HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use COMPLERA safely and effectively. See full prescribing information for COMPLERA.

COMPLERA® (emtricitabine, rilpivirine, tenofovir disoproxil fumarate) tablets, for oral use
Initial U.S. Approval: 2011

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B
See full prescribing information for complete boxed warning.

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate, a component of COMPLERA. (5.1)**
- **COMPLERA is not approved for the treatment of chronic hepatitis B virus (HBV) infection. Severe acute exacerbations of hepatitis B have been reported in patients coinfected with HIV-1 and HBV who have discontinued EMTRIVA or VIREAD, two of the components of COMPLERA. Hepatic function should be monitored closely in these patients. If appropriate, initiation of anti-hepatitis B therapy may be warranted. (5.2)**

----------**RECENT MAJOR CHANGES**----------

Indications and Usage (1)	02/2016
Dosage and Administration (2)	02/2016
Warnings and Precautions (5.3)	05/2015
Warnings and Precautions (5.6, 5.8)	02/2016

----------**INDICATIONS AND USAGE**----------

COMPLERA, a combination of two nucleoside analog HIV-1 reverse transcriptase inhibitors (emtricitabine and tenofovir disoproxil fumarate) and one non-nucleoside reverse transcriptase inhibitor (rilpivirine), is indicated for use as a complete regimen for the treatment of HIV-1 infection in (1) patients 12 years of age and older with no antiretroviral treatment history and with HIV-1 RNA less than or equal to 100,000 copies/mL at the start of therapy, and (2) in certain virologically-suppressed (HIV-1 RNA <50 copies/mL) patients on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen *[see below]*. (1, 14)

The following points should be considered when initiating therapy with COMPLERA in patients with no antiretroviral treatment history (1, 12.4, 14):

- More rilpivirine-treated subjects with HIV-1 RNA greater than 100,000 copies/mL at the start of therapy experienced virologic failure (HIV-1 RNA ≥50 copies/mL) compared to rilpivirine-treated subjects with HIV-1 RNA less than or equal to 100,000 copies/mL.
- Regardless of HIV-1 RNA level at the start of therapy, more rilpivirine-treated subjects with CD4+ cell count less than 200 cells/mm^3 at the start of therapy experienced virologic failure compared to subjects with CD4+ cell count greater than or equal to 200 cells/mm^3.
- The observed virologic failure rate in rilpivirine-treated subjects conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz.
- More subjects treated with rilpivirine developed tenofovir- and lamivudine/emtricitabine-associated resistance compared to efavirenz.

The efficacy of COMPLERA was established in patients who were virologically-suppressed (HIV-1 RNA <50 copies/mL) on stable ritonavir-boosted protease inhibitor-containing regimen. The following points should be met when considering replacing the current regimen with COMPLERA in virologically-suppressed (HIV-1 RNA <50 copies/mL) patients (1,14):

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

Additional monitoring of HIV-1 RNA and regimen tolerability is recommended after replacing therapy to assess for potential virologic failure or rebound. (1)

----------**DOSAGE AND ADMINISTRATION**----------

- Dose in patients 12 years of age and older: One tablet (containing 200 mg of emtricitabine, 25 mg of rilpivirine, and 300 mg of tenofovir disoproxil fumarate) taken once daily with food. (2)
- Dose in renal impairment: Should not be administered in patients with estimated creatinine clearance below 50 mL per minute. (2)
- With rifabutin coadministration, an additional 25 mg tablet of rilpivirine (Edurant) once per day is recommended to be taken concomitantly with COMPLERA and with a meal for the duration of the rifabutin coadministration. (2,7.5,12.3)

----------**DOSAGE FORMS AND STRENGTHS**----------

Tablets: 200 mg of emtricitabine, 25 mg of rilpivirine, and 300 mg of tenofovir disoproxil fumarate. (3)

----------**CONTRAINDICATIONS**----------

Coadministration of COMPLERA is contraindicated with drugs where significant decreases in rilpivirine plasma concentrations may occur, which may result in loss of virologic response and possible resistance and cross-resistance. (4)

----------**WARNINGS AND PRECAUTIONS**----------

- Skin and Hypersensitivity Reactions: Severe skin and hypersensitivity reactions have been reported during postmarketing experience, including cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Immediately discontinue treatment if hypersensitivity or rash with systemic symptoms or elevations in hepatic serum biochemistries develops and closely monitor clinical status, including hepatic serum biochemistries. (5.3)
- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Assess estimated creatinine clearance before initiating treatment with COMPLERA. In patients at risk for renal dysfunction, assess estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein before initiating treatment with COMPLERA and periodically during treatment. Avoid administering COMPLERA with concurrent or recent use of nephrotoxic drugs. (5.4)
- Caution should be given to prescribing COMPLERA with drugs that may reduce the exposure of rilpivirine. (5.5)
- Caution should be given to prescribing COMPLERA with drugs with a known risk of Torsade de Pointes. (5.5)
- Depressive disorders: Severe depressive disorders have been reported. Immediate medical evaluation is recommended for severe depressive disorders. (5.6)
- Hepatotoxicity: Hepatic adverse events have been reported in patients receiving a rilpivirine-containing regimen. Monitor liver-associated tests before and during treatment with COMPLERA in patients with underlying hepatic disease or marked elevations in liver-associated tests. Also consider monitoring liver-associated tests in patients without risk factors. (5.7)
- Decreases in bone mineral density (BMD): Consider monitoring BMD in patients with a history of pathologic fracture or other risk factors of osteoporosis or bone loss. (5.8)
- Coadministration with other products: Do not use with drugs containing emtricitabine or tenofovir disoproxil fumarate, including ATRIPLA, EMTRIVA, STRIBILD, TRUVADA, and VIREAD, or with drugs containing lamivudine. Do not administer in combination with HEPSERA. Do not coadminister in combination with rilpivirine (Edurant) unless required for dose adjustment when coadministered with rifabutin. (5.9)
- Redistribution/accumulation of body fat: Observed in patients receiving antiretroviral therapy. (5.10)

Reference ID: 3891182

- Immune reconstitution syndrome: May necessitate further evaluation and treatment. (5.11)

----------**ADVERSE REACTIONS**----------

Most common adverse reactions to rilpivirine (incidence greater than or equal to 2%, Grades 2–4) are depressive disorders, insomnia, and headache. (6.1)

Most common adverse reactions to emtricitabine and tenofovir disoproxil fumarate (incidence greater than or equal to 10%) are diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------**DRUG INTERACTIONS**----------

- COMPLERA is a complete regimen for the treatment of HIV-1 infection; therefore, COMPLERA should not be administered with other antiretroviral medications for treatment of HIV-1 infection.
- CYP3A4 inducers or inhibitors: Drugs that induce or inhibit CYP3A4 may affect the plasma concentrations of rilpivirine. (7.1)
- Drugs that increase gastric pH: Drugs that increase gastric pH may decrease plasma concentrations of rilpivirine. (7.2)

----------**USE IN SPECIFIC POPULATIONS**----------

- Pregnancy: Use during pregnancy only if the potential benefit justifies the potential risk. (8.1)
- Nursing mothers: Women infected with HIV should be instructed not to breastfeed due to the potential for HIV transmission. (8.3)
- Pediatrics: Safety and effectiveness have not been established in patients less than 12 years of age. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 02/2016

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FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate, a component of COMPLERA, in combination with other antiretrovirals *[See Warnings and Precautions (5.1)]*.

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-1. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued EMTRIVA or VIREAD, which are components of COMPLERA. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue COMPLERA. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[See Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

COMPLERA, a combination of two nucleoside analog HIV-1 reverse transcriptase inhibitors (NRTIs) (emtricitabine and tenofovir disoproxil fumarate) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) (rilpivirine), is indicated for use as a complete regimen for the treatment of HIV-1 infection in patients 12 years of age and older with no antiretroviral treatment history and with HIV-1 RNA less than or equal to 100,000 copies/mL at the start of therapy, and in certain virologically-suppressed (HIV-1 RNA <50 copies/mL) patients on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen (see below).

- The following points should be considered when initiating therapy with COMPLERA in patients with no antiretroviral treatment history:
    - More rilpivirine-treated subjects with HIV-1 RNA greater than 100,000 copies/mL at the start of therapy experienced virologic failure (HIV-1 RNA ≥50 copies/mL) compared to rilpivirine-treated subjects with HIV-1 RNA less than or equal to 100,000 copies/mL *[See Clinical Studies (14)]*.
    - Regardless of HIV-1 RNA level at the start of therapy, more rilpivirine-treated subjects with CD4+ cell count less than 200 cells/mm^3 experienced virologic failure compared to rilpivirine-treated subjects with CD4+ cell count greater than or equal to 200 cells/mm^3 *[See Clinical Studies (14)]*.
    - The observed virologic failure rate in rilpivirine-treated subjects conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz *[See Microbiology (12.4)]*.

Reference ID: 3891182

    - More subjects treated with rilpivirine developed tenofovir- and lamivudine/emtricitabine-associated resistance compared to efavirenz *[See Microbiology (12.4)]*.

- The efficacy of COMPLERA was established in patients who were virologically-suppressed (HIV-1 RNA <50 copies/mL) on stable ritonavir-boosted protease inhibitor (PI)-containing regimen. The following points should be met when considering replacing the current regimen with COMPLERA in virologically-suppressed patients *[See Clinical Studies (14)]*:
    - Patients should have no history of virologic failure.
    - Patients should have been stably suppressed (HIV-1 RNA <50 copies/mL) for at least 6 months prior to switching therapy.
    - Patients should currently be on their first or second antiretroviral regimen prior to switching therapy.
    - Patients should have no current or past history of resistance to any of the three components of COMPLERA.

Additional monitoring of HIV-1 RNA and regimen tolerability is recommended after replacing therapy to assess for potential virologic failure or rebound.

2 DOSAGE AND ADMINISTRATION

The recommended dose of COMPLERA in patients 12 years of age and older and weighing at least 35 kg is one tablet taken orally once daily with food *[See Use in Specific Populations (8.4) and Clinical Pharmacology (12.3)].*

Renal Impairment: Because COMPLERA is a fixed-dose combination, it should not be prescribed for patients requiring dose reduction, such as those with moderate or severe renal impairment (estimated creatinine clearance below 50 mL per minute).

Rifabutin Coadministration: If COMPLERA is coadministered with rifabutin, an additional 25 mg tablet of rilpivirine (Edurant®) once per day is recommended to be taken concomitantly with COMPLERA and with a meal for the duration of the rifabutin coadministration *[See Drug Interactions (7.5) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

COMPLERA is available as tablets. Each tablet contains 200 mg of emtricitabine (FTC), 27.5 mg of rilpivirine hydrochloride (equivalent to 25 mg of rilpivirine), and 300 mg of tenofovir disoproxil fumarate (tenofovir DF or TDF, equivalent to 245 mg of tenofovir disoproxil).

The tablets are purplish pink, capsule shaped, film coated, debossed with “GSI” on one side, and plain faced on the other side.

4 CONTRAINDICATIONS

COMPLERA should not be coadministered with the following drugs, as significant decreases in rilpivirine plasma concentrations may occur due to CYP3A enzyme induction or gastric pH increase, which may result in loss of virologic response and possible resistance to COMPLERA or to the class of NNRTIs *[See Drug Interactions (7) and Clinical Pharmacology (12.3)]*:

- the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- the antimycobacterials rifampin, rifapentine
- proton pump inhibitors, such as dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole
- the glucocorticoid systemic dexamethasone (more than a single dose)
- St. John's wort (*Hypericum perforatum*)

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir DF, a component of COMPLERA, in combination with other antiretrovirals. 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).

5.2 Patients Coinfected with HIV-1 and HBV

It is recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B virus 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 coinfected with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued emtricitabine or tenofovir DF, two of the components of COMPLERA. In some patients infected with HBV and treated with EMTRIVA®, the exacerbations of hepatitis B were associated with liver decompensation and liver failure. Patients who are coinfected with HIV-1 and HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with COMPLERA. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Reference ID: 3891182

5.3 Skin and Hypersensitivity Reactions

Severe skin and hypersensitivity reactions have been reported during the postmarketing experience, including cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) with rilpivirine-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 3 clinical trials, treatment-related rashes with at least Grade 2 severity were reported in 1% of subjects receiving rilpivirine plus emtricitabine/tenofovir DF. Overall, most rashes were Grade 1 or 2 and occurred in the first four to six weeks of therapy *[see Adverse Reactions (6.1 and 6.2)]*.

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.

