Product Monograph

PrCOMPLERA®

(emtricitabine/rilpivirine/tenofovir disoproxil fumarate) tablets

200 mg emtricitabine
25 mg rilpivirine as rilpivirine hydrochloride
300 mg tenofovir disoproxil fumarate

Antiretroviral Agent

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PART I. HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients[a]
Oral	Tablet emtricitabine 200 mg /rilpivirine[a] 25 mg/tenofovir disoproxil fumarate 300 mg	Lactose monohydrate, pregelatinized starch (gluten free).

[a] For the salt concentration of the drug substance and a complete listing of nonmedicinal ingredients, see the DOSAGE FORMS, COMPOSITION, AND PACKAGING section.

INDICATIONS AND CLINICAL USE

COMPLERA® (emtricitabine [FTC]/rilpivirine [RPV]/tenofovir disoproxil fumarate [TDF]) is indicated for use as a complete regimen for the treatment of adults infected with HIV-1 with no known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or FTC, and with a viral load less than or equal to 100,000 copies/mL.

The safety and efficacy of COMPLERA has not been established in patients with a prior history of virologic failure.

The following points should be considered prior to the initiation of therapy in adult patients:

(i) With no antiretroviral treatment history:

- Regardless of HIV-1 RNA at the start of therapy, more RPV-treated patients with CD4+ cell count less than 200 cells/mm^3 at the start of therapy experienced virologic failure compared to patients with CD4+ cell count greater than or equal to 200 cells/mm^3.

- The observed virologic failure rate in RPV-treated patients conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to the control (efavirenz [EFV]) (see **WARNINGS AND PRECAUTIONS, Resistance/Cross-resistance, MICROBIOLOGY, Resistance, Cross-resistance**).

- More patients treated with RPV developed tenofovir and lamivudine/FTC associated resistance compared to the control (see **WARNINGS AND PRECAUTIONS, Resistance/Cross-resistance, MICROBIOLOGY, Resistance, Cross-resistance**).

(ii) Who are virologically-suppressed (HIV-1 RNA <50 copies/mL):

- The efficacy of COMPLERA was established in patients who were virologically-suppressed on a ritonavir-boosted protease inhibitor-containing regimen. Patients were

virologically-suppressed for at least 6 months prior to the initiation of therapy and were on their first or second antiretroviral regimen.

Geriatrics (≥65 years of age):

COMPLERA should be used with caution in patients 65 years and older since clinical studies of the components of COMPLERA did not include sufficient numbers of these patients to determine whether they respond differently from adult patients <65 years of age (see **WARNINGS AND PRECAUTIONS**, **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**).

Pediatrics (<18 years of age):

The safety and efficacy in pediatric patients have not been established.

CONTRAINDICATIONS

COMPLERA is contraindicated in patients with previously demonstrated hypersensitivity to FTC, RPV, TDF or to any of the excipients. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

Coadministration of COMPLERA is contraindicated with drugs which induce CYP3A enzymes or increase gastric pH as this may result in significant decreases in the plasma concentrations of RPV, a loss of virologic response and possible resistance to RPV and to the NNRTI class of antiretrovirals. These drugs are listed in Table 1 (see **DRUG INTERACTIONS**).

Table 1. Drugs that Are Contraindicated with RPV

Drug Class	Drugs Within Class That Are Contraindicated with RPV
Anticonvulsants	carbamazepine, oxcarbazepine, phenobarbital, phenytoin
Antimycobacterials	rifapentine, rifampin
Glucocorticoids	systemic dexamethasone (more than a single dose)
Herbal products	St. John's wort (*Hypericum perforatum*)
Proton pump inhibitors	dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole

WARNINGS AND PRECAUTIONS

- **Lactic Acidosis and Severe Hepatomegaly with Steatosis**

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs including TDF, a component of COMPLERA, in combination with other antiretrovirals (see **WARNINGS AND PRECAUTIONS: Hepatic/Biliary/Pancreatic**).

- **Post-treatment Exacerbation of Hepatitis B**

COMPLERA is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of COMPLERA have not been established in patients coinfected with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV after the discontinuation of FTC or TDF, two of the components of COMPLERA. Hepatic function should be closely monitored with both clinical and laboratory follow-up for at least several months in patients who discontinue COMPLERA and are coinfected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted (see **WARNINGS AND PRECAUTIONS: Special Populations**).

- **Nephrotoxicity**

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia) has been reported with the use of TDF during clinical practice (see **WARNINGS AND PRECAUTIONS: Renal**).

General

As a fixed-dose combination of FTC, RPV and TDF, COMPLERA should not be administered concurrently with other medicinal products containing any of the same active components (ATRIPLA®, EMTRIVA®, STRIBILD®, TRUVADA®, and VIREAD®) or with medicinal products containing tenofovir alafenamide (TAF) (BIKTARVY®, DESCOVY®, GENVOYA®, ODEFSEY®, Symtuza™, and VEMLIDY®). COMPLERA should not be administered with RPV (Edurant®) unless needed for dose adjustment (e.g. with rifabutin) (see **DOSAGE AND ADMINISTRATION** and **DRUG INTERACTIONS**). Due to similarities between FTC and lamivudine, COMPLERA should not be administered with drugs containing lamivudine, including Combivir®, 3TC®, Heptovir®, Kivexa®, Triumeq® and Trizivir®. Caution should be given to prescribing COMPLERA with drugs that may reduce the exposure of RPV (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS**).

COMPLERA should not be administered with HEPSERA® (adefovir dipivoxil).

Carcinogenesis and Mutagenesis

Rilpivirine induced benign and malignant tumors in the liver of mice and rats. These tumors are caused by the enzyme induction that RPV caused in these species which may be rodent-specific. In rats, RPV caused benign and malignant tumors of the thyroid follicular cells. These tumors are the result of continuous stimulation of the follicular cells due to the increased clearance of thyroxine caused by RPV in this species. This effect is considered rat-specific.

Cardiovascular

COMPLERA should be administered with caution to patients who are suspected to be at an increased risk of experiencing proarrhythmic conditions such as clinically significant bradycardia, congenital prolongation of QTc interval, acute myocardial ischemia, hypokalemia or congestive heart failure (see **ADVERSE REACTIONS, DRUG INTERACTIONS** and **ACTION AND CLINICAL PHARMACOLOGY).**

In healthy subjects, RPV has been associated with prolongation of the QT interval of the electrocardiogram at doses of 75 mg and 300 mg once daily. In antiretroviral naïve, HIV-1 infected patients receiving RPV 25 mg once daily in Phase III clinical trials, which excluded subjects with high risk factors for proarrhythmia, the mean QTc interval increased gradually over 48 weeks and remained stable through Week 96. An increase of >60 ms in QTcF interval resulting in abnormal values of >480 ms was reported in one patient. Prolongation of QT interval may increase the risk of cardiac arrhythmias.

There is limited information available on the potential for a pharmacodynamic interaction between RPV and drugs that prolong the QTc interval of the electrocardiogram.

COMPLERA should be used with caution when coadministered with drugs with a known risk of Torsade de Pointes.

Depressive Disorders

During the Phase III trials of RPV in adult patients (N=686) through 96 weeks, the incidence of depressive disorder adverse drug reactions (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) of at least moderate intensity (Grades 2 to 4) was 5%. The incidence of discontinuation due to depressive disorders was 1%. Suicide attempt was reported in 2 subjects while suicide ideation was reported in 4 subjects taking in RPV. The incidence of these events was similar in the control group.

Patients with severe depressive symptoms should seek immediate medical evaluation to assess the possibility that the symptoms are related to RPV, and if so, to determine whether the risks of continued therapy with COMPLERA outweigh the benefits.

Drug Interactions

Use with Certain HCV Regimens:

Tenofovir exposure is increased when COMPLERA is coadministered with HARVONI® (ledipasvir/sofosbuvir), EPCLUSA® (sofosbuvir/velpatasvir), or VOSEVI® (sofosbuvir/velpatasvir/voxilaprevir). Patients receiving COMPLERA concomitantly with HARVONI, EPCLUSA or VOSEVI, particularly those at increased risk for renal dysfunction, should be monitored for tenofovir-associated adverse reactions (see **DRUG INTERACTIONS**).

Endocrine and Metabolism

Fat Redistribution:

Redistribution/accumulation of body fat (lipodystrophy) 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 currently unknown. A causal relationship has not been established.

Hepatic/Biliary/Pancreatic

Hepatic Impairment:

Emtricitabine has not been evaluated in patients with hepatic impairment; however, FTC has not been shown to be metabolized by liver enzymes, so the impact of liver impairment is likely to be limited.

Rilpivirine is primarily metabolized and eliminated by the liver. No dose adjustment of COMPLERA is required in patients with mild or moderate hepatic impairment. Rilpivirine has not been studied in subjects with severe hepatic impairment (Child-Pugh score C) and the use of COMPLERA is not recommended in this population. However, given that the metabolism of RPV is cytochrome P450-mediated and that clinical experience in patients with mild or moderate hepatic impairment is limited, caution should be exercised when administering COMPLERA to this population (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency**).

Tenofovir and tenofovir disoproxil are not metabolized by liver enzymes. Clinically relevant pharmacokinetic changes in patients with hepatic impairment are not observed.

The safety and efficacy of COMPLERA have not been established or specifically studied in patients with underlying liver disorders. Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products (see **WARNINGS AND PRECAUTIONS: Special Populations**).

Hepatotoxicity:

Hepatic adverse events have been reported in patients receiving an RPV-containing regimen. Patients with underlying hepatitis B or C, or marked elevations in transaminases prior to treatment may be at increased risk for worsening or development of transaminase elevations with use of RPV. A few cases of hepatic toxicity have been reported in patients receiving an RPV-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 RPV is recommended in patients with underlying hepatic disease such as hepatitis B or C, or in patients with marked elevations in transaminases prior to treatment initiation. Liver enzyme monitoring should also be considered for patients without pre-existing hepatic dysfunction or other risk factors.

Lactic Acidosis/Severe Hepatomegaly with Steatosis:

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

Pancreatitis:

Pancreatitis has occurred during therapy with combination regimens that included TDF. Caution should be used when administering nucleoside analogues (including COMPLERA) to patients with a history of pancreatitis or risk factors for the development of pancreatitis. Therapy should be suspended in patients with suspected pancreatitis.

Immune

Immune Reconstitution Inflammatory Syndrome:

Immune reconstitution inflammatory syndrome has been reported in patients treated with combination antiretroviral therapy, including the components of COMPLERA. During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infections, cytomegalovirus, *Pneumocystis jiroveci* pneumonia (PCP), and tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.

Musculoskeletal

Bone Effects:

Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk for osteopenia. 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 then appropriate consultation should be obtained.

In a 144-week study of treatment-naïve patients, decreases from baseline in bone mineral density (BMD) were seen at the lumbar spine and hip in both arms of the study. At Week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in patients in the TDF+lamivudine+EFV group compared with patients in the stavudine+lamivudine+EFV group. In both groups, the majority of the reduction in BMD occurred in the first 24–48 weeks of the study and this reduction was sustained through Week 144. Twenty-eight percent of TDF-treated patients vs. 21% of the stavudine-treated patients lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 patients in the TDF group and 6 patients in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide) in the TDF group relative to the stavudine group, suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in the TDF group. Except for bone specific alkaline phosphatase, these changes resulted in values that remained within the normal range. The effects of TDF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown.

Cases of osteomalacia (associated with proximal renal tubulopathy and infrequently contributing to fractures) have been reported in association with the use of TDF (see **ADVERSE REACTIONS, Post Market Adverse Drug Reactions: Tenofovir disoproxil fumarate**).

For additional information, please consult the VIREAD Product Monograph.

Renal

Nephrotoxicity:

COMPLERA should not be administered to 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 FTC and TDF that cannot be achieved with the combination tablet.

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported in association with the use of TDF (see **ADVERSE REACTIONS, Post Marketing Experience**). The majority of these cases

occurred in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents, however, some cases occurred in patients without identified risk factors.

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

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

Particular caution should be exercised when administering COMPLERA to patients with known risk factors for renal disease and a history of renal dysfunction. COMPLERA should be avoided with concurrent or recent use of a nephrotoxic agent.

Resistance/Cross-resistance

In the pooled analysis from two Phase III trials, the emergence of resistance among subjects was greater in the RPV arm as compared to the control (EFV) arm at Week 48 (10.6%, 5.3%, respectively) and at Week 96 (14%, 7.6%, respectively). More RPV-treated subjects with baseline HIV-1 RNA>100,000 copies/mL experienced virologic failure compared to subjects with HIV RNA≤100,000 copies/mL at baseline.

The observed virologic failures in RPV-treated subjects conferred a higher cross resistance to the NNRTI class as compared to those in control-treated subjects. More subjects treated with RPV developed lamivudine/FTC associated resistance as compared to those treated with the comparator (see **VIROLOGY (MICROBIOLOGY)**, **Resistance**, **Cross-resistance**).

Skin and Hypersensitivity Reactions

Severe skin and hypersensitivity reactions have been reported during the post-marketing experience, including cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), with RPV-containing regimens. While some skin reactions were accompanied by constitutional symptoms such as fever, other skin reactions were associated with organ dysfunctions, including elevations in hepatic serum biochemistries. During the Phase III clinical trials, treatment-related rashes with at least Grade 2 severity were reported in 3% of subjects receiving RPV plus FTC/TDF. No Grade 4 rashes were reported. Overall, most rashes were Grade 1 or 2 and occurred in the first four to six weeks of therapy (see **ADVERSE REACTIONS**).

Discontinue COMPLERA immediately if signs or symptoms of severe skin or hypersensitivity reactions develop, including but not limited to, severe rash or rash accompanied by fever, blisters, mucosal involvement, conjunctivitis, facial edema,

angioedema, hepatitis or eosinophilia. Clinical status including laboratory parameters should be monitored and appropriate therapy should be initiated.

