicide ideation.

Rilpivirine: Treatment-emergent adverse drug reactions of at least moderate intensity (≥ Grade 2) that occurred in less than 2% of subjects treated with rilpivirine plus any of the allowed background regimens (N=686) in clinical studies C209 and C215 include (grouped by Body System): vomiting, diarrhea, abdominal discomfort, abdominal pain, fatigue, cholecystitis, cholelithiasis, decreased appetite, somnolence, sleep disorders, anxiety, glomerulonephritis membranous, glomerulonephritis mesangioproliferative, and nephrolithiasis.

Emtricitabine and Tenofovir Disoproxil Fumarate: The following adverse reactions were observed in clinical trials of emtricitabine or tenofovir DF in combination with other antiretroviral agents:

The most common adverse drug reactions occurring in at least 10% of HIV-1-infected treatment-naïve adult subjects in a Phase 3 clinical trial of emtricitabine and tenofovir DF in combination with another antiretroviral agent are diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash. In addition, adverse drug reactions that occurred in at least 5% of treatment-experienced or treatment-naïve subjects receiving emtricitabine or tenofovir DF with other antiretroviral agents in clinical trials include abdominal pain, dyspepsia, vomiting, fever, pain, nasopharyngitis, pneumonia, sinusitis, upper respiratory tract infection, arthralgia, back pain, myalgia, paresthesia, peripheral neuropathy (including peripheral neuritis and neuropathy), anxiety, increased cough, and rhinitis.

Skin discoloration has been reported with higher frequency among emtricitabine-treated subjects; it was manifested by hyperpigmentation on the palms and/or soles and was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

Laboratory Abnormalities: The percentage of subjects treated with rilpivirine + emtricitabine/tenofovir DF or efavirenz + emtricitabine/tenofovir DF in studies C209 and C215 with selected treatment-emergent laboratory abnormalities (Grades 1 to 4), representing worst grade toxicity, are presented in Table 3.

Table 3: Selected Laboratory Abnormalities (Grades 1-4) Reported in Subjects Who Received Rilpivirine or Efavirenz in Combination with Emtricitabine/Tenofovir DF in Studies C209 and C215 (Week 96 Analysis)

		Rilpivirine + FTC/TDF	**Efavirenz + FTC/TDF**
Laboratory Parameter Abnormality, (%)	**DAIDS Toxicity Range**	**N=550**	**N=546**
BIOCHEMISTRY			

Increased Creatinine			
Grade 1	1.1-1.3 x ULN[a]	6%	1%
Grade 2	>1.3-1.8 x ULN	1%	1%
Grade 3	>1.8-3.4 x ULN	<1%	0
Grade 4	>3.4 x ULN	0	<1%
Increased AST			
Grade 1	1.25-2.5 x ULN	16%	19%
Grade 2	>2.5-5.0 x ULN	4%	7%
Grade 3	>5.0-10.0 x ULN	2%	3%
Grade 4	>10.0 x ULN	1%	1%
Increased ALT			
Grade 1	1.25-2.5 x ULN	19%	22%
Grade 2	>2.5-5.0 x ULN	5%	7%
Grade 3	>5.0-10.0 x ULN	1%	2%
Grade 4	>10.0 x ULN	1%	1%
Increased Total Bilirubin			
Grade 1	1.1-1.5 x ULN	6%	<1%
Grade 2	>1.5-2.5 x ULN	3%	1%
Grade 3	>2.5-5.0 x ULN	1%	<1%
Increased Total Cholesterol (fasted)			
Grade 1	200-239 mg/dL	14%	31%
Grade 2	240-300 mg/dL	6%	18%
Grade 3	>300 mg/dL	<1%	2%
Increased LDL Cholesterol (fasted)			
Grade 1	130-159 mg/dL	13%	28%
Grade 2	160-190 mg/dL	5%	13%
Grade 3	>190 mg/dL	1%	4%
Increased Triglycerides (fasted)			
Grade 2	500-750 mg/dL	1%	2%
Grade 3	751-1,200 mg/dL	1%	2%
Grade 4	>1,200 mg/dL	0	1%

N = number of subjects per treatment group

[a] ULN = Upper limit of normal value.