5.4 New Onset or Worsening Renal Impairment

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir DF *[See Adverse Reactions (6.2)]*.

It is recommended that estimated creatinine clearance be assessed in all patients prior to initiating therapy and as clinically appropriate during therapy with COMPLERA. In patients at risk of renal dysfunction, including patients who have previously experienced renal events while receiving HEPSERA®, it is recommended that estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein be assessed prior to initiation of COMPLERA and periodically during COMPLERA therapy.

COMPLERA should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple nonsteroidal anti-inflammatory drugs [NSAIDs]) *[See Drug Interactions (7.3)].* Cases of acute renal failure after initiation of high-dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on tenofovir DF. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.

Persistent or worsening bone pain, pain in extremities, fractures, and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in at-risk patients.

Emtricitabine and tenofovir are principally eliminated by the kidney; however, rilpivirine is not. Since COMPLERA is a combination product and the dose of the individual components cannot be altered, patients with estimated creatinine clearance below 50 mL per minute should not receive COMPLERA.

5.5 Drug Interactions

Caution should be given to prescribing COMPLERA with drugs that may reduce the exposure of rilpivirine *[See Contraindications (4), Drug Interactions (7), and Clinical Pharmacology (12.3)]*.

In healthy subjects, supratherapeutic doses of rilpivirine (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval of the electrocardiogram *[See Drug Interactions (7) and Clinical Pharmacology (12.2)]*. COMPLERA should be used with caution when coadministered with a drug with a known risk of Torsade de Pointes.

5.6 Depressive Disorders

The adverse reaction depressive disorders (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) has been reported with rilpivirine. Patients with severe depressive symptoms should seek immediate medical evaluation to assess the possibility that the symptoms are related to COMPLERA, and if so, to determine whether the risks of continued therapy outweigh the benefits.

During the Phase 3 trials in adults (N=1368) through 96 weeks, the incidence of depressive disorders (regardless of causality, severity) reported among rilpivirine (n=686) or efavirenz (n=682) was 9% and 8%, respectively. Most events were mild or moderate in severity. The incidence of Grades 3 and 4 depressive disorders (regardless of causality) was 1% for both rilpivirine and efavirenz. The incidence of discontinuation due to depressive disorders among rilpivirine or efavirenz was 1% in each arm. Suicidal ideation was reported in 4 subjects in each arm while suicide attempt was reported in 2 subjects in the rilpivirine arm.

During the Phase 2 trial in pediatric subjects 12 to less than 18 years of age (N=36) receiving rilpivirine through 48 weeks, the incidence of depressive disorders (regardless of causality, severity) was 19.4% (7/36). Most events were mild or moderate in severity. The incidence of Grade 3 and 4 depressive disorders (regardless of causality) was 5.6% (2/36). None of the subjects discontinued due to depressive disorders. Suicidal ideation and suicide attempt were reported in 1 subject.

5.7 Hepatotoxicity

Hepatic adverse events have been reported in patients receiving a rilpivirine-containing regimen. Patients with underlying hepatitis B or C, or marked elevations in liver-associated tests prior to treatment, may be at increased risk for worsening or development of liver-associated test elevations with use of COMPLERA. A few cases of hepatic toxicity have been reported in adult patients receiving a rilpivirine-containing regimen who had no pre-existing hepatic disease or other identifiable risk factors. Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with COMPLERA is recommended in patients with underlying hepatic disease such as hepatitis B or C, or in patients with marked elevations in liver-associated tests prior to treatment initiation. Liver-associated test monitoring should

also be considered for patients without pre-existing hepatic dysfunction or other risk factors.

5.8 Bone Effects of Tenofovir DF

Bone Mineral Density

In clinical trials in HIV-1-infected adults, tenofovir DF was associated with slightly greater decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving tenofovir DF. For more information, please consult the VIREAD® prescribing information.

Clinical trials evaluating tenofovir DF in pediatric and adolescent subjects were conducted. Under normal circumstances, BMD increases rapidly in pediatric patients. In HIV-1-infected subjects aged 2 years to less than 18 years, bone effects were similar to those observed in adult subjects and suggest increased bone turnover. Total body BMD gain was less in the tenofovir DF-treated HIV-1-infected pediatric subjects as compared to the control groups. Similar trends were observed in chronic hepatitis B-infected adolescent subjects aged 12 years to less than 18 years. In all pediatric trials, skeletal growth (height) appeared to be unaffected. For more information, please consult the VIREAD prescribing information.

The effects of tenofovir DF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Assessment of BMD should be considered for adult and pediatric patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and Vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected, then appropriate consultation should be obtained.

Mineralization Defects

Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of tenofovir DF *[See Adverse Reactions (6.2)].* Arthralgias and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing tenofovir DF *[See Warnings and Precautions (5.4)].*

5.9 Coadministration with Other Products

COMPLERA should not be administered concurrently with other medicinal products containing the active components emtricitabine or tenofovir DF (ATRIPLA®, EMTRIVA, STRIBILD®, TRUVADA®, VIREAD), with medicinal products containing lamivudine

(Epivir®, Epivir-HBV®, Epzicom®, Combivir®, Triumeq®, Trizivir®), or with adefovir dipivoxil (HEPSERA). COMPLERA should not be administered with rilpivirine (Edurant) unless needed for dose adjustment (e.g., with rifabutin) *[See Dosage and Administration (2) and Drug Interactions (7.5)].*

5.10 Fat Redistribution

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

5.11 Immune Reconstitution Syndrome

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

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré 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.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[See Boxed Warning, Warnings and Precautions (5.1)]*.
- Severe Acute Exacerbations of Hepatitis B *[See Boxed Warning, Warnings and Precautions (5.2)]*.
- Skin and Hypersensitivity Reactions *[See Warnings and Precautions (5.3)].*
- New Onset or Worsening Renal Impairment *[See Warnings and Precautions (5.4)]*.
- Depressive Disorders *[See Warnings and Precautions (5.6)].*
- Hepatotoxicity *[See Warnings and Precautions (5.7)]*.
- Bone Effects of Tenofovir DF *[See Warnings and Precautions (5.8)]*.
- Immune Reconstitution Syndrome *[See Warnings and Precautions (5.11)]*.

6.1 Adverse Reactions from Clinical Trials Experience in Adult Subjects

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

In HIV-1-Infected Adult Subjects With No Antiretroviral Treatment History

Studies C209 and C215

Treatment-Emergent Adverse Drug Reactions: The safety assessment of rilpivirine, used in combination with other antiretroviral drugs, is based on the Week 96 pooled data from 1368 subjects in the Phase 3 trials TMC278-C209 (ECHO) and TMC278-C215 (THRIVE) in antiretroviral treatment-naïve HIV-1-infected adult subjects. A total of 686 subjects received rilpivirine in combination with other antiretroviral drugs as background regimen; most (N=550) received emtricitabine/tenofovir DF as background regimen. The number of subjects randomized to the control arm efavirenz was 682, of which 546 received emtricitabine/tenofovir DF as background regimen *[See Clinical Studies (14)]*. The median duration of exposure for subjects in either treatment arm was 104 weeks.

Adverse reactions observed at Week 96 in subjects who received rilpivirine or efavirenz + emtricitabine/tenofovir DF as background regimen are shown in Table 1. No new types of adverse reactions were identified between Week 48 and Week 96. The adverse reactions observed in this subset of subjects were generally consistent with those seen for the overall patient population participating in these studies (refer to the prescribing information for Edurant).

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

Common Adverse Reactions: Clinical adverse reactions to rilpivirine or efavirenz of at least moderate intensity (≥Grade 2) reported in at least 2% of adult subjects are shown in Table 1.

Table 1 Selected Treatment-Emergent Adverse Reactions[a] (Grades 2–4) Reported in ≥2% of Adult Subjects Receiving Rilpivirine or Efavirenz in Combination with Emtricitabine/Tenofovir DF in Studies C209 and C215 (Week 96 Analysis)

System Organ Class Preferred Term	Rilpivirine + FTC/TDF	Efavirenz + FTC/TDF
	N=550	N=546
Gastrointestinal Disorders		
Nausea	1%	2%
Nervous System Disorders		
Headache	2%	2%
Dizziness	1%	7%
Psychiatric Disorders		
Depressive disorders[b]	2%	2%
Insomnia	2%	2%
Abnormal dreams	1%	3%
Skin and Subcutaneous Tissue Disorders		
Rash	1%	5%

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

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

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

<u>In Virologically-Suppressed HIV-1-Infected Adult Subjects</u>

No new adverse reactions to COMPLERA were identified in stable, virologically-suppressed subjects switching to COMPLERA from a regimen containing a ritonavir-boosted protease inhibitor; however, the frequency of adverse reactions increased by 20% (Study 106) after switching to COMPLERA.

Emtricitabine and Tenofovir Disoproxil Fumarate: The most common adverse reactions that occurred in at least 10% of HIV-1-infected treatment-naïve adult subjects in a Phase 3 clinical trial of emtricitabine and tenofovir DF in combination with another antiretroviral agent were diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash. Adverse reactions that occurred in at least 5% of treatment-experienced or treatment-naïve subjects receiving emtricitabine or tenofovir DF with other antiretroviral agents in clinical trials included abdominal pain, dyspepsia, vomiting, fever, pain, nasopharyngitis, pneumonia, sinusitis, upper respiratory tract

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infection, arthralgia, back pain, myalgia, paresthesia, peripheral neuropathy (including peripheral neuritis and neuropathy), anxiety, increased cough, and rhinitis.

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

6.2 Laboratory Abnormalities in Adult Subjects

The percentage of subjects treated with rilpivirine + emtricitabine/tenofovir DF or efavirenz + emtricitabine/tenofovir DF in studies C209 and C215 with selected treatment-emergent laboratory abnormalities (Grades 1–4), representing worst-grade toxicity, is presented in Table 2.

Table 2 Selected Laboratory Abnormalities (Grades 1–4) Reported in Adult Subjects Who Received Rilpivirine or Efavirenz in Combination with Emtricitabine/Tenofovir DF in Studies C209 and C215 (Week 96 Analysis)

Laboratory Parameter Abnormality	DAIDS Toxicity Range	Rilpivirine + FTC/TDF	Efavirenz + FTC/TDF
		N=550	N=546
BIOCHEMISTRY			
Increased Creatinine			
Grade 1	1.1–1.3 x ULN[a]	6%	1%
Grade 2	>1.3–1.8 x ULN	1%	1%
Grade 3	>1.8–3.4 x ULN	<1%	0
Grade 4	>3.4 x ULN	0	<1%
Increased AST			
Grade 1	1.25–2.5 x ULN	16%	19%
Grade 2	>2.5–5.0 x ULN	4%	7%
Grade 3	>5.0–10.0 x ULN	2%	3%
Grade 4	>10.0 x ULN	1%	1%
Increased ALT			
Grade 1	1.25–2.5 x ULN	19%	22%
Grade 2	>2.5–5.0 x ULN	5%	7%
Grade 3	>5.0–10.0 x ULN	1%	2%
Grade 4	>10.0 x ULN	1%	1%
Increased Total Bilirubin			
Grade 1	1.1–1.5 x ULN	6%	<1%
Grade 2	>1.5–2.5 x ULN	3%	1%
Grade 3	>2.5–5.0 x ULN	1%	<1%
Increased Total Cholesterol (fasted)			
Grade 1	200–239 mg/dL	14%	31%
Grade 2	240–300 mg/dL	6%	18%
Grade 3	>300 mg/dL	<1%	2%
Increased LDL Cholesterol (fasted)			
Grade 1	130–159 mg/dL	13%	28%

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Laboratory Parameter Abnormality	DAIDS Toxicity Range	Rilpivirine + FTC/TDF	Efavirenz + FTC/TDF
		N=550	N=546
Grade 2	160–190 mg/dL	5%	13%
Grade 3	>190 mg/dL	1%	4%
Increased Triglycerides (fasted)			
Grade 2	500–750 mg/dL	1%	2%
Grade 3	751–1200 mg/dL	1%	2%
Grade 4	>1200 mg/dL	0	1%

N=number of subjects per treatment group

a. ULN=Upper limit of normal value.

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

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

Adrenal Function: In the pooled Phase 3 trials of C209 and C215, in subjects treated with rilpivirine plus any of the allowed background regimens (N=686), at Week 96 there was an overall mean change from baseline in basal cortisol of –0.69 (−1.12, 0.27) micrograms/dL in the rilpivirine group, and of −0.02 (−0.48, 0.44) micrograms/dL in the efavirenz group.

