CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21752Orig1s060

Trade Name:	**Truvada**
Generic or Proper Name:	Emtricitabine and tenofovir fumarate
Sponsor:	GILEAD SCIENCES INC
Approval Date:	July 1, 2019

Indication:

Truvada (emtricitabine and tenofavir fumarate) is a two-drug combination of emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF), both HIV-1nucleoside analog reverse transcriptase inhibitors, and is indicated:

- in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 17 kg

HIV-1 PrEP

- Truvada is indicated in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection. Individuals must have a negative HIV-1 test immediately prior to initiating Truvada for HIV-1 PrEP.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

NDA 021752/S-060

SUPPLEMENT APPROVAL

Gilead Sciences, Inc.
Attention: Linda Fletcher, PharmD
Senior Associate, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Fletcher:

Please refer to your supplemental new drug application (sNDA) dated and received on March 27, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TRUVADA® (emtricitabine and tenofovir disoproxil fumarate) tablets, for oral use.

This Prior Approval supplemental new drug application provides for proposed modifications to the approved emtricitabine/tenofovir disoproxil fumarate Single Shared System (SSS) REMS. We acknowledge that your application included a rationale to support the proposed REMS modifications.

APPROVAL

We have completed our review of this application, as amended. It is approved, effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for TRUVADA® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) for a pre-exposure prophylaxis (PrEP) indication was originally approved on July 16, 2012, and the SSS REMS for emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg was approved on June 8, 2017. The REMS consists of elements to assure safe use (ETASU) and a timetable for submission of assessments of the REMS. Your proposed modification to the SSS REMS consists of eliminating the ETASU, including educational and training materials.

Elements to Assure Safe Use: We have determined that elements to assure safe use are no longer necessary because:

- Since approval, non-REMS educational programs (e.g., Centers for Disease Control and Prevention and local health departments; Department of Health and Human Services initiative) and clinical guidelines for PrEP have become readily available and support greater awareness, education, and knowledge of PrEP

among healthcare professionals (HCPs), PrEP users, and public health communities. These materials and guidelines convey:
    - the importance of strict adherence to the recommended dosing schedule
    - importance of regular monitoring of HIV-1 serostatus to avoid continuing to take emtricitabine/tenofovir disoproxil fumarate alone if seroconversion has occurred
    - that emtricitabine/tenofovir disoproxil fumarate for a PrEP indication should only be used as part of a comprehensive prevention strategy that includes other preventive measures
- The REMS assessments have been completed and the available information indicates that prescribers and uninfected individuals understand the important key messages with regards to appropriate use of emtricitabine/tenofovir disoproxil fumarate for a PrEP indication.

Therefore, because the elements to assure safe use are no longer necessary to ensure the benefits of the drug outweigh the risks, a REMS is no longer required for emtricitabine/tenofovir disoproxil fumarate tablets, for oral use.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Alicia Moruf, PharmD, MPH, Regulatory Project Manager, at 301-796-3953.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21752rig1s060

LABELING

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

TRUVADA® (emtricitabine and tenofovir disoproxil fumarate) tablets, for oral use
Initial U.S. Approval: 2004

WARNING: POSTTREATMENT ACUTE EXACERBATION OF HEPATITIS B and RISK OF DRUG RESISTANCE WITH USE OF TRUVADA FOR HIV-1 PRE-EXPOSURE PROPHYLAXIS (PrEP) IN UNDIAGNOSED EARLY HIV-1 INFECTION
See full prescribing information for complete boxed warning.

- **Severe acute exacerbations of hepatitis B (HBV) have been reported in HBV-infected individuals who have discontinued TRUVADA. Hepatic function should be monitored closely in these individuals who discontinue TRUVADA. If appropriate anti-hepatitis B therapy may be warranted. (5.1)**
- **TRUVADA used for HIV-1 PrEP must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiating and at least every 3 months during use. Drug-resistant HIV-1 variants have been identified with the use of TRUVADA for HIV-1 PrEP following undetected acute HIV-1 infection. Do not initiate TRUVADA for HIV-1 PrEP if signs or symptoms of acute HIV infection are present unless negative infection status is confirmed. (5.2)**

----------INDICATIONS AND USAGE----------
HIV-1 Treatment (1.1)
TRUVADA is a two-drug combination of emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF), both HIV-1 nucleoside analog reverse transcriptase inhibitors, and is indicated:
- in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 17 kg.

HIV-1 PrEP (1.2):
- TRUVADA is indicated in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection. Individuals must have a negative HIV-1 test immediately prior to initiating TRUVADA for HIV-1 PrEP.

----------DOSAGE AND ADMINISTRATION----------
- Testing: Prior to or when initiating TRUVADA test for hepatitis B virus infection. Prior to initiation and during use of TRUVADA, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all individuals. In individuals with chronic kidney disease, also assess serum phosphorus. (2.1)
- HIV-1 Screening: Screen all individuals for HIV-1 infection immediately prior to initiating TRUVADA for HIV-1 PrEP and at least once every 3 months while taking TRUVADA, and upon diagnosis of any other sexually transmitted infections (STIs). (2.2)

Treatment of HIV-1 Infection
- Recommended dosage in adults and pediatric patients weighing at least 35 kg: One TRUVADA tablet (containing 200 mg of FTC and 300 mg of TDF) once daily taken orally with or without food. (2.3)
- Recommended dosage in pediatric patients weighing at least 17 kg: One TRUVADA low-strength tablet (100 mg/150 mg, 133 mg/200 mg, or 167 mg/250 mg based on body weight) once daily taken orally with or without food. (2.4)
- Recommended dosage in renally impaired HIV-1 infected adult patients:
  - Creatinine clearance (CrCl) 30–49 mL/min: 1 tablet every 48 hours. (2.6)
  - CrCl below 30 mL/min or hemodialysis: TRUVADA is not recommended. (2.6)

HIV-1 Pre-Exposure Prophylaxis (PrEP)
- Recommended dosage in HIV-1 uninfected adults and adolescents weighing at least 35 kg: One TRUVADA tablet (containing 200 mg of FTC and 300 mg of TDF) once daily taken orally with or without food. (2.5)
- Recommended dosage in renally impaired HIV-uninfected individuals: TRUVADA is not recommended in HIV-uninfected individuals if CrCl is below 60 mL/min. (2.6)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 200 mg/300 mg, 167 mg/250 mg, 133 mg/200 mg, and 100 mg/150 mg of emtricitabine and tenofovir disoproxil fumarate, respectively. (3)

----------CONTRAINDICATIONS----------
TRUVADA for HIV-1 PrEP is contraindicated in individuals with unknown or positive HIV-1 status. (4)

----------WARNINGS AND PRECAUTIONS----------
- Comprehensive management to reduce the risk of acquiring HIV-1 when TRUVADA is used for HIV-1 PrEP: Use as part of a comprehensive prevention strategy including other prevention measures; strictly adhere to dosing schedule. (5.2)
- Management to reduce the risk of acquiring HIV-1 drug resistance when TRUVADA is used for HIV-1 PrEP: refer to full prescribing information for additional detail. (5.2)
- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Avoid administering TRUVADA with concurrent or recent use of nephrotoxic drugs. (5.3)
- Immune reconstitution syndrome during treatment of HIV-1 infection: May necessitate further evaluation and treatment. (5.4)
- Decreases in bone mineral density (BMD): Consider assessment of BMD in individuals with a history of pathologic fracture or other risk factors for osteoporosis or bone loss. (5.5)
- Lactic acidosis/severe hepatomegaly with steatosis: Discontinue TRUVADA in individuals who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.6)

----------ADVERSE REACTIONS----------
- In HIV-1 infected patients, the most common adverse reactions (incidence greater than or equal to 10%) are diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash. (6.1)
- In HIV-1 uninfected adults in PrEP trials, adverse reactions that were reported by more than 2% of TRUVADA participants and more frequently than by placebo participants were headache, abdominal pain, and weight decreased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-445-3235 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------
- Tenofovir disoproxil fumarate increases didanosine concentrations. Dose reduction and close monitoring for didanosine toxicity are warranted. (7.2)
- Coadministration decreases atazanavir concentrations. When coadministered with TRUVADA, use atazanavir given with ritonavir. (7.2)
- Coadministration of TRUVADA with certain HIV-1 protease inhibitors or certain drugs to treat HCV increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity. (7.2)
- Consult Full Prescribing Information prior to and during treatment for important drug interactions. (7.2)

----------USE IN SPECIFIC POPULATIONS----------
Lactation: Mothers infected with HIV-1 or suspected of having acquired HIV-1 infection should be instructed not to breastfeed due to the potential for HIV transmission. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: POSTTREATMENT ACUTE EXACERBATION OF HEPATITIS B and RISK OF DRUG RESISTANCE WITH USE OF TRUVADA FOR HIV-1 PRE-EXPOSURE PROPHYLAXIS (PrEP) IN UNDIAGNOSED EARLY HIV-1 INFECTION

Severe acute exacerbations of hepatitis B (HBV) have been reported in HBV-infected individuals who have discontinued TRUVADA. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in individuals who are infected with HBV and discontinue TRUVADA. If appropriate, anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.1)]*.

TRUVADA used for HIV-1 PrEP must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiating and at least every 3 months during use. Drug-resistant HIV-1 variants have been identified with use of TRUVADA for HIV-1 PrEP following undetected acute HIV-1 infection. Do not initiate TRUVADA for HIV-1 PrEP if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

1.1 Treatment of HIV-1 Infection

TRUVADA is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 17 kg *[see Clinical Studies (14)]*.

1.2 HIV-1 Pre-Exposure Prophylaxis (PrEP)

TRUVADA is indicated in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection. Individuals must have a negative HIV-1 test immediately prior to initiating TRUVADA for HIV-1 PrEP *[see Dosage and Administration (2.2), Warnings and Precautions (5.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation of TRUVADA for Treatment of HIV-1 Infection or for HIV-1 PrEP

Prior to or when initiating TRUVADA, test individuals for hepatitis B virus infection *[see Warnings and Precautions (5.1)]*.