Special Populations

Patients with HIV and Hepatitis B Virus Coinfection:

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 after the discontinuation of FTC and TDF, two of the components of COMPLERA. In some patients infected with HBV and treated with FTC, the exacerbations of hepatitis B were associated with liver decompensation and liver failure. Hepatic function should be closely monitored with both clinical and laboratory follow-up for at least several months in patients who discontinue COMPLERA and are co-infected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, post-treatment exacerbation of hepatitis may lead to hepatic decompensation. Therefore, in these patients, discontinuation of treatment without initiation of alternative anti-hepatitis B therapy is not recommended.

Pregnant Women:

There are no adequate and well-controlled studies of COMPLERA in pregnant women. COMPLERA should not be used in pregnant women unless the benefits outweigh the potential risks to the fetus.

Emtricitabine: The incidence of fetal variations and malformations was not increased in embryo-fetal toxicity studies performed with FTC in mice at exposures (AUC) approximately 60-times higher and in rabbits at approximately 120-times 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 **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Pregnancy and Postpartum**).

Studies in animals have shown no evidence of embryonic or fetal toxicity or an effect on reproductive function. There was no teratogenicity with RPV in rats and rabbits. The exposures at the embryo-fetal No Observed Adverse Effects Levels in rats and rabbits were respectively 15 and 70 times higher than the exposure in humans at the recommended dose of 25 mg 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. Reduced pup body weights, survival and delay in sexual maturation was observed in a peri- and postnatal toxicity study in rats at the maternally toxic doses of 450 and 600 mg/kg (approximately 14 and 19 times the human dose based on body surface area comparisons).

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to ART (antiretroviral therapy) including COMPLERA, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.

Nursing Women:

HIV-1 infected mothers should not breast-feed their infants to avoid risking postnatal transmission of HIV.

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

Rilpivirine: It is not known whether RPV 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 breastfed by mothers being treated with TDF are unknown.

Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving COMPLERA.**

Pediatrics (<18 years of age): The safety and efficacy in pediatric patients have not been established.

Geriatrics (≥65 years of age): Clinical studies of FTC, RPV or TDF did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from adult subjects <65 years of age. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Drug Reaction Overview

HIV-1 Infected Patients with no Antiretroviral History

The safety assessment of RPV at Week 48 and Week 96 is based on pooled data from 686 patients in the Phase III controlled trials TMC278-C209 (ECHO) and TMC278-C215 (THRIVE) in adult patients with no antiretroviral treatment history who received RPV (25 mg once daily) in combination with other antiretroviral drugs; most (550) received FTC+TDF as background regimen (see **CLINICAL TRIALS**). In the Week 96 analysis, the median duration of exposure was 104 weeks. The proportion of patients who discontinued treatment with RPV in combination with FTC and TDF due to adverse drug reactions (ADRs) was 2%. Most ADRs occurred during the first 48 weeks of treatment and no new ADR terms were identified between 48 weeks and 96 weeks. Adverse reactions observed in these studies were generally consistent with those seen in previous studies of the individual components (Table 2).

In addition to the events reported here, please consult the Edurant and TRUVADA Product Monographs.

Table 2. Selected Treatment-Emergent Adverse Reactions[a] (Grades 2–4) Reported in ≥1% of Patients Receiving RPV or EFV in Combination with FTC/TDF in Studies C209 and C215 (Week 96)

	RPV+FTC/TDF	EFV+FTC/TDF
	N=550	N=546
Gastrointestinal Disorder		
Abdominal Pain	2%	2%
Nausea	2%	3%
Vomiting	1%	2%
General Disorders and Administration Site		

	RPV+FTC/TDF	EFV+FTC/TDF
	N=550	N=546
Condition		
Fatigue	2%	3%
Nervous System Disorders		
Dizziness[b]	1%	7%
Headache	4%	4%
Somnolence	<1%	1%
Psychiatric Disorders		
Abnormal dreams	2%	5%
Depression	5%	3%
Insomnia	3%	3%
Sleep Disorders	1%	1%
Skin and Subcutaneous Tissue Disorders		
Rash[b]	3%	10%
Metabolism and Nutrition Disorders		
Decreased Appetite	1%	1%

a Frequencies of adverse reactions are based on all Grades 2-4 treatment-emergent adverse events, regardless of relationship to study drug.

b p-value <0.0001 based on Fisher's exact test.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Psychiatric Disorders: Depressed Mood
Gastrointestinal Disorders: Abdominal Discomfort

In addition to the adverse reactions in C209 and C215, the following adverse reactions were observed in clinical trials of FTC or TDF or RPV in combination with other antiretroviral agents.

Emtricitabine and Tenofovir disoproxil fumarate: Adverse reactions that occurred in at least 3-5% of patients receiving FTC or TDF with other antiretroviral agents in clinical trials include: anorexia, anxiety, arthralgia, asthenia, increased cough, depressive disorders, dyspepsia, fever, vomiting, flatulence, myalgia, pain, abdominal pain, back pain, chest pain, paresthesia, peripheral neuropathy (including peripheral neuritis and neuropathy), pneumonia, rhinitis, rash event (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash and allergic reaction), sweating, and weight loss. Skin discoloration has been reported with higher frequency among FTC treated patients. Skin discoloration, manifested by hyperpigmentation on the palms and/or soles was generally mild and asymptomatic and of little clinical significance. The mechanism is unknown.

For information on the effects of FTC and TDF on limb fat, please consult the TRUVADA Product Monograph.

For information on the effects of TDF on bone mineral density, please see **WARNINGS and PRECAUTIONS**, **Musculoskeletal** and consult the VIREAD and TRUVADA Product Monographs.

Rilpivirine: No additional adverse reactions occurred in patients receiving RPV with other antiretroviral agents in clinical trials.

This list is not all inclusive. For additional safety information about EMTRIVA, Edurant or VIREAD, consult the Product Monographs for these products.

Laboratory Abnormalities: Laboratory abnormalities observed in studies C209 and C215 were generally consistent with those seen in other studies of the individual components (Table 3).

Table 3. Significant Laboratory Abnormalities (Grades 3-4) Reported in Patients Who Received RPV or EFV in Combination with FTC/TDF in Studies C209 and C215 (Week 96)

	Division of AIDS (DAIDS) Toxicity Range	RPV+FTC/TDF	EFV+FTC/TDF
		N=550	N=546
Creatinine	>1.8 ULN[a]	0.2%	0.2%
Pancreatic Amylase	>2 ULN	4.2%	4.9%
Lipase	>3 ULN	0.9%	1.5%
Decreased Hemoglobin	<4.5 mmol/L	0.2%	0.6%
Decreased Platelet Count	<49999/mm^3	0.0%	0.2%
Decreased White Blood Cell Count	<1499/mm^3	0.2%	0.2%
AST	>5 ULN	2.6%	3.6%
ALT	>5 ULN	1.6%	3.5%
Increased Bilirubin	>2.5 ULN	0.5%	0.4%
Total Cholesterol (fasted)	>300 mg/dL	0.2%	2.2%
LDL-Cholesterol (fasted)	≥191 mg/dL	0.9%	3.9%
Triglycerides (fasted)	≥751 mg/dL	0.5%	2.6%

a ULN = Upper limit of normal value.

Adrenal Function

In the pooled analysis of Phase III trials, at Week 48, the overall mean change from baseline in basal cortisol showed a decrease of 13.1 nmol/L in the RPV group and an increase of 9.0 nmol/L in the control (EFV) group. At Week 96, the overall mean change from baseline in basal cortisol showed a decrease of 19.1 nmol/L in the RPV group and a decrease of 0.6 nmol/L in the control group. At Week 48 and Week 96, the mean change from baseline in ACTH-stimulated cortisol levels was lower in the RPV group (+16.5±6.14 nmol/L and +18.4±8.36 nmol/L, respectively) than in the control group (+58.1±6.66 nmol/L and +54.1±7.24 nmol/L, respectively). Mean values for both basal and ACTH-stimulated cortisol values at Week 48 and 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. The effects on adrenal function are specific to RPV and not dependent on the background regimen.

Emtricitabine and Tenofovir disoproxil fumarate: In addition to the laboratory abnormalities described for Studies C209 and C215 (Table 3), serum glucose (<40 or >250 mg/dL), creatine kinase (M:>990 U/L; F:>845 U/L), serum amylase (>175 U/L), hematuria (>75 RBC/HPF), alkaline phosphatase (>550 U/L), neutrophils (<750/mm^3), and urine glucose (≥3+) occurred in up to 3% of patients treated with FTC or TDF with other antiretroviral agents in other clinical trials. For detailed information, please consult the respective Product Monographs.

Rilpivirine: Changes from baseline in total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides are presented in Table 4. The mean changes from baseline were smaller in the RPV arm versus the EFV arm. The impact of such findings has not been demonstrated.

Table 4. Lipid Values Reported in Patients Receiving RPV or EFV in Combination with FTC/TDF in Studies C209 and C215 (Week 96)

	Pooled Data from the C209 and C215 Trials			
	RPV+FTC/TDF N=550		EFV+FTC/TDF N=546	
	Baseline	Week 96	Baseline	Week 96
	Mean (mg/dL)	Mean Change[a] (mg/dL)	Mean (mg/dL)	Mean Change[a] (mg/dL)
Total Cholesterol (fasted)[b]	162	1	161	27
HDL-cholesterol (fasted)[b]	41	4	40	11
LDL-cholesterol (fasted)[b]	97	-0.7	96	14
Triglycerides (fasted)[b]	124	-14	132	8

a The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 96 values.

b p-value <0.0001, Wilcoxon rank-sum test for treatment comparison of change from baseline.

Virologically-Suppressed HIV-1 Infected Patients

No new adverse reactions to COMPLERA were identified in stable, virologically-suppressed patients who switched to COMPLERA from a regimen containing a ritonavir-boosted protease inhibitor; however, the frequency of adverse reactions increased by 20% (GS-US-264-0106) after switching to COMPLERA.

Patients coinfected with Hepatitis B and/or Hepatitis C virus

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

Electrocardiogram Findings

In a Phase II clinical trial in antiretroviral treatment-naïve HIV-1 infected patients, RPV at doses of 25 mg, 75 mg, and 150 mg once daily was associated with dose-dependent QTc prolongation. A pooled analysis of data from two Phase III clinical trials of antiretroviral treatment-naïve HIV-1 infected patients who received either RPV 25 mg once daily or control (EFV), showed statistically significant mean increase from baseline in the QTc

interval at Weeks 48 and 96. During treatment with RPV 25 mg, the mean change from baseline in QTc increased through Week 48 without reaching plateau and remained stable between Week 48 and Week 96 (11.4 ms (95% CI 10.1, 12.8) and 12.4 ms (95% CI 11.0, 13.7), respectively). These trials excluded patients with high risk factors for proarrhythmia. The clinical relevance of these findings is unknown (see **WARNINGS AND PRECAUTIONS, Cardiovascular; DRUG INTERACTIONS, QT Prolonging Drugs; ACTION AND CLINICAL PHARMACOLOGY, Effects on Electrocardiogram**).

Post-Market Adverse Drug Reactions

In addition to the adverse reaction reports from clinical trials, the following possible adverse reactions have been identified during post-approval use of FTC, TDF, RPV or COMPLERA. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been considered possible adverse reactions due to a combination of their seriousness, frequency of reporting or potential causal relationship with treatment.

Emtricitabine:

Blood and lymphatic system disorders:	Thrombocytopenia
Gastrointestinal disorders:	Pancreatitis
General disorders and administrative site conditions:	Pyrexia
Metabolism and nutrition disorders:	Lactic acidosis

Tenofovir DF:

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
Blood and lymphatic system disorders:	Thrombocytopenia
Hepatobiliary disorders:	Hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT, GGT)
Skin and Subcutaneous Tissue Disorders:	Rash
Musculoskeletal and Connective Tissue Disorders:	Rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing 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 administrative site conditions:	Asthenia

Rilpivirine:

Renal and Genitourinary Disorders:	Nephrotic syndrome

COMPLERA (FTC/RPV/TDF):

Metabolism and Nutrition Disorders:	Weight increased
Skin and Subcutaneous Tissue Disorders:	Severe skin reactions with systemic symptoms (including rashes accompanied by fever, blisters, conjunctivitis, angioedema, elevated liver function tests, and/or eosinophilia).

The following adverse reactions, listed under the system organ class headings above, sometimes appeared to be concurrent with proximal renal tubulopathy: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), hypokalemia, muscular weakness, myopathy, and hypophosphatemia.

There have been three post marketing reports of acute renal failure in patients on concomitant NSAIDS therapy where a relationship to TDF could not be excluded. These events mostly occurred in medically complex patients, where underlying disease processes confound interpretation.

DRUG INTERACTIONS

Drug-Drug Interactions

COMPLERA is a complete regimen for the treatment of HIV-1 infection; therefore, COMPLERA should not be administered with other antiretroviral medications unless needed for dose adjustment (e.g., with rifabutin) (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). Please refer to the product monographs of the individual components. The drug interactions described in Table 5 and Table 6 are based on studies conducted with FTC, RPV or TDF as individual agents or with COMPLERA as a

combination product or are potential drug interactions. The tables include potentially significant interactions, but may not be inclusive of all potential interactions.

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 RPV (see **ACTION AND CLINICAL PHARMACOLOGY**). Coadministration of RPV and drugs that induce CYP3A may result in decreased plasma concentrations of RPV and loss of virologic response and possible resistance to RPV or to the NNRTI class of antiretrovirals which could potentially reduce the therapeutic effect of COMPLERA. Coadministration of RPV and drugs that inhibit CYP3A may result in increased plasma concentrations of RPV.