Note: Percentages were calculated versus the number of subjects in ITT population with emtricitabine + tenofovir DF as background regimen.

Emtricitabine or Tenofovir Disoproxil Fumarate: The following laboratory abnormalities have been previously reported in subjects treated with emtricitabine or tenofovir DF with other antiretroviral agents in other clinical trials: Grade 3 or 4 laboratory abnormalities of increased pancreatic amylase (>2.0 x ULN), increased serum amylase (>175 U/L), increased lipase (>3.0 x ULN), increased alkaline phosphatase (>550 U/L), increased or decreased serum glucose (<40 or >250 mg/dL), increased glycosuria (≥3+), increased creatine kinase (M: >990 U/L; F: >845 U/L), decreased neutrophils (<750/mm^3) and increased hematuria (>75 RBC/HPF) occurred.

Adrenal Function

In the pooled Phase 3 trials of C209 and C215, in subjects 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 (95% CI: -30.9; -7.4) nmol/L in the rilpivirine group, and of -0.6 (95% CI: -13.3; 12.2) 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 subjects 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 with a mean change of 0.1 mg/dL (range: -0.3 mg/dL to 0.6 mg/dL) observed through Week 96. In subjects who entered the trial 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 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 and triglycerides are presented in Table 4.

Table 4: Lipid Values Reported in Subjects Receiving Rilpivirine or Efavirenz in Combination with Emtricitabine/Tenofovir DF in Studies C209 and C215[a]

	Pooled Data from the Week 96 Analysis of C209 and C215 Trials							
	Rilpivirine + FTC/TDF N=550				**Efavirenz + FTC/TDF N=546**			
	N	**Baseline**	**Week 96**		**N**	**Baseline**	**Week 96**	
Mean		Mean (mg/dL)	Mean (mg/dL)	Mean Change[b] (mg/dL)		Mean (mg/dL)	Mean (mg/dL)	Mean Change[b] (mg/dL)
Total Cholesterol (fasted)	430	162	164	2	401	160	186	26
HDL-cholesterol (fasted)	429	42	45	4	399	40	50	11
LDL-cholesterol (fasted)	427	97	97	-1	397	96	110	14
Triglycerides (fasted)	430	123	109	-14	401	127	133	6

N = number of subjects per treatment group

[a] Excludes subjects 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.

Subjects 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 subjects receiving rilpivirine who were not coinfected. The same increase was also observed in the efavirenz arm. The pharmacokinetic exposure of rilpivirine in coinfected subjects was comparable to that in subjects without coinfection.

In Virologically-Suppressed HIV-1-Infected Subjects

No new adverse reactions to COMPLERA™ 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 (efavirenz/emtricitabine/tenofovir disoproxil fumarate) (GS-US-264-0111, N = 49) to COMPLERA™.

Pediatric Patients

Emtricitabine

Assessment of adverse reactions is based on Week 48 data from one single-arm, open-label study of 116 pediatric patients 3 months to 17 years of age (Study FTC-203). In addition to the adverse reactions reported in adults, anemia was common and hyperpigmentation was very common in pediatric patients.

Rilpivirine

The safety assessment is based on Week 48 data from one single-arm, open-label study (Study TMC278-C213) 36 pediatric patients 12 to less than 18 years of age and weighing at least 32 kg. No patients discontinued treatment due to adverse reactions. No new adverse reactions were identified compared to those seen in adults.

Most adverse reactions were Grade 1 or 2. Adverse reactions (all grades) of very common frequency were headache, depression, somnolence, and nausea. No Grade 3 to 4 laboratory abnormalities for AST/ALT or Grade 3 to 4 adverse reactions of transaminase increased were reported.

Tenofovir disoproxil fumarate

Assessment of adverse reactions is based on one randomized study (Study GS-US-104-0321) in 87 pediatric patients 12 to <18 years of age who received VIREAD or placebo for 48 weeks. The adverse reactions observed in pediatric patients were consistent with those observed in clinical studies of VIREAD in adults (see Warnings and Precautions – Bone effects).