Prior to initiation, and during use of TRUVADA, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all individuals. In individuals with chronic kidney disease, also assess serum phosphorus *[see Warnings and Precautions (5.3)].*

2.2 HIV-1 Screening for Individuals Receiving TRUVADA for HIV-1 PrEP

Screen all individuals for HIV-1 infection immediately prior to initiating TRUVADA for HIV-1 PrEP and at least once every 3 months while taking TRUVADA, and upon diagnosis of any other sexually transmitted infections (STIs) *[see Indications and Usage (1.2), Contraindications (4), and Warnings and Precautions (5.2)].*

If recent (<1 month) exposures to HIV-1 are suspected or clinical symptoms consistent with acute HIV-1 infection are present, use a test approved or cleared by the FDA as an aid in the diagnosis of

acute or primary HIV-1 infection *[see Warnings and Precautions (5.2), Use in Specific Populations (8.4), and Clinical Studies (14.3 and 14.4)]*.

2.3 Recommended Dosage for Treatment of HIV-1 Infection in Adults and Pediatric Patients Weighing at Least 35 kg

TRUVADA is a two-drug fixed dose combination product containing emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF). The recommended dosage of TRUVADA in adults and in pediatric patients weighing at least 35 kg is one tablet (containing 200 mg of FTC and 300 mg of TDF) once daily taken orally with or without food *[see Clinical Pharmacology (12.3)]*.

2.4 Recommended Dosage for Treatment of HIV-1 Infection in Pediatric Patients Weighing at Least 17 kg and Able to Swallow a Tablet

The recommended oral dosage of TRUVADA for pediatric patients weighing at least 17 kg and who can swallow a tablet is presented in Table 1. Tablets should be taken once daily with or without food. Weight should be monitored periodically and the TRUVADA dose adjusted accordingly.

Table 1 Dosing for Treatment of HIV-1 Infection in Pediatric Patients Weighing 17 kg to less than 35 kg

Body Weight (kg)	Dosing of TRUVADA (FTC/TDF)
17 to less than 22	one 100 mg /150 mg tablet once daily
22 to less than 28	one 133 mg /200 mg tablet once daily
28 to less than 35	one 167 mg /250 mg tablet once daily

2.5 Recommended Dosage for HIV-1 PrEP in Adults and Adolescents Weighing at Least 35 kg

The dosage of TRUVADA for HIV-1 PrEP is one tablet (containing 200 mg of FTC and 300 mg of TDF) once daily taken orally with or without food in HIV-1 uninfected adults and adolescents weighing at least 35 kg *[see Clinical Pharmacology (12.3)]*.

2.6 Dosage Adjustment in Individuals with Renal Impairment

Treatment of HIV-1 Infection

Table 2 provides dosage interval adjustment for patients with renal impairment. No dosage adjustment is necessary for HIV-1 infected patients with mild renal impairment (creatinine clearance 50–80 mL/min). The safety and effectiveness of the dosing interval adjustment recommendations in patients with moderate renal impairment (creatinine clearance 30–49 mL/min) have not been clinically evaluated; therefore, clinical response to treatment and renal function should be closely monitored in these patients *[see Warnings and Precautions (5.3)]*.

No data are available to make dosage recommendations in pediatric patients with renal impairment.

Table 2 Dosage Interval Adjustment for HIV-1 Infected Adult Patients with Altered Creatinine Clearance

	Creatinine Clearance (mL/min)[a]		
	≥50	**30–49**	**<30 (Including Patients Requiring Hemodialysis)**
Recommended Dosing Interval	Every 24 hours	Every 48 hours	TRUVADA is not recommended.

a. Calculated using ideal (lean) body weight

HIV-1 PrEP

TRUVADA for HIV-1 PrEP is not recommended in HIV-1 uninfected individuals with estimated creatinine clearance below 60 mL/min *[see Warnings and Precautions (5.3)]*.

If a decrease in estimated creatinine clearance is observed in uninfected individuals while using TRUVADA for HIV-1 PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use *[see Warnings and Precautions (5.3)]*.

3 DOSAGE FORMS AND STRENGTHS

TRUVADA tablets are available in four dose strengths.

- 100 mg/150 mg Tablets: 100 mg of emtricitabine (FTC) and 150 mg of tenofovir disoproxil fumarate (TDF) (equivalent to 123 mg of tenofovir disoproxil): blue, oval shaped, film coated, debossed with “GSI” on one side and with “703” on the other side.
- 133 mg/200 mg Tablets: 133 mg of FTC and 200 mg of TDF (equivalent to 163 mg of tenofovir disoproxil): blue, rectangular shaped, film coated, debossed with “GSI” on one side and with “704” on the other side.
- 167 mg/250 mg Tablets: 167 mg of FTC and 250 mg of TDF (equivalent to 204 mg of tenofovir disoproxil): blue, modified capsule shaped, film coated, debossed with “GSI” on one side and with “705” on the other side.
- 200 mg/300 mg Tablets: 200 mg of FTC and 300 mg of TDF (equivalent to 245 mg of tenofovir disoproxil): blue, capsule shaped, film coated, debossed with “GILEAD” on one side and with “701” on the other side.

4 CONTRAINDICATIONS

TRUVADA for HIV-1 PrEP is contraindicated in individuals with unknown or positive HIV-1 status *[see Warnings and Precautions (5.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Severe Acute Exacerbation of Hepatitis B in Individuals with HBV Infection

All individuals should be tested for the presence of chronic hepatitis B virus (HBV) before or when initiating TRUVADA *[see Dosage and Administration (2.1)]*.

Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in HBV-infected individuals who have discontinued TRUVADA. Individuals infected with HBV who discontinue TRUVADA should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, anti-hepatitis B therapy may be warranted, especially in individuals with advanced liver disease or cirrhosis, since posttreatment

exacerbation of hepatitis may lead to hepatic decompensation and liver failure. HBV-uninfected individuals should be offered vaccination.

5.2 Comprehensive Management to Reduce the Risk of Sexually Transmitted Infections, Including HIV-1, and Development of HIV-1 Resistance When TRUVADA Is Used for HIV-1 PrEP

Use TRUVADA for HIV-1 PrEP to reduce the risk of HIV-1 infection as part of a comprehensive prevention strategy that includes other prevention measures, including adherence to daily administration and safer sex practices, including condoms, to reduce the risk of sexually transmitted infections (STIs). The time from initiation of TRUVADA for HIV-1 PrEP to maximal protection against HIV-1 infection is unknown.

Risk for HIV-1 acquisition includes behavioral, biological, or epidemiologic factors including but not limited to condomless sex, past or current STIs, self-identified HIV risk, having sexual partners of unknown HIV-1 viremic status, or sexual activity in a high prevalence area or network.

Counsel individuals on the use of other prevention measures (e.g., consistent and correct condom use, knowledge of partner(s)' HIV-1 status, including viral suppression status, regular testing for STIs that can facilitate HIV-1 transmission). Inform uninfected individuals about and support their efforts in reducing sexual risk behavior.

Use TRUVADA to reduce the risk of acquiring HIV-1 only in individuals confirmed to be HIV-negative**.** HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only TRUVADA, because TRUVADA alone does not constitute a complete regimen for HIV-1 treatment *[see Microbiology (12.4)];* therefore, care should be taken to minimize the risk of initiating or continuing TRUVADA before confirming the individual is HIV-1 negative.

- Some HIV-1 tests only detect anti-HIV antibodies and may not identify HIV-1 during the acute stage of infection. Prior to initiating TRUVADA for HIV-1 PrEP, ask seronegative individuals about recent (in past month) potential exposure events (e.g., condomless sex or condom breaking during sex with a partner of unknown HIV-1 status or unknown viremic status, or a recent STI), and evaluate for current or recent signs or symptoms consistent with acute HIV-1 infection (e.g., fever, fatigue, myalgia, skin rash).
- If recent (<1 month) exposures to HIV-1 are suspected or clinical symptoms consistent with acute HIV-1 infection are present, use a test approved or cleared by the FDA as an aid in the diagnosis of acute or primary HIV-1 infection.

While using TRUVADA for HIV-1 PrEP, HIV-1 testing should be repeated at least every 3 months, and upon diagnosis of any other STIs.

- If an HIV-1 test indicates possible HIV-1 infection, or if symptoms consistent with acute HIV-1 infection develop following a potential exposure event, convert the HIV-1 PrEP regimen to an HIV treatment regimen until negative infection status is confirmed using a test approved or cleared by the FDA as an aid in the diagnosis of acute or primary HIV-1 infection.

Counsel HIV-1 uninfected individuals to strictly adhere to the once daily TRUVADA dosing schedule. The effectiveness of TRUVADA in reducing the risk of acquiring HIV-1 is strongly correlated with adherence, as demonstrated by measurable drug levels in clinical trials of TRUVADA for HIV-1 PrEP. Some individuals, such as adolescents, may benefit from more frequent visits and counseling to support adherence *[see Use in Specific Populations (8.4), Microbiology (12.4), and Clinical Studies (14.3 and 14.4)]*.

5.3 New Onset or Worsening Renal Impairment

Emtricitabine and tenofovir are principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of TDF, a component of TRUVADA *[see Adverse Reactions (6.2)]*.

Prior to initiation and during use of TRUVADA, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all individuals. In individuals with chronic kidney disease, also assess serum phosphorus.

TRUVADA should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple non-steroidal anti-inflammatory drugs [NSAIDs]) *[see Drug Interactions (7.1)]*. 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 TDF. 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 individuals at risk of renal dysfunction.

Treatment of HIV-1 Infection

Dosing interval adjustment of TRUVADA and close monitoring of renal function are recommended in all patients with estimated creatinine clearance 30–49 mL/min *[see Dosage and Administration (2.6)]*. No safety or efficacy data are available in patients with renal impairment who received TRUVADA using these dosing guidelines, so the potential benefit of TRUVADA therapy should be assessed against the potential risk of renal toxicity. TRUVADA is not recommended in patients with estimated creatinine clearance below 30 mL/min or patients requiring hemodialysis.