Drugs Increasing Gastric pH

Coadministration of RPV and drugs that increase gastric pH may result in decreased plasma concentrations of RPV and loss of virologic response and possible resistance to RPV or to the NNRTI class of antiretrovirals (see **DRUG INTERACTIONS, Drug-Drug Interactions,** Table 6).

Drugs Affecting Renal Function

Since FTC and tenofovir are primarily eliminated by the kidneys, coadministration of COMPLERA with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of FTC, tenofovir, and/or other renally eliminated drugs. Some examples include, but are not limited to, acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, and valganciclovir.

QT Prolonging Drugs

There is limited information available on the potential for a pharmacodynamic interaction between RPV and drugs that prolong the QTc interval of the electrocardiogram. In a study of healthy subjects, RPV (75 mg once daily and 300 mg once daily) was shown to prolong the QTc interval of the electrocardiogram (see **ACTION AND CLINICAL PHARMACOLOGY, Effects on Electrocardiogram**).

Rilpivirine is a substrate for CYP3A4. Plasma levels of RPV can be increased by inhibitors of CYP3A4. Drugs that inhibit CYP3A4 include, but are not limited to, azole antifungal agents (e.g., ketoconazole, fluconazole, voriconazole), clarithromycin, erythromycin, and telithromycin. Caution should be observed if these drugs are to be used concomitantly with COMPLERA.

Caution should be observed when using COMPLERA with drugs that can disrupt electrolyte levels, including, but not limited to, the following: loop, thiazide, and related diuretics; laxatives and enemas; amphotericin B; high dose corticosteroids.

COMPLERA should be used with caution when coadministered with a drug with a known risk of Torsade de Pointes (see **WARNINGS AND PRECAUTIONS, Cardiovascular**).

Drugs that Should not be Coadministered with COMPLERA and Established and Other Potentially Significant Drug Interactions

Important drug interaction information for COMPLERA is summarized in Table 5 and Table 6. The drug interactions described are based on studies conducted with FTC, RPV, or TDF as individual agents or with COMPLERA as a combination product or are potential drug interactions; (for pharmacokinetic data, see Table 7 and Table 8). The tables include potentially significant interactions, but are not all inclusive.

Table 5. Drugs that Should not be Coadministered with COMPLERA

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Anticonvulsants: carbamazepine oxcarbazepine phenobarbital phenytoin	↓ rilpivirine	COMPLERA is contraindicated with these anticonvulsants as coadministration may cause significant decreases in RPV plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of COMPLERA and possible development of resistance to RPV and other NNRTIs.
Antimycobacterials: rifampin[c,d] rifapentine	↓ rilpivirine	COMPLERA is contraindicated with rifampin or rifapentine as coadministration may cause significant decreases in RPV plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of COMPLERA and possible development of resistance to RPV and other NNRTIs.
Glucocorticoids: dexamethasone (systemic)	↓ rilpivirine	COMPLERA is contraindicated in combination with systemic dexamethasone as coadministration may cause significant decreases in RPV plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of COMPLERA and possible development of resistance to RPV and other NNRTIs. Alternatives should be considered, particularly for long-term use.
Proton Pump Inhibitors: omeprazole[c,d] lansoprazole rabeprazole pantoprazole esomeprazole	↓ rilpivirine ↓ omeprazole	COMPLERA is contraindicated with proton pump inhibitors as coadministration may cause significant decreases in RPV plasma concentrations (increase in gastric pH). This may result in loss of therapeutic effect of COMPLERA and possible development of resistance to RPV and other NNRTIs.
Herbal Products: St. John's wort (*Hypericum perforatum*)	↓ rilpivirine	COMPLERA is contraindicated with products containing St. John's wort as coadministration may cause significant decreases in RPV plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of COMPLERA and possible development of resistance to RPV and other NNRTIs.

a This table is not all inclusive.

b ↑ = increase, ↓ = decrease
c The interaction was evaluated in a clinical study. All other drug-drug interactions shown are predicted.
d This interaction study has been performed with a dose higher than the recommended dose for RPV assessing the maximal effect on the coadministered drug. The dosing recommendation is applicable to the recommended dose of RPV 25 mg once daily.

Table 6. Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Azole Antifungal Agents: ketoconazole[c,d] fluconazole voriconazole itraconazole posaconazole	↑ rilpivirine ↓ ketoconazole	Concomitant use of COMPLERA with azole antifungal agents may cause an increase in the plasma concentrations of RPV (inhibition of CYP3A enzymes). An interaction trial between RPV (150 mg q.d.) and ketoconazole (400 mg q.d.) demonstrated that ketoconazole increased the mean exposure of RPV by 1.49-fold. The concomitant use of COMPLERA with other azole antifungals is expected to result in increased mean exposure (AUC) of RPV (see **QT prolonging drugs**). Caution should be exercised when these drugs are coadministered with COMPLERA. Clinical monitoring for breakthrough infections is recommended when azole antifungals are coadministered with COMPLERA.
Hepatitis C Antiviral Agents: ledipasvir/sofosbuvir sofosbuvir/velpatasvir sofosbuvir/velpatasvir/voxilaprevir	↑ tenofovir[c]	Patients receiving COMPLERA with HARVONI (ledipasvir/sofosbuvir), EPCLUSA (sofosbuvir/velpatasvir) or VOSEVI (sofosbuvir/velpatasvir/voxilaprevir) should be monitored for adverse reactions associated with TDF. HARVONI, EPCLUSA, and VOSEVI had no effect on FTC exposure.
Macrolide antibiotics: clarithromycin erythromycin troleandomycin	↑ rilpivirine	Concomitant use of COMPLERA with clarithromycin, erythromycin and troleandomycin may cause an increase in the plasma concentrations of RPV (inhibition of CYP3A enzymes). Where possible, alternatives such as azithromycin should be considered.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
H_2-Receptor Antagonists: famotidine[c,d] cimetidine nizatidine ranitidine	↔ rilpivirine (famotidine taken 12 hours before rilpivirine) ↓ rilpivirine (famotidine taken 2 hours before rilpivirine) ↔ rilpivirine (famotidine taken 4 hours after rilpivirine)	The combination of COMPLERA and H_2-receptor antagonists should be used with caution as coadministration may cause significant decreases in RPV plasma concentrations (increase in gastric pH). H_2-receptor antagonists should only be administered at least 12 hours before or at least 4 hours after COMPLERA.
Antacids: antacids (e.g., aluminium, magnesium hydroxide, or calcium carbonate)	↓ rilpivirine	The combination of COMPLERA and antacids should be used with caution as coadministration may cause significant decreases in RPV plasma concentrations (increase in gastric pH). Antacids should only be administered either at least 2 hours before or at least 4 hours after COMPLERA.
Antimycobacterials: Rifabutin[c]	↓ rilpivirine	Concomitant use of COMPLERA with rifabutin may cause significant decreases in RPV plasma concentrations (inductions of CYPA3A enzymes). This may result in loss of therapeutic effect of COMPLERA. If COMPLERA is coadministered with rifabutin, an additional 25 mg tablet of RPV (Edurant) per day is recommended to be taken concomitantly with COMPLERA, for the duration of rifabutin coadministration.
Narcotic Analgesics: methadone[c]	↓ R(−) methadone ↓ S(+) methadone	No dose adjustments are required when initiating coadministration of methadone with COMPLERA. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.

a This table is not all inclusive.
b ↑ = increase, ↓ = decrease, ↔ = no effect
c The interaction was evaluated in a clinical study. All other drug-drug interactions shown are predicted.
d This interaction study has been performed with a dose higher than the recommended dose for RPV assessing the maximal effect on the coadministered drug. The dosing recommendation is applicable to the recommended dose of RPV 25 mg once daily.

Emtricitabine and Tenofovir disoproxil fumarate:

In vitro and clinical pharmacokinetic drug-drug interaction studies have shown that the potential for CYP450 mediated interactions involving FTC and tenofovir with other medicinal products is low.

No drug-drug interactions due to competition for renal excretion have been observed.

Rilpivirine:

No clinically significant drug interactions have been observed between RPV and acetaminophen, atorvastatin, didanosine, digoxin, ethinyl estradiol, ledipasvir/sofosbuvir, metformin, norethindrone, sildenafil, simeprevir, sofosbuvir, sofosbuvir/velpatasvir, or sofosbuvir/velpatasvir/voxilaprevir.

The effects of coadministration of other drugs on the AUC, C_{max}, and C_{min} values of RPV are summarized in Table 7. The effect of coadministration of RPV on the AUC, C_{max}, and C_{min} values of other drugs are summarized in Table 8. For information regarding clinical recommendations, see **DRUG INTERACTIONS**, **Drug-Drug Interactions**.

Table 7. Drug Interactions: Changes in Pharmacokinetic Parameters for RPV in the Presence of the Coadministered Drugs

Coadministered Drug	Dose of Coadministered Drug	Dose of RPV	N[a]	Mean % Change of RPV Pharmacokinetic Parameters[b] (90% CI)		
				C_{max}	AUC	C_{min}
Famotidine	40 mg single dose taken 12 hours before RPV	150 mg single dose[c]	24	↔	↔	NA
	40 mg single dose taken 2 hours before RPV	150 mg single dose[c]	23	↓ 85 (↓ 88 to ↓ 81)	↓ 76 (↓ 80 to ↓ 72)	NA
	40 mg single dose taken 4 hours after RPV	150 mg single dose[c]	24	↔	↔	NA
Ketoconazole	400 mg once daily	150 mg once daily[c]	15	↑ 30 (↑ 13 to ↑ 48)	↑ 49 (↑ 31 to ↑ 70)	↑ 76 (↑ 57 to ↑ 97)
Ledipasvir/sofosbuvir	90 mg/400 mg once daily	25 mg once daily	14	↓ 3 (↓ 12 to ↑ 7)	↑ 2 (↓ 6 to ↑ 11)	↑ 12 (↑ 3 to ↑ 21)
Sofosbuvir/velpatasvir	400 mg /100 mg once daily	25 mg once daily	24	↓ 7 (↓ 12 to ↓ 2)	↓ 5 (↓ 10 to 0)	↓ 4 (↓ 10 to ↑ 3)
Methadone	60 mg-100 mg once daily individualized dose	25 mg once daily	12	↔[d]	↔[d]	↔[d]
Omeprazole	20 mg once daily	150 mg once daily[c]	16	↓ 40 (↓ 52 to ↓ 27)	↓ 40 (↓ 49 to ↓ 29)	↓ 33 (↓ 42 to ↓ 22)
Rifabutin	300 mg once daily	25 mg once daily	18	↓ 31 (↓ 38 to ↓ 24)	↓ 42 (↓ 48 to ↓ 35)	↓ 48 (↓ 54 to ↓ 41)
	300 mg once daily	50 mg once daily[c]	18	↑ 43 (↑ 30 to ↑56)[e]	↑ 16 (↑ 6 to ↑ 26)[e]	↓ 7 (↓ 15 to ↑ 1)[e]
Rifampin	600 mg once daily	150 mg once daily[c]	16	↓ 69 (↓ 73 to ↓ 64)	↓ 80 (↓ 82 to ↓ 77)	↓ 89 (↓ 90 to ↓ 87)
Simeprevir	25 once daily	150 once daily	23	↑ 4 (↓ 5 to ↑ 13)	↑ 12 (↑ 5 to ↑ 19)	↑ 25 (↑ 16 to ↑ 35)
Sofosbuvir	400 mg once daily	25 mg once daily	17	↑ 5 (↓ 3 to ↑ 15)	↑ 6 (↑ 2 to ↑ 9)	↓ 1 (↓ 6 to ↑4)
Sofosbuvir/ velpatasvir/ voxilaprevir	400 mg/100 mg/100 mg + voxilaprevir[f] 100 mg once daily	25 mg once daily[g]	30	↓ 21 (↓ 26 to ↓ 16)	↓ 20 (↓ 24 to ↓ 15)	↓ 18 (↓ 23 to ↓ 13)

NA = not available

a N = maximum number of subjects for C_{max}, AUC, or C_{min}.

b Increase = ↑; Decrease = ↓; No Effect = ↔

c The Interaction study has been performed with a dose higher than the recommended dose for Edurant (25 mg once daily) assessing the maximal effect on the coadministered drug.

d Comparison based on historic controls.

e Compared to RPV 25 mg once daily alone.

f Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

g Study conducted with ODEFSEY (FTC/RPV/TAF fixed dose combination).