Postmarketing Experience

The following adverse reactions have been identified during postmarketing experience in patients receiving rilpivirine-or tenofovir DF-containing regimens. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

COMPLERA:

Metabolism and Nutrition Disorders
Weight increased

Skin and Subcutaneous Tissue Disorders

Severe skin and hypersensitivity reactions including DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms)

Rilpivirine:

Renal and Urinary Disorders
nephrotic syndrome

Emtricitabine:

No postmarketing adverse reactions have been identified for inclusion in this section.

Tenofovir Disoproxil Fumarate:

Immune System Disorders
allergic reaction, including angioedema

Metabolism and Nutrition Disorders
lactic acidosis, hypokalemia, hypophosphatemia

Respiratory, Thoracic, and Mediastinal Disorders
dyspnea

Gastrointestinal Disorders
pancreatitis, increased amylase, abdominal pain

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, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy

Renal and Urinary Disorders
acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria

General Disorders and Administration Site Conditions
asthenia

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

Overdose

Treatment

If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with COMPLERA™ 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.

Emtricitabine

Emtricitabine can be removed by hemodialysis, which removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing. 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. Treatment of overdose with rilpivirine 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. Since rilpivirine is highly bound to plasma protein, dialysis is unlikely to result in significant removal of the active substance.

Tenofovir disoproxil fumarate

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of tenofovir disoproxil fumarate, a 4-hour hemodialysis session removed approximately 10% of the administered tenofovir dose. The elimination of tenofovir by peritoneal dialysis has not been studied.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

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

Mechanism of action

Emtricitabine and tenofovir disoproxil fumarate

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.

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 reverse transcriptase, resulting in DNA chain termination.

Both emtricitabine triphosphate and tenofovir diphosphate are weak inhibitors of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there was no evidence of toxicity to mitochondria *in vitro* and *in vivo*.

Rilpivirine

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

Antiviral activity

Emtricitabine, rilpivirine, and tenofovir disoproxil fumarate

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

Emtricitabine

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 clades 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), non-nucleoside reverse transcriptase inhibitors (NNRTIs) (delavirdine, efavirenz, nevirapine, and rilpivirine), and protease inhibitors (PIs) (amprenavir, nelfinavir, ritonavir, and saquinavir), additive to synergistic effects were observed.

Rilpivirine

Rilpivirine exhibited activity against laboratory strains of wild-type HIV-1 in an acutely infected T-cell line with a median EC_{50} value for HIV-1/IIIB of 0.73 nM (0.27 ng/mL). Although rilpivirine demonstrated limited *in vitro* activity against HIV-2 with EC_{50} values ranging from 2510 to 10830 nM (920 to 3970 ng/mL), 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 (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 rilpivirine was not antagonistic when combined with the N(t)RTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, zidovudine and tenofovir; the PIs amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and tipranavir; the NNRTIs efavirenz, etravirine and nevirapine; the fusion inhibitor enfuvirtide; the CCR5 co-receptor antagonist maraviroc; and the integrase strand transfer inhibitor raltegravir.

Tenofovir disoproxil fumarate

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 clades 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

Emtricitabine and tenofovir disoproxil fumarate

HIV-1 isolates with reduced susceptibility to emtricitabine or tenofovir have been selected in cell culture. Reduced susceptibility to emtricitabine was associated with M184V/I substitutions in HIV-1 RT. HIV-1 isolates selected by tenofovir expressed a K65R substitution in HIV-1 RT and showed a 2-4 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.

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.

Resistance to rilpivirine was determined as a fold change in EC_{50} value (FC) above the biological cut off (BCO) of the assay.

In treatment-naïve adult patients

Emtricitabine, rilpivirine, and tenofovir disoproxil fumarate

Considering all of the available *in vitro* and *in vivo* data, the following resistance-associated substitutions, when present at baseline, are likely to affect the activity of COMPLERA™: K65R, K70E, K101E, K101P, E138A, E138G, E138K, E138Q, E138R, V179L, Y181C, Y181I, Y181V, M184I, M184V, Y188L, H221Y, F227C, M230I, M230L, and the combination of L100I+K103N.

Study TMC278-C209 and TMC278-C215

In the Week 48 pooled resistance analysis for patients receiving rilpivirine in combination with emtricitabine/tenofovir disoproxil fumarate in clinical trials TMC278-C209 and TMC278-C215 (see *Pharmacological Properties - Clinical Studies*), the resistance analysis population included 62 virologic failures with resistance information available for 54 of those, and the Week 96 resistance analysis population included 78 virologic failures with resistance information available for 66 of those.