HIV-1 PrEP

TRUVADA for HIV-1 PrEP is not recommended in uninfected individuals with estimated creatinine clearance less than 60 mL/min. If a decrease in estimated creatinine clearance is observed while using TRUVADA for HIV-1 PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use *[see Dosage and Administration (2.6)]*.

5.4 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in HIV-1 infected patients treated with combination antiretroviral therapy, including TRUVADA. During the initial phase of combination antiretroviral treatment, HIV-1 infected 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, Guillain-Barré syndrome, and autoimmune hepatitis) 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.

5.5 Bone Loss and Mineralization Defects

Bone Mineral Density

In clinical trials in HIV-1 infected adults and in a clinical trial of HIV-1 uninfected individuals, TDF (a component of TRUVADA) 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 *[see Adverse Reactions (6.1)]*. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving TDF.

Clinical trials evaluating TDF 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 TDF-treated HIV-1 infected pediatric subjects as compared to the control groups. Similar trends were observed in adolescent subjects aged 12 years to less than 18 years treated for chronic hepatitis B. In all pediatric trials, skeletal growth (height) appeared to be unaffected.

The effects of TDF-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. If bone abnormalities are suspected, 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 TDF use *[see Adverse Reactions (6.1)]*. Arthralgia 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 TDF-containing products *[see Warnings and Precautions (5.3)].*

5.6 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 FTC and TDF, components of TRUVADA, alone or in combination with other antiretrovirals. Treatment with TRUVADA should be suspended in any individual 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).

5.7 Risk of Adverse Reactions Due to Drug Interactions

The concomitant use of TRUVADA and other drugs may result in known or potentially significant drug interactions, some of which may lead to possible clinically significant adverse reactions from greater exposures of concomitant drugs *[see Drug Interactions (7.2)].*

See Table 7 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with TRUVADA; review concomitant medications during therapy with TRUVADA; and monitor for adverse reactions associated with the concomitant drugs.

6 ADVERSE REACTIONS

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

- Severe Acute Exacerbations of Hepatitis B in Patients with HBV Infection *[see Warnings and Precautions (5.1)]*.
- New Onset or Worsening Renal Impairment *[see Warnings and Precautions (5.3)]*.
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.4)]*.

- Bone Loss and Mineralization Defects *[see Warnings and Precautions (5.5)]*.
- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[see Warnings and Precautions (5.6)]*.

6.1 Clinical Trials Experience

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

Adverse Reactions from Clinical Trials Experience in HIV-1 Infected Subjects

Clinical Trials in Adult Subjects

In Study 934, 511 antiretroviral-naïve subjects received efavirenz (EFV) administered in combination with either FTC+TDF (N=257) or zidovudine (AZT)/lamivudine (3TC) (N=254) for 144 weeks. The most common adverse reactions (incidence greater than or equal to 10%, all grades) included diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash. Table 3 provides the treatment-emergent adverse reactions (Grades 2–4) occurring in greater than or equal to 5% of subjects treated in any treatment group.

Skin discoloration, manifested by hyperpigmentation, occurred in 3% of subjects taking FTC+TDF, and was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

Table 3 Selected Adverse Reactions[a] (Grades 2–4) Reported in ≥5% in Any Treatment Group in Study 934 (0–144 Weeks)

	FTC+TDF+EFV[b]	AZT/3TC+EFV
	N=257	N=254
Fatigue	9%	8%
Depression	9%	7%
Nausea	9%	7%
Diarrhea	9%	5%
Dizziness	8%	7%
Upper respiratory tract infections	8%	5%
Sinusitis	8%	4%
Rash event[c]	7%	9%
Headache	6%	5%
Insomnia	5%	7%
Nasopharyngitis	5%	3%
Vomiting	2%	5%

a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.
b. From Weeks 96 to 144 of the trial, subjects received TRUVADA with efavirenz in place of FTC+TDF with efavirenz.
c. Rash event includes rash, exfoliative rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, and rash vesicular.

Laboratory Abnormalities: Laboratory abnormalities observed in this trial were generally consistent with those seen in other trials of TDF and/or FTC (Table 4).

Table 4 Significant Laboratory Abnormalities Reported in ≥1% of Subjects in Any Treatment Group in Study 934 (0–144 Weeks)

	FTC+TDF+EFV[a]	AZT/3TC+EFV
	N=257	N=254
Any ≥ Grade 3 Laboratory Abnormality	30%	26%
Fasting Cholesterol (>240 mg/dL)	22%	24%
Creatine Kinase (M: >990 U/L) (F: >845 U/L)	9%	7%
Serum Amylase (>175 U/L)	8%	4%
Alkaline Phosphatase (>550 U/L)	1%	0%
AST (M: >180 U/L) (F: >170 U/L)	3%	3%
ALT (M: >215 U/L) (F: >170 U/L)	2%	3%
Hemoglobin (<8.0 mg/dL)	0%	4%
Hyperglycemia (>250 mg/dL)	2%	1%
Hematuria (>75 RBC/HPF)	3%	2%
Glycosuria (≥3+)	<1%	1%
Neutrophils (<750/mm^3)	3%	5%
Fasting Triglycerides (>750 mg/dL)	4%	2%

a. From Weeks 96 to 144 of the trial, subjects received TRUVADA with efavirenz in place of FTC+TDF with efavirenz.

Clinical Trials 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 months to less than 18 years of age) who received treatment with FTC in the larger of two open-label, uncontrolled pediatric trials (N=116).

Tenofovir Disoproxil Fumarate: In pediatric clinical trials (Studies 352 and 321) conducted in 184 HIV-1 infected subjects 2 to less than 18 years of age, the adverse reactions observed in pediatric subjects who received treatment with TDF were consistent with those observed in clinical trials of TDF in adults.

In Study 352 (2 to less than 12 years of age), 89 pediatric subjects received TDF for a median exposure of 104 weeks. Of these, 4 subjects discontinued from the trial due to adverse reactions consistent with proximal renal tubulopathy. Three of these 4 subjects presented with hypophosphatemia and had decreases in total body or spine BMD Z-score *[see Warnings and Precautions (5.5)].* Total body BMD gain at Week 48 was less in the TDF group compared to the stavudine (d4T) or zidovudine (AZT) treatment groups. The mean rate of BMD gain in lumbar spine was similar between treatment groups. One TDF-treated subject and none of the d4T- or AZT-treated subjects experienced significant (greater than 4%) lumbar spine BMD loss at Week 48. Changes from baseline in BMD Z-scores were −0.012 for lumbar spine and −0.338 for total body in the 64 subjects who were treated with TDF for 96 weeks.

In Study 321 (12 to less than 18 years of age), the mean rate of BMD gain at Week 48 was less in the TDF compared to the placebo treatment group. Six TDF-treated subjects and one placebo-treated subject had significant (greater than 4%) lumbar spine BMD loss at Week 48. Changes from baseline BMD Z-scores were −0.341 for lumbar spine and −0.458 for total body in the 28 subjects who were treated with TDF for 96 weeks.

In both trials, skeletal growth (height) appeared to be unaffected.

Adverse Reactions from Clinical Trial Experience in Uninfected Subjects Taking TRUVADA for HIV-1 PrEP

Clinical Trials in Adult Subjects

The safety profile of TRUVADA for HIV-1 PrEP was comparable to that observed in clinical trials of HIV-infected subjects based on two randomized placebo-controlled clinical trials (iPrEx, Partners PrEP) in which 2,830 HIV-1 uninfected adults received TRUVADA once daily for HIV-1 PrEP. Subjects were followed for a median of 71 weeks and 87 weeks, respectively. Table 5 provides a list of selected adverse events that occurred in 2% or more of subjects in any treatment group in the iPrEx trial, with an incidence greater than placebo.

Table 5 Selected Adverse Events (All Grades) Reported in ≥2% in Any Treatment Group in the iPrEx Trial and Greater than Placebo

	FTC/TDF (N=1251)	Placebo (N=1248)
Headache	7%	6%
Abdominal pain	4%	2%
Weight decreased	3%	2%

In the Partners PrEP trial, the frequency of adverse events in the TRUVADA treatment group was generally either less than or the same as in the placebo group.

Laboratory Abnormalities: Table 6 provides a list of Grade 2-4 laboratory abnormalities observed in the iPrEx and Partners PrEP trials. Six subjects in the TDF-containing arms of the Partners PrEP trial discontinued from the trial due to an increase in serum creatinine compared with no discontinuations in the placebo group. One subject in the TRUVADA arm of the iPrEx trial discontinued from the trial due to an increase in serum creatinine and another subject discontinued due to low serum phosphorus. Grades 2−3 proteinuria (2-4+) and/or glycosuria (3+) occurred in less than 1% of subjects treated with TRUVADA in the iPrEx trial and Partners PrEP trial.

Table 6 Laboratory Abnormalities (Highest Toxicity Grade Reported for Each Subject) in the iPrEx Trial and Partners PrEP Trial

Grade 2-4[a]	iPrEx Trial		Partners PrEP Trial	
	FTC/TDF (N=1251)	Placebo (N=1248)	FTC/TDF (N=1579)	Placebo (N=1584)
Creatinine (>1.4 × ULN)	<1%	<1%	<1%	<1%
Phosphorus (<2.0 mg/dL)	10%	8%	9%	9%
AST (>2.6 × ULN)	5%	5%	<1%	<1%
ALT (>2.6 × ULN)	7%	7%	<1%	<1%
Hemoglobin (<9.4 mg/dL)	1%	2%	2%	2%
Neutrophils (<750/mm^3)	<1%	<1%	5%	3%

a. Grading is per DAIDS criteria.