Table 8. Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of RPV

Coadministered Drug	Dose of Coadministered Drug	Dose of RPV	N[a]	Mean % Change of Coadministered Drug Pharmacokinetic Parameters[b] (90% CI)		
				C_{max}	AUC	C_{min}
Digoxin	0.5 mg single dose	25 mg once daily	22	↑ 6 (↓ 3 to ↑ 17)	↓ 2 (↓ 7 to ↑ 4)[c]	NA
Ketoconazole	400 mg once daily	150 mg once daily[d]	14	↓ 15 (↓ 20 to ↓ 10)	↓ 24 (↓ 30 to ↓ 18)	↓ 66 (↓ 75 to ↓ 54)
Ledipasvir	90 mg/400 mg once daily	25 mg once daily	15	↑ 1 (↓ 5 to ↑ 7)	↑ 8 (↑ 2 to ↑ 15)	↑ 16 (↑ 8 to ↑ 25)
Sofosbuvir				↑ 5 (↓ 7 to ↑ 20)	↑ 10 (↑ 1 to ↑ 21)	NA
GS-331007[e]				↑ 6 (↑ 1 to ↑ 11)	↑ 15 (↑ 11 to ↑ 19)	↑ 18 (↑ 13 to ↑ 24)
Sofosbuvir	400 mg/100 mg once daily	25 mg once daily	24	↑ 9 (↓ 5 to ↑ 25)	↑ 16 (↑ 9 to ↑ 24)	NA
GS-331007[e]				↓ 4 (↓ 10 to ↑ 1)	↑ 4 (0 to ↑ 7)	↑ 12 (↑ 7 to ↑ 17)
Velpatasvir				↓ 4 (↓ 15 to ↑ 10)	↓ 1 (↓ 12 to ↑ 11)	↑ 2 (↓ 9 to ↑ 15)
R(-) methadone	60 mg-100 mg once daily individualized dose	25 mg once daily	13	↓ 14 (↓ 22 to ↓ 5)	↓ 16 (↓ 26 to ↓ 5)	↓ 22 (↓ 33 to ↓ 9)
S(+) methadone			13	↓ 13 (↓ 22 to ↓ 3)	↓ 16 (↓ 26 to ↓ 4)	↓ 21 (↓ 33 to ↓ 8)
Metformin	850 mg single dose	25 mg once daily	20	↑ 2 (↓ 5 to ↑10)	↓ 3 (↓ 10 to ↑6)	NA
Omeprazole	20 mg once daily	150 mg once daily[d]	15	↓ 14 (↓ 32 to ↑ 9)	↓ 14 (↓ 24 to ↓ 3)	NA
Rifabutin	300 mg once daily	150 mg once daily[d]	17	↔	↔	↔
25-*O*-desacetyl-rifabutin			17	↔	↔	↔
Rifampin	600 mg once daily	150 mg once daily[d]	16	↔	↔	NA
25-desacetylrifampin			16	↔	↔	NA
Sofosbuvir	400 mg once daily	25 mg once daily	17	↑ 21 (↓ 10 to ↑ 62)	↑ 9 (↓ 6 to ↑ 27)	NA

Sofosbuvir	400 mg/100 mg/100 mg + voxilaprevir[f] 100 mg once daily	25 mg once daily[g]	30	↓ 5 (↓ 14 to ↑ 5)	↑ 1 (↓ 3 to ↑ 6)	NA
GS-331007				↑ 2 (↓ 2 to ↑ 6)	↑ 4 (↑ 1 to ↑ 6)	NA
Velpatasvir				↑ 5 (↓ 4 to ↑ 16)	↑ 1 (↓ 6 to ↑ 7)	↑ 1 (↓ 5 to ↑ 9)
Voxilaprevir				↓ 4 (↓ 16 to ↑ 11)	↓ 6 (↓ 16 to ↑ 5)	↑ 2 (↓ 8 to ↑ 12)

NA = not available

a N = maximum number of subjects for C_{max}, AUC, or C_{min}.

b Increase = ↑; Decrease = ↓; No Effect = ↔

c $AUC_{(0\text{-last})}$

d The Interaction study has been performed with a dose higher than the recommended dose for Edurant (25 mg once daily) assessing the maximal effect on the coadministered drug.

e The predominant circulating nucleoside metabolite of sofosbuvir.

f Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

g Study conducted with ODEFSEY (FTC/RPV/TAF fixed-dose combination).

Drug-Food Interactions

Effect of Food on Oral Absorption

COMPLERA should be taken with food.

Relative to fasting conditions, the administration of COMPLERA to healthy adult subjects with a light meal (390 Kcal, 12 g fat) resulted in increased exposures of RPV and tenofovir. The C_{max} and AUC of RPV 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 effect of a protein-rich nutritional drink on the exposure to COMPLERA was not examined. When Edurant was taken as a single agent with only a protein-rich nutritional drink, exposures were 50% lower than when taken with food. **These decreases in plasma concentration of RPV may lead to a loss of virologic response and possible resistance to Edurant and the NNRTI class of antiretrovirals.**

Drug-Herb Interactions

COMPLERA should not be used in combination with products containing St. John's wort (*Hypericum perforatum*) as coadministration may cause significant decreases in RPV plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of COMPLERA (see **DRUG INTERACTIONS**, **Drug-Drug Interactions**, **Table 5**).

Drug-Laboratory Interactions

Interactions of COMPLERA with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

The recommended dose of COMPLERA is one tablet, once daily, **which must be taken with food to obtain optimal absorption** (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

When dose modification is necessary, separate preparations of RPV, FTC, and TDF should be used (see **DRUG INTERACTIONS, Drug-Drug Interactions**).

Rifabutin Coadminstration: If COMPLERA is coadministered with rifabutin, an additional 25 mg tablet of RPV (Edurant) per day is recommended to be taken concomitantly with COMPLERA, for the duration of the rifabutin coadministration (see **DRUG INTERACTIONS, Drug-Drug Interactions**).

Dose Adjustment for Renal Impairment

Because COMPLERA is a fixed-dose combination, it should not be prescribed for patients requiring dosage reduction such as those with moderate or severe renal impairment (creatinine clearance <50 mL/min) (see **WARNINGS AND PRECAUTIONS**).

Missed Dose

If the patient misses a dose of COMPLERA within 12 hours of the time it is usually taken, the patient should take COMPLERA with food 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, the patient should not take the missed dose, but resume the usual dosing schedule.

OVERDOSAGE

For management of a suspected drug overdose, please contact your regional Poison Control Centre.

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:

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

Hemodialysis treatment removes approximately 30% of the FTC dose over a 3-hour dialysis period starting within 1.5 hours of FTC dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min), however, a single treatment does not significantly affect FTC C_{max} or AUC. It is not known whether FTC can be removed by peritoneal dialysis.

Rilpivirine:

There is no specific antidote for overdose with RPV. Human experience of overdose with Edurant is limited. Since RPV is highly bound to plasma protein, dialysis is unlikely to result in significant removal of RPV.

Tenofovir disoproxil fumarate:

Limited clinical experience at doses higher than the therapeutic dose of VIREAD 300 mg is available. In one study, 600 mg TDF was administered to 8 patients orally for 28 days. No severe adverse reactions were reported. The effects of higher doses are not known.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

COMPLERA is a fixed-dose combination of antiretroviral drugs FTC, RPV, and TDF.

Emtricitabine:

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

Rilpivirine:

Rilpivirine is a diarylpyrimidine NNRTI of HIV-1. Rilpivirine activity is mediated by non-competitive inhibition of HIV-1 RT. Rilpivirine does not inhibit the human cellular DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Tenofovir disoproxil fumarate:

Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form

tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 RT by competing with the natural substrate deoxyadenosine 5′-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Pharmacodynamics

Effects on Electrocardiogram

The effect of RPV on the QTc interval of the ECG was evaluated in two Phase I studies in healthy adult volunteers. Rilpivirine at the recommended therapeutic dose of 25 mg q.d. was examined in a double-blind, double-dummy, randomized, placebo- and active-controlled three-way crossover study in healthy adult volunteers (N=60, 35M/25F), with 13 ECG recordings over 24 hours on day 11 of treatment (steady-state). Rilpivirine at the dose of 25 mg q.d. was not associated with a statistically significant or clinically relevant effect on the QTc interval. Rilpivirine at doses of 75 mg q.d. and 300 mg q.d. was studied in a double-blind, double-dummy, randomized, placebo and active controlled, three-way crossover study in healthy adult volunteers (N=40, 22F/19M), with 13 ECG recordings over 24 hours on day 1 and day 11 of treatment. On day 11 of treatment (steady-state), the maximum mean QTc interval prolongation (baseline- and placebo-adjusted) was 10.7 (90% CI 6.1, 15.3) ms in the 75 mg q.d. treatment arm and 23.3 (90% CI 18.0, 28.7) ms at 4.5 h post-dosing in the 300 mg q.d. arm.

For QTc interval effects with long-term treatment in the target patient population, see **ADVERSE REACTIONS**, **Electrocardiogram Findings**. See also **WARNINGS AND PRECAUTIONS**, **Cardiovascular** and **DRUG INTERACTIONS**, **QT Prolonging Drugs**.

Antiviral Activity *In Vitro*: See also **DETAILED PHARMACOLOGY: VIROLOGY section.**

Pharmacokinetics

COMPLERA:

The bioavailability of one COMPLERA Tablet was comparable to one EMTRIVA Capsule (200 mg) plus one Edurant Tablet (25 mg) plus one VIREAD Tablet (300 mg) following single-dose administration to fed healthy subjects (N=34) (see **CLINICAL TRIALS**) but not comparable when administered under fasting conditions (N=15).

See also **DRUG INTERACTIONS, Drug-Food Interactions** section.

Emtricitabine:

Following oral administration, FTC is rapidly absorbed with peak plasma concentrations occurring at 1–2 hours post-dose. Emtricitabine systemic exposure (AUC) was unaffected while C_{max} decreased by 29% and T_{max} was delayed by 1.5 hours when EMTRIVA was administered with food (an approximately 1000 kcal high-fat meal). *In vitro* binding of FTC

to human plasma proteins is <4% and is independent of concentration over the range of 0.02–200 μg/mL. Following administration of radiolabelled FTC, approximately 86% is recovered in the urine and 13% is recovered as metabolites. The metabolites of FTC include 3′-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose, the plasma FTC half-life is approximately 10 hours.

Rilpivirine:

The pharmacokinetic properties of RPV have been evaluated in adult healthy subjects and in adult antiretroviral treatment-naïve HIV-1 infected subjects at 96 weeks. Exposure to RPV was generally lower in HIV-1 infected subjects than in healthy subjects. After oral administration, the C_{max} of RPV is achieved within 4–5 hours. The mean C_{0h} and AUC_{24h} values in HIV-1 infected subjects were 0.079±0.035 μg/mL and 2.24±0.85 μg•hr/mL, respectively. In a number of healthy subjects, multiple absorption peaks and/or an increase in absorption between 12 and 24 hours post-dose is observed. The underlying mechanism for these observations is unknown. The absolute bioavailability of Edurant is unknown. The exposure to RPV as a single agent is approximately 40% lower when taken in a fasted condition as compared to a normal caloric meal (533 kcal) or high-fat, high-caloric meal (928 kcal). When RPV was taken with only a protein-rich nutritional drink, exposures were 50% lower than when taken with a meal.

Rilpivirine is approximately 99.7% bound to plasma proteins *in vitro*, primarily to albumin. *In vitro* experiments indicate that RPV primarily undergoes oxidative metabolism by the cytochrome P450 (CYP) 3A system. The terminal elimination half-life of RPV is approximately 45 hours. After single dose oral administration of ^{14}C-RPV, on average 85% and 6.1% of the radioactivity could be retrieved in feces and urine, respectively. In feces, unchanged RPV accounted for on average 25% of the administered dose. Only trace amounts of unchanged RPV (<1% of dose) were detected in urine.

Tenofovir disoproxil fumarate:

Following oral administration of VIREAD, maximum tenofovir serum concentrations are achieved in 1.0±0.4 hour and C_{max} and AUC values are 296±90 ng/mL and 2287±685 ng•hr/mL, respectively. Administration of TDF following a high-fat meal (~700 to 1000 kcal containing 40–50% fat) increases the oral bioavailability, with an increase in tenofovir $AUC_{0-\infty}$ of approximately 40% and an increase in C_{max} of approximately 14%. Food delays the time to tenofovir C_{max} by approximately 1 hour. C_{max} and AUC of tenofovir are 326±119 ng/mL and 3324±1370 ng•hr/mL following multiple doses of TDF 300 mg once daily in the fed state, when meal content was not controlled. *In vitro* binding of tenofovir to human plasma proteins is <0.7% and is independent of concentration over the range of 0.01–25 μg/mL. Approximately 70-80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of TDF, the terminal elimination half-life of tenofovir is approximately 17 hours.

Special Populations and Conditions

Pediatrics: Emtricitabine has been studied in pediatric patients from 3 months to 17 years of age. Tenofovir disoproxil fumarate has been studied in adolescent patients (12 to <18 years of age). COMPLERA is not recommended for pediatric administration.

Geriatrics: Pharmacokinetics of FTC and tenofovir have not been fully evaluated in the elderly (≥65 years). Clinical studies of RPV did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from adult subjects <65 years of age. COMPLERA should be used with caution in this population.

Race:

Emtricitabine: No pharmacokinetic differences due to race have been identified following the administration of FTC.

Rilpivirine: Population pharmacokinetic analysis of RPV in HIV-1 infected subjects indicated that race had no clinically relevant effect on the exposure to RPV.

Tenofovir disoproxil fumarate*:* There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations following administration of VIREAD.

Gender: No clinically relevant pharmacokinetic differences have been observed between men and women for FTC, RPV, and TDF.

Renal Insufficiency:

Emtricitabine and Tenofovir disoproxil fumarate: The pharmacokinetics of FTC and tenofovir are altered in patients with renal insufficiency (see **WARNINGS AND PRECAUTIONS, Renal, Nephrotoxicity**). In patients with creatinine clearance <50 mL/min, C_{max} and $AUC_{0-\infty}$ of FTC and tenofovir were increased. Because COMPLERA is a fixed dose combination, it should not be prescribed for patients requiring dosage adjustment such as those with moderate to severe renal impairment (creatinine clearance <50 mL/min).

Rilpivirine*:* The pharmacokinetics of RPV have not been studied in subjects with renal insufficiency. Renal elimination of RPV is negligible. Therefore, the impact of renal impairment on RPV elimination is expected to be minimal.

Hepatic Insufficiency:

Emtricitabine: The pharmacokinetics of FTC have not been studied in patients with hepatic impairment; however, FTC has not been shown to be significantly metabolized by liver enzymes, so the impact of liver impairment should be limited (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**).

Rilpivirine: Rilpivirine is primarily metabolized and eliminated by the liver. In a study comparing 8 subjects with mild hepatic impairment (Child-Pugh score A) to 8 matched controls and 8 subjects with moderate hepatic impairment (Child-Pugh score B) to 8 matched controls, the multiple dose exposure of RPV was 47% higher in subjects with mild hepatic impairment and 5% higher in subjects with moderate hepatic impairment. No dose adjustment is required in patients with mild or moderate hepatic impairment. Rilpivirine has not been studied in subjects with severe hepatic impairment (Child-Pugh score C).