The amino acid substitutions associated with NNRTI resistance that developed most commonly in these patients were: V90I, K101E, E138K/Q, V179I, Y181C, V189I, and H221Y, and F227C.

The most common mutations were the same in the week 48 and week 96 analyses. However, in the trials, the presence of the substitutions V90I and V189I, at baseline, did not affect response. The E138K substitution emerged most frequently during rilpivirine treatment, commonly in combination with the M184I substitution. 52% of patients with virologic failure in the rilpivirine arm developed concomitant NNRTI and NRTI mutations. The 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 ≤ 100000 copies/mL had emerging resistance-associated substitutions and/or phenotypic resistance to rilpivirine (7/288) than patients with baseline viral load > 100000 copies/mL (30/262). Among those patients who developed resistance to rilpivirine, 4/7 patients with baseline viral load ≤ 100000 copies/mL and 28/30 patients with baseline viral load > 100000 copies/mL had cross-resistance to other NNRTIs.

More patients who failed virologically on rilpivirine than who failed virologically on efavirenz developed lamivudine/emtricitabine associated resistance.

Virologically suppressed adult patients

Study GS-US-264-0106

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

Of the 24 patients treated with COMPLERA™ that had the NNRTI-associated K103N substitution pre-existing at baseline, 17 of 18 patients in the COMPLERA™ arm and 5 of 6 patients in the stay on baseline regimen (SBR) arm maintained virologic suppression after switching to COMPLERA™ 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 COMPLERA™ from ATRIPLA (0 of 49 patients).

Cross resistance

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

In cell culture

Emtricitabine

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

Viruses harboring 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 substitutions associated with NNRTI resistance, including those associated with rilpivirine resistance, was 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 and Y181V/I. 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.

Tenofovir disoproxil fumarate

The K65R and K70E substitutions result in reduced susceptibility to abacavir, didanosine, lamivudine, emtricitabine, and tenofovir, but retain sensitivity to zidovudine.

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

Multinucleoside-resistant HIV-1 with a T69S double insertion mutation in the RT showed reduced susceptibility to tenofovir.

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 adult patients

Resistance outcomes, including cross resistance to other NNRTIs, in patients receiving rilpivirine hydrochloride in combination with emtricitabine/tenofovir disoproxil fumarate in Phase III studies (C209 and C215 pooled data) and experiencing virological failure, are shown in Table 5 below.

Table 5: Phenotypic resistance and cross-resistance outcomes from studies C209 and C215 (pooled data) for patients receiving rilpivirine hydrochloride in combination with emtricitabine/tenofovir disoproxil fumarate at week 96 (based on resistance analysis)

	In patients with	In patients with BL VL[1]	In patients with BL VL[1]

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

[1] BLVL = Baseline viral load

[2] Phenotypic resistance to rilpivirine (> 3.7-fold change compared to control)

[3] Phenotypic resistance (Antivirogram)

Virologically suppressed adult patients

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

Effects on electrocardiogram

The effect of rilpivirine at the recommended dose of 25 mg once daily on the QTcF interval was evaluated in a randomized, 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.

Pharmacodynamic effects

Clinical experience

Treatment-naïve HIV-1 infected adult patients

The efficacy of COMPLERA™ is based on the analyses of 96 week data from two randomised, double-blind, controlled studies C209 and C215. Antiretroviral treatment-naïve HIV-1 infected patients were enrolled (n = 1,368) who had a plasma HIV-1 RNA ≥ 5,000 copies/mL and were screened for susceptibility to N(t)RTI and for absence of specific NNRTI resistance-associated

mutations. The studies are identical in design with the exception of the background regimen (BR). Patients were randomised in a 1:1 ratio to receive either rilpivirine hydrochloride 25 mg (n = 686) once daily or efavirenz 600 mg (n = 682) once daily in addition to a BR. In study C209 (n = 690), the BR was emtricitabine/tenofovir disoproxil 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 6 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 6: Demographic and baseline characteristics of antiretroviral treatment-naïve HIV-1 infected adult patients in studies C209 and C215 (pooled data for patients receiving rilpivirine hydrochloride or efavirenz in combination with emtricitabine/tenofovir disoproxil fumarate) at week 96