Changes in Bone Mineral Density: In clinical trials of HIV-1 uninfected individuals, decreases in BMD were observed. In the iPrEx trial, a substudy of 503 subjects found mean changes from baseline in BMD ranging from –0.4% to –1.0% across total hip, spine, femoral neck, and trochanter in the TRUVADA group compared with the placebo group, which returned toward baseline after discontinuation of treatment. Thirteen percent of TRUVADA-treated subjects versus 6% of placebo-treated subjects lost at least 5% of BMD at the spine during treatment. Bone fractures were reported in 1.7% of the TRUVADA group compared with 1.4% in the placebo group. No correlation between BMD and fractures was noted *[see Clinical Studies (14.3)]*. The Partners PrEP trial found similar fracture rates between the treatment and placebo groups (0.8% and 0.6%, respectively); no BMD evaluations were performed in this trial *[see Clinical Studies (14.4)]*.

Clinical Trials in Adolescent Subjects

In a single-arm, open-label clinical trial (ATN113), in which 67 HIV-1 uninfected adolescent (15 to 18 years of age) men who have sex with men received TRUVADA once daily for HIV-1 PrEP, the safety profile of TRUVADA was similar to that observed in adults. Median duration to exposure of TRUVADA was 47 weeks *[see Use in Specific Populations (8.4)].*

In the ATN113 trial, median BMD increased from baseline to Week 48, +2.58% for lumbar spine and +0.72% for total body. One subject had significant (greater than or equal to 4%) total body BMD loss at Week 24. Median changes from baseline BMD Z-scores were 0.0 for lumbar spine and −0.2 for total body at Week 48. Three subjects showed a worsening (change from > −2 to ≤ −2) from baseline in their lumbar spine or total body BMD Z-scores at Week 24 or 48. Interpretation of these data, however, may be limited by the low rate of adherence to TRUVADA by Week 48.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of TDF. No additional adverse reactions have been identified during postapproval use of FTC. 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.

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

7.1 Drugs Affecting Renal Function

FTC and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion *[see Clinical Pharmacology (12.3)]*. No drug-drug interactions due to competition for renal excretion have been observed; however, coadministration of TRUVADA with drugs that are eliminated by active tubular secretion may increase concentrations of FTC, tenofovir, and/or the coadministered drug. Some examples 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 (5.3)]*. Drugs that decrease renal function may increase concentrations of FTC and/or tenofovir.

7.2 Established and Significant Interactions

Table 7 provides a listing of established or clinically significant drug interactions. The drug interactions described are based on studies conducted with either TRUVADA, the components of TRUVADA (FTC and TDF) as individual agents and/or in combination, or are predicted drug interactions that may occur with TRUVADA *[see Clinical Pharmacology (12.3)].*

Table 7 Established and Significant[a] Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Trials

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
NRTI: didanosine[c]	↑ didanosine	Patients receiving TRUVADA and didanosine should be monitored closely for didanosine-associated adverse reactions. Discontinue didanosine in patients who develop didanosine-associated adverse reactions. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis, and neuropathy. Suppression of CD4+ cell counts has been observed in patients receiving TDF with didanosine 400 mg daily. In patients weighing greater than 60 kg, reduce the didanosine dose to 250 mg when it is coadministered with TRUVADA. Data are not available to recommend a dose adjustment of didanosine for adult or pediatric patients weighing less than 60 kg. When coadministered, TRUVADA and Videx EC may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat).
HIV-1 Protease Inhibitors: atazanavir[c]	↓ atazanavir	When coadministered with TRUVADA, atazanavir 300 mg should be given with ritonavir 100 mg.
lopinavir/ritonavir[c] atazanavir/ritonavir[c] darunavir/ritonavir[c]	↑ tenofovir	Monitor patients receiving TRUVADA concomitantly with lopinavir/ritonavir, ritonavir-boosted atazanavir, or ritonavir-boosted darunavir for TDF-associated adverse reactions. Discontinue TRUVADA in patients who develop TDF-associated adverse reactions.
Hepatitis C Antiviral Agents: sofosbuvir/velpatasvir[c] sofosbuvir/velpatasvir/voxilaprevir[c]	↑ tenofovir	Monitor patients receiving TRUVADA concomitantly with EPCLUSA® (sofosbuvir/velpatasvir) or VOSEVI® (sofosbuvir/velpatasvir/voxilaprevir) for adverse reactions associated with TDF.
ledipasvir/sofosbuvir[c]		Monitor patients receiving TRUVADA concomitantly with HARVONI® (ledipasvir/sofosbuvir) without an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination for adverse reactions associated with TDF. In patients receiving TRUVADA concomitantly with HARVONI and an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination, consider an alternative HCV or antiretroviral therapy, as the safety of increased tenofovir concentrations in this setting has not been established. If coadministration is necessary, monitor for adverse reactions associated with TDF.

a. This table is not all inclusive.
b. ↑=Increase, ↓=Decrease
c. Indicates that a drug-drug interaction trial was conducted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to TRUVADA during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

Data on the use of TRUVADA during pregnancy from observational studies have shown no increased risk of major birth defects. Available data from the APR show no significant difference in the overall risk of major birth defects with first trimester exposure for emtricitabine (FTC) (2.3%) or tenofovir disoproxil fumarate (TDF) (2.1%) compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) *(see Data)*. The rate of miscarriage for individual drugs is not reported in the APR. In the U.S. general population, the estimated background risk of miscarriage in clinically recognized pregnancies is 15–20%.

In animal reproduction studies, no adverse developmental effects were observed when the components of TRUVADA were administered separately at doses/exposures ≥60 (FTC), ≥14 (TDF) and 2.7 (tenofovir) times those of the recommended daily dose of TRUVADA (*see Data*).

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

HIV-1 PrEP: Published studies indicate an increased risk of HIV-1 infection during pregnancy and an increased risk of mother to child transmission during acute HIV-1 infection. In women at risk of acquiring HIV-1, consideration should be given to methods to prevent acquisition of HIV, including continuing or initiating TRUVADA for HIV-1 PrEP, during pregnancy.

Data

Human Data

TRUVADA for HIV-1 PrEP: In an observational study based on prospective reports to the APR, 78 HIV-seronegative women exposed to TRUVADA during pregnancy delivered live-born infants with no major malformations. All but one were first trimester exposures, and the median duration of exposure was 10.5 weeks. There were no new safety findings in the women receiving TRUVADA for HIV-1 PrEP compared with HIV-1 infected women treated with other antiretroviral medications.

Emtricitabine: Based on prospective reports to the APR of exposures to FTC-containing regimens during pregnancy resulting in live births (including over 3,300 exposed in the first trimester and over 1,300 exposed in the second/third trimester), the prevalence of major birth defects in live births was 2.6% (95% CI: 2.1% to 3.2%) and 2.3% (95% CI: 1.6% to 3.3%) following first and second/third trimester exposure, respectively, to FTC-containing regimens.

Tenofovir Disoproxil Fumarate: Based on prospective reports to the APR of exposures to TDF-containing regimens during pregnancy resulting in live births (including over 4,000 exposed in the first trimester and over 1,700 exposed in the second/third trimester), the prevalence of major birth defects in live births was 2.4% (95% CI: 2.0% to 2.9%) and 2.4% (95% CI: 1.7% to 3.2%) following first and second/third trimester exposure, respectively, to TDF-containing regimens.

Methodologic limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates women and infants from a limited geographic area, and does not include outcomes for births that occurred at <20 weeks gestation.

Additionally, published observational studies on emtricitabine and tenofovir exposure in pregnancy have not shown an increased risk for major malformations.

Animal Data

Emtricitabine: FTC was administered orally to pregnant mice (at 0, 250, 500, or 1,000 mg/kg/day), and rabbits (at 0, 100, 300, or 1,000 mg/kg/day) through organogenesis (on gestation days 6 through 15, and 7 through 19, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with FTC in mice at exposures (AUC) approximately 60 times higher and in rabbits at approximately 120 times higher than human exposures at the recommended daily dose. In a pre/postnatal development study in mice, FTC was administered orally at doses up to 1,000 mg/kg/day; no significant adverse effects directly related to drug were observed in the offspring exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 60 times higher than human exposures at the recommended daily dose.

Tenofovir Disoproxil Fumarate: TDF was administered orally to pregnant rats (at 0, 50, 150, or 450 mg/kg/day) and rabbits (at 0, 30, 100, or 300 mg/kg/day) through organogenesis (on gestation days 7 through 17, and 6 through 18, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with TDF in rats at doses up to 14 times the human dose based on body surface area comparisons and in rabbits at doses up to 19 times the human dose based on body surface area comparisons. In a pre/postnatal development study in rats, TDF was administered orally through lactation at doses up to 600 mg/kg/day; no adverse effects were observed in the offspring at tenofovir exposures of approximately 2.7 times higher than human exposures at the recommended daily dose of TRUVADA.

8.2 Lactation

Risk Summary

Based on published data, FTC and tenofovir have been shown to be present in human breast milk *(see Data).* It is not known if the components of TRUVADA affect milk production or have effects on the breastfed child.

Treatment of HIV-1 Infection:

The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1.

Because of the potential for: (1) HIV transmission (in HIV-negative infants); (2) developing viral resistance (in HIV-positive infants); and (3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are taking TRUVADA for the treatment of HIV-1.

HIV-1 PrEP:

In HIV-uninfected women, the developmental and health benefits of breastfeeding and the mother's clinical need for TRUVADA for HIV-1 PrEP should be considered along with any potential adverse effects on the breastfed child from TRUVADA and the risk of HIV-1 acquisition due to nonadherence and subsequent mother to child transmission.

Women should not breastfeed if acute HIV-1 infection is suspected because of the risk of HIV-1 transmission to the infant.

Data

HIV-1 PrEP: In a study of 50 breastfeeding women who received TRUVADA for HIV-1 PrEP between 1 and 24 weeks postpartum (median 13 weeks), after 7 days of treatment, tenofovir was undetectable but FTC was detectable in the plasma of most infants. In these infants, the average FTC plasma

concentration was less than 1% of the FTC C_{max} observed in HIV-infected infants (up to 3 months of age) receiving the therapeutic dose of FTC (3 mg/kg/day). There were no serious adverse events. Two infants (4%) had an adverse event of mild diarrhea which resolved.