Tenofovir disoproxil fumarate: The pharmacokinetics of tenofovir following a 300 mg single dose of VIREAD have been studied in non-HIV infected subjects with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects.

Hepatitis B and/or Hepatitis C Virus Co-infection: Pharmacokinetics of FTC and TDF have not been fully evaluated in hepatitis B and/or C virus-coinfected patients. Population pharmacokinetic analysis indicated that hepatitis B and/or C virus coinfection had no clinically relevant effect on the exposure to RPV.

Pregnancy and Postpartum

The exposure to total rilpivirine after intake of rilpivirine 25 mg once daily as part of an antiretroviral regimen was lower during pregnancy (similar for the 2nd and 3rd trimesters) compared with postpartum (see Table 9). The decrease in unbound (i.e., active) rilpivirine pharmacokinetic parameters during pregnancy compared to postpartum was less pronounced than for total rilpivirine.

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

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

Pharmacokinetics of Total Rilpivirine[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. Mean across subjects.

STORAGE AND STABILITY

Store at 15-30 °C (59-86 °F).

- Keep container tightly closed.
- Dispense only in original container.
- Do not use if seal over bottle opening is broken or missing.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

COMPLERA is available as tablets. Each tablet contains 200 mg of FTC, 25 mg of RPV (as 27.5 mg of RPV hydrochloride) and 300 mg of TDF (equivalent to 245 mg of tenofovir disoproxil) as active ingredients.

The tablets also include the following inactive ingredients: pregelatinized starch, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, povidone, and polysorbate 20. The tablets are film-coated with polyethylene glycol, hypromellose, lactose monohydrate, triacetin, titanium dioxide, red iron oxide, FD&C Blue #2 aluminum lake, FD&C Yellow #6 aluminum lake.

The tablets are purplish-pink, capsule-shaped and film-coated, debossed with “GSI” on one side and plain-faced on the other side. Each high density polyethylene (HDPE) bottle

contains 30 tablets, silica gel desiccant, polyester fiber coil and is closed with a child-resistant closure fitted with an induction sealed, aluminum-faced liner.

PART II. SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

COMPLERA is a fixed-dose combination tablet containing FTC, RPV and TDF. EMTRIVA is the brand name for FTC, a synthetic nucleoside analog of cytidine. Edurant is the brand name for RPV, a non-nucleoside reverse transcriptase inhibitor. VIREAD is the brand name for TDF, which is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate. VIREAD and EMTRIVA are the components of TRUVADA.

COMPLERA tablets are for oral administration. Each tablet contains 200 mg of FTC, 25 mg of RPV (as 27.5 mg of RPV hydrochloride), and 300 mg of TDF (equivalent to 245 mg of tenofovir disoproxil), as active ingredients. The tablets also include the following inactive ingredients: pregelatinized starch, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, povidone, and polysorbate 20. The tablets are film-coated with a coating material containing polyethylene glycol, hypromellose, lactose monohydrate, triacetin, titanium dioxide, iron oxide red, FD&C Blue #2 aluminum lake, FD&C Yellow #6 aluminum lake.

Emtricitabine:

Drug Substance

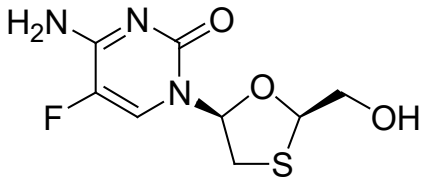
Common Name: emtricitabine (INN)

Chemical Name: 5-fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (IUPAC)

Empirical Formula: $C_8H_{10}FN_3O_3S$

Molecular Weight: 247.24

Structural Formula:



Physicochemical Properties:

Description: Emtricitabine is a white to off-white crystalline powder.

Solubility: The solubility is approximately 112 mg/mL in water at 25 °C.

Dissociation Constant: The dissociation constant (pKa) is 2.65.

Partition Coefficient: The partition coefficient (log P) is -0.43.

Rilpivirine:

Drug Substance

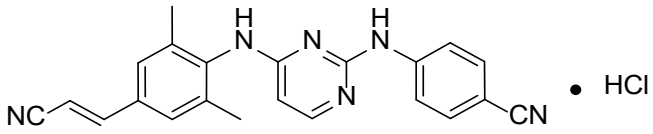
Common Name: rilpivirine hydrochloride (INN)

Chemical Name: 4-[[4-[[4-[(E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile monohydrochloride (IUPAC)

Empirical Formula: $C_{22}H_{18}N_6 \bullet HCl$

Molecular Weight: 402.88

Structural Formula:



Physicochemical Properties:

Description: Rilpivirine hydrochloride is a white to almost white powder.

Solubility: Rilpivirine hydrochloride is practically insoluble in water over a wide pH range. The solubility is approximately 0.01 mg/mL in water at 25 °C.

Dissociation Constant: The pKa is 5.6 (pyrimidine moiety).

Partition Coeffficient: The log P is 4.86.

Tenofovir disoproxil fumarate:

Drug Substance

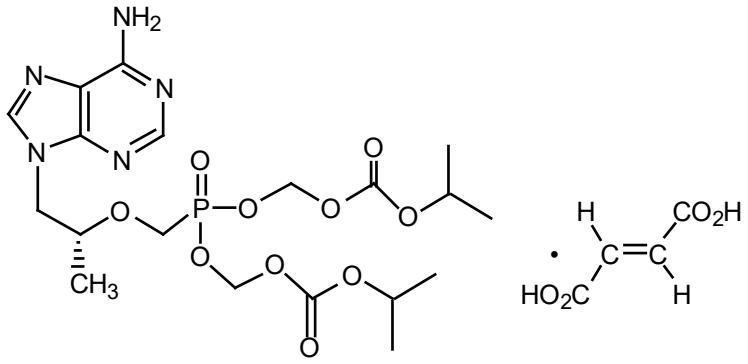
Common Name: Tenofovir disoproxil fumarate (INN)

Chemical Name: 9-[(*R*)-2-[[bis[[(isopropoxycarbonyl)oxy]methoxy] phosphinyl]-methoxy]propyl]adenine fumarate (1:1) (IUPAC)

Empirical Formula: $C_{19}H_{30}N_5O_{10}P \bullet C_4H_4O_4$

Molecular Weight: 635.52

Structural Formula:



Physicochemical Properties:

Description: Tenofovir disoproxil fumarate is a white to off-white crystalline powder.

Solubility: The solubility is 13.4 mg/mL in water at 25 °C.

Dissociation Constant: The pKa is 3.75.

Partition Coefficient: The log P is 1.25.

CLINICAL TRIALS

Study Demographics and Trial Design

Description of Clinical Studies

For safety and efficacy studies using EMTRIVA, Edurant or VIREAD in combination with other antiretroviral agents, also consult the Product Monographs for these products.

HIV-1 Infected Patients with No Antiretroviral History

The efficacy of COMPLERA in HIV-1 infected patients with no antiretroviral history is based on the analyses of 96 week data from two Phase III, randomized, double-blind, double-dummy, active controlled international studies in antiretroviral treatment naïve, HIV-1 infected patients. Similar efficacy for Edurant was seen in each trial demonstrating non-inferiority to comparator.

Patients with plasma HIV-1 RNA ≥5000 copies/mL, who were screened for susceptibility to N(t)RTIs and for absence of specific NNRTI RAMs, were included in the trials.

Demographic characteristics for patients who received FTC/TDF in Studies C209 and C215 are provided in Table 10.

Table 10. Study Treatment and Demographic Characteristics of Antiretroviral Treatment-Naïve HIV-1-Infected Adult Patients in Studies C209 (ECHO) and C215 (THRIVE)

Study	Dosage, Route of Administration	Demographics	
		Treatment Arm	Control Arm
TMC278 C209 (ECHO)	**RPV 25 mg, oral, once daily plus BR[a] (Treatment arm)** **or** **EFV 600 mg, oral, once daily plus BR[1] (Comparator arm)**	**N=346** **Gender: n (%)** Male 268 (77.5) Female 78 (22.5) **Age: median (range)** 36.0 (18–78) **Race:** White – 214 (61.8) Black – 89 (25.7) Asian – 33 (9.5) Other – 3 (0.9) Missing – 7 (2.0)	**N=344** **Gender: n (%)** Male 275 (79.9) Female 69 (20.1) **Age: median (range)** 36.0 (19–67) **Race:** White – 206 (59.9) Black – 80 (23.3) Asian – 48 (14.0) Other – 4 (1.2) Missing - 6 (1.7)
TMC278 C215 (THRIVE)	**RPV 25 mg, oral, once daily plus BR of FTC/TDF[b] (Treatment arm)** **or** **EFV 600 mg, oral, once daily plus BR of FTC/TDF[2] (Comparator arm)**	**N=204** **Gender: n (%)** Male 161 (78.9) Female 43 (21.1) **Age: median (range)** 36.0 (20-62)	**N=202** **Gender: n (%)** Male 156 (77.2) Female 46 (22.8) **Age: median (range)** 38.0 (19-69)

Study	Dosage, Route of Administration	Demographics	
		Treatment Arm	**Control Arm**
		Race: White – 134 (66.3) Black – 45 (22.3) Asian – 21 (10.4) Other – 2 (1.0) Missing - 2	**Race:** White – 128 (63.4) Black – 48 (23.8) Asian – 22 (10.9) Other – 3 (1.5) Missing – 1 (0.5)

a. In Study C209, the BR was FTC/TDF.

b. In Study C215, the BR consisted of 2 NRTIs: FTC/TDF or lamivudine/zidovudine or abacavir plus lamivudine. Only the results for FTC/ TDF are presented here.

Virologically-Suppressed HIV-1 Infected Patients

Study GS-US-264-0106

The efficacy and safety of switching from a ritonavir-boosted protease inhibitor (PI) in combination with two NRTIs to COMPLERA was evaluated in a randomized, open-label study of 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 (Stay on Baseline Regimen, SBR, N=159) before switching to COMPLERA for an additional 24 weeks (SBR Rollover to COMPLERA, N=152).

Demographic characteristics for subjects in study GS-US-264-0106 are provided in Table 11.

Table 11. Study Treatment and Demographic Characteristics of Antiretroviral HIV-1-Infected Virologically-Suppressed Adult Patients in GS-US-264-0106

Study	Dosage, Route of Administration	Demographics		
		Total	**Treatment Arm**	**Stayed on Baseline Regimen**
GS-US-264-0106	**COMPLERA, oral (Treatment arm)** **or** **PI/r + NRTIs, oral (Stay on Baseline Regimen)**	**N=476** **Gender: n (%)** Male 417 (87.6) Female 59 (12.4) **Age: median (range)** 42 (19-73) **Race: n (%)** White – 365 (76.7) Black – 83 (17.4)	**N=317** **Gender: n (%)** Male 273 (86.1) Female 44 (13.9) **Age: median (range)** 42 (19-73) **Race: n (%)** White – 241 (76.0) Black – 61 (19.2)	**N=159** **Gender: n (%)** Male 144 (90.6) Female 15 (9.4) **Age: median (range)** 43 (20-71) **Race: n (%)** White – 124 (78.0) Black – 22 (13.8)

Study	Dosage, Route of Administration	Demographics		
		Total	Treatment Arm	Stayed on Baseline Regimen
		Other – 28 (5.9)	Other – 15 (4.7)	Other – 13 (8.2)

The mean baseline CD4+ cell count was 584 cells/mm^3 (range 42–1484). Randomization was stratified by use of TDF and/or lopinavir/ritonavir in the baseline regimen.

Study Result

HIV-1 Infected Patients with No Antiretroviral History

Study C209 and C215: FTC + TDF + RPV Compared with FTC + TDF + EFV

Efficacy at Week 48 and Week 96 for subjects in the RPV and EFV arms for the pooled data are shown in Table 12. The response rate (confirmed undetectable viral load HIV-1 RNA <50 copies/mL) at Week 96 was comparable between the RPV arm and the EFV arm. The incidence of virologic failure was higher in the RPV arm than the EFV arm at Week 96; however, most of the virologic failures occurred within the first 48 weeks of treatment.

Table 12. Virologic Outcome of Randomized Treatment of Studies C209 and C215 (Pooled Data for Patients Receiving RPV or EFV in Combination with FTC/TDF) at Week 48 and Week 96[a]

	Outcome at Week 48		Outcome at Week 96	
	RPV+FTC/TDF	EFV+FTC/TDF	RPV+FTC/TDF	EFV+FTC/TDF
	N=550	N=546	N=550	N=546
Confirmed Undetectable Viral Load (<50 HIV-1 RNA copies/mL)[a, b]	459 (83.5%)	450 (82.4%)	423 (76.9%)	422 (77.3%)
Virologic failure[c]	52 (9.5%)	23 (4.2%)	63 (11.5%)	28 (5.1%)
Death	0	1 (0.2%)	0	4 (0.7%)
Discontinued study due to adverse event (AE)	12 (2.2%)	39 (7.1%)	20 (3.6%)	44 (8.1%)
Discontinued study for other reasons	27 (4.9%)	33 (6.0%)	44 (8.0%)	48 (8.8%)

N = number of subjects per treatment group

a Subject with 2 consecutive viral load values <50 copies/mL (ITT TLOVR - Intention to Treat Time to Loss of Virologic Response)

b The difference of response rate is -3% to 6% (95% confidence interval) for Week 48 and -5% to 5% for Week 96, respectively, using normal approximation.

c Includes subjects who were rebounder (confirmed viral load ≥50 copies/mL after being responder) or who were never suppressed (no confirmed viral load <50 copies/mL).

Virologic response by baseline plasma viral load is presented in Table 13.