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

A subgroup analysis of the virologic response (< 50 HIV-1 RNA copies/mL) at both 48 weeks and 96 weeks, and virologic failure by baseline viral load (pooled data from the two Phase III clinical studies, C209 and C215, for patients receiving the emtricitabine/tenofovir disoproxil fumarate background regimen) is presented in Table 7. The response rate (confirmed undetectable viral load < 50 HIV-1 RNA copies/mL) at week 96 was comparable between the rilpivirine arm and the efavirenz arm. The incidence of virologic failure was higher in the rilpivirine arm than in the efavirenz arm at week 96; however, most of the virologic failures

occurred within the first 48 weeks of treatment. Discontinuations due to adverse events were higher in the efavirenz arm at week 96 than in the rilpivirine arm.

Table 7: 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 (primary) and week 96

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

n = total number of patients per treatment group.

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

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

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

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

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

Emtricitabine/tenofovir disoproxil 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.

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

There were no new cross resistance patterns at week 96 compared to week 48. The resistance outcome for patients with protocol defined virological failure and phenotypic resistance at week 96 are shown in Table 8.

Table 8: Phenotypic 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 96 (based on resistance analysis)

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

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

Pregnancy

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.

Virologically suppressed adult patients

Study GS-US-264-0106

The efficacy and safety of switching from a ritonavir-boosted protease inhibitor in combination with two NRTIs to COMPLERA™ was evaluated in a randomized, 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 COMPLERA™, and must have been stably suppressed (HIV-1 RNA < 50 copies/mL) for at least 6 months prior to screening. Patients were

randomized in a 2:1 ratio to either switch to COMPLERA™ at baseline (COMPLERA™, N = 317), or stay on their baseline antiretroviral regimen for 24 weeks (SBR, N = 159) before switching to COMPLERA™ 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). Randomization was stratified by use of tenofovir DF and/or lopinavir/ritonavir in the baseline regimen.

Treatment outcomes through 24 weeks are presented in Table 9. Switching to COMPLERA™ 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 9: Virologic Outcomes of Randomized Treatment of Study GS-US-264-0106 at Week 24[a]

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

[c] 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. No deaths were reported.

[d] 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.

By Week 24, median CD4+ cell counts had increased significantly from baseline in both the COMPLERA™ arm (+10 cells/mm^3, p = 0.046) and the SBR arm (+22 cells/mm^3, p = 0.008) in the on-treatment analysis. The difference in median CD4+ cell count change between the COMPLERA™ and SBR treatment arms 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 COMPLERA™, 92% (140/152) of patients had HIV-1 RNA < 50 copies/mL after 24 weeks of COMPLERA™, consistent with the Week 24 results for patients who switched to COMPLERA™ at baseline.

At Week 48, 89% (283/317) of patients randomized to switch to COMPLERA™ at baseline (COMPLERA™) 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, 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 COMPLERA™ were 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 COMPLERA™, and have HIV-1 RNA < 50 copies/mL at screening.

Patients were switched from ATRIPLA to COMPLERA™ without a washout period. Consistent with the CYP3A induction by efavirenz, rilpivirine mean trough concentrations (C_{trough}) were initially lower at 1 week post-switch (32 ng/mL), but were in the range of historical data starting 2 weeks post-switch. Simultaneously, efavirenz concentrations remained above its protein-binding adjusted IC_{90} (10 ng/mL) for 4 weeks post-switch, consistent with the established half-life for efavirenz. Among 49 patients who received at least one dose of COMPLERA™, 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 subject (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. The efficacy data indicate that the brief period of lower rilpivirine exposure does not impact antiviral efficacy of COMPLERA™, and no dose adjustment is required following the switch from an efavirenz-containing regimen.