8.4 Pediatric Use

Treatment of HIV-1 Infection

No pediatric clinical trial was conducted to evaluate the safety and efficacy of TRUVADA in patients with HIV-1 infection. Data from previously conducted trials with the individual drug products, FTC and TDF, were relied upon to support dosage recommendations for TRUVADA. For additional information, consult the prescribing information for EMTRIVA and VIREAD.

TRUVADA should only be administered to HIV-1 infected pediatric patients with body weight greater than or equal to 17 kg and who are able to swallow a tablet. Because it is a fixed-dose combination tablet, TRUVADA cannot be adjusted for patients of lower weight *[see Warnings and Precautions (5.5), Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*. TRUVADA is not approved for use in pediatric patients weighing less than 17 kg.

HIV-1 PrEP

The safety and effectiveness of TRUVADA for HIV-1 PrEP in at-risk adolescents weighing at least 35 kg is supported by data from adequate and well-controlled studies of TRUVADA for HIV-1 PrEP in adults with additional data from safety and pharmacokinetic studies in previously conducted trials with the individual drug products, FTC and TDF, in HIV-1 infected adults and pediatric subjects *[see Dosage and Administration (2.5), Adverse Reactions (6.1), Clinical Pharmacology (12.3 and 12.4), and Clinical Studies (14.3 and 14.4)].*

Safety, adherence, and resistance were evaluated in a single-arm, open-label clinical trial (ATN113) in which 67 HIV-1 uninfected at-risk adolescent men who have sex with men received TRUVADA once daily for HIV-1 PrEP. The mean age of subjects was 17 years (range 15 to 18 years); 46% were Hispanic, 52% Black, and 37% White. The safety profile of TRUVADA in ATN113 was similar to that observed in the adult HIV-1 PrEP trials *[see Adverse Reactions (6.1)]*.

In the ATN113 trial, HIV-1 seroconversion occurred in 3 subjects. Tenofovir diphosphate levels in dried blood spot assays indicate that these subjects had poor adherence. No tenofovir- or FTC-associated HIV-1 resistance substitutions were detected in virus isolated from the 3 subjects who seroconverted *[see Microbiology (12.4)].*

Adherence to study drug, as demonstrated by tenofovir diphosphate levels in dried blood spot assays, declined markedly after Week 12 once subjects switched from monthly to quarterly visits, suggesting that adolescents may benefit from more frequent visits and counseling *[see Warnings and Precautions (5.2)]*.

Safety and effectiveness of Truvada for HIV-1 PrEP in pediatric patients weighing less than 35 kg have not been established.

8.5 Geriatric Use

Clinical trials of FTC, TDF, or TRUVADA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8.6 Renal Impairment

Treatment of HIV-1 Infection

The dosing interval for TRUVADA should be modified in HIV-infected adult individuals with estimated creatinine clearance of 30–49 mL/min. TRUVADA is not recommended in individuals with estimated

creatinine clearance below 30 mL/min and in individuals with end-stage renal disease requiring dialysis *[see Dosage and Administration (2.6)]*.

HIV-1 PrEP

TRUVADA for HIV-1 PrEP is not recommended in HIV-1 uninfected individuals with estimated creatinine clearance below 60 mL/min. If a decrease in estimated creatinine clearance is observed in uninfected individuals while using TRUVADA for HIV-1 PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use *[see Dosage and Administration (2.6)]*.

10 OVERDOSAGE

If overdose occurs, the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

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

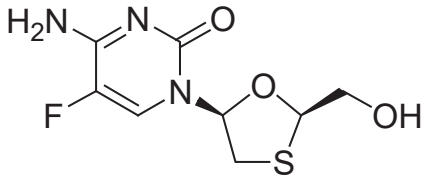
Tenofovir Disoproxil Fumarate: Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of TDF, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

11 DESCRIPTION

TRUVADA tablets are fixed-dose combination tablets containing emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF). FTC is a synthetic nucleoside analog of cytidine. TDF is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate. Both FTC and tenofovir exhibit inhibitory activity against HIV-1 reverse transcriptase.

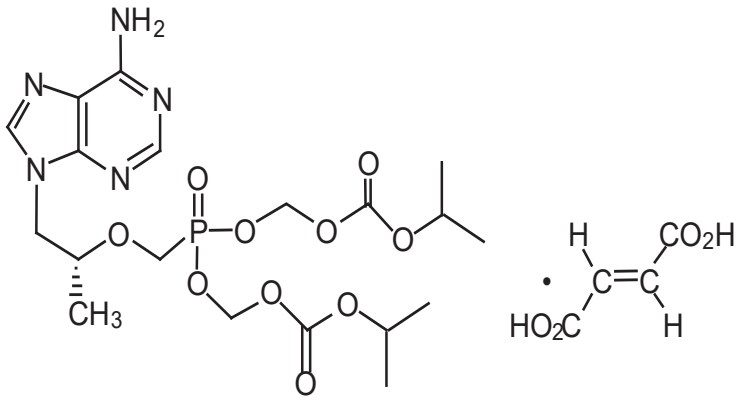
Emtricitabine: The chemical name of FTC is 5-fluoro-1-(2*R*,5*S*)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. FTC is the (-) enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5-position.

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:



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

Tenofovir Disoproxil Fumarate: TDF 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 disoproxil fumarate is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in water at 25 °C. The partition coefficient (log p) for tenofovir disoproxil is 1.25 and the pKa is 3.75. All dosages are expressed in terms of TDF except where otherwise noted.

TRUVADA tablets are for oral administration, and are available in the following strengths:

- Film-coated tablet containing 200 mg of FTC and 300 mg of TDF (which is equivalent to 245 mg of tenofovir disoproxil) as active ingredients
- Film-coated tablet containing 167 mg of FTC and 250 mg of TDF (which is equivalent to 204 mg of tenofovir disoproxil) as active ingredients
- Film-coated tablet containing 133 mg of FTC and 200 mg of TDF (which is equivalent to 163 mg of tenofovir disoproxil) as active ingredients
- Film-coated tablet containing 100 mg of FTC and 150 mg of TDF (which is equivalent to 123 mg of tenofovir disoproxil) as active ingredients

All strengths of TRUVADA tablets also include the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch (gluten free). The 200 mg/300 mg strength tablets are coated with Opadry II Blue Y-30-10701, which contains FD&C Blue #2 aluminum lake, hypromellose 2910, lactose monohydrate, titanium dioxide, and triacetin. The 167 mg/250 mg, 133 mg/200 mg, and 100 mg/150 mg strength tablets are coated with Opadry II Blue, which contains FD&C Blue #2 aluminum lake, hypromellose 2910, lactose monohydrate, titanium dioxide, and triacetin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

TRUVADA is a fixed-dose combination of antiviral drugs FTC and TDF *[see Microbiology (12.4)].*

12.3 Pharmacokinetics

TRUVADA: One TRUVADA tablet was comparable to one FTC capsule (200 mg) plus one TDF tablet (300 mg) following single-dose administration to fasting healthy subjects (N=39).

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

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

Table 8 Single Dose Pharmacokinetic Parameters for FTC and Tenofovir in Adults[a]

	FTC	Tenofovir
Fasted Oral Bioavailability[b] (%)	92 (83.1–106.4)	25 (NC–45.0)
Plasma Terminal Elimination Half-Life[b] (hr)	10 (7.4–18.0)	17 (12.0–25.7)
C_{max}[c] (μg/mL)	1.8±0.72[d]	0.30±0.09
AUC[c] (μg·hr/mL)	10.0±3.12[d]	2.29±0.69
CL/F[c] (mL/min)	302±94	1043±115
CL_{renal}[c] (mL/min)	213±89	243±33

a. NC=Not calculated
b. Median (range)
c. Mean (± SD)
d. Data presented as steady state values

Effects of Food on Oral Absorption

TRUVADA may be administered with or without food. Administration of TRUVADA following a high fat meal (784 kcal; 49 grams of fat) or a light meal (373 kcal; 8 grams of fat) delayed the time of tenofovir C_{max} by approximately 0.75 hour. The mean increases in tenofovir AUC and C_{max} were approximately 35% and 15%, respectively, when administered with a high fat or light meal, compared to administration in the fasted state. In previous safety and efficacy trials, TDF (tenofovir) was taken under fed conditions. FTC systemic exposures (AUC and C_{max}) were unaffected when TRUVADA was administered with either a high fat or a light meal.

Specific Populations

Race

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

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 TDF.

Gender

Emtricitabine and Tenofovir Disoproxil Fumarate: FTC and tenofovir pharmacokinetics are similar in male and female subjects.

Pediatric Patients

Treatment of HIV-1 Infection: The pharmacokinetic data for tenofovir and FTC following administration of TRUVADA in pediatric subjects weighing 17 kg and above are not available. The dosage recommendations of TRUVADA in this population are based on the dosage recommendations of FTC and TDF in this population. Refer to the EMTRIVA and VIREAD prescribing information for pharmacokinetic information on the individual products in pediatric patients.

HIV-1 PrEP: The pharmacokinetic data for tenofovir and FTC following administration of TRUVADA in HIV-1 uninfected adolescents weighing 35 kg and above are not available. The dosage recommendations of TRUVADA for HIV-1 PrEP in this population are based on safety and adherence data from the ATN113 trial *[see Use in Specific Populations (8.4)]* and known pharmacokinetic information in HIV-infected adolescents taking TDF and FTC for treatment.

Geriatric Patients

Pharmacokinetics of FTC and tenofovir have not been fully evaluated in the elderly (65 years of age and older).

Patients with Renal Impairment

The pharmacokinetics of FTC and tenofovir are altered in subjects with renal impairment *[see Warnings and Precautions (5.3)]*. In adult subjects with creatinine clearance below 50 mL/min, C_{max} and $AUC_{0-\infty}$ of FTC and tenofovir were increased. No data are available to make dosage recommendations in pediatric patients with renal impairment.