Table 13. Virological Outcomes of Studies C209 and C215 (Pooled Data for Patients Receiving RPV or EFV in Combination with FTC /TDF) at 48 Weeks and 96 Weeks by Baseline Viral Load and Baseline CD4+ Cell Count

	Outcome at Week 48*		Outcome at Week 96*	
	RPV+FTC/TDF	**EFV+FTC/TDF**	**RPV+FTC/TDF**	**EFV+FTC/TDF**
Virologic Response	459/550 (83.5%)	450/546 (82.4%)	423/550 (76.9%)	422/546 (77.3%)
By baseline viral load (copies/mL)				
≤100,000	258/288 (89.6%)	217/256 (84.8%)	241/288 (83.7%)	206/255 (80.8%)
>100,000	201/262 (76.7%)	233/290 (80.3%)	182/262 (69.5%)	216/291 (74.2%)
By baseline CD4+ cell count (cells/mm^3)				
<200	138/181 (76.2%)	132/164 (80.5%)	122/181 (67.4%)	119/164 (72.6%)
≥200	321/368 (87.2%)	318/382 (83.2%)	301/368 (81.8%)	303/382 (79.3%)
Virologic Failure[a]	52/550 (9.5%)	23/546 (4.2%)	63/550 (11.5%)	28/546 (5.1%)
By baseline viral load (copies/mL)				
≤100,000	12/288 (4.2%)	6/256 (2.3%)	17/288 (5.9%)	6/255 (2.4%)
>100,000	40/262 (15.3%)	17/290 (5.9%)	46/262 (17.6%)	22/291 (7.6%)
By baseline CD4+ cell count (cells/mm^3)				
<200	28/181 (15.5%)	12/164 (7.3%)	36/181 (19.9%)	14/164 (8.5%)
≥200	24/368 (6.5%)	11/382 (2.9%)	27/368 (7.3%)	14/382 (3.7%)

N = number of subjects per treatment group

* Imputations according to the TLOVR algorithm

a Includes subjects who were rebounder (confirmed viral load ≥50 copies/mL after being responder) or who were never suppressed (no confirmed viral load <50 copies/mL).

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

Based on the pooled data from the C209 and C215 trials at 96 weeks of treatment, the mean CD4+ cell count increase from baseline was 226 cells/mm^3 for RPV plus FTC/TDF-treated subjects and 222 cells/mm^3 for EFV plus FTC/TDF-treated subjects [estimated treatment difference (95% CI): +8 (-13 to 28)].

Virologically-Suppressed HIV-1 Infected Patients

Study GS-US-264-0106

Treatment outcomes (FDA Snapshot analysis) are presented in Table 14.

Table 14. Virologic Outcomes of Randomized Treatment in Study GS-US-264-0106

	COMPLERA Week 48[a]	Stayed on Baseline Regimen Week 24[b]
	N=317	N=159
Virologic Success[c] HIV-1 RNA <50 copies/mL	283 (89.3%)	143 (89.9%)
Virologic Failure[d]	8 (2.5%)	8 (5.0%)
No Virologic Data at Week 24 Window		
Discontinued Study Drug Due to AE or Death[e]	7 (2.2%)	0%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[f]	16 (5.0%)	5 (3.1%)
Missing Data During Window but on Study Drug	3 (0.9%)	3 (1.9%)

a. Week 48 window is between Day 295 and 378 (inclusive).

b. For subjects in the SBR arm who maintained their baseline regimen for 24 weeks and then switched to COMPLERA, the Week 24 window is between Day 127 and first dose day on COMPLERA.

c. Predicted difference (95% CI) of response rate for switching to COMPLERA at Week 48 compared to staying on baseline regimen at Week 24 (in absence of Week 48 results from the SBR group by study design) is -0.7% (-6.4% to 5.1%).

d. Includes patients who had HIV-1 RNA ≥50 copies/mL in the time window, patients who discontinued earlier due to lack or loss of efficacy, and patients who discontinued for reasons other than an adverse event or death, who at the time of discontinuation had HIV-1 RNA of ≥50 copies/mL.

e. 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.

f. 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).

Pivotal Comparative Bioavailability Study

A randomized, single dose, open-label, three-way crossover comparative bioavailability study under low fat, low calorie fed conditions (13 g fat; 400 cal) was conducted in 36 healthy male and female volunteers. The rate and extent of absorption of FTC, RPV and TDF, based on the metabolite tenofovir were measured and compared following a single oral dose of 1 x COMPLERA (FTC/RPV hydrochloride/TDF) 200 mg/25 mg/300 mg fixed dose combination tablets and concomitant administration of EMTRIVA (FTC) 200 mg capsules, Edurant (RPV hydrochloride) 25 mg tablets and VIREAD (TDF) 300 mg tablets. The bioavailability results from 34 subjects are provided in the following tables.

Table 15. Summary of FTC Pharmacokinetic Parameters (GS-US-264-0103) – Fed

FTC 200 mg From Measured Data Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test Treatment B[a]**	**Reference Treatment A[b]**	**% Ratio of Geometric Means[c]**	**90% Confidence Interval[c]**
AUC_T (ng•h/mL)	9360.88 9416.5 (14.3)	9366.29 9417.5 (13.9)	99.94	(97.77, 102.16)
AUC_I (ng•h/mL)	9581.10 9636.3 (14.1)	9594.63 9644.5 (13.6)	99.86	(97.67, 102.09)
C_{max} (ng/mL)	1714.21 1753.9 (23.6)	1625.23 1652.8 (21.9)	105.47	(100.46, 110.74)
T_{max}[d] (h)	2.50 (2.00–3.00)	2.00 (2.00–2.50)		
$T_{½}$[e] (h)	17.85 (24.5)	19.31 (33.4)		

a Treatment B = 200 mg FTC/25 mg RPV/300 mg TDF combination tablet administered to fed subjects.
b Treatment A = concurrent administration of EMTRIVA (FTC) 200 mg capsule, Edurant (RPV) 25 mg tablet and VIREAD (TDF) 300 mg tablet to fed subjects.
c Based on geometric least squares mean.
d Expressed as the median (range) only.
e Expressed as the arithmetic mean (CV%) only.

Table 16. Summary of RPV Pharmacokinetic Parameters (GS-US-264-0103) – Fed

RPV 25 mg From Measured Data Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test Treatment B[a]**	**Reference Treatment A[b]**	**% Ratio of Geometric Means[c]**	**90% Confidence Interval[c]**
AUC_{0-72} (ng•h/mL)	1899.73 1971.3 (27.0)	1657.57 1723.1 (26.4)	114.61	(108.32-121.27)
AUC_I (ng•h/mL)	3166.87 3389.3 (39.4)	2738.56 2923.3 (38.6)	115.64	(108.71-123.01)

C_{max} (ng/mL)	109.57 115.5 (29.6)	94.56 99.8 (30.5)	115.87	(108.21, 124.06)
T_{max}[d] (h)	4.50 (4.00–4.50)	4.50 (4.00-4.50)		
$T_{½}$[e] (h)	52.79 (32.6)	54.97 (37.4)		

a Treatment B = 200 mg FTC/25 mg RPV/300 mg TDF combination tablet administered to fed subjects
b Treatment A = concurrent administration of EMTRIVA (FTC) 200 mg capsule, Edurant (RPV) 25 mg tablet and VIREAD (TDF) 300 mg tablet to fed subjects.
c Based on geometric least squares mean.
d Expressed as the median (range) only.
e Expressed as the arithmetic mean (CV%) only.

Table 17. Summary of Tenofovir Pharmacokinetic Parameters (GS-US-264-0103) - Fed

Tenofovir 300mg From Measured Data Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test Treatment B[a]**	**Reference Treatment A[b]**	**% Ratio of Geometric Means[c]**	**90% Confidence Interval[c]**
AUC_T (ng•h/mL)	3053.10 3108.2 (21.1)	2989.16 3040.3 (21.3)	102.14	(99.00, 105.38)
AUC_I (ng•h/mL)	3264.17 3313.6 (19.7)	3200.52 3246.8 (19.7)	101.99	(99.06, 105.00)
C_{max} (ng/mL)	315.41 324.7 (26.0)	284.13 291.1 (26.4)	111.01	(104.19, 118.28)
T_{max}[d] (h)	2.00 (2.00-2.50)	1.50 (1.00–2.00)		
$T_{½}$[e] (h)	18.21 (15.2)	18.15 (16.8)		

a Treatment B = 200 mg FTC/25 mg RPV/300 mg TDF combination tablet administered to fed subjects
b Treatment A = concurrent administration of EMTRIVA (FTC) 200 mg capsule, Edurant (RPV) 25 mg tablet and VIREAD (TDF) 300 mg tablet to fed subjects.
c Based on geometric least squares mean.
d Expressed as the median (range) only.
e Expressed as the arithmetic mean (CV%) only.

DETAILED PHARMACOLOGY

See also **ACTION AND CLINICAL PHARMACOLOGY: Mechanism of Action**.

VIROLOGY (MICROBIOLOGY)

Antiviral Activity

Emtricitabine, Rilpivirine and Tenofovir disoproxil fumarate: The triple combination of FTC, RPV, and tenofovir demonstrated synergistic antiviral activity in cell culture.

Emtricitabine: The *in vitro* antiviral activity of FTC against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The EC_{50} values for FTC were in the range of 0.0013–0.64 μM (0.0003–0.158 μg/mL). In drug combination studies of FTC with nucleoside reverse transcriptase inhibitors (abacavir, lamivudine, stavudine, zalcitabine, and zidovudine), NNRTIs (delavirdine, EFV, nevirapine, and RPV), and protease inhibitors (amprenavir, nelfinavir, ritonavir, and saquinavir), additive to synergistic effects were observed. Most of these drug combinations have not been studied in humans. Emtricitabine displayed antiviral activity *in vitro* against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007–0.075 μM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.007–1.5 μM).

Rilpivirine: Rilpivirine exhibited activity against laboratory strains of wild-type HIV-1 in an acutely infected T-cell line with a median EC_{50} value for HIV-1/IIIB of 0.73 nM. Rilpivirine demonstrated antiviral activity against a broad panel of HIV-1 group M (subtype A, B, C, D, F, G, H) primary isolates with EC_{50} values ranging from 0.07 to 1.01 nM and group O primary isolates with EC_{50} values ranging from 2.88 to 8.45 nM. Rilpivirine showed additive to synergistic antiviral activity in combination with the N(t)RTIs abacavir, didanosine, FTC, lamivudine, stavudine, tenofovir, and zidovudine; the PIs amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and tipranavir; the NNRTIs EFV, etravirine and nevirapine; the fusion inhibitor enfuvirtide; the entry inhibitor maraviroc; and the integrase inhibitor raltegravir.

Tenofovir disoproxil fumarate: The *in vitro* antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC_{50} values for tenofovir were in the range of 0.04–8.5 μM. In drug combination studies of tenofovir with N(t)RTIs (abacavir, didanosine, lamivudine, stavudine, zalcitabine, and zidovudine), NNRTIs (delavirdine, EFV, nevirapine and RPV), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, and saquinavir), additive to synergistic effects were observed. Most of these drug combinations have not been studied in humans. Tenofovir displayed antiviral activity *in vitro* against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values ranged from 0.5–2.2 μM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 1.6 μM to 4.9 μM).

Resistance

In Cell Culture

Emtricitabine and Tenofovir disoproxil fumarate: HIV-1 isolates with reduced susceptibility to FTC or tenofovir have been selected in cell culture. Reduced susceptibility to FTC 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 subsititution in HIV-1 reverse transcripase has been selected by tenofovir and results in low-level reduced susceptibility to abacavir, FTC, 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.

HIV-1 Infected Patients with No Antiretroviral History

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

In the pooled analysis from two Phase III trials, the emergence of resistance was greater among patients receiving RPV in combination with FTC/TDF as compared to the control (EFV in combination with FTC/TDF) arm at Week 48 (11.5%, 4.2%, repectively) and at Week 96 (14.2%, 6.8%, respectively). Fewer virologic failures due to resistance occurred between Week 48 and Week 96 in each treatment arm (2.7% and 2.6% in the RPV and control arms, respectively). Through Week 96, fewer patients with baseline viral load ≤100,000 copies/mL had genotypic and/or phenotypic resistance to RPV (2.4%) as compared to patients with baseline viral load >100,000 copies/mL (11.4%).

In the Week 96 pooled resistance analysis for patients treated with RPV/FTC/TDF, resistance data were available for 71 of the 78 virologic failures. The most common emergent NNRTI substitutions in these patients included V90I, K101E, E138K/Q, V179I, Y181C, V189I, H221Y, and F227C/L. However, in the trials, the presence of the substitutions V90I and V189I at baseline did not affect the virologic response. The E138K substitution emerged most frequently during RPV treatment at Week 48 and Week 96, commonly in combination with the M184I mutation. The amino acid substitutions associated with NRTI resistance that developed in 3 or more patients treated with RPV were: K65R, K70E, M184V/I, and K219E. The most common mutations were the same in the Week 48 and Week 96 analyses.

Virologically-Suppressed HIV-1 Infected 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 had genotypic and phenotypic data available. Through Week 24, 2 patients who switched to COMPLERA at baseline (2/317, 0.6%) and 1 patient who maintained their protease inhibitor-based regimen (1/159 patients, 0.6%) developed genotypic and/or phenotypic resistance to study drugs. After Week 24, 2 additional patients who switched to COMPLERA at baseline 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.

Cross-resistance

Emtricitabine, Rilpivirine, and Tenofovir disoproxil fumarate:

In Cell Culture

Cross-resistance has been recognized among NNRTIs. Considering all available data, the following amino acid substitutions in RT, when present at baseline, are likely to affect the activity of RPV: K101E, K101P, E138A, E138G, E138K, E138R, E138Q, V179L, Y181C, Y181I, Y181V, Y188L, H221Y, F227C, M230I, and M230L. Cross-resistance has also been recognized among certain NRTIs. The M184V/I and/or K65R substitutions selected *in vitro* by the combination of FTC and tenofovir are also observed in some HIV-1 isolates from subjects failing treatment with tenofovir in combination with either lamivudine or FTC, and either abacavir or didanosine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors either or both of these amino acid substitutions.