Pediatric Patients

Studies FTC-202, FTC-203, and FTC-211

In three open-label, non-randomized clinical studies (Studies FTC-202, FTC-203, and FTC-211), EMTRIVA was administered to 169 HIV-1 infected treatment-naïve and experienced (defined as virologically suppressed on a lamivudine containing regimen for which EMTRIVA was substituted for lamivudine) patients between 3 months and 21 years of age, including 34 patients ages 12 to less than 18 years. Patients received once daily EMTRIVA oral solution (6 mg/kg to a maximum of 240 mg/day) or EMTRIVA capsules (a single 200 mg capsule once daily) in combination with at least two other antiretroviral agents.

Patients had a mean age of 7.9 years (range 0.3 to 21), 49% were male, 15% Caucasian, 61% Black, and 24% Hispanic. Patients had a median baseline HIV-1 RNA of 4.6 $\log_{10}$ copies/mL (range 1.7 to 6.4) and a mean baseline CD4 cell count of 745 cells/mm^3 (range 2 to 2650). Through 48 weeks of therapy, the overall proportion of patients who achieved and sustained an HIV-1 RNA <400 copies/mL was 86%, and <50 copies/mL was 73%. The mean increase from baseline in CD4 cell count was 232 cells/mm^3 (range −945, +1512).

Study TMC278-C213

The pharmacokinetics, safety, tolerability, and efficacy of rilpivirine 25 mg once daily, in combination with an investigator-selected background regimen (BR) containing two NRTIs, were evaluated in trial TMC278-C213, a single-arm, open-label Phase 2 trial in antiretroviral treatment-naïve HIV-1 infected pediatric patients 12 to less than 18 years of age and weighing at least 32 kg. This analysis included 36 patients who had completed at least 48 weeks of treatment or discontinued earlier. The median duration of exposure for patients was 63.5 weeks.

The 36 patients had a median age of 14.5 years (range 12 to 17 years) and were 55.6% female, 88.9% Black, and 11.1% Asian. The median baseline plasma HIV-1 RNA was 4.8 $\log_{10}$ copies/mL, and the median baseline CD4+ cell count was 414 x 10^6 cells/l (range 25 to 983 x 10^6 cells/l). The proportion of patients with HIV-1 RNA <50 copies/mL at Week 48 (TLOVR) was 72.2% (26/36). The combination of NRTIs most frequently used together with rilpivirine was FTC/TDF (24 subjects [66.7%]), followed by 3TC/TDF (8 subjects [22.2%]) and 3TC/AZT (4 subjects [11.1%]).

The proportion of responders was higher in subjects with a baseline viral load ≤100000 copies/mL (78.6%, 22/28) as compared to those with a baseline viral load >100000 copies/mL (50.0%, 4/8). The proportion of virologic failures was 22.2% (8/36). The proportion of virologic failures was lower in subjects with a baseline viral load ≤100000 copies/mL (17.9%, 5/28) as compared to those with a baseline viral load >100000 copies/mL (37.5%, 3/8). One subject discontinued due to an adverse event and 1 subject discontinued due to reasons other than an adverse event or virologic failure. At Week 48, the mean increase in CD4+ cell count from baseline was 201.2 x 10^6 cells/L.

Study GS-US-104-0321

In Study GS-US-104-0321, 87 treatment-experienced patients 12 to less than 18 years of age were treated with VIREAD (N=45) or placebo (N=42) in combination with an optimized background regimen (OBR) for 48 weeks. The mean baseline CD4 cell count was 374 cells/mm3 and the mean baseline plasma HIV-1 RNA was 4.6 log10 copies/mL. The median time-weighted average (DAVG) change from baseline through Weeks 24 and 48 (DAVG24 and DAVG48) in plasma HIV-1 RNA were −1.58 and −1.42 log10 copies/mL for the VIREAD treatment group compared to −1.55 and −1.35 log10 copies/mL for the placebo group, at Weeks 24 and 48, respectively. The lack of difference in virologic response between the two groups was primarily attributable to greater activity of the OBR in the placebo group compared to the VIREAD treatment group. In patients with partially active or non-active OBR (genotypic sensitivity score ≤1), the addition of VIREAD or placebo resulted in a median DAVG24 in plasma HIV RNA of −1.66 and −1.14 log10 copies/mL, respectively.