Patients with Hepatic Impairment

The pharmacokinetics of tenofovir following a 300 mg dose of TDF 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. The pharmacokinetics of TRUVADA or FTC have not been studied in subjects with hepatic impairment; however, FTC is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.

Assessment of Drug Interactions

The steady state pharmacokinetics of FTC and tenofovir were unaffected when FTC and TDF were administered together versus each agent dosed alone.

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

TDF is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters. When TDF is coadministered with an inhibitor of these transporters, an increase in absorption may be observed.

No clinically significant drug interactions have been observed between FTC and famciclovir, indinavir, stavudine, TDF, and zidovudine (Tables 9 and 10). Similarly, no clinically significant drug interactions have been observed between TDF and efavirenz, methadone, nelfinavir, oral contraceptives, ribavirin, or sofosbuvir in trials conducted in healthy volunteers (Tables 11 and 12).

Table 9 Drug Interactions: Changes in Pharmacokinetic Parameters for FTC in the Presence of the Coadministered Drug[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	FTC Dose (mg)	N	% Change of FTC Pharmacokinetic Parameters[b] (90% CI)		
				C_{max}	AUC	C_{min}
TDF	300 once daily × 7 days	200 once daily × 7 days	17	⇔	⇔	↑ 20 (↑ 12 to ↑ 29)
Zidovudine	300 twice daily × 7 days	200 once daily × 7 days	27	⇔	⇔	⇔
Indinavir	800 × 1	200 × 1	12	⇔	⇔	NA
Famciclovir	500 × 1	200 × 1	12	⇔	⇔	NA
Stavudine	40 × 1	200 × 1	6	⇔	⇔	NA

a. All interaction trials conducted in healthy volunteers
b. ↑ = Increase; ⇔ = No Effect; NA = Not Applicable

Table 10 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of FTC[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	FTC Dose (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters[b] (90% CI)		
				C_{max}	AUC	C_{min}
TDF	300 once daily × 7 days	200 once daily × 7 days	17	⇔	⇔	⇔
Zidovudine	300 twice daily × 7 days	200 once daily × 7 days	27	↑ 17 (↑ 0 to ↑ 38)	↑ 13 (↑ 5 to ↑ 20)	⇔
Indinavir	800 × 1	200 × 1	12	⇔	⇔	NA
Famciclovir	500 × 1	200 × 1	12	⇔	⇔	NA
Stavudine	40 × 1	200 × 1	6	⇔	⇔	NA

a. All interaction trials conducted in healthy volunteers
b. ↑ = Increase; ⇔ = No Effect; NA = Not Applicable

Table 11 Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir[a] in the Presence of the Coadministered Drug

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters[b] (90% CI)		
			C_{max}	AUC	C_{min}
Atazanavir[c]	400 once daily × 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Atazanavir/ Ritonavir[c]	300/100 once daily	12	↑ 34 (↑ 20 to ↑ 51)	↑ 37 (↑ 30 to ↑ 45)	↑ 29 (↑ 21 to ↑ 36)
Darunavir/ Ritonavir[d]	300/100 twice daily	12	↑ 24 (↑ 8 to ↑ 42)	↑ 22 (↑ 10 to ↑ 35)	↑ 37 (↑ 19 to ↑ 57)
Indinavir	800 three times daily × 7 days	13	↑ 14 (↓ 3 to ↑ 33)	⇔	⇔
Ledipasvir/ Sofosbuvir[e,f]	90/400 once daily × 10 days	24	↑ 47 (↑ 37 to ↑ 58)	↑ 35 (↑ 29 to ↑42)	↑ 47 (↑ 38 to ↑ 57)
Ledipasvir/ Sofosbuvir[e,g]		23	↑ 64 (↑ 54 to ↑ 74)	↑ 50 (↑ 42 to ↑ 59)	↑ 59 (↑ 49 to ↑ 70)
Ledipasvir/ Sofosbuvir[h]	90/400 once daily × 14 days	15	↑ 79 (↑ 56 to ↑ 104)	↑ 98 (↑ 77 to ↑ 123)	↑ 163 (↑ 132 to ↑ 197)
Ledipasvir/ Sofosbuvir[i]	90/400 once daily × 10 days	14	↑ 32 (↑ 25 to ↑ 39)	↑ 40 (↑ 31 to ↑ 50)	↑ 91 (↑ 74 to ↑ 110)
Ledipasvir/ Sofosbuvir[j]	90/400 once daily × 10 days	29	↑ 61 (↑ 51 to ↑ 72)	↑ 65 (↑ 59 to ↑ 71)	↑ 115 (↑ 105 to ↑ 126)
Lopinavir/ Ritonavir	400/100 twice daily × 14 days	24	⇔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)
Saquinavir/ Ritonavir	1000/100 twice daily × 14 days	35	⇔	⇔	↑ 23 (↑ 16 to ↑ 30)
Sofosbuvir[k]	400 single dose	16	↑ 25 (↑ 8 to ↑ 45)	⇔	⇔
Sofosbuvir/ Velpatasvir[l]	400/100 once daily	24	↑ 44 (↑ 33 to ↑ 55)	↑ 40 (↑ 34 to ↑ 46)	↑ 84 (↑ 76 to ↑ 92)
Sofosbuvir/ Velpatasvir[m]	400/100 once daily	30	↑ 46 (↑ 39 to ↑ 54)	↑ 40 (↑ 34 to ↑ 45)	↑ 70 (↑ 61 to ↑ 79)
Sofosbuvir/ Velpatasvir/ Voxilaprevir[n]	400/100/100 + Voxilaprevir[o] 100 once daily	29	↑ 48 (↑ 36 to ↑ 61)	↑ 39 (↑ 32 to ↑ 46)	↑ 47 (↑ 38 to ↑ 56)
Tacrolimus	0.05 mg/kg twice daily × 7 days	21	↑ 13 (↑ 1 to ↑ 27)	⇔	⇔
Tipranavir/ Ritonavir[p]	500/100 twice daily	22	↓ 23 (↓ 32 to ↓ 13)	↓ 2 (↓ 9 to ↑ 5)	↑ 7 (↓ 2 to ↑ 17)
	750/200 twice daily (23 doses)	20	↓ 38 (↓ 46 to ↓ 29)	↑ 2 (↓ 6 to ↑ 10)	↑ 14 (↑ 1 to ↑ 27)

a. Subjects received VIREAD 300 mg once daily.
b. Increase = ↑; Decrease = ↓; No Effect = ⇔
c. Reyataz Prescribing Information.
d. Prezista Prescribing Information.
e. Data generated from simultaneous dosing with HARVONI (ledipasvir/sofosbuvir). Staggered administration (12 hours apart) provided similar results.
f. Comparison based on exposures when administered as atazanavir/ritonavir + FTC/TDF.
g. Comparison based on exposures when administered as darunavir/ritonavir + FTC/TDF.
h. Study conducted with ATRIPLA (efavirenz/FTC/TDF) coadministered with HARVONI.
i. Study conducted with COMPLERA (FTC/rilpivirine/TDF) coadministered with HARVONI.
j. Study conducted with TRUVADA (FTC/TDF) + dolutegravir coadministered with HARVONI.
k. Study conducted with ATRIPLA coadministered with SOVALDI® (sofosbuvir).
l. Study conducted with COMPLERA coadministered with EPCLUSA; coadministration with EPCLUSA also results in comparable increases in tenofovir exposures when TDF is administered as ATRIPLA, STRIBILD, TRUVADA + atazanavir/ritonavir, or TRUVADA + darunavir/ritonavir.
m. Administered as raltegravir + FTC/TDF.
n. Comparison based on exposures when administered as darunavir + ritonavir + FTC/TDF.
o. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients
p. Aptivus Prescribing Information.

No effect on the pharmacokinetic parameters of the following coadministered drugs was observed with TRUVADA: abacavir, didanosine (buffered tablets), FTC, entecavir, and lamivudine.

Table 12 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Tenofovir

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters[a] (90% CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	↑ 12 (↓ 1 to ↑ 26)	⇔	NA
Atazanavir[b]	400 once daily × 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
Atazanavir[b]	Atazanavir/Ritonavir 300/100 once daily × 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓ 25[c] (↓ 42 to ↓ 3)	↓ 23[c] (↓ 46 to ↑ 10)
Darunavir[d]	Darunavir/Ritonavir 300/100 once daily	12	↑ 16 (↓ 6 to ↑ 42)	↑ 21 (↓ 5 to ↑ 54)	↑ 24 (↓ 10 to ↑ 69)
Didanosine[e]	250 once, simultaneously with TDF and a light meal[f]	33	↓ 20[g] (↓ 32 to ↓ 7)	⇔[g]	NA
Emtricitabine	200 once daily × 7 days	17	⇔	⇔	↑ 20 (↑ 12 to ↑ 29)
Indinavir	800 three times daily × 7 days	12	↓ 11 (↓ 30 to ↑ 12)	⇔	⇔
Entecavir	1 once daily × 10 days	28	⇔	↑ 13 (↑ 11 to ↑ 15)	⇔
Lamivudine	150 twice daily × 7 days	15	↓ 24 (↓ 34 to ↓ 12)	⇔	⇔
Lopinavir Ritonavir	Lopinavir/Ritonavir 400/100 twice daily × 14 days	24	⇔ ⇔	⇔ ⇔	⇔ ⇔
Saquinavir Ritonavir	Saquinavir/Ritonavir 1000/100 twice daily × 14 days	32	↑ 22 (↑ 6 to ↑41) ⇔	↑ 29[h] (↑ 12 to ↑ 48) ⇔	↑ 47[h] (↑ 23 to ↑ 76) ↑ 23 (↑ 3 to ↑ 46)
Tacrolimus	0.05 mg/kg twice daily × 7 days	21	⇔	⇔	⇔
Tipranavir[i]	Tipranavir/Ritonavir 500/100 twice daily	22	↓ 17 (↓ 26 to ↓ 6)	↓ 18 (↓ 25 to ↓ 9)	↓ 21 (↓ 30 to ↓ 10)
	Tipranavir/Ritonavir 750/200 twice daily (23 doses)	20	↓ 11 (↓ 16 to ↓ 4)	↓ 9 (↓ 15 to ↓ 3)	↓ 12 (↓ 22 to 0)

a. Increase = ↑; Decrease = ↓; No Effect = ⇔; NA = Not Applicable
b. Reyataz Prescribing Information.
c. In HIV-infected subjects, addition of TDF to atazanavir 300 mg plus ritonavir 100 mg resulted in AUC and C_{min} values of atazanavir that were 2.3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.
d. Prezista Prescribing Information.
e. Videx EC Prescribing Information. Subjects received didanosine enteric-coated capsules. When didanosine 250 mg enteric-coated capsules were administered with TDF, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions.
f. 373 kcal, 8.2 g fat
g. Compared with didanosine (enteric-coated) 400 mg administered alone under fasting conditions.

h. Increases in AUC and C_{min} are not expected to be clinically relevant; hence, no dose adjustments are required when TDF and ritonavir-boosted saquinavir are coadministered.
i. Aptivus Prescribing Information.