HIV-1 Infected Patients with No Antiretroviral History

In the Week 96 pooled analysis for patients receiving RPV in combination with FTC/TDF in the two Phase III trials of 66 patients with virologic failure for whom phenotypic resistance data were available, 40 (60%) had reduced susceptibility to FTC, 31 (47%) to RPV, 39 (59%) to lamivudine, and 2 (3%) to tenofovir. Of the 29 patients with virologic failure on EFV (control) in combination with FTC/TDF for whom phenotypic resistance data was available, 12 (41.4%) had reduced susceptibility to EFV, 5 (17.2%) to FTC, 6 (20.7%) to lamivudine, and 1 (3.4%) to tenofovir. Of the 31 patients who had reduced susceptibility to RPV, 31 (100%) were resistant to etravirine, 28 (90%) to EFV, and 13 (42%) to nevirapine. Of the 12 patients who lost susceptibility to EFV, 1 (8%) was resistant to etravirine, none to RPV, and 12 (100%) to nevirapine.

In the Week 96 pooled analyses, fewer patients with baseline viral load ≤100,000 copies/mL had phenotypic cross-resistance to other NNRTIs (4/7) as compared to patients with baseline viral load >100,000 copies/mL (28/30).

Virologically-Suppressed HIV-1 Infected Patients

In Study GS-US-264-0106, 4 of the 469 patients who 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 lost susceptibility to FTC and 2 lost susceptibility to RPV. Patients with resistance to FTC also were resistant to lamivudine. These patients with resistance to RPV developed phenotypic cross-resistance to the other NNRTIs delavirdine, EFV, and nevirapine, but remained susceptible to etravirine in 1 of 2 cases.

***Emtricitabine*:** Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine and zalcitabine but retained susceptibility in cell culture to didanosine, stavudine, tenofovir, zidovudine, and NNRTIs (delavirdine, EFV, nevirapine, and RPV). Isolates from heavily treatment-experienced patients containing the M184V/I amino acid substitution in the context of other NRTI resistance-associated substitutions may retain susceptibility to tenofovir. HIV-1 isolates containing the K65R substitution, selected *in vivo* by abacavir, didanosine, tenofovir and zalcitabine, demonstrated reduced susceptibility to inhibition by FTC. Viruses harboring substitutions conferring reduced susceptibility to stavudine and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E), or didanosine (L74V) remained sensitive to

FTC. HIV-1 containing the substitutions associated with NNRTI resistance K103N or RPV-associated substitutions were susceptible to FTC.

***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, RPV showed antiviral activity against 64 (96%) of these strains. The single amino acid substitutions associated with a loss of susceptibility to RPV were: K101P, Y181I and Y181V. The K103N substitution did not result in reduced susceptibility to RPV by itself, but the combination of K103N with L100I resulted in a 7-fold reduced susceptibility to RPV. In another study, the Y188L substitution resulted in a reduced susceptibility to RPV of 9-fold for clinical isolates and 6-fold for site directed mutants.

***Tenofovir disoproxil fumarate*:** The K65R and K70E substitutions selected by tenofovir are also selected in some HIV-1 infected patients treated with abacavir, didanosine or zalcitabine. HIV-1 isolates with the K65R and K70E mutations also showed reduced susceptibility to FTC and lamivudine. Therefore, cross-resistance among these NRTIs may occur in patients whose virus harbors the K65R mutation. HIV-1 isolates from patients (N=20) whose HIV-1 expressed a mean of 3 zidovudine-associated RT amino acid substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N) showed a 3.1-fold decrease in the susceptibility to tenofovir. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the RT showed reduced susceptibility to tenofovir.

Subjects whose virus expressed an L74V substitution without zidovudine resistance associated substitutions (N=8) had reduced response to VIREAD. Limited data are available for patients whose virus expressed a Y115F substitution (N=3), Q151M substitution (N=2), or T69 insertion (N=4), all of whom had a reduced response.

HIV-1 containing the substitutions associated with NNRTI resistance K103N and Y181C, or RPV-associated substitutions were susceptible to tenofovir.

TOXICOLOGY

For additional information on toxicology including reproductive toxicology, mutagenicity and carcinogenicity, please consult the Product Monographs for EMTRIVA, Edurant, VIREAD and TRUVADA.

Carcinogenesis

Emtricitabine: In long-term oral carcinogenicity studies of FTC, no drug-related increase in tumor incidence was found in mice at doses up to 750 mg/kg/day (26 times the human systemic exposure at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (31 times the human systemic exposure at the therapeutic dose).

***Rilpivirine*:** Rilpivirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 20, 60 and 160 mg/kg/day were administered to mice and doses of 40, 200, 500 and 1500 mg/kg/day were administered to rats. An increase in the incidences of hepatocellular adenomas and carcinomas was

observed in both mice and rats. An increase in the incidences of follicular cell adenomas and/or carcinomas in the thyroid gland was observed in rats. Administration of RPV did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. The observed hepatocellular findings in mice and rats may be rodent-specific, associated with liver enzyme induction. The follicular cell findings may be rat-specific, associated with increased clearance of thyroxine and are not considered to be relevant for humans. At the lowest tested doses in the carcinogenicity studies, the systemic exposures (based on AUC) to RPV were 21 fold (mice) and 3 fold (rats), relative to those observed in humans at the recommended dose (25 mg once daily).

***Tenofovir disoproxil fumarate*:** Long-term oral carcinogenicity studies were conducted in mice and rats receiving TDF. In the mouse study, one male and two female mice in the 600 mg/kg/day group (15 times the human systemic exposure at the recommended human dose of 300 mg/day) had duodenal tumors. The mechanism underlying this effect is uncertain but may relate to high local drug concentrations in the gastrointestinal tract. No treatment-related tumors were seen in mice in the 100 or 300 mg/kg/day groups. In the rat study at doses of 30, 100, and 300 mg/kg/day (approximately 5 times human exposure), no treatment-related increase in tumor incidence was observed.

Mutagenesis

Emtricitabine: Emtricitabine was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or mouse micronucleus assays.

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

Tenofovir disoproxil fumarate: Tenofovir disoproxil fumarate was negative in the *in vitro* bacterial mutation (Ames) assay (*Salmonella-Eschericia coli*/Mammalian-Microsome Reverse Mutation Assay) but positive in the *in vitro* mouse lymphoma assay (L5178Y TK +/- Forward Mutation Assay), with and without metabolic activation. Tenofovir disoproxil fumarate was negative in the *in vivo* mouse micronucleus assay at plasma exposure levels of more than 10× the human exposure.

Impairment of Fertility

Emtricitabine: Emtricitabine did not affect fertility in male rats at approximately 140-fold or in male and female mice at approximately 60-fold higher exposures (AUC) than in humans given the recommended 200 mg daily dose. Fertility was normal in the offspring of mice exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 60-fold higher than human exposures at the recommended 200 mg daily dose.

Rilpivirine: In a study conducted in rats, there were no effects on mating or fertility with RPV up to 400 mg/kg/day, a dose of RPV that showed maternal toxicity. This dose is associated with an exposure that is approximately 40 times higher than the exposure in humans at the recommended dose of 25 mg once daily. In a pre and postnatal development assessment in rats, RPV had no effect on development of offspring during lactation or post weaning when the mothers were dosed up to 400 mg/kg/day.

Tenofovir disoproxil fumarate: Tenofovir disoproxil fumarate had no adverse effects on fertility or general reproductive performance in rats at doses up to 600 mg/kg/day. In a study of effects on peri- and postnatal development in rats, effects considered due to maternal toxicity (450-600 mg/kg/day) were reduced survival and a slight delay in sexual maturation in the F1 generation. There were no adverse effects on growth, development, behavior, or reproductive parameters at non-maternally toxic doses (150 mg/kg/day) at exposures that were approximately 4-fold higher than human exposures.

Pregnancy

Emtricitabine: The incidence of fetal variations and malformations was not increased in embryofetal toxicity studies performed with FTC 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: There was no teratogenicity with RPV in rats and rabbits. The exposures at the embryo-fetal No Observed Adverse Effects 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 once daily. In a pre- and postnatal development assessment in rats, RPV had no effect on development of offspring during lactation or post weaning when the mothers were dosed up to 400 mg/kg/day.

Tenofovir disoproxil fumarate: Tenofovir disoproxil fumarate had no adverse effects on embryo-fetal development in rats at doses up to 450 mg/kg/day and in rabbits at doses up to 300 mg/kg/day (14 and 19 times the human dose based on body surface area comparisons). Reduced pup body weights, survival and delay in sexual maturation was observed in a peri- and postnatal toxicity study in rats at the maternally toxic doses of 450 and 600 mg/kg (approximately 14 and 19 times the human dose based on body surface area comparisons).

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IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

PrCOMPLERA®
(emtricitabine/rilpivirine/tenofovir disoproxil fumarate) tablets

This leaflet is Part III of a three-part "Product Monograph" published when COMPLERA was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about COMPLERA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
COMPLERA contains 3 medicines, EMTRIVA® (emtricitabine), Edurant® (rilpivirine) and VIREAD® (tenofovir disoproxil fumarate [tenofovir DF]), combined in one pill. EMTRIVA and VIREAD are HIV (human immunodeficiency virus) nucleotide/nucleoside analog reverse transcriptase inhibitors (NRTI) and Edurant is an HIV non-nucleoside analog reverse transcriptase inhibitor (NNRTI). VIREAD and EMTRIVA are components of TRUVADA®. COMPLERA is used as a complete regimen to treat people with HIV infection. COMPLERA is for adults age 18 and older. COMPLERA has not been studied in children under age 18 or in a sufficient number of adults over age 65 to determine whether they respond differently from adults under 65 years.

What it does:
COMPLERA helps block HIV reverse transcriptase, a chemical in your body (enzyme) that is needed for HIV to multiply. COMPLERA lowers the amount of HIV in the blood (viral load). Lowering the amount of HIV in the blood lowers the chance of infections that happen when your immune system is weak (opportunistic infections). COMPLERA may also help to increase the number of T cells (CD4+ cells).

HIV infection destroys CD4+ (T) cells, which are important to the immune system. The immune system helps fight infection. After a large number of T cells are destroyed, acquired immune deficiency syndrome (AIDS) develops.

COMPLERA does not cure HIV infection or AIDS. The long-term effects of COMPLERA are not known at this time. People taking COMPLERA may still get opportunistic infections or other conditions that happen with HIV infection. Opportunistic infections are infections that develop because the immune system is weak. Some of these conditions are pneumonia, herpes virus infections, and *Mycobacterium avium* complex (MAC) infections. **It is very important that you see your doctor regularly while taking COMPLERA.**

COMPLERA does not reduce the risk of passing HIV to others through sexual contact or blood contamination. Continue to practice safe sex by using a latex or polyurethane condom or other barrier to lower the chance of sexual contact with semen, vaginal secretions or blood and do not use or share needles.

When it should not be used:
Together with your doctor, you need to decide whether COMPLERA is right for you.

Do not take COMPLERA if:
- you are already taking any of the following drugs:

Type of Drug	Examples of Generic Names
Anticonvulsants (to treat epilepsy and prevent seizures)	carbamazepine, oxcarbazepine, phenytoin, phenobarbital
Antimycobacterials	rifapentine, rifampin
Glucocorticoids	systemic dexamethasone (more than a single dose)
Herbal products	St. John's wort (*Hypericum perforatum*)
Proton Pump Inhibitors (to prevent or treat stomach ulcers, heartburn or acid reflux disease)	omeprazole, lansoprazole, dexlansoprazole, rabeprazole, pantoprazole, esomeprazole

- you are on other medications that may affect your kidneys and have not discussed this with your doctor.
- you have or are at known risk for any type of bone disease or bone related problems and have not discussed this with your doctor.
- you are allergic to COMPLERA or any of its ingredients. The medicinal ingredients are emtricitabine, rilpivirine and tenofovir DF (See**: What the important nonmedicinal ingredients are**).
- you are already taking ATRIPLA®, BIKTARVY®, DESCOVY®, EMTRIVA, GENVOYA®, ODEFSEY®, Symtuza™, STRIBILD®, TRUVADA, VEMLIDY®, VIREAD, Combivir®, 3TC®, Heptovir®, Kivexa®, or

Trizivir®, because these medicines contain the same or similar active ingredients.
- you are also taking HEPSERA® to treat your HBV infection.
- you are already taking Edurant unless recommended by your doctor and you are taking rifabutin with COMPLERA.

What the medicinal ingredients are:
emtricitabine
rilpivirine hydrochloride
tenofovir DF

What the important nonmedicinal ingredients are:
pregelatinized starch, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, povidone, polysorbate 20. The film coating contains polyethylene glycol, hypromellose, lactose monohydrate, triacetin, titanium dioxide, iron oxide red, FD&C Blue #2 aluminum lake, FD&C Yellow #6 aluminum lake.