Pharmacokinetic Properties

Absorption

Emtricitabine, rilpivirine, and tenofovir disoproxil fumarate

The separate pharmaceutical forms of emtricitabine, rilpivirine, and tenofovir disoproxil fumarate were used to determine the pharmacokinetics of emtricitabine, rilpivirine, and tenofovir disoproxil fumarate in HIV-1 infected patients. The bioequivalence of one COMPLERA™ film-coated tablet with one emtricitabine 200 mg capsule plus one rilpivirine 25 mg (as the hydrochloride salt) tablet plus one tenofovir disoproxil 300 mg tablet was established following single dose administration to fed healthy subjects.

Emtricitabine

Emtricitabine is absorbed following oral administration with peak plasma concentrations occurring at 1 to 2 hours postdose. Following multiple dose oral administration of emtricitabine to 20 HIV-1 infected patients, the (mean ± SD) steady state plasma emtricitabine C_{max} were 1.8 ± 0.7 μg/mL and AUC over a 24-hour dosing interval was 10.0 ± 3.1 hr•μg/mL.

The mean absolute bioavailability of the emtricitabine 200 mg capsule in fasted patients was 93%.

Rilpivirine

The pharmacokinetic properties of rilpivirine have been evaluated in adult healthy subjects, in adult antiretroviral treatment-naïve HIV-1 infected patients, and antiretroviral treatment-naïve HIV-1 infected pediatric patients 12 years of age and older and weighing at least 32 kg. Exposure to rilpivirine was generally lower in HIV-1 infected patients than in healthy subjects.

After oral administration, the maximum plasma concentration of rilpivirine is generally achieved within 4 to 5 hours. The absolute bioavailability of rilpivirine hydrochloride is unknown.

Tenofovir disoproxil fumarate

Following oral administration of tenofovir disoproxil fumarate to HIV-1 infected patients, tenofovir disoproxil fumarate is rapidly absorbed and converted to tenofovir. Maximum tenofovir concentrations are observed in serum within one hour of dosing in the fasted state. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted patients was approximately 25%.

Effects of Food on Oral Absorption

The food effect trial for COMPLERA™ evaluated two types of meals. The trial defined a meal with 390 kcal containing 12 g fat as a light meal, and a meal with 540 kcal containing 21 g fat as a standard meal. Relative to fasting conditions, the administration of COMPLERA™ to healthy adult subjects with both types of meals resulted in increased exposures of rilpivirine and tenofovir. The C_{max} and AUC of rilpivirine increased 34% and 9% with a light meal, while increasing 26% and 16% with a standard meal, respectively. The C_{max} and AUC of tenofovir increased 12% and 28% with a light meal, while increasing 32% and 38% with a standard meal, respectively. Emtricitabine exposures were not affected by food.

The effects on rilpivirine, emtricitabine and tenofovir exposure when COMPLERA™ is administered with a high fat meal were not evaluated.

COMPLERA™ should be taken with food.

Distribution

Emtricitabine

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.

Rilpivirine

Rilpivirine is approximately 99.7% bound to plasma proteins *in vitro*, primarily to albumin. The distribution of rilpivirine into compartments other than plasma (e.g., cerebrospinal fluid, genital tract secretions) has not been evaluated in humans.

Tenofovir disoproxil fumarate

Following intravenous administration the steady-state volume of distribution of tenofovir was estimated to be approximately 800 mL/kg. *In vitro* protein binding of tenofovir to plasma protein was less than 0.7%, over the tenofovir concentration range 0.01 to 25 μg/mL.

Metabolism

Emtricitabine

In vitro studies indicate that emtricitabine is not an inhibitor of human CYP450 enzymes. Following administration of ^{14}C-emtricitabine, complete recovery of the emtricitabine dose was achieved in urine (~ 86%) and feces (~ 14%). Thirteen percent of the dose was recovered in the urine as three putative metabolites. The biotransformation of emtricitabine includes oxidation of the thiol moiety to form the 3'-sulfoxide diastereomers (~ 9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (~ 4% of dose). No other metabolites were identifiable.

Rilpivirine

In vitro experiments indicate that rilpivirine primarily undergoes oxidative metabolism mediated by the cytochrome P450 (CYP) 3A system.

Tenofovir disoproxil fumarate

In vitro studies have determined that neither tenofovir disoproxil fumarate nor tenofovir are substrates for the CYP450 enzymes.