12.4 Microbiology

Mechanism of Action

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

Tenofovir Disoproxil Fumarate: TDF is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. TDF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate (TFV-DP), which 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. TFV-DP is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Antiviral Activity

Emtricitabine and Tenofovir Disoproxil Fumarate: No antagonism was observed in combination studies evaluating the cell culture antiviral activity of FTC and tenofovir together.

Emtricitabine: The antiviral activity of FTC 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 FTC were in the range of 0.0013–0.64 μM (0.0003–0.158 μg/mL). In drug combination studies of FTC with nucleoside RT inhibitors (abacavir, lamivudine, stavudine, zidovudine), non-nucleoside RT inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, saquinavir), no antagonism was observed. 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).

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. In drug combination studies of tenofovir with nucleoside RT inhibitors (abacavir, didanosine, lamivudine, stavudine, zidovudine), non-nucleoside RT inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), no antagonism was observed. 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 μM to 5.5 μM).

Prophylactic Activity in a Nonhuman Primate Model of HIV-1 Transmission

Emtricitabine and Tenofovir Disoproxil Fumarate: The prophylactic activity of the combination of daily oral FTC and TDF was evaluated in a controlled study of macaques inoculated once weekly for 14 weeks with SIV/HIV-1 chimeric virus (SHIV) applied to the rectal surface. Of the 18 control animals, 17 became infected after a median of 2 weeks. In contrast, 4 of the 6 animals treated daily with oral FTC and TDF remained uninfected and the two infections that did occur were significantly delayed until 9 and 12 weeks and exhibited reduced viremia. An M184I-expressing FTC-resistant variant emerged in 1 of the 2 macaques after 3 weeks of continued drug exposure.

Resistance

Emtricitabine and Tenofovir Disoproxil Fumarate: HIV-1 isolates with reduced susceptibility to the combination of FTC and tenofovir have been selected in cell culture. Genotypic analysis of these isolates identified the M184V/I and/or K65R amino acid substitutions in the viral RT. In addition, a K70E substitution in the HIV-1 RT has been selected by tenofovir and results in reduced susceptibility to tenofovir.

In Study 934, a clinical trial of treatment-naïve subjects *[see Clinical Studies (14.2)]*, resistance analysis was performed on HIV-1 isolates from all confirmed virologic failure subjects with greater than 400 copies/mL of HIV-1 RNA at Week 144 or early discontinuation. Development of efavirenz resistance-associated substitutions occurred most frequently and was similar between the treatment arms. The M184V amino acid substitution, associated with resistance to FTC and lamivudine, was observed in 2/19 analyzed subject isolates in the FTC+TDF group and in 10/29 analyzed subject isolates in the zidovudine/lamivudine group. Through 144 weeks of Study 934, no subjects have developed a detectable K65R or K70E substitution in their HIV-1 as analyzed through standard genotypic analysis.

Emtricitabine: FTC-resistant isolates of HIV-1 have been selected in cell culture and in vivo. Genotypic analysis of these isolates showed that the reduced susceptibility to FTC was associated with a substitution in the HIV-1 RT gene at codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I).

Tenofovir Disoproxil Fumarate: HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R substitution in RT and showed a 2- to 4-fold reduction in susceptibility to tenofovir.

In treatment-naïve subjects, isolates from 8/47 (17%) analyzed subjects developed the K65R substitution in the TDF arm through 144 weeks; 7 occurred in the first 48 weeks of treatment and 1 at Week 96. In treatment-experienced subjects, 14/304 (5%) isolates from subjects failing TDF through Week 96 showed greater than 1.4-fold (median 2.7) reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a K65R amino acid substitution in the HIV-1 RT.

iPrEx Trial: In the iPrEx trial, a clinical trial of HIV-1 seronegative adult subjects *[see Clinical Studies (14.3)]*, no amino acid substitutions associated with resistance to FTC or TDF were detected at the time of seroconversion among 48 subjects in the TRUVADA group and 83 subjects in the placebo group who became infected with HIV-1 during the trial. Ten subjects were observed to be HIV-1 infected at time of enrollment. The M184V/I substitutions associated with resistance to FTC were observed in 3 of the 10 subjects (2 of 2 in the TRUVADA group and 1 of 8 in the placebo group). One of the two subjects in the TRUVADA group harbored wild type virus at enrollment and developed the M184V substitution 4 weeks after enrollment. The other subject had indeterminate resistance at enrollment but was found to have the M184I substitution 4 weeks after enrollment.

Partners PrEP Trial: In the Partners PrEP trial, a clinical trial of HIV-1 seronegative adult subjects *[see Clinical Studies (14.4)],* no variants expressing amino acid substitutions associated with resistance to FTC or TDF were detected at the time of seroconversion among 12 subjects in the TRUVADA group, 15 subjects in the TDF group, and 51 subjects in the placebo group. Fourteen subjects were observed to be HIV-1 infected at the time of enrollment (3 in the TRUVADA group, 5 in the TDF group, and 6 in the placebo group). One of the three subjects in the TRUVADA group who was infected with wild type virus at enrollment selected an M184V expressing virus by Week 12. Two of the five subjects in the TDF group had tenofovir-resistant viruses at the time of seroconversion; one subject infected with wild type virus at enrollment developed a K65R substitution by Week 16, while the second subject had virus expressing the combination of D67N and K70R substitutions upon seroconversion at Week 60, although baseline virus was not genotyped and it is unclear if the

resistance emerged or was transmitted. Following enrollment, 4 subjects (2 in the TDF group, 1 in the TRUVADA group, and 1 in the placebo group) had virus expressing K103N or V106A substitutions, which confer high-level resistance to NNRTIs but have not been associated with FTC or TDF and may have been present in the infecting virus.

ATN113 Trial: In ATN113, a clinical trial of HIV-1 seronegative adolescent subjects *[see Use in Specific Populations (8.4)],* no amino acid substitutions associated with resistance to FTC or TDF were detected at the time of seroconversion from any of the 3 subjects who became infected with HIV-1 during the trial. All 3 subjects who seroconverted were nonadherent to the recommended TRUVADA dosage.

Cross Resistance

Emtricitabine and Tenofovir Disoproxil Fumarate: Cross-resistance among certain NRTIs has been recognized. The M184V/I and/or K65R substitutions selected in cell culture by the combination of FTC and tenofovir are also observed in some HIV-1 isolates from subjects failing treatment with tenofovir in combination with either FTC or lamivudine, and either abacavir or didanosine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors either or both of these amino acid substitutions.

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

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 FTC and lamivudine. Therefore, cross-resistance among these NRTIs may occur in patients whose virus harbors the K65R or K70E substitutions. HIV-1 isolates from subjects (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 TDF. 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

FTC 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.

Tenofovir Disoproxil Fumarate: Long-term oral carcinogenicity studies of TDF 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.

TDF 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, TDF was negative when administered to male mice.

There were no effects on fertility, mating performance, or early embryonic development when TDF 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 and TDF 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 four 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 Overview of Clinical Trials

The efficacy and safety of TRUVADA have been evaluated in the studies summarized in Table 13.

Table 13 Trials Conducted with TRUVADA for HIV-1 Treatment and HIV-1 PrEP

Trial	Population	Study Arms (N)[a]	Timepoint
Study 934[b] (NCT00112047)	HIV-infected, treatment-naïve adults	FTC+TDF + efavirenz (257) zidovudine/lamivudine + efavirenz (254)	48 Weeks
iPrEx[c] (NCT00458393)	HIV-seronegative men or transgender women who have sex with men	TRUVADA (1,251) Placebo (1,248)	4,237 person-years
Partners PrEP[c] (NCT00557245)	HIV serodiscordant heterosexual couples	TRUVADA (1,583) Placebo (1,586)	7,827 person-years

a. Randomized and dosed.
b. Randomized, open label, active-controlled trial.
c. Randomized, double-blind, placebo-controlled trial.

14.2 Clinical Trial Results for Treatment of HIV-1: Study 934

Data through 144 weeks are reported for Study 934, a randomized, open-label, active-controlled multicenter trial comparing FTC+TDF administered in combination with efavirenz (EFV) versus

zidovudine (AZT)/lamivudine (3TC) fixed-dose combination administered in combination with EFV in 511 antiretroviral-naïve adult subjects. From Weeks 96 to 144 of the trial, subjects received TRUVADA with EFV in place of FTC+TDF with EFV. Subjects had a mean age of 38 years (range 18–80); 86% were male, 59% were Caucasian, and 23% were Black. The mean baseline CD4+ cell count was 245 cells/mm^3 (range 2–1,191) and median baseline plasma HIV-1 RNA was 5.01 $\log_{10}$ copies/mL (range 3.56–6.54). Subjects were stratified by baseline CD4+ cell count (< or ≥200 cells/mm^3); 41% had CD4+ cell counts <200 cells/mm^3 and 51% of subjects had baseline viral loads >100,000 copies/mL. Treatment outcomes through 48 and 144 weeks for those subjects who did not have EFV resistance at baseline are presented in Table 14.