In the rilpivirine group, 43/588 (7.3%) of subjects with a normal 250 micrograms ACTH stimulation test at baseline developed an abnormal 250 micrograms ACTH stimulation test (peak cortisol level <18.1 micrograms/dL) during the trial compared to 18/561 (3.2%) in the efavirenz group. Of the subjects who developed an abnormal 250 micrograms ACTH stimulation test during the trial, 14 subjects in the rilpivirine group and 9 subjects in the efavirenz group had an abnormal 250 micrograms ACTH stimulation test at Week 96. Overall, there were no serious adverse events, deaths, or treatment discontinuations that could clearly be attributed to adrenal insufficiency. The clinical significance of the higher abnormal rate of 250 micrograms ACTH stimulation tests in the rilpivirine group is not known.

Serum Creatinine: In the pooled Phase 3 trials of C209 and C215 in subjects treated with rilpivirine plus any of the allowed background regimens (N=686), there was a small increase in serum creatinine over 96 weeks of treatment with rilpivirine. Most of this

increase occurred within the first 4 weeks of treatment, with a mean change of 0.1 mg/dL (range –0.3 to 0.6 mg/dL) observed through Week 96. In subjects who entered the trial with mild or moderate renal impairment, the serum creatinine increase observed was similar to that seen in subjects with normal renal function. These changes are not considered to be clinically relevant, and no subject discontinued treatment due to increases in serum creatinine. Creatinine increases were comparable by background N(t)RTIs.

Serum Lipids: Changes from baseline in total cholesterol, LDL-cholesterol, and triglycerides are presented in Table 3.

Table 3 Lipid Values Reported in Adult Subjects Receiving Rilpivirine or Efavirenz in Combination with Emtricitabine/Tenofovir DF in Studies C209 and C215[a]

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

N=number of subjects per treatment group

a. Excludes subjects who received lipid lowering agents during the treatment period.

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

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

6.3 Clinical Trials Experience in Pediatric Subjects

Emtricitabine: In addition to the adverse reactions reported in adults, anemia and hyperpigmentation were observed in 7% and 32%, respectively, of pediatric subjects (3

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months to less than 18 years of age) who received treatment with EMTRIVA in the larger of two open-label, uncontrolled pediatric trials (N=116). For additional information, please consult the EMTRIVA prescribing information.

Rilpivirine: The safety assessment is based on the Week 48 analysis of the single-arm, open-label Phase 2 trial, TMC278-C213, in which 36 antiretroviral treatment-naïve HIV-1-infected subjects 12 to less than 18 years of age and weighing at least 32 kg received rilpivirine (25 mg once daily) in combination with other antiretroviral agents. The median duration of exposure for subjects was 63.5 weeks. No subjects discontinued treatment due to adverse reactions. No new adverse reactions were identified compared to those seen in adults.

Adverse reactions were reported in 19 pediatric subjects (52.8%). Most adverse reactions were Grade 1 or 2. The most common adverse reactions reported in at least 2 subjects (regardless of severity) include headache (19.4%), depression (19.4%), somnolence (13.9%), nausea (11.1%), dizziness (8.3%), abdominal pain (8.3%), vomiting (5.6%), and rash (5.6%).

Observed laboratory abnormalities were comparable to those in adults. For additional information, please consult the Edurant prescribing information.

Adrenal Function

In trial TMC278-C213, at Week 48, the overall mean change from baseline in basal cortisol showed an increase of 1.59 (0.24, 2.93) micrograms/dL.

Six of 30 (20%) subjects with a normal 250 micrograms ACTH stimulation test at baseline developed an abnormal 250 micrograms ACTH stimulation test (peak cortisol level <18.1 micrograms/dL) during the trial. Three of these subjects had an abnormal 250 micrograms ACTH stimulation test at Week 48. Overall, there were no serious adverse events, deaths, or treatment discontinuations that could clearly be attributed to adrenal insufficiency. The clinical significance of the abnormal 250 micrograms ACTH stimulation tests is not known.

Tenofovir Disoproxil Fumarate: In a pediatric clinical trial conducted in subjects 12 to less than 18 years of age, the adverse reactions observed in pediatric subjects who received treatment with VIREAD were consistent with those observed in clinical trials of VIREAD in adults *[See Warnings and Precautions (5.8)].* For additional information, including information on bone mineral density changes, please consult the VIREAD prescribing information.

6.4 Postmarketing Experience

The following adverse reactions have been identified during postmarketing experience in patients receiving rilpivirine- or tenofovir DF-containing regimens. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is

not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

COMPLERA:

Metabolism and Nutrition Disorders
weight increased

Skin and Subcutaneous Tissue Disorders
severe skin and hypersensitivity reactions including DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms)

Rilpivirine:

Renal and Urinary Disorders
nephrotic syndrome

Emtricitabine:

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

Tenofovir Disoproxil Fumarate:

Immune System Disorders
allergic reaction, including angioedema

Metabolism and Nutrition Disorders
lactic acidosis, hypokalemia, hypophosphatemia

Respiratory, Thoracic, and Mediastinal Disorders
dyspnea

Gastrointestinal Disorders
pancreatitis, increased amylase, abdominal pain

Hepatobiliary Disorders
hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT, gamma GT)

Skin and Subcutaneous Tissue Disorders
rash

Musculoskeletal and Connective Tissue Disorders
rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy

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

General Disorders and Administration Site Conditions
asthenia

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

7 DRUG INTERACTIONS

COMPLERA is a complete regimen for the treatment of HIV-1 infection; therefore, COMPLERA should not be administered with other antiretroviral medications. Information regarding potential drug-drug interactions with other antiretroviral medications is not provided. Please refer to the Edurant, VIREAD, and EMTRIVA prescribing information as needed.

This section describes clinically relevant drug interactions with COMPLERA. Drug interaction studies were conducted with the components of COMPLERA (emtricitabine, rilpivirine, and tenofovir DF as single agents) or with COMPLERA as a combination product *[See Dosage and Administration (2), Contraindications (4), and Clinical Pharmacology (12.3)]*.

7.1 Drugs Inducing or Inhibiting CYP3A Enzymes

Rilpivirine is primarily metabolized by cytochrome P450 (CYP) 3A, and drugs that induce or inhibit CYP3A may thus affect the clearance of rilpivirine *[See Clinical Pharmacology (12.3), Contraindications (4)]*. Coadministration of rilpivirine and drugs that induce CYP3A may result in decreased plasma concentrations of rilpivirine and loss of virologic response and possible resistance to rilpivirine or to the class of NNRTIs. Coadministration of rilpivirine and drugs that inhibit CYP3A may result in increased plasma concentrations of rilpivirine.

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

7.2 Drugs Increasing Gastric pH

Coadministration of rilpivirine with drugs that increase gastric pH may decrease plasma concentrations of rilpivirine and loss of virologic response and possible resistance to rilpivirine or to the class of NNRTIs *[See Table 4].*

7.3 Drugs Affecting Renal Function

Because emtricitabine and tenofovir are primarily eliminated by the kidneys through a combination of glomerular filtration and active tubular secretion, coadministration of COMPLERA with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of emtricitabine, tenofovir, and/or other renally eliminated drugs. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs *[See Warnings and Precautions (5.4)]*.

7.4 QT Prolonging Drugs

There is limited information available on the potential for a pharmacodynamic interaction between rilpivirine and drugs that prolong the QTc interval of the electrocardiogram. In a study of healthy subjects, supratherapeutic doses of rilpivirine (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval of the electrocardiogram *[See Clinical Pharmacology (12.2)]*. COMPLERA should be used with caution when coadministered with a drug with a known risk of Torsade de Pointes.

7.5 Established and Other Potentially Significant Drug Interactions

Important drug interaction information for COMPLERA is summarized in Table 4. The drug interactions described are based on studies conducted with emtricitabine, rilpivirine, or tenofovir DF as individual medications or with COMPLERA as a combination product, or are potential drug interactions *[for pharmacokinetic data see Clinical Pharmacology (12.3)*, *Tables 7–8]*. Table 4 includes potentially significant interactions, but is not all inclusive.

Table 4 Established and Other Potentially Significant[a] 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
Antacids: antacids (e.g., aluminium, magnesium hydroxide, or calcium carbonate)	↔ rilpivirine (antacids taken at least 2 hours before or at least 4 hours after rilpivirine) ↓ rilpivirine (concomitant intake)	The combination of COMPLERA and antacids should be used with caution as coadministration may cause significant decreases in rilpivirine 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	↓ rilpivirine[c]	Concomitant use of COMPLERA with rifabutin may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). If COMPLERA is coadministered with rifabutin, an additional 25 mg tablet of rilpivirine (Edurant) once per day is recommended to be taken concomitantly with COMPLERA and with a meal for the duration of rifabutin coadministration.
Azole Antifungal Agents: fluconazole itraconazole ketoconazole posaconazole voriconazole	↑ rilpivirine[c,d] ↓ ketoconazole[c,d]	Concomitant use of COMPLERA with azole antifungal agents may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). No dose adjustment is required when COMPLERA is coadministered with azole antifungal agents. Clinically monitor for breakthrough fungal infections when azole antifungals are coadministered with COMPLERA.
Hepatitis C Antiviral Agents: ledipasvir/sofosbuvir	↑ tenofovir[c]	Patients receiving COMPLERA concomitantly with HARVONI® (ledipasvir/sofosbuvir) should be monitored for adverse reactions associated with tenofovir disoproxil fumarate.

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Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
H_2-Receptor Antagonists: cimetidine famotidine nizatidine ranitidine	↔ rilpivirine[c,d] (famotidine taken 12 hours before rilpivirine or 4 hours after rilpivirine) ↓ rilpivirine[c,d] (famotidine taken 2 hours before rilpivirine)	The combination of COMPLERA and H_2-receptor antagonists should be used with caution as coadministration may cause significant decreases in rilpivirine plasma concentrations (increase in gastric pH). H_2-receptor antagonists should only be administered at least 12 hours before or at least 4 hours after COMPLERA.
Macrolide or Ketolide Antibiotics: clarithromycin erythromycin telithromycin	↑ rilpivirine ↔ clarithromycin ↔ erythromycin ↔ telithromycin	Concomitant use of COMPLERA with clarithromycin, erythromycin, or telithromycin may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). Where possible, alternatives such as azithromycin should be considered.
Narcotic Analgesics: methadone	↓ R(–) methadone[c] ↓ S(+) methadone[c] ↔ rilpivirine[c] ↔ methadone[c] (when used with tenofovir)	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 rilpivirine. The dosing recommendation is applicable to the recommended dose of rilpivirine 25 mg once daily.

7.6 Drugs with No Observed or Predicted Interactions with COMPLERA

No clinically significant drug interactions have been observed between emtricitabine and the following medications: famciclovir, ledipasvir/sofosbuvir, or tenofovir DF.

No clinically significant drug interactions have been observed between tenofovir DF and the following medications: entecavir, methadone, oral contraceptives, ribavirin, sofosbuvir, or tacrolimus in studies conducted in healthy subjects.

No clinically significant drug interactions have been observed between rilpivirine and the following medications: acetaminophen, atorvastatin, chlorzoxazone, ethinyl estradiol, ledipasvir/sofosbuvir, norethindrone, sildenafil, simeprevir, sofosbuvir, telaprevir, or tenofovir DF. Rilpivirine did not have a clinically significant effect on the pharmacokinetics of digoxin or metformin. No clinically relevant drug-drug interaction is expected when rilpivirine is coadministered with ribavirin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

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

Rilpivirine: Studies in animals have shown no evidence of embryonic or fetal toxicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with rilpivirine during pregnancy and lactation, there were no toxicologically significant effects on developmental endpoints. 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.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, COMPLERA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV.

Emtricitabine: Samples of breast milk obtained from 5 HIV-1-infected mothers show that emtricitabine is secreted in human milk. Breastfeeding infants whose mothers are being treated with emtricitabine may be at risk for developing viral resistance to emtricitabine. Other emtricitabine-associated risks in infants breastfed by mothers being treated with emtricitabine are unknown.

Rilpivirine: Studies in lactating rats and their offspring indicate that rilpivirine was present in rat milk. It is not known whether rilpivirine is secreted in human milk.

Tenofovir Disoproxil Fumarate: Samples of breast milk obtained from 5 HIV-1-infected mothers in the first postpartum week show that tenofovir is excreted in human milk. The impact of this exposure in breastfed infants is 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 breastfeed if they are receiving COMPLERA**.