What dosage forms it comes in:
COMPLERA is available as tablets. Each tablet contains 200 mg of emtricitabine, 25 mg of rilpivirine (which is equivalent to 27.5 mg of rilpivirine hydrochloride) and 300 mg of tenofovir DF (which is equivalent to 245 mg of tenofovir disoproxil), as active ingredients. The tablets are pink, modified capsule-shaped, film-coated, debossed with "GSI" on one side and plain-faced on the other side. Each bottle contains 30 tablets, silica gel desiccant and polyester coil and is closed with a child-resistant closure.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- The most serious possible side effect is harm to the kidneys, including damage to kidney cells, kidney tissue inflammation and kidney failure. Your doctor may monitor your kidney function before beginning and while receiving COMPLERA. Some patients treated with tenofovir DF (a component of COMPLERA) have had kidney problems. Your doctor may need to perform additional blood tests if you have had kidney problems in the past or need to take another drug that can cause kidney problems.
- **If you are also infected with the Hepatitis B Virus, "flare-ups" of Hepatitis B Virus infection**, in which the disease suddenly returns in a worse way than before, can occur if you stop taking COMPLERA. Do not stop taking COMPLERA without your doctor's advice. If you stop taking COMPLERA, tell your doctor immediately about any new, unusual or worsening symptoms that you notice after stopping treatment. After you stop taking COMPLERA, your doctor will still need to check your health and take blood tests to check your liver. COMPLERA is not approved for the treatment of hepatitis B virus infection.
- The class of medicines to which emtricitabine and tenofovir DF, two of the components of COMPLERA, belong (NRTIs) can cause a condition called lactic acidosis (build up of acid in the blood). The symptoms that may be signs of lactic acidosis include: feeling very weak, tired or uncomfortable; unusual or unexpected stomach discomfort; feeling cold; feeling dizzy or lightheaded; suddenly developing a slow or irregular heartbeat. This rare but serious side effect has occasionally been fatal.
- Severe liver problems can happen in people who take COMPLERA or similar medicines. You may develop an enlarged liver (hepatomegaly) or a fatty liver (steatosis). Non-specific symptoms such as yellowing of skin and eyes, nausea, vomiting and stomach pain might indicate the development of liver problems. Lactic acidosis or severe liver problems occurs more often in women, particularly if they are very overweight. You should consult your doctor immediately if such symptoms occur while you are receiving COMPLERA. If you notice these symptoms, stop taking COMPLERA and consult a doctor immediately.

- Tenofovir DF caused harm to the bones of animals. Tenofovir DF reduced bone density in humans. If you notice bone pain, suffer a bone fracture, or other bone problem, consult your doctor. If you have bone problems, you may wish to discuss calcium and/or vitamin D supplements with your doctors.
- Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amounts of fat in the upper back and neck ("buffalo hump"), breast, and around the trunk. Loss of fat from the legs, arms and face may also happen. The cause and long term health effects of these conditions are not known at this time.

BEFORE you use COMPLERA (emtricitabine/rilpivirine/tenofovir DF) talk to your doctor or pharmacist:

If you have an eating disorder or are following a strict diet.

If you have any drug allergies.

If you are pregnant or planning to become pregnant*:* The effects of COMPLERA on pregnant women or their unborn babies are not known. Pregnant women should not take COMPLERA unless specifically directed by the doctor. If you use COMPLERA while you are pregnant, talk to your doctor about how you can be on the COMPLERA Antiviral Pregnancy Registry.

If you are breastfeeding or plan to breastfeed: Do not breastfeed if you are taking COMPLERA or have HIV. Tenofovir and emtricitabine pass into your baby in your breast milk. You should not breastfeed because of the risk of passing HIV to your baby. Talk to your doctor about the best way to feed your baby.

If you have a heart disease or a heart condition, including a heart rhythm disorder (QT prolongation) or family history of heart rhythm disorders (QT prolongation) or sudden (heart) death under 50 years of age.

If you have other medical conditions: Let your doctor know if you have other medical conditions, especially liver problems, including hepatitis B or C virus infection, pancreatitis (inflammation of the pancreas), have or are at risk for bone disease or bone related problems, have kidney problems or are undergoing kidney dialysis treatment, or have or develop feelings of depression.

If you are taking other medicines: Some medicines can interact when taken together, including prescription and non-prescription medicines, herbal products and dietary supplements **(see INTERACTIONS WITH THIS MEDICATION).**

INTERACTIONS WITH THIS MEDICATION

Drugs that should not be taken with COMPLERA:

- Do not take COMPLERA if you are on other medications that may affect your kidneys and have not discussed this with your doctor.
- ATRIPLA, BIKTARVY, DESCOVY, EMTRIVA, GENVOYA, ODEFSEY, Symtuza, STRIBILD, TRUVADA, VEMLIDY, VIREAD, Combivir (lamivudine/zidovudine), 3TC or Heptovir (lamivudine), Kivexa (abacavir sulfate/lamivudine), HEPSERA, Trizivir (abacavir sulfate/lamivudine/ zidovudine) and Triumeq (dolutegravir/abacavir sulfate/lamivudine) **should not be used with those medicines.**
- Edurant, unless recommended by your doctor and you are taking rifabutin with COMPLERA.

Tell your doctor if you are taking any of the following medicines. Some of these medicines may be obtained without a prescription and some of these may be available under other names. It is important that you carefully read the package leaflets that are provided with these medicines.

Type of Drug	Examples of Generic Names (Brand Names)
Antacids (to treat heartburn from acid reflux)	aluminum magnesium hydroxide calcium carbonate
Antimycobacterials (to treat some bacterial infections)	rifabutin
Azole antifungal agents	ketoconazole, fluconazole, voriconazole, itraconazole, posaconazole
Corticosteroids (to treat inflammation or asthma)	fluticasone propionate (Advair Diskus®, Cutivate®, Flonase®, Flovent Diskus®)
H_2-Receptor Antagonists (to treat stomach ulcers or used to relieve heartburn from acid reflux)	cimetidine (Tagamet®) famotidine (Pepcid®) nizatidine (Axid AR®) ranitidine (Zantac®)
Hepatitis C Antiviral Agents (to treat hepatitis C)	ledipasvir/sofosbuvir (HARVONI®) sofosbuvir/velpatasvir (EPCLUSA®) sofosbuvir/velpatasvir/ voxilaprevir (VOSEVI®)
Macrolide Antibiotics (to treat bacterial infections)	clarithromycin (Biaxin®) erythromycin (Benzamycin®, AK Mycin®, EES®-200/400, EES-600, ERYC®, Erythro-S®, Erythro-ES®, Erybid®, PCE®)
Narcotic Analgesic	methadone (Methadol®, Metadol-D®, Cophylac® drops)

These are not all the medicines that may cause problems if you take COMPLERA. Be sure to tell your doctor about all the medicines you take.

Keep a complete list of all the prescription and nonprescription medicines as well as any herbal medicines that you are taking, how much you take and how often you take them. Make a new list when medicines or herbal medicines are added or stopped, or if the dose changes. Give copies of this list to all your doctors and pharmacists **every** time you visit them or fill a prescription. This will give your doctor a complete picture of the medicines you use. Then he or she can decide the best approach for the situation.

PROPER USE OF THIS MEDICATION

Stay under a doctor's care when taking COMPLERA. Do not change your treatment or stop treatment without first talking with your doctor.

Take COMPLERA every day exactly as your doctor prescribed it. Follow the directions from your doctor, exactly as written on the label. Set up a dosing schedule and follow it carefully.

Always take COMPLERA with food. COMPLERA must be taken with food which will help make sure the medicine is absorbed into your body. A protein drink is not a substitute for food. An example of suitable foods to take with COMPLERA would be 2 pieces of toast with a butter substitute, with 250 mL (8 ounces) of 2% milk and 4 ounces of apple juice. There are other food options that can be taken to achieve the food requirement. Talk to your doctor.

When your COMPLERA supply starts to run low, get more from your doctor or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to COMPLERA and become harder to treat.

Only take medicine that has been prescribed specifically for you. Do not give COMPLERA to others or take medicine prescribed for someone else.

If you take an antacid (a medicine to treat heartburn from acid reflux such as aluminum/magnesium hydroxide, calcium carbonate), take the antacid either at least 2 hours before or at least 4 hours after COMPLERA. If you take an H_2-receptor antagonist (medicines used to treat stomach ulcers, heartburn or acid reflux disease such as cimetidine, famotidine, nizatidine or ranitidine), take the H_2-receptor antagonist at least 12 hours before or at least 4 hours after COMPLERA. Importantly, proton pump inhibitors (such as omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole) also available for these conditions should not be taken with COMPLERA.

For patients receiving rifabutin, an additional 25 mg tablet of Edurant per day is recommended to be taken concomitantly with COMPLERA for the duration of the rifabutin coadministration.

Do not use if seal over bottle opening is broken or missing.

Usual Adult Dose:

- The usual dose of COMPLERA is one tablet orally (by mouth) once a day. Swallow with plenty of water.

- **Always take COMPLERA with food;** food is important to make sure the medicine is absorbed into your body. A protein drink is not a substitute for food. See further instructions above.

Overdosage:

In case of drug overdose, contact your healthcare practitioner (e.g. doctor), hospital emergency department or regional poison control centre, even if there are no symptoms.

As with all medicines, COMPLERA should be kept out of reach of children.

Missed Dose:
It is important that you do not miss any doses. If you miss a dose of COMPLERA within 12 hours of the time it is usually taken, you should take COMPLERA with food as soon as possible. Take the next dose of COMPLERA at the regularly scheduled time.

If you miss a dose of COMPLERA by more than 12 hours of the time you usually take it, wait and then take the next dose of COMPLERA at the regularly scheduled time. Do not double the next dose to make up for a missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects of COMPLERA are abdominal pain, depression, headache, rash and sleeping problems (including difficulty falling asleep).

Other side effects include vomiting, nausea, intestinal gas, dizziness, allergic reaction (including skin rash, redness, irritation, swelling of the face, lips, tongue or throat, difficulty in breathing), sleepiness, abnormal dreams, stomach pain or discomfort, indigestion, diarrhea, skin discoloration (small spot or freckles), pain, weakness, decreased appetite, increased weight and fatigue.

Severe skin and allergic reactions have been reported with COMPLERA. If you develop a rash and any of the following symptoms, stop taking COMPLERA and contact your doctor right away:
- swelling of the face, lips, tongue, mouth or throat, eyes (pink eye), hands or feet
- difficulty breathing
- blisters, mouth sores, fever
- liver problems (hepatitis) with symptoms such as stomach pain, nausea, vomiting, yellowing of the skin and eyes (jaundice)
- increased eosinophils (type of white blood cells) in the blood with symptoms such as reddened skin, fever, and enlarged lymph nodes

Changes in your immune system (Immune Reconstitution Inflammatory Syndrome) can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time, or you could develop an autoimmune disease in which your immune system reacts against your own body [e.g. Grave's disease (which affects the thyroid gland), Guillain-Barre syndrome (which affects the nervous system) or polymyositis (which affects the muscles)] and it may develop at any time, sometimes months later after the start of HIV therapy. Sometimes symptoms can be severe, so if you develop high temperature (fever), joint or muscle pain, redness, rash, swelling or fatigue, or any new symptoms, contact your doctor right away.

Other common side effects reported for EMTRIVA and VIREAD are:
- Inflammation of the pancreas
- Shortness of breath
- Allergic reaction (see above)

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

	Symptoms / Effect	Talk with your doctor or pharmacist: Only if severe	Talk with your doctor or pharmacist: In all cases	Stop taking drug and call your doctor or pharmacist
Rare	**Effect: Lactic acidosis Symptoms**			
	• Feeling very weak or tired		✓	
	• Unusual muscle pain		✓	
	• Stomach pain with nausea and vomiting		✓	
	• Feeling cold especially in arms and legs		✓	
	• Feeling dizzy or lightheaded		✓	
	• Fast or irregular heartbeat		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
		Talk with your doctor or pharmacist		
	Symptoms / Effect	Only if severe	In all cases	Stop taking drug and call your doctor or pharmacist
Very Rare	**Effect: Hepatotoxicity (severe liver problems) with hepatomegaly (liver enlargement) and steatosis (fat in the liver)** **Symptoms** • Jaundice (skin or the white part of eyes turn yellow) • Urine turns dark • Bowel movements (stools) turn light in color • Loss of appetite for several days or longer • Feeling sick to your stomach (nausea) • Lower stomach pain		✓ ✓ ✓ ✓ ✓ ✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
		Talk with your doctor or pharmacist		
	Symptoms / Effect	Only if severe	In all cases	Stop taking drug and call your doctor or pharmacist
Very Rare	**Effect: Flare-ups of hepatitis B virus infection following drug discontinuation** **Symptoms** • Jaundice (skin or the white part of eyes turn yellow) • Urine turns dark • Bowel movements (stools) turn light in color • Loss of appetite for several days or longer • Feeling sick to your stomach (nausea) • Lower stomach pain		✓ ✓ ✓ ✓ ✓ ✓	
Rare	**Effect: Kidney problems** **Symptoms** • You may have increased or decreased urination as well as increased thirst • You may have swelling of your legs and feet • You may feel listless and tired		✓ ✓ ✓	

Lactic acidosis is a medical emergency and must be treated in the hospital. You may be more likely to get lactic acidosis or serious liver problems if you are very overweight (obese) or have been taking nucleoside analog medicines, like COMPLERA, for a long time.

Muscle pain, muscle weakness, bone pain and softening of the bone (infrequently contributing to fractures) have also been reported due to tenofovir DF (a component of COMPLERA).

There have been other side effects in patients taking EMTRIVA, Edurant or VIREAD. This is **not** a complete list of side effects. If you have questions about side effects, ask your doctor, nurse, or pharmacist. You should report any new or continuing symptoms to your doctor right away. Your doctor may be able to help you manage these side effects.

HOW TO STORE IT

- Keep COMPLERA and all other medications out of reach and sight of children.
- COMPLERA should be stored at 15–30 °C (59–86 °F). It should remain stable until the expiration date printed on the label.
- Do not keep your medicine in places that are too hot or cold.
- Do not keep medicine that is out of date or that you no longer need. If you throw any medicines away make sure that children will not find them.
- Keep COMPLERA in its original container and keep the container tightly closed.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **— Fax toll-free to 1-866-678-6789, or**
  - **— Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 1908C
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the Medeffect™ Canada Web site at www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada

NOTE: Should you require information related to the management of side effects, please contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals, can be found at: www.gilead.ca, or by contacting the sponsor, Gilead Sciences Canada, Inc., at: 1-866-207-4267

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