Table 14 Virologic Outcomes of Randomized Treatment at Weeks 48 and 144 (Study 934)

Outcomes	At Week 48		At Week 144	
	FTC+TDF +EFV (N=244)	AZT/3TC +EFV (N=243)	FTC+TDF +EFV (N=227)[a]	AZT/3TC +EFV (N=229)[a]
Responder[b]	84%	73%	71%	58%
Virologic failure[c]	2%	4%	3%	6%
Rebound	1%	3%	2%	5%
Never suppressed	0%	0%	0%	0%
Change in antiretroviral regimen	1%	1%	1%	1%
Death	<1%	1%	1%	1%
Discontinued due to adverse event	4%	9%	5%	12%
Discontinued for other reasons[d]	10%	14%	20%	22%

a. Subjects who were responders at Week 48 or Week 96 (HIV-1 RNA <400 copies/mL) but did not consent to continue trial after Week 48 or Week 96 were excluded from analysis.
b. Subjects achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Weeks 48 and 144.
c. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Weeks 48 and 144.
d. Includes lost to follow-up, subject withdrawal, noncompliance, protocol violation, and other reasons.

Through Week 48, 84% and 73% of subjects in the FTC+TDF group and the AZT/3TC group, respectively, achieved and maintained HIV-1 RNA <400 copies/mL (71% and 58% through Week 144). The difference in the proportion of subjects who achieved and maintained HIV-1 RNA <400 copies/mL through 48 weeks is largely due to the higher number of discontinuations due to adverse events and other reasons in the AZT/3TC group in this open-label trial. In addition, 80% and 70% of subjects in the FTC+TDF group and the AZT/3TC group, respectively, achieved and maintained HIV-1 RNA <50 copies/mL through Week 48 (64% and 56% through Week 144). The mean increase from baseline in CD4+ cell count was 190 cells/mm^3 in the FTC+TDF group and 158 cells/mm^3 in the AZT/3TC group at Week 48 (312 and 271 cells/mm^3 at Week 144).

Through 48 weeks, 7 subjects in the FTC+TDF group and 5 subjects in the AZT/3TC group experienced a new CDC Class C event (10 and 6 subjects through 144 weeks).

14.3 Clinical Trial Results for HIV-1 PrEP: iPrEx

The iPrEx trial was a randomized, double-blind, placebo-controlled multinational study evaluating TRUVADA in 2,499 HIV-seronegative men or transgender women who have sex with men and with evidence of high-risk behavior for HIV-1 infection. Evidence of high-risk behavior included any one of the following reported to have occurred up to six months prior to study screening: no condom use during anal intercourse with an HIV-1 positive partner or a partner of unknown HIV status; anal intercourse with more than 3 sex partners; exchange of money, gifts, shelter, or drugs for anal sex;

sex with male partner and diagnosis of sexually transmitted infection; no consistent use of condoms with sex partner known to be HIV-1 positive.

All subjects received monthly HIV-1 testing, risk-reduction counseling, condoms, and management of sexually transmitted infections. Of the 2,499 enrolled subjects, 1,251 received TRUVADA and 1,248 received placebo. The mean age of subjects was 27 years; 5% were Asian, 9% Black, 18% White, and 72% Hispanic/Latino.

Subjects were followed for 4,237 person-years. The primary outcome measure was the incidence of documented HIV seroconversion. At the end of treatment, emergent HIV-1 seroconversion was observed in 131 subjects, of which 48 occurred in the TRUVADA group and 83 occurred in the placebo group, indicating a 42% (95% CI: 18–60%) reduction in risk. Risk reduction was found to be higher (53%; 95% CI: 34–72%) among subjects who reported previous unprotected anal intercourse (URAI) at screening (732 and 753 subjects reported URAI within the last 12 weeks at screening in the TRUVADA and placebo groups, respectively). In a post-hoc case control study of plasma and intracellular drug levels in about 10% of study subjects, risk reduction appeared to be greatest in subjects with detectable intracellular tenofovir diphosphate concentrations. Efficacy was therefore strongly correlated with adherence.

14.4 Clinical Trial Results for HIV-1 PrEP: Partners PrEP

The Partners PrEP trial was a randomized, double-blind, placebo-controlled 3-arm trial conducted in 4,758 HIV-1 serodiscordant heterosexual couples in Kenya and Uganda to evaluate the efficacy and safety of TDF (N=1,589) and FTC/TDF (N=1,583) versus (parallel comparison) placebo (N=1,586) in preventing HIV-1 acquisition by the uninfected partner.

All uninfected partner subjects received monthly HIV-1 testing, evaluation of adherence, assessment of sexual behavior, and safety evaluations. Women were also tested monthly for pregnancy. Women who became pregnant during the trial had study drug interrupted for the duration of the pregnancy and while breastfeeding. The uninfected partner subjects were predominantly male (61–64% across study drug groups) and had a mean age of 33–34 years.

Following 7,827 person-years of follow-up, 82 emergent HIV-1 seroconversions were reported, with an overall observed seroincidence rate of 1.05 per 100 person-years. Of the 82 seroconversions, 13 and 52 occurred in partner subjects randomized to TRUVADA and placebo, respectively. Two of the 13 seroconversions in the TRUVADA arm and 3 of the 52 seroconversions in the placebo arm occurred in women during treatment interruptions for pregnancy. The risk reduction for TRUVADA relative to placebo was 75% (95% CI: 55–87%). In a post-hoc case control study of plasma drug levels in about 10% of study subjects, risk reduction appeared to be greatest in subjects with detectable plasma tenofovir concentrations. Efficacy was therefore strongly correlated with adherence.

16 HOW SUPPLIED/STORAGE AND HANDLING

TRUVADA tablets are available in bottles containing 30 tablets with child-resistant closure as follows:

- 100 mg of FTC and 150 mg of TDF (equivalent to 123 mg of tenofovir disoproxil) tablets are blue, oval shaped, film coated, debossed with “GSI” on one side and with “703” on the other side (NDC 61958-0703-1).
- 133 mg of FTC and 200 mg of TDF (equivalent to 163 mg of tenofovir disoproxil) tablets are blue, rectangular shaped, film coated, debossed with “GSI” on one side and with “704” on the other side (NDC 61958-0704-1).

- 167 mg of FTC and 250 mg of TDF (equivalent to 204 mg of tenofovir disoproxil) tablets are blue, modified capsule shaped, film coated, debossed with “GSI” on one side and with “705” on the other side (NDC 61958-0705-1).
- 200 mg of FTC and 300 mg of TDF (equivalent to 245 mg of tenofovir disoproxil) tablets are blue, capsule shaped, film coated, debossed with “GILEAD” on one side and with “701” on the other side (NDC 61958-0701-1).

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.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Important Information for Uninfected Individuals Taking TRUVADA for HIV-1 PrEP

Advise HIV-uninfected individuals about the following *[see Warnings and Precautions (5.2)]*:

- The need to confirm that they are HIV-negative before starting to take TRUVADA to reduce the risk of acquiring HIV-1.
- That HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking TRUVADA, because TRUVADA alone does not constitute a complete regimen for HIV-1 treatment.
- The importance of taking TRUVADA on a regular dosing schedule and strict adherence to the recommended dosing schedule to reduce the risk of acquiring HIV-1. Uninfected individuals who miss doses are at greater risk of acquiring HIV-1 than those who do not miss doses.
- That TRUVADA does not prevent other sexually acquired infections and should only be used as part of a complete prevention strategy including other prevention measures.
- To use condoms consistently and correctly to lower the chances of sexual contact with any body fluids such as semen, vaginal secretions, or blood.
- The importance of knowing their HIV-1 status and the HIV-1 status of their partner(s).
- The importance of virologic suppression in their partner(s) with HIV-1.
- The need to get tested regularly for HIV-1 (at least every 3 months, or more frequently for some individuals such as adolescents) and to ask their partner(s) to get tested as well.
- To report any symptoms of acute HIV-1 infection (flu-like symptoms) to their healthcare provider immediately.
- That the signs and symptoms of acute infection include fever, headache, fatigue, arthralgia, vomiting, myalgia, diarrhea, pharyngitis, rash, night sweats, and adenopathy (cervical and inguinal).
- To get tested for other sexually transmitted infections, such as syphilis, chlamydia, and gonorrhea, that may facilitate HIV-1 transmission.
- To assess their sexual risk behavior and get support to help reduce sexual risk behavior.

Severe Acute Exacerbation of Hepatitis B in Patients Infected with HBV

Inform individuals that severe acute exacerbations of hepatitis B have been reported in patients who are infected with HBV and have discontinued TRUVADA *[see Warnings and Precautions (5.1)]*. Advise HBV-infected individuals to not discontinue TRUVADA without first informing their healthcare provider.

New Onset or Worsening Renal Impairment

Inform HIV-1 infected patients and uninfected individuals that renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported in association with the use of TDF, a component of TRUVADA. Advise patients to avoid TRUVADA with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple NSAIDs) *[see Warnings and Precautions (5.3)]*. The dosing interval of TRUVADA may need adjustment in HIV-1 infected patients with renal impairment. TRUVADA for HIV-1 PrEP should not be used in HIV-1 uninfected individuals if estimated creatinine clearance is less than 60 mL/min. If a decrease in estimated creatinine clearance is observed in uninfected individuals while using TRUVADA for HIV-1 PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use *[see Dosage and Administration (2.6)]*.

Immune Reconstitution Syndrome

Inform HIV-1 infected 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 (5.4)].*

Bone Loss and Mineralization Defects

Inform patients that decreases in bone mineral density have been observed with the use of TDF or TRUVADA. Consider bone monitoring in patients and uninfected individuals who have a history of pathologic bone fracture or at risk for osteopenia *[see Warnings and Precautions (5.5)].*

Lactic Acidosis and Severe Hepatomegaly

Inform HIV-1 infected patients and uninfected individuals that lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Treatment with