8.4 Pediatric Use

Because COMPLERA is a fixed-dose combination tablet, it is not recommended for patients requiring dose adjustments. Safety and efficacy for COMPLERA have not been established in pediatric patients less than 12 years of age or weighing less than 35 kg *[See Adverse Reactions (6.3) and Clinical Pharmacology (12.3)]*. For additional information, please consult the Edurant, EMTRIVA, and VIREAD prescribing information.

8.5 Geriatric Use

Clinical studies of emtricitabine, rilpivirine, or tenofovir DF did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for elderly patients should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[See Clinical Pharmacology (12.3)].*

8.6 Renal Impairment

Because COMPLERA is a fixed-dose combination, it should not be prescribed for patients requiring dosage adjustment, such as those with moderate, severe, or end-stage renal impairment (estimated creatinine clearance below 50 mL per minute) or that require dialysis *[See Warnings and Precautions (5.4*), *Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dose adjustment of COMPLERA is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. COMPLERA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) *[See Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

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 emtricitabine 1200 mg were administered to 11 subjects. No severe adverse reactions were reported. The effects of higher doses are not known.

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

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

Administration of activated charcoal may be used to aid in removal of unabsorbed active substance.

Tenofovir Disoproxil Fumarate: Limited clinical experience at doses higher than the therapeutic dose of VIREAD 300 mg is available. In one study, 600 mg tenofovir DF was administered to 8 subjects orally for 28 days, and 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 4-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

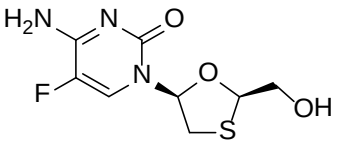
11 DESCRIPTION

COMPLERA is a fixed-dose combination tablet containing emtricitabine, rilpivirine hydrochloride, and tenofovir DF. EMTRIVA is the brand name for emtricitabine, a synthetic nucleoside analog of cytidine. Edurant is the brand name for rilpivirine, a non-nucleoside reverse transcriptase inhibitor. VIREAD is the brand name for tenofovir DF, 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 emtricitabine, 27.5 mg of rilpivirine hydrochloride (equivalent to 25 mg of rilpivirine), and 300 mg of tenofovir DF (equivalent to 245 mg of tenofovir disoproxil) as active ingredients. The tablets include the following inactive ingredients: pregelatinized starch, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, povidone, 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: The chemical name of emtricitabine is 5-fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. Emtricitabine is the (-) enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5-position.

It has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24. It has the following structural formula:



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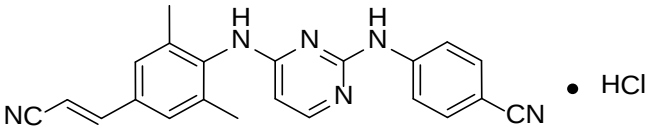
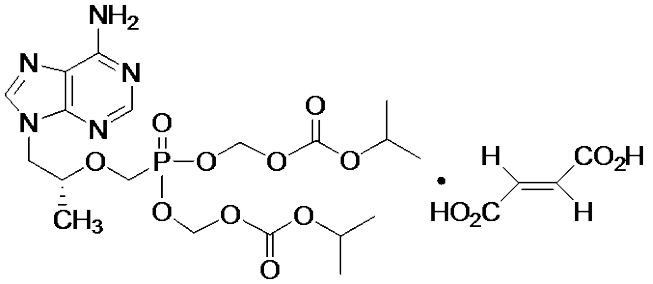
Emtricitabine is a white to off-white crystalline powder with a solubility of approximately 112 mg per mL in water at 25 °C.

Rilpivirine: Rilpivirine is available as the hydrochloride salt. The chemical name for rilpivirine hydrochloride is 4-[[4-[[4-[(E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile monohydrochloride. Its molecular formula is $C_{22}H_{18}N_6 \bullet HCl$ and its molecular weight is 402.88. Rilpivirine hydrochloride has the following structural formula:



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

Tenofovir Disoproxil Fumarate: Tenofovir DF is a fumaric acid salt of the bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. The chemical name of tenofovir DF is 9-[(*R*)-2 [[bis[[(isopropoxycarbonyl)oxy]-methoxy]phosphinyl]methoxy]propyl]adenine fumarate (1:1). It has a molecular formula of $C_{19}H_{30}N_5O_{10}P \bullet C_4H_4O_4$ and a molecular weight of 635.52. It has the following structural formula:



Tenofovir DF is a white to off-white crystalline powder with a solubility of 13.4 mg per mL in water at 25 °C. All dosages are expressed in terms of tenofovir DF except where otherwise noted.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

COMPLERA is a fixed-dose combination of the antiretroviral drugs emtricitabine, rilpivirine, and tenofovir disoproxil fumarate *[See Microbiology (12.4)].*

12.2 Pharmacodynamics

<u>Effects on Electrocardiogram</u>

The effect of rilpivirine at the recommended dose of 25 mg once daily on the QTcF interval was evaluated in a randomized, placebo-, and active- (moxifloxacin 400 mg once daily) controlled crossover study in 60 healthy adults, with 13 measurements over 24 hours at steady state. The maximum mean time-matched (95% upper confidence bound) differences in QTcF interval from placebo after baseline correction was 2.0 (5.0) milliseconds (i.e., below the threshold of clinical concern).

When supratherapeutic doses of 75 mg once daily and 300 mg once daily of rilpivirine were studied in healthy adults, the maximum mean time-matched (95% upper confidence bound) differences in QTcF interval from placebo after baseline correction were 10.7 (15.3) and 23.3 (28.4) milliseconds, respectively. Steady-state administration of rilpivirine 75 mg once daily and 300 mg once daily resulted in a mean steady-state C_{max} approximately 2.6-fold and 6.7-fold, respectively, higher than the mean C_{max} observed with the recommended 25 mg once daily dose of rilpivirine *[See Warnings and Precautions (5.5)]*.

12.3 Pharmacokinetics

COMPLERA: Under fed conditions (total calorie content of the meal was approximately 400 kcal with approximately 13 grams of fat), rilpivirine, emtricitabine, and tenofovir exposures were bioequivalent when comparing COMPLERA to EMTRIVA capsules (200 mg) plus Edurant tablets (25 mg) plus VIREAD tablets (300 mg) following single-dose administration to healthy subjects (N=34).

Single-dose administration of COMPLERA tablets to healthy subjects under fasted conditions provided approximately 25% higher exposure of rilpivirine compared to administration of EMTRIVA capsules (200 mg) plus Edurant tablets (25 mg) plus VIREAD tablets (300 mg), while exposures of emtricitabine and tenofovir were comparable (N=15).

Emtricitabine: Following oral administration, emtricitabine is absorbed with peak plasma concentrations occurring at 1–2 hours postdose. Following multiple-dose oral administration of EMTRIVA to 20 HIV-1-infected subjects, the mean steady-state plasma emtricitabine C_{max} was 1.8 ± 0.7 μg per mL and the AUC over a 24-hour dosing interval was 10.0 ± 3.1 μg•hr per mL. The mean steady-state plasma trough concentration at 24 hours postdose was 0.09 μg per mL. The mean absolute bioavailability of EMTRIVA capsules was 93%. Less than 4% of emtricitabine binds to human plasma proteins in vitro over the range of 0.02–200 μg per mL. Following administration of radiolabelled emtricitabine, recovery was approximately 86% in the urine, approximately 14% in the feces, and 13% as metabolites in the urine. The metabolites of emtricitabine include 3′-sulfoxide diastereomers (approximately 9% of the dose) and the glucuronic acid conjugate (approximately 4% of the dose). Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion, with a renal clearance in adults with creatinine clearance above 80 mL per minute of 213 ± 89 mL per minute (mean ± SD). The plasma emtricitabine half-life is approximately 10 hours.

Rilpivirine: The pharmacokinetic properties of rilpivirine have been evaluated in adult healthy subjects and in adult antiretroviral treatment-naïve HIV-1-infected subjects *[See Table 5].* Exposure to rilpivirine was generally lower in HIV-1-infected subjects than in healthy subjects. After oral administration, the C_{max} of rilpivirine is achieved within 4–5 hours. The absolute bioavailability of rilpivirine is unknown.

Table 5 Population Pharmacokinetic Estimates of Rilpivirine 25 mg Once Daily in Antiretroviral Treatment-Naïve HIV-1-infected Adult Subjects (Pooled Data from Phase 3 Trials through Week 96)

Parameter	**Rilpivirine 25 mg Once Daily N=679**
AUC_{24h} (ng•h/mL)	
Mean ± standard deviation	2235 ± 851
Median (range)	2096 (198–7307)
C_{0h} (ng/mL)	
Mean ± standard deviation	79 ± 35
Median (range)	73 (2–288)

Rilpivirine is approximately 99.7% bound to plasma proteins in vitro, primarily to albumin. In vitro experiments indicate that rilpivirine primarily undergoes oxidative metabolism by the cytochrome CYP3A system. The terminal elimination half-life of rilpivirine is approximately 50 hours. After single-dose oral administration of ^{14}C-rilpivirine, on average 85% and 6.1% of the radioactivity could be retrieved in feces and urine, respectively. In feces, unchanged rilpivirine accounted for on average 25% of the administered dose. Only trace amounts of unchanged rilpivirine (less than 1% of dose) were detected in urine.

Tenofovir Disoproxil Fumarate: Following oral administration of a single 300 mg dose of VIREAD to HIV-1-infected subjects in the fasted state, C_{max} was achieved in 1 hour. C_{max} and AUC values were 0.30 ± 0.09 μg per mL and 2.29 ± 0.69 μg•hr per mL, respectively. The oral bioavailability of tenofovir from VIREAD in fasted subjects is approximately 25%. Less than 0.7% of tenofovir binds to human plasma proteins in vitro over the range of 0.01–25 μg per mL. Approximately 70–80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine within 72 hours of dosing. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion, with a renal clearance in adults with creatinine clearance above 80 mL per minute of 243.5 ± 33.3 mL per minute (mean ± SD). Following a single oral dose, the terminal elimination half-life of tenofovir is approximately 17 hours.

Effects of Food on Oral Absorption

The food effect trial for COMPLERA evaluated two types of meals. The trial defined a meal with 390 kcal containing 12 g fat as a light meal, and a meal with 540 kcal containing 21 g fat as a standard meal. Relative to fasting conditions, the administration of COMPLERA to healthy adult subjects with both types of meals resulted in increased exposures of rilpivirine and tenofovir. The C_{max} and AUC of rilpivirine increased 34%

and 9% with a light meal, while increasing 26% and 16% with a standard meal, respectively. The C_{max} and AUC of tenofovir increased 12% and 28% with a light meal, while increasing 32% and 38% with a standard meal, respectively. Emtricitabine exposures were not affected by food.

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

COMPLERA should be taken with food.

Specific Populations

Race

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

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

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 the administration of VIREAD.

Sex

No clinically relevant pharmacokinetic differences have been observed between men and women for emtricitabine, rilpivirine, and tenofovir DF.

Pediatric Patients

Pediatric trials have not been conducted using the emtricitabine, rilpivirine, tenofovir disoproxil fumarate fixed-dose combination tablets. Pediatric information is based on trials conducted with the individual entities. In pediatric subjects, emtricitabine has been studied from 0 months to 17 years of age and tenofovir DF has been studied in 2 years of age and older. Information on the pharmacokinetics of rilpivirine is currently available only for pediatric subjects from 12 to less than 18 years of age *[See Use in Specific Populations (8.4)]*.

Emtricitabine: The pharmacokinetics of emtricitabine at steady state were determined in 27 HIV-1-infected pediatric subjects 13 to 17 years of age receiving a daily dose of 6 mg/kg up to a maximum dose of 240 mg oral solution or a 200 mg capsule; 26 of 27 subjects in this age group received the 200 mg emtricitabine capsule. Mean (± SD) C_{max} and AUC were 2.7 ± 0.9 µg/mL and 12.6 ± 5.4 µg•hr/mL, respectively. Exposures achieved in pediatric subjects 12 to less than 18 years of age were similar to those achieved in adults receiving a once daily dose of 200 mg.

Rilpivirine: The pharmacokinetics of rilpivirine in antiretroviral treatment-naïve HIV-1-infected pediatric subjects 12 to less than 18 years of age receiving rilpivirine 25 mg once daily were comparable to those in treatment-naïve HIV-1-infected adults receiving rilpivirine 25 mg once daily *[See Table 6]*. There was no clinically significant impact of

body weight on rilpivirine pharmacokinetics in pediatric subjects in trial C213 (33 to 93 kg).