Elimination

Emtricitabine

The plasma emtricitabine half-life was approximately 10 hours.
Emtricitabine is primarily excreted by the kidney by both glomerular filtration and active tubular secretion.

Rilpivirine

The terminal elimination half-life of rilpivirine is approximately 45 hours. After single dose oral administration of ^{14}C-rilpivirine, on average 85% and 6.1% of the radioactivity could be retrieved in feces and urine, respectively. In feces, 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 disoproxil fumarate

Tenofovir is primarily excreted by the kidneys by both filtration and an active tubular transport system with approximately 70 to 80% of the dose excreted unchanged in urine following intravenous administration. Following a single oral dose, the terminal elimination half-life of tenofovir is approximately 17 hours.

Special populations

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

Pediatrics

The pharmacokinetics of rilpivirine in antiretroviral treatment-naïve HIV-1 infected pediatric patients 12 to less than 18 years of age receiving rilpivirine 25mg once daily was comparable to that in treatment-naïve HIV-1 infected adults receiving rilpivirine 25mg once daily. There was no impact of body weight on rilpivirine pharmacokinetics in pediatric patients in trial C213 (33 to 93 kg), similar to what was observed in adults. The pharmacokinetics of rilpivirine in pediatric patients less than 12 years of age is under investigation.

Elderly

Population pharmacokinetic analysis in HIV-1 infected patients showed that rilpivirine pharmacokinetics is not different across the age range (12 to 78 years) evaluated. Pharmacokinetic studies for emtricitabine and tenofovir disoproxil fumarate have not been performed in the elderly (over 65 years of age).

Renal impairment

***Emtricitabine and Tenofovir Disoproxil Fumarate*:** Tenofovir and emtricitabine are principally eliminated by renal excretion and the exposure to tenofovir and emtricitabine increases in patients with renal impairment.

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

COMPLERA™ is not recommended for patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min, including patients who require hemodialysis). Patients with moderate or severe renal impairment require dose interval adjustment of emtricitabine and tenofovir disoproxil fumarate that cannot be achieved with the combination tablet.

Hepatic impairment

Emtricitabine: No data are available on which to make an emtricitabine dose recommendation for patients with hepatic impairment.

Rilpivirine: Rilpivirine is primarily metabolized and eliminated by the liver. In a study in adults 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. However, it may not be excluded that the pharmacologically active, unbound, rilpivirine exposure is significantly increased in moderate hepatic impairment. No dose adjustment is suggested but caution is advised in patients with moderate hepatic impairment. Rilpivirine has not been studied in patients with severe hepatic impairment (Child Pugh score C). Therefore, rilpivirine is not recommended in patients with severe hepatic impairment.

Tenofovir Disoproxil Fumarate: Clinically relevant pharmacokinetic changes in patients with hepatic impairment were not observed. Therefore, no tenofovir disoproxil fumarate dose adjustment is required in patients with hepatic impairment.

Hepatitis B and/or hepatitis C virus co-infection

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

Pregnancy and postpartum

Rilpivirine: 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 trimester) compared with postpartum (see Table 10). 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 10: 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[a] (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

a. Arithmetic mean across subjects.

NON-CLINICAL INFORMATION

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.

PHARMACEUTICAL INFORMATION

List of Excipients

Tablet Core	Pregelatinised Starch Lactose Monohydrate Microcrystalline Cellulose Croscarmellose Sodium Magnesium Stearate Povidone Polysorbate 20
Film Coating	Polyethylene Glycol Hypromellose Lactose Monohydrate Triacetin Titanium Dioxide Red Iron Oxide Indigo Carmine Aluminium Lake Sunset Yellow Aluminium Lake

Incompatibilities

Not applicable.

Shelf Life
See expiry date on the outer pack.

Storage Conditions
Do not store above 30ºC.
Store in the original bottle to protect from light and moisture. Keep the bottle tightly closed.

Keep out of the sight and reach of children.

Nature and Contents of Container
COMPLERA™ tablets are supplied in high density polyethylene (HDPE) bottles with a child-resistant closure containing 30 film-coated tablets with a silica gel desiccant.

Instructions for Use and Handling
No special requirements.

PRODUCT REGISTRANT

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BATCH RELEASER

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