Table 6 Population Pharmacokinetic Estimates of Rilpivirine 25 mg once daily in Antiretroviral Treatment-Naïve HIV-1-Infected Pediatric Subjects aged 12 to less than 18 years (Data from Phase 2 Trial through Week 48)

Parameter	**Rilpivirine 25 mg once daily N=34**
AUC_{24h} (ng•h/mL)	
Mean ± Standard Deviation	2424 ± 1024
Median (Range)	2269 (417−5166)
C_{0h} (ng/mL)	
Mean ± Standard Deviation	85 ± 40
Median (Range)	79 (7− 202)

Tenofovir Disoproxil Fumarate: Steady-state pharmacokinetics of tenofovir were evaluated in 8 HIV-1-infected pediatric subjects (12 to less than 18 years). Mean (± SD) C_{max} and AUC_{tau} are 0.38 ± 0.13 µg/mL and 3.39 ± 1.22 µg•hr/mL, respectively. Tenofovir exposure achieved in these pediatric subjects receiving oral daily doses of VIREAD 300 mg was similar to exposures achieved in adults receiving once-daily doses of VIREAD 300 mg.

Geriatric Patients

The pharmacokinetics of emtricitabine, rilpivirine, and tenofovir have not been fully evaluated in the elderly (65 years of age and older) *[See Use in Specific Populations (8.5)].*

Patients with Renal Impairment

Emtricitabine and Tenofovir Disoproxil Fumarate: The pharmacokinetics of emtricitabine and tenofovir DF are altered in subjects with renal impairment. In subjects with creatinine clearance below 50 mL per minute or with end stage renal disease requiring dialysis, C_{max} and AUC of emtricitabine and tenofovir were increased *[See Warnings and Precautions (5.4) and Use in Specific Populations (8.6)]*.

Rilpivirine: Population pharmacokinetic analysis indicated that rilpivirine exposure was similar in HIV-1-infected subjects with mild renal impairment relative to HIV-1-infected subjects with normal renal function. There is limited or no information regarding the pharmacokinetics of rilpivirine in patients with moderate or severe renal impairment or in patients with end-stage renal disease, and rilpivirine concentrations may be increased due to alteration of drug absorption, distribution, and metabolism secondary to renal dysfunction *[See Use in Specific Populations (8.6)]*.

Patients with Hepatic Impairment

Emtricitabine: The pharmacokinetics of emtricitabine have not been studied in subjects with hepatic impairment; however, emtricitabine is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.

Rilpivirine: Rilpivirine is primarily metabolized and eliminated by the liver. In a study comparing 8 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 rilpivirine was 47% higher in subjects with mild hepatic impairment and 5% higher in subjects with moderate hepatic impairment *[See Use in Specific Populations (8.7)]*.

Tenofovir Disoproxil Fumarate: The pharmacokinetics of tenofovir following a 300 mg 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 Coinfection

The pharmacokinetics of emtricitabine and tenofovir DF 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 rilpivirine.

Drug Interaction Studies

COMPLERA is a complete regimen for the treatment of HIV-1 infection; therefore, COMPLERA should not be administered with other HIV antiretroviral medications. Information regarding potential drug-drug interactions with other HIV antiretroviral medications is not provided. Please refer to the Edurant, VIREAD, and EMTRIVA prescribing information as needed.

The drug interaction studies described were conducted with COMPLERA as a combination product or with emtricitabine, rilpivirine, or tenofovir DF as individual agents.

COMPLERA: A drug interaction study for COMPLERA was performed with HARVONI (ledipasvir/sofosbuvir). No effect on the pharmacokinetic parameters of ledipasvir, sofosbuvir, and GS-331007 (the predominant circulating metabolite of sofosbuvir) was observed. There was no effect on the C_{max}, AUC, and C_{min} of emtricitabine or rilpivirine; tenofovir C_{max} increased by 32% (90% confidence interval [CI]: [↑25% to ↑39%]), tenofovir AUC increased by 40% (90% CI: [↑31% to ↑50%]), and tenofovir C_{min} increased by 91% (90% CI: [↑74% to ↑110%]) *[See Drug Interactions (7.5)].*

Emtricitabine and Tenofovir Disoproxil Fumarate: In vitro and clinical pharmacokinetic drug-drug interaction studies have shown that the potential for CYP-mediated interactions involving emtricitabine and tenofovir with other medicinal products is low.

Emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No drug-drug interactions due to competition for renal excretion have been observed; however, coadministration of emtricitabine and tenofovir DF with drugs that are eliminated by active tubular secretion

may increase concentrations of emtricitabine, tenofovir, and/or the coadministered drug *[See Drug Interactions (7.3, 7.6)]*.

Drugs that decrease renal function may increase concentrations of emtricitabine and/or tenofovir.

Drug interaction studies were performed for emtricitabine and the following medications: tenofovir DF and famciclovir. Tenofovir increased the C_{min} of emtricitabine by 20% (90% CI: [↑12% to ↑29%]) and had no effect on emtricitabine C_{max} and AUC. Emtricitabine had no effect on the C_{max}, AUC, and C_{min} of tenofovir. Coadministration of emtricitabine and famciclovir had no effect on the C_{max} or AUC of either medication.

Drug interaction studies were performed for tenofovir DF and the following medications: entecavir, methadone, oral contraceptives (ethinyl estradiol/norgestimate), ribavirin, and tacrolimus. Tacrolimus increased the C_{max} of tenofovir by 13% (90% CI: [↑1% to ↑27%]) and had no effect on the tenofovir AUC and C_{min}. Tenofovir had no effect on the C_{max}, AUC, and C_{min} of tacrolimus.

The C_{max}, AUC, and C_{min} of tenofovir were not affected in the presence of entecavir. Tenofovir increased the AUC of entecavir by 13% (90% CI: [↑11% to ↑15%]) and had no effect on the entecavir C_{max} and C_{min}.

Tenofovir had no effect on the C_{max}, AUC, and C_{min} of methadone or ethinyl estradiol/norgestimate or the C_{max} and AUC of ribavirin.

Rilpivirine: Rilpivirine is primarily metabolized by cytochrome CYP3A, and drugs that induce or inhibit CYP3A may thus affect the clearance of rilpivirine. Coadministration of COMPLERA and drugs that induce CYP3A may result in decreased plasma concentrations of rilpivirine and loss of virologic response and possible resistance. Coadministration of COMPLERA and drugs that inhibit CYP3A may result in increased plasma concentrations of rilpivirine. Coadministration of COMPLERA with drugs that increase gastric pH may result in decreased plasma concentrations of rilpivirine and loss of virologic response and possible resistance to rilpivirine and to the class of NNRTIs.

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

The effects of coadministration of other drugs on the AUC, C_{max}, and C_{min} values of rilpivirine are summarized in Table 7. The effect of coadministration of rilpivirine 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 (7)*.

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

Coadministered Drug	Dose of Coadministered Drug	Dose of Rilpivirine	N[a]	Mean % Change of Rilpivirine Pharmacokinetic Parameters[b] (90% CI)		
				C_{max}	AUC	C_{min}
Acetaminophen	500 mg single dose	150 mg once daily[c]	16	↑9 (↑1 to ↑18)	↑16 (↑10 to ↑22)	↑26 (↑16 to ↑38)
Atorvastatin	40 mg once daily	150 mg once daily[c]	16	↓9 (↓21 to ↑6)	↓10 (↓19 to ↓1)	↓10 (↓16 to ↓4)
Chlorzoxazone	500 mg single dose taken 2 hours after rilpivirine	150 mg once daily[c]	16	↑17 (↑8 to ↑27)	↑25 (↑16 to ↑35)	↑18 (↑9 to ↑28)
Ethinyl Estradiol/ Norethindrone	0.035 mg once daily/1 mg once daily	25 mg once daily	16	↔[d]	↔[d]	↔[d]
Famotidine	40 mg single dose taken 12 hours before rilpivirine	150 mg single dose[c]	24	↓1 (↓16 to ↑16)	↓9 (↓22 to ↑7)	NA
	40 mg single dose taken 2 hours before rilpivirine	150 mg single dose[c]	23	↓85 (↓88 to ↓81)	↓76 (↓80 to ↓72)	NA
	40 mg single dose taken 4 hours after rilpivirine	150 mg single dose[c]	24	↑21 (↑6 to ↑39)	↑13 (↑1 to ↑27)	NA
Ketoconazole	400 mg once daily	150 mg once daily[c]	15	↑30 (↑13 to ↑48)	↑49 (↑31 to ↑70)	↑76 (↑57 to ↑97)
Methadone	60–100 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	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 mg once daily	150 mg once daily	23	↑ 4 (↓ 5 to ↑ 13)	↑ 12 (↑ 5 to ↑ 19)	↑ 25 (↑ 16 to ↑ 35)

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Sildenafil	50 mg single dose	75 mg once daily	16	↓8 (↓15 to ↓1)	↓2 (↓8 to ↑5)	↑4 (↓2 to ↑9)
Telaprevir	750 mg every 8 hours	25 mg once daily	16	↑49 (↑20 to ↑84)	↑78 (↑44 to ↑120)	↑93 (↑55 to ↑141)
Tenofovir Disoproxil Fumarate	300 mg once daily	150 mg once daily[c]	16	↓4 (↓19 to ↑13)	↑1 (↓13 to ↑18)	↓1 (↓17 to ↑16)

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 rilpivirine (25 mg once daily) assessing the maximal effect on the coadministered drug.

d. Comparison based on historic controls.

e. Reference arm for comparison was 25 mg q.d. rilpivirine administered alone.

Table 8 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Rilpivirine

Coadministered Drug	Dose of Coadministered Drug (mg)	Dose of Rilpivirine	N[a]	Mean % Change of Coadministered Drug Pharmacokinetic Parameters[b] (90% CI)		
				C_{max}	AUC	C_{min}
Atorvastatin	40 mg once daily	150 mg once daily[c]	16	↑ 35 (↑ 8 to ↑ 68)	↑ 4 (↓ 3 to ↑ 12)	↓ 15 (↓ 31 to ↑ 3)
2-hydroxy-atorvastatin			16	↑ 58 (↑ 33 to ↑ 87)	↑ 39 (↑ 29 to ↑ 50)	↑ 32 (↑ 10 to ↑ 58)
4-hydroxy-atorvastatin			16	↑ 28 (↑ 15 to ↑ 43)	↑ 23 (↑ 13 to ↑ 33)	NA
Ethinyl estradiol	0.035 mg once daily	25 mg once daily	17	↑ 17 (↑ 6 to ↑ 30)	↑ 14 (↑ 10 to ↑ 19)	↑ 9 (↑ 3 to ↑ 16)
Ketoconazole	400 mg once daily	150 mg once daily[c]	14	↓ 15 (↓ 20 to ↓ 10)	↓ 24 (↓ 30 to ↓ 18)	↓ 66 (↓ 75 to ↓ 54)
R(-) methadone	60-100 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)
Omeprazole	20 mg once daily	150 mg once daily[c]	15	↓ 14 (↓ 32 to ↑ 9)	↓ 14 (↓ 24 to ↓ 3)	NA
Rifampin	600 mg once daily	150 mg once daily[c]	16	↑ 2 (↓ 7 to ↑ 12)	↓ 1 (↓ 8 to ↑ 7)	NA
25-desacetylrifampin			16	↔ (↓ 13 to ↑ 15)	↓ 9 (↓ 23 to ↑ 7)	NA
Simeprevir	150 mg once daily	25 mg once daily	21	↑ 10 (↓ 3 to ↑ 26)	↑ 6 (↓ 6 to ↑ 19)	↓ 4 (↓ 17 to ↑ 11)
Telaprevir	750 mg every 8 hours	25 mg once daily	13	↓ 3 (↓ 21 to ↑ 21)	↓ 5 (↓ 24 to ↑ 18)	↓ 11 (↓ 33 to ↑ 18)
Tenofovir Disoproxil Fumarate	300 mg once daily	150 mg once daily[c]	16	↑19 (↑6 to ↑34)	↑23 (↑16 to ↑31)	↑24 (↑10 to ↑38)

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 rilpivirine (25 mg once daily).

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No effect on the pharmacokinetic parameters of the following coadministered drugs was observed with rilpivirine: acetaminophen, chlorzoxazone (administered 2 hours after rilpivirine), digoxin, ledipasvir, norethindrone, metformin, sildenafil (and its metabolite, N-desmethyl-sildenafil), and sofosbuvir (and its predominant circulating metabolite, GS-331007).

12.4 Microbiology

Mechanism of Action

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 polymerase α, β, ε, and mitochondrial DNA polymerase γ.

Rilpivirine: Rilpivirine is a diarylpyrimidine non-nucleoside reverse transcriptase inhibitor of HIV-1 and inhibits HIV-1 replication 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 DF is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir DF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of 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.

Antiviral Activity

Emtricitabine, Rilpivirine, and Tenofovir Disoproxil Fumarate: The triple combination of emtricitabine, rilpivirine, and tenofovir was not antagonistic in cell culture.

Emtricitabine: The antiviral activity of emtricitabine against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The 50% effective concentration (EC_{50}) values for emtricitabine were in the range of 0.0013–0.64 μM. Emtricitabine displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007–0.075 μM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.007–1.5 μM). In drug combination studies of emtricitabine with nucleoside reverse transcriptase inhibitors (abacavir, lamivudine, stavudine, tenofovir, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine, and rilpivirine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, saquinavir), no antagonistic effects were observed.

Reference ID: 3891182

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 limited activity in cell culture against HIV-2 with a median EC_{50} value of 5220 nM (range 2510–10,830 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 0.07–1.01 nM and was less active against group O primary isolates with EC_{50} values ranging from 2.88–8.45 nM. The antiviral activity of rilpivirine was not antagonistic when combined with the NNRTIs efavirenz, etravirine, or nevirapine; the N(t)RTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, or zidovudine; the PIs amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, or tipranavir; the fusion inhibitor enfuvirtide; the CCR5 co-receptor antagonist maraviroc; or the integrase strand transfer inhibitor raltegravir.

Tenofovir Disoproxil Fumarate: The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells, and peripheral blood lymphocytes. The EC_{50} values for tenofovir were in the range of 0.04–8.5 μM. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values ranged from 0.5–2.2 μM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 1.6–5.5 μM). In drug combination studies of tenofovir with NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, and zidovudine), NNRTIs (delavirdine, efavirenz, nevirapine, and rilpivirine), and PIs (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), no antagonistic effects were observed.

Resistance

In Cell Culture

Emtricitabine and Tenofovir Disoproxil Fumarate: HIV-1 isolates with reduced susceptibility to emtricitabine or tenofovir have been selected in cell culture. Reduced susceptibility to emtricitabine was associated with M184V/I substitutions in HIV-1 RT. HIV-1 isolates selected by tenofovir expressed a K65R substitution in HIV-1 RT and showed a 2–4 fold reduction in susceptibility to tenofovir. In addition, a K70E substitution in HIV-1 RT has been selected by tenofovir and results in low-level reduced susceptibility to abacavir, emtricitabine, lamivudine, and tenofovir.

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 frequently observed amino acid substitutions that emerged and conferred decreased phenotypic susceptibility to rilpivirine included: L100I, K101E, V106I and A, V108I, E138K and G, Q, R, V179F and I, Y181C and I, V189I, G190E, H221Y, F227C, and M230I and L.

In HIV-1-Infected Adult Subjects With No Antiretroviral Treatment History

In the Week 96 pooled resistance analysis for adult subjects receiving rilpivirine or efavirenz in combination with emtricitabine/tenofovir DF in the Phase 3 clinical trials C209 and C215, the emergence of resistance was greater among subjects' viruses in the rilpivirine + emtricitabine/tenofovir DF arm compared to the efavirenz +

emtricitabine/tenofovir DF arm and was dependent on baseline viral load. In the pooled resistance analysis, 61% (47/77) of the subjects who qualified for resistance analysis (resistance analysis subjects) in the rilpivirine + emtricitabine/tenofovir DF arm had virus with genotypic and/or phenotypic resistance to rilpivirine compared to 42% (18/43) of the resistance analysis subjects in the efavirenz + emtricitabine/tenofovir DF arm who had genotypic and/or phenotypic resistance to efavirenz. Moreover, genotypic and/or phenotypic resistance to emtricitabine or tenofovir emerged in viruses from 57% (44/77) of the resistance analysis subjects in the rilpivirine arm compared to 26% (11/43) in the efavirenz arm.

Emerging NNRTI substitutions in the rilpivirine resistance analysis of subjects' viruses included V90I, K101E/P/T, E138K/A/Q/G, V179I/L, Y181C/I, V189I, H221Y, F227C/L, and M230L, which were associated with a rilpivirine phenotypic fold change range of 2.6–621. The E138K substitution emerged most frequently during rilpivirine treatment, commonly in combination with the M184I substitution. The emtricitabine and lamivudine resistance-associated substitutions M184I or V and NRTI resistance-associated substitutions (K65R/N, A62V, D67N/G, K70E, Y115F, K219E/R) emerged more frequently in the rilpivirine resistance analysis subjects than in efavirenz resistance analysis subjects *[See Table 9].*

NNRTI- and NRTI-resistance substitutions emerged less frequently in the resistance analysis of viruses from subjects with baseline viral loads of ≤100,000 copies/mL compared to viruses from subjects with baseline viral loads of >100,000 copies/mL: 23% (10/44) compared to 77% (34/44) of NNRTI-resistance substitutions and 20% (9/44) compared to 80% (35/44) of NRTI-resistance substitutions. This difference was also observed for the individual emtricitabine/lamivudine and tenofovir resistance substitutions: 22% (9/41) compared to 78% (32/41) for M184I/V and 0% (0/8) compared to 100% (8/8) for K65R/N. Additionally, NNRTI and/or NRTI-resistance substitutions emerged less frequently in the resistance analysis of the viruses from subjects with baseline CD4+ cell counts ≥200 cells/mm^3 compared to the viruses from subjects with baseline CD4+ cell counts <200 cells/mm^3: 32% (14/44) compared to 68% (30/44) of NNRTI-resistance substitutions and 27% (12/44) compared to 73% (32/44) of NRTI-resistance substitutions.

Table 9 Proportion of Frequently Emerging Reverse Transcriptase Substitutions in the HIV-1 Virus of Resistance Analysis Adult Subjects[a] Who Received Rilpivirine or Efavirenz in Combination with Emtricitabine/Tenofovir DF from Pooled Phase 3 TMC278-C209 and TMC278-C215 Trials in the Week 96 Analysis

	C209 and C215 N=1096	
	Rilpivirine + FTC/TDF	**Efavirenz + FTC/TDF**
	N=550	**N=546**
Subjects who Qualified for Resistance Analysis	14% (77/550)	8% (43/546)
Subjects with Evaluable Postbaseline Resistance Data	70	31
Emergent NNRTI Substitutions[b]		
Any	63% (44/70)	55% (17/31)
V90I	14% (10/70)	0
K101E/P/T/Q	19% (13/70)	10% (3/31)
K103N	1% (1/70)	39% (12/31)
E138K/A/Q/G	40% (28/70)	0
E138K+M184I[c]	30% (21/70)	0
V179I/D	6% (4/70)	10% (3/31)
Y181C/I/S	13% (9/70)	3% (1/31)
V189I	9% (6/70)	0
H221Y	10% (7/70)	0
Emergent NRTI Substitutions[d]		
Any	63% (44/70)	32% (10/31)
M184I/V	59% (41/70)	26% (8/31)
K65R/N	11% (8/70)	6% (2/31)
A62V, D67N/G, K70E, Y115F, or K219E/R[e]	20% (14/70)	3% (1/31)

a. Subjects who qualified for resistance analysis

b. V90, L100, K101, K103, V106, V108, E138, V179, Y181, Y188, V189, G190, H221, P225, F227, and M230

c. This combination of NRTI and NNRTI substitutions is a subset of those with the E138K.

d. A62V, K65R/N, D67N/G, K70E, L74I, Y115F, M184V/I, L210F, K219E/R

e. These substitutions emerged in addition to the primary substitutions M184V/I or K65R; A62V (n=2), D67N/G (n=3), K70E (n=4), Y115F (n=2), K219E/R (n=8) in rilpivirine resistance analysis subjects.

Reference ID: 3891182

In Virologically-Suppressed HIV-1-Infected Adult Subjects

Study 106: Through Week 48, 4 subjects who switched to COMPLERA (4 of 469 subjects, 0.9%) and 1 subject who maintained their ritonavir-boosted protease inhibitor-based regimen (1 of 159 subjects, 0.6%) developed genotypic and/or phenotypic resistance to a study drug. All 4 of the subjects who had resistance emergence on COMPLERA had evidence of emtricitabine resistance and 3 of the subjects had evidence of rilpivirine resistance.

Cross Resistance

Rilpivirine, Emtricitabine, and Tenofovir Disoproxil Fumarate:

In Cell Culture

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

Rilpivirine:

Site-Directed NNRTI Mutant Virus

Cross-resistance has been observed among NNRTIs. The single NNRTI substitutions K101P, Y181I, and Y181V conferred 52-fold, 15-fold, and 12-fold decreased susceptibility to rilpivirine, respectively. The combination of E138K and M184I showed 6.7-fold reduced susceptibility to rilpivirine compared to 2.8-fold for E138K alone. The K103N substitution did not show reduced susceptibility to rilpivirine by itself. However, the combination of K103N and L100I resulted in a 7-fold reduced susceptibility to rilpivirine. In another study, the Y188L substitution resulted in a reduced susceptibility to rilpivirine of 9-fold for clinical isolates and 6-fold for site-directed mutants. Combinations of 2 or 3 NNRTI resistance-associated substitutions gave decreased susceptibility to rilpivirine (fold change range of 3.7–554) in 38% and 66% of mutants, respectively.

In HIV-1-Infected Adult Subjects With No Antiretroviral Treatment History

Considering all of the available cell culture and clinical data, any of the following amino acid substitutions, when present at baseline, are likely to decrease the antiviral activity of rilpivirine: K101E, K101P, E138A, E138G, E138K, E138R, E138Q, V179L, Y181C, Y181I, Y181V, Y188L, H221Y, F227C, M230I, M230L, and the combination of L100I+K103N.

Cross-resistance to efavirenz, etravirine, and/or nevirapine is likely after virologic failure and development of rilpivirine resistance. In a pooled 96-week analysis for adult subjects receiving rilpivirine in combination with emtricitabine/tenofovir DF in the Phase 3 clinical trials TMC278-C209 and TMC278-C215, 43 of the 70 (61%) rilpivirine resistance analysis subjects with postbaseline resistance data had virus with decreased susceptibility to rilpivirine (≥2.5 fold). Of these, 84% (n=36/43) were resistant to efavirenz (≥3.3-fold change), 88% (n=38/43) were resistant to etravirine (≥3.2-fold change), and 60% (n=26/43) were resistant to nevirapine (≥6-fold change). In the efavirenz arm, 3 of the 15 (20%) efavirenz resistance analysis subjects had viruses with

resistance to etravirine and rilpivirine, and 93% (14/15) had resistance to nevirapine. Virus from subjects experiencing virologic failure on rilpivirine in combination with emtricitabine/tenofovir DF developed more NNRTI resistance-associated substitutions conferring more cross-resistance to the NNRTI class and had a higher likelihood of cross-resistance to all NNRTIs in the class than subjects who failed on efavirenz.

Emtricitabine: Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine but retained susceptibility in cell culture to didanosine, stavudine, tenofovir, zidovudine, and NNRTIs (delavirdine, efavirenz, nevirapine, and rilpivirine). HIV-1 isolates containing the K65R substitution, selected in vivo by abacavir, didanosine, and tenofovir, demonstrated reduced susceptibility to inhibition by emtricitabine. Viruses harboring substitutions conferring reduced susceptibility to stavudine and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E), or didanosine (L74V), remained sensitive to emtricitabine. HIV-1 containing the substitutions associated with NNRTI resistance K103N or rilpivirine-associated substitutions were susceptible to emtricitabine.

Tenofovir Disoproxil Fumarate: The K65R and K70E substitutions selected by tenofovir are also selected in some HIV-1-infected patients treated with abacavir or didanosine. HIV-1 isolates with the K65R and K70E substitutions also showed reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these NRTIs may occur in patients whose virus harbors the K65R substitution. 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.

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 rilpivirine-associated substitutions, were susceptible to tenofovir.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

Reference ID: 3891182

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: 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 per kg per day were administered to mice and doses of 40, 200, 500, and 1500 mg per kg per day were administered to rats. In rats, there were no drug-related neoplasms. In mice, rilpivirine was positive for hepatocellular neoplasms in both males and females. The observed hepatocellular findings in mice may be rodent-specific. At the lowest tested doses in the carcinogenicity studies, the systemic exposures (based on AUC) to rilpivirine were 21 fold (mice) and 3 fold (rats), relative to those observed in humans at the recommended dose (25 mg once daily).

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

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

Tenofovir Disoproxil Fumarate: Long-term oral carcinogenicity studies of tenofovir DF in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.

Tenofovir DF was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus assay, tenofovir DF was negative when administered to male mice.

There were no effects on fertility, mating performance, or early embryonic development when tenofovir DF was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day 7 of gestation. There was, however, an alteration of the estrous cycle in female rats.

13.2 Animal Toxicology and/or Pharmacology

Tenofovir Disoproxil Fumarate: Tenofovir and tenofovir DF administered in toxicology studies to rats, dogs, and monkeys at exposures (based on AUCs) greater than or equal to 6-fold those observed in humans caused bone toxicity. In monkeys the bone toxicity

was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

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

14 CLINICAL STUDIES

14.1 Adult Subjects

In HIV-1-Infected Adult Subjects With No Antiretroviral Treatment History

The efficacy of COMPLERA is based on the analyses of 48- and 96-week data from two randomized, double-blind, controlled studies (Study C209 [ECHO] and TRUVADA subset of Study C215 [THRIVE]) in treatment-naïve, HIV-1-infected subjects (N=1368). The studies are identical in design with the exception of the background regimen (BR). Subjects were randomized in a 1:1 ratio to receive either rilpivirine 25 mg (N=686) once daily or efavirenz 600 mg (N=682) once daily in addition to a BR. In Study C209 (N=690), the BR was emtricitabine/tenofovir DF. In Study C215 (N=678), the BR consisted of 2 NRTIs: emtricitabine/tenofovir DF (60%, n=406), lamivudine/zidovudine (30%, n=204), or abacavir + lamivudine (10%, n=68).

For subjects who received emtricitabine/tenofovir DF (N=1096) in studies C209 and C215, the mean age was 37 years (range 18–78), 78% were male, 62% were White, 24% were Black, and 11% were Asian. The mean baseline CD4+ cell count was 265 cells/mm^3 (range 1–888) and 31% had CD4+ cell counts <200 cells/mm^3. The median baseline plasma HIV-1 RNA was 5 $\log_{10}$ copies/mL (range 2–7). Subjects were stratified by baseline HIV-1 RNA. Fifty percent of subjects had baseline viral load ≤100,000 copies/mL, 39% of subjects had baseline viral load between 100,000 copies/mL to 500,000 copies/mL, and 11% of subjects had baseline viral load >500,000 copies/mL.

Treatment outcomes through 96 weeks for the subset of subjects receiving emtricitabine/tenofovir DF in studies C209 and C215 (Table 10) are generally consistent with treatment outcomes for all participating subjects (presented in the prescribing information for Edurant). The incidence of virologic failure was higher in the rilpivirine arm than the efavirenz arm at Week 96. Virologic failures and discontinuations due to adverse events mostly occurred in the first 48 weeks of treatment.

Table 10 Virologic Outcome of Randomized Treatment of Studies C209 and C215 (Pooled Data for Subjects Receiving Rilpivirine or Efavirenz in Combination with Emtricitabine/Tenofovir DF) at Week 96[a]

	Rilpivirine + FTC/TDF	Efavirenz + FTC/TDF
	N=550	N=546
HIV-1 RNA <50 copies/mL[b]	77%	77%
HIV-1 RNA ≥50 copies/mL[c]	14%	8%
No Virologic Data at Week 96 Window		
Reasons		
Discontinued study due to adverse event or death[d]	4%	9%
Discontinued study for other reasons[e] and the last available HIV-1 RNA <50 copies/mL (or missing)	4%	6%
Missing data during window but on study	<1%	<1%
HIV-1 RNA <50 copies/mL by Baseline HIV-1 RNA (copies/mL)		
≤100,000	83%	80%
>100,000	71%	74%
HIV-1 RNA ≥50 copies/mL[c] by Baseline HIV-1 RNA (copies/mL)		
≤100,000	7%	5%
>100,000	22%	12%
HIV-1 RNA <50 copies/mL by Baseline CD4+ Cell Count (cells/mm^3)		
<200	68%	72%
≥200	82%	79%
HIV-1 RNA ≥50 copies/mL[c] by Baseline CD4+ Cell Count (cells/mm^3)		
<200	27%	12%
≥200	8%	7%

a. Analyses were based on the last observed viral load data within the Week 96 window (Week 90–103).

b. Predicted difference (95% CI) of response rate is 0.5% (–4.5% to 5.5%) at Week 96.

c. Includes subjects who had ≥50 copies/mL in the Week 96 window, subjects who discontinued early due to lack or loss of efficacy, subjects who discontinued for reasons other than an adverse event, death, or lack or loss of efficacy and at the time of discontinuation had a viral load value of ≥50 copies/mL, and subjects who had a switch in background regimen that was not permitted by the protocol.

d. Includes subjects who discontinued due to an adverse event or death if this resulted in no on-treatment virologic data in the Week 96 window.

e. Includes subjects 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.

Reference ID: 3891182

Based on the pooled data from studies C209 and C215, the mean CD4+ cell count increase from baseline at Week 96 was 226 cells/mm^3 for rilpivirine + emtricitabine/tenofovir DF-treated subjects and 223 cells/mm^3 for efavirenz + emtricitabine/tenofovir DF-treated subjects.

In Virologically-Suppressed HIV-1-Infected Adult Subjects

The efficacy and safety of switching from a ritonavir-boosted protease inhibitor in combination with two NRTIs to COMPLERA was evaluated in Study 106, a randomized, open-label study in virologically-suppressed HIV-1-infected adults. Subjects 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 suppressed (HIV-1 RNA <50 copies/mL) for at least 6 months prior to screening. Subjects were randomized in a 2:1 ratio to either switch to COMPLERA at baseline (COMPLERA arm, N=317), or stay on their baseline antiretroviral regimen for 24 weeks (SBR arm, N=159) and then switch to COMPLERA for an additional 24 weeks (N=52). Subjects had a mean age of 42 years (range 19–73), 88% were male, 77% were White, 17% were Black, and 17% were Hispanic/Latino. The mean baseline CD4+ cell count was 584 cells/mm^3 (range 42–1484). Randomization was stratified by use of tenofovir DF and/or lopinavir/ritonavir in the baseline regimen.

Treatment outcomes are presented in Table 11.

Table 11 Virologic Outcomes of Randomized Treatment in Study GS-US-264-0106

	COMPLERA **Week 48[a]**	**Stayed on Baseline Regimen (SBR)** **Week 24[b]**
	N=317	**N=159**
HIV-1 RNA <50 copies/mL[c]	89% (283/317)	90% (143/159)
HIV-1 RNA ≥50 copies/mL[d]	3% (8/317)	5% (8/159)
No Virologic Data at Week 24 Window		
Discontinued study drug due to AE or death[e]	2% (7/317)	0%
Discontinued study drug due to other reasons and last available HIV-1 RNA <50 copies/mL[f]	5% (16/317)	3% (5/159)
Missing data during window but on study drug	1% (3/317)	2% (3/159)

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%).

Reference ID: 3891182

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

e. Includes subjects 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 subjects 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.

14.2 Pediatric Subjects

The pharmacokinetics, safety, and efficacy of rilpivirine in combination with other antiretroviral agents was evaluated in a single-arm, open-label Phase 2 trial in antiretroviral treatment-naïve HIV-1-infected pediatric subjects 12 to less than 18 years of age and weighing at least 32 kg (TMC-C213). Thirty-six (36) subjects were enrolled with a median age of 14.5 years (range 12 to 17 years), and were 55.6% female, 88.9% Black, and 11.1% Asian. The majority of subjects (24/36) received rilpivirine in combination with emtricitabine and tenofovir DF. Of these 24 subjects, 20 had baseline HIV RNA ≤100,000 copies/mL. The baseline characteristics and efficacy outcomes at Week 48 are further described below for the 20 subjects.

The median baseline plasma HIV-1 RNA and CD4+ cell count were 49,550 (range 2060 to 92,600 copies/mL) and 437.5 cells/mm^3 (range 123 to 983 cells/mm^3), respectively. At Week 48, 80% (16/20) of the subjects had HIV RNA <50 copies/mL, 15% (3/20) had HIV RNA ≥50 copies/mL, and one subject discontinued therapy prior to Week 48 and before reaching virologic suppression (HIV RNA <50 copies/mL). At Week 48, the mean increase in CD4+ cell count from baseline was 225 cells/mm^3.

16 HOW SUPPLIED/STORAGE AND HANDLING

COMPLERA tablets are purplish pink, capsule shaped, film coated, debossed with “GSI” on one side, and plain faced on the other side. Each bottle contains 30 tablets (NDC 61958-1101-1), a silica gel desiccant, and a polyester fiber coil, and is closed with a child-resistant closure.

Store at 25 °C (77 °F), excursions permitted to 15 °C–30 °C (59 °F–86 °F) *[see USP Controlled Room Temperature].*

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

A statement to patients and healthcare providers is included on the product's bottle label: **ALERT: Find out about medicines that should NOT be taken with**

COMPLERA. A Patient Package Insert for COMPLERA is available for patient information.

Information for Patients

Advise patients to remain under the care of a healthcare provider when using COMPLERA.

Inform patients that COMPLERA is not a cure for HIV infection. Patients should stay on continuous HIV therapy to control HIV infection and decrease HIV-related illnesses. Inform patients that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death.

Advise patients to continue to practice safer sex, and to use latex or polyurethane condoms to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood. Advise patients to never re-use or share needles.

Inform patients that there is a pregnancy exposure registry available that monitors outcomes in women exposed to COMPLERA during pregnancy *[See Use in Specific Populations (8.1)].*

Nursing Mothers

Advise patients not to breastfeed because at least two of the drugs contained in COMPLERA can be passed to the baby in breast milk. It is not known whether this could harm the baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in breast milk.

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Inform patients that lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Treatment with COMPLERA should be suspended in any patients who develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity (including nausea, vomiting, unusual or unexpected stomach discomfort, and weakness) *[See Warnings and Precautions (5.1)]*.

Patients Coinfected with HIV-1 and HBV

Inform patients with HIV-1 that they should be tested for hepatitis B virus (HBV) before initiating antiretroviral therapy. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and who have discontinued EMTRIVA or VIREAD *[See Warnings and Precautions (5.2)]*. Patients should not discontinue COMPLERA without first informing their healthcare provider.

Severe Skin Reactions and Hypersensitivity

Inform patients that skin reactions ranging from mild to severe, including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), have been reported with COMPLERA. Instruct patients to immediately stop taking COMPLERA and seek medical attention if they develop a rash associated with any of the following symptoms: fever, blisters, mucosal involvement, eye inflammation (conjunctivitis), severe allergic reaction causing swelling of the face, eyes, lips, mouth, tongue or throat which may lead

to difficulty swallowing or breathing, and any signs and symptoms of liver problems, as they may be a sign of a more serious reaction. Patients should understand that if severe rash occurs, they will be closely monitored, laboratory tests will be performed and appropriate therapy will be initiated *[See Warnings and Precautions (5.3)].*

New Onset or Worsening Renal Impairment

Inform patients that renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported in association with the use of VIREAD. COMPLERA should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple NSAIDs) *[See Warnings and Precautions (5.4)]*.

Drug Interactions

Inform patients that:

- COMPLERA may interact with many drugs; therefore, patients should report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John's wort *[See Warnings and Precautions (5.5)]*.
- COMPLERA should not be coadministered with the following drugs, as significant decreases in rilpivirine plasma concentrations may occur due to CYP3A enzyme induction or gastric pH increase, which may result in loss of virologic response and possible resistance to COMPLERA or to the class of NNRTIs: the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, and phenytoin; the antimycobacterials rifampin and rifapentine; proton pump inhibitors, such as esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole; the glucocorticoid systemic dexamethasone (more than a single dose); or St. John's wort (*Hypericum perforatum*) *[See Contraindications (4)]*.
- COMPLERA should not be coadministered with ATRIPLA, EMTRIVA, STRIBILD, TRUVADA, or VIREAD; or with drugs containing lamivudine, including Combivir, Epivir or Epivir-HBV, Epzicom, Triumeq, or Trizivir; or with HEPSERA. COMPLERA should not be coadministered with rilpivirine (Edurant) unless needed for dose adjustment (e.g., with rifabutin) *[See Warnings and Precautions (5.9)]*.
- For patients receiving rifabutin, an additional 25 mg tablet of rilpivirine (Edurant) once per day is recommended to be taken concomitantly with COMPLERA and with a meal for the duration of rifabutin coadministration.

Depressive Disorders

Inform patients that depressive disorders (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) have been reported with COMPLERA. If they experience depressive symptoms, they should seek immediate medical evaluation *[See Warnings and Precautions (5.6)].*

Hepatotoxicity

Inform patients that hepatotoxicity has been reported with COMPLERA *[See Warnings and Precautions (5.7)]*.

Bone Effects

Inform patients that decreases in bone mineral density have been observed with the use of VIREAD. Bone mineral density (BMD) monitoring should be considered in patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss *[See Warnings and Precautions (5.8)].* Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, and that the cause and long-term health effects of these conditions are not known *[See Warnings and Precautions (5.10)]*.

Inflammation in Patients with AIDS

Inform patients that, in some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. Advise patients to inform their healthcare provider immediately of any symptoms of infection *[See Warnings and Precautions (5.11)].*

Dosing Instructions

Advise patients that:

- It is important to take COMPLERA on a regular dosing schedule with food and to avoid missing doses. A protein drink is not a substitute for food. If the healthcare provider decides to stop COMPLERA and the patient is switched to new medicines to treat HIV that include rilpivirine tablets, the rilpivirine tablets should be taken only with a meal.
- 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. Inform the patient that he or she should not take more or less than the prescribed dose of COMPLERA at any one time. For patients receiving rifabutin, an additional 25 mg tablet of rilpivirine (Edurant) once per day is recommended to be taken concomitantly with COMPLERA and with a meal for the duration of rifabutin coadministration.

Manufactured and distributed by:

Gilead Sciences, Inc.

Foster City, CA 94404

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Patient Information
COMPLERA® (kom-PLEH-rah)
(emtricitabine, rilpivirine, tenofovir disoproxil fumarate)
tablets

Important: Ask your healthcare provider or pharmacist about medicines that should not be taken with COMPLERA. For more information, see the section "What should I tell my healthcare provider before taking COMPLERA?"

Read this Patient Information before you start taking COMPLERA and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about COMPLERA?

COMPLERA can cause serious side effects, including:

- **Build-up of an acid in your blood (lactic acidosis).** Lactic acidosis can happen in some people who take COMPLERA or similar medicines (nucleoside analogs). **Lactic acidosis** is a serious medical emergency that can lead to death.

  Lactic acidosis can be hard to identify early, because the symptoms could seem like symptoms of other health problems. **Call your healthcare provider right away if you get any of the following symptoms which could be signs of lactic acidosis:**
  - feel very weak or tired
  - have unusual (not normal) muscle pain
  - have trouble breathing
  - have stomach pain with nausea and vomiting
  - feel cold, especially in your arms and legs
  - feel dizzy or lightheaded
  - have a fast or irregular heartbeat

- **Severe liver problems.** Severe liver problems can happen in people who take COMPLERA or similar medicines. In some cases these liver problems can lead to death. Your liver may become large (hepatomegaly) and you may develop fat in your liver (steatosis).

Call your healthcare provider right away if you have any of the following symptoms of liver problems:
  - your skin or the white part of your eyes turns yellow (jaundice)
  - dark or "tea-colored" urine
  - light colored stools (bowel movements)
  - loss of appetite
  - nausea
  - pain, aching, or tenderness on the right side of your stomach area

- **You may be more likely to get lactic acidosis or severe liver problems if you are female, are very overweight (obese), or have been taking nucleoside analog medicines for a long time.**

  Worsening of Hepatitis B infection. If you have both HIV-1 and hepatitis B virus (HBV) infections, your HBV may get worse (flare-up) if you stop taking COMPLERA. A "flare-up" is when your HBV infection suddenly returns in a worse way than before. COMPLERA is not approved for the treatment of HBV, so you must discuss your HBV therapy with your healthcare provider.
  - Do not run out of COMPLERA. Refill your prescription or talk to your healthcare provider before your COMPLERA is all gone.
  - Do not stop taking COMPLERA without first talking to your healthcare provider.
  - If you stop taking COMPLERA, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your HBV infection. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking COMPLERA.

For more information about side effects, see the section "**What are the possible side effects of COMPLERA?**".

What is COMPLERA?

COMPLERA is a prescription HIV-1 (Human Immunodeficiency Virus) medicine. HIV-1 is the virus that causes AIDS (Acquired Immunodeficiency Syndrome).

COMPLERA is used to treat HIV-1 infection in people 12 years of age and older who:

- have **never** taken HIV-1 medicines before, **and** who have an amount of HIV-1 in their blood (this is called 'viral load') that is no more than 100,000 copies/mL before they start taking COMPLERA,
  and
- in certain people who have a viral load that is less than 50 copies/mL when they start taking COMPLERA, to replace their current HIV-1 medicines.

Your healthcare provider will measure your viral load.

COMPLERA contains 3 medicines (emtricitabine, rilpivirine, tenofovir disoproxil fumarate) combined in one tablet. Emtricitabine (EMTRIVA®) and tenofovir disoproxil fumarate (VIREAD®) are HIV-1 nucleoside analog reverse transcriptase inhibitors (NRTIs). Rilpivirine (Edurant®) is an HIV-1 non-nucleoside analog reverse transcriptase inhibitor (NNRTI).

It is not known if COMPLERA is safe and effective in children less than 12 years of age or who weigh less than 77 lb (35 kg).

COMPLERA may help:

- Reduce the amount of HIV-1 in your blood. This is called "viral load".
- Increase the number of CD4+ (T) cells in your blood that help fight off other infections.

Reducing the amount of HIV-1 and increasing the CD4+ (T) cells in your blood may help improve your immune system. This may reduce your risk of death or getting infections that can happen when your immune system is weak (opportunistic infections).

COMPLERA does not cure HIV-1 infections or AIDS. You must keep taking HIV-1 medicines to control HIV-1 infection and decrease HIV-related illnesses.

Avoid doing things that can spread HIV-1 infection to others:

- Do not share or re-use needles or other injection equipment.
- Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.
- Do not have any kind of sex without protection. Always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood.

Ask your healthcare provider if you have any questions about how to prevent passing HIV-1 to other people.

Who should not take COMPLERA?

Do not take COMPLERA if:

- you are taking any of the following medicines:
  - anti-seizure medicines:
    - carbamazepine (Carbatrol®, Epitol® Equetro®, Tegretol®, Tegretol- XR®, Teril®)
    - oxcarbazepine (Oxtellar XR®, Trileptal®)
    - phenobarbital (Luminal®)
    - phenytoin (Dilantin®, Dilantin-125®, Phenytek®)
  - anti-tuberculosis (anti-TB) medicines:
    - rifampin (Rifater®, Rifamate®, Rimactane®, Rifadin®)
    - rifapentine (Priftin®)
  - proton pump inhibitor (PPI) medicine for certain stomach or intestinal problems:
    - dexlansoprazole (Dexilant®)
    - esomeprazole (Nexium®, Vimovo®)
    - lansoprazole (Prevacid®, Prevpac®)
    - omeprazole (Prilosec®, Zegerid®)
    - pantoprazole sodium (Protonix®)
    - rabeprazole (Aciphex®, Aciphex Sprinkle®)
  - more than 1 dose of the steroid medicine dexamethasone or dexamethasone sodium phosphate
  - St. John's wort (*Hypericum perforatum*)

What should I tell my healthcare provider before taking COMPLERA?

Before you take COMPLERA, tell your healthcare provider if you:

- have liver problems, including hepatitis B or C virus infection
- have kidney problems
- have ever had a mental health problem
- have bone problems
- are pregnant or plan to become pregnant. It is not known if COMPLERA can harm your unborn child.

  Pregnancy Registry. There is a pregnancy registry for women who take antiretroviral medicines during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.
- are breastfeeding or plan to breastfeed. You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby. Do not breastfeed if you are taking COMPLERA. At least two of the medicines contained in COMPLERA can be passed to your baby in your breast milk. We do not know whether this could harm your baby. Talk to your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some medicines interact with COMPLERA. Keep a list of your medicines to show your healthcare provider and pharmacist.

- You can ask your healthcare provider or pharmacist for a list of medicines that can interact with COMPLERA.
- Do not start taking a new medicine without telling your healthcare provider. Your healthcare provider can tell you if it is safe to take COMPLERA with other medicines.

How should I take COMPLERA?

- **Stay under the care of your healthcare provider during treatment with COMPLERA.**
- **Take COMPLERA exactly as your healthcare provider tells you to take it.**
- **Always take COMPLERA with food.** Taking COMPLERA with food is important to help get the right amount of medicine in your body. A protein drink does not replace food. If your healthcare provider decides to stop COMPLERA and you are switched to new medicines to treat HIV-1 that include rilpivirine tablets, the rilpivirine tablets should be taken only with a meal.
- Do not change your dose or stop taking COMPLERA without first talking with your healthcare provider. See your healthcare provider regularly while taking COMPLERA.
- If you miss a dose of COMPLERA within 12 hours of the time you usually take it, take your dose of COMPLERA **with food** as soon as possible. Then, take your 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 take more than your prescribed dose to make up for a missed dose.
- When your COMPLERA supply starts to run low, get more from your healthcare provider or pharmacy. It is very important not to run out of COMPLERA. The amount of virus in your blood may increase if the medicine is stopped for even a short time.
- If you take too much COMPLERA, contact your local poison control center or go to the nearest hospital emergency room right away.

What are the possible side effects of COMPLERA?

COMPLERA can cause serious side effects, including:

- **See "What is the most important information I should know about COMPLERA?"**
  Severe skin rash and allergic reactions. Skin rash is a common side effect of COMPLERA. Rash can be serious. Call your healthcare provider right away if you get a rash. In some cases, rash and allergic reaction may need to be treated in a hospital. **If you get a rash with any of the following symptoms, stop taking COMPLERA and call your healthcare provider or get medical help right away:**
  - fever
  - skin blisters
  - mouth sores
  - redness or swelling of the eyes (conjunctivitis)
  - swelling of the face, lips, mouth, tongue or throat
  - trouble breathing or swallowing
  - pain on the right side of the stomach (abdominal) area
  - dark or "tea colored" urine
- **New or worse kidney problems, including kidney failure,** can happen in some people who take COMPLERA. Your healthcare provider should do blood tests to check your kidneys before starting treatment with COMPLERA. If you have had kidney problems in the past or need to take another medicine that can cause kidney problems, your healthcare provider may need to do blood tests to check your kidneys during your treatment with COMPLERA.
- **Depression or mood changes. Tell your healthcare provider right away if you have any of the following symptoms:**
  - feel sad or hopeless
  - feel anxious or restless
  - have thoughts of hurting yourself (suicide) or have tried to hurt yourself
- **Change in liver enzymes**. People with a history of hepatitis B or C virus infection or who have certain liver enzyme changes may have an increased risk of developing new or worsening liver problems during treatment with COMPLERA. Liver problems can also happen during treatment with COMPLERA in people without a history of liver disease. Your healthcare provider may need to do tests to check your liver enzymes before and during treatment with COMPLERA.
- **Bone problems** can happen in some people who take COMPLERA. Bone problems include bone pain, softening, or thinning (which may lead to fractures). Your healthcare provider may need to do additional tests to check your bones.
- **Changes in body fat** can happen in people taking HIV-1 medicine. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the middle part of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term health effect of these conditions are not known.
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having new symptoms after starting your HIV-1 medicine.

The most common side effects of rilpivirine, one of the medicines in COMPLERA, include:

- depression
- trouble sleeping
- headache

The most common side effects of emtricitabine and tenofovir disoproxil fumarate, two of the medicines in COMPLERA, include:

- diarrhea
- nausea
- tiredness
- headache
- dizziness
- depression
- trouble sleeping
- abnormal dreams
- rash

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of COMPLERA. For more information, ask your healthcare provider or pharmacist.
Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store COMPLERA?

- Store COMPLERA at room temperature between 68 °F to 77 °F (20 °C to 25 °C).
- Keep COMPLERA in its original container and keep the container tightly closed.
- Do not use COMPLERA if the seal over the bottle opening is broken or missing.

Keep COMPLERA and all other medicines out of reach of children.

General information about safe and effective use of COMPLERA

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use COMPLERA for a condition for which it was not prescribed. Do not give COMPLERA to other people, even if they have the same symptoms you have. It may harm them.

If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about COMPLERA that is written for health professionals. For more information, call 1-800-445-3235 or go to www.COMPLERA.com.

What are the ingredients of COMPLERA?

Active ingredients: emtricitabine, rilpivirine hydrochloride, and tenofovir disoproxil fumarate.

Inactive ingredients: pregelatinized starch, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, povidone, polysorbate 20. The tablet 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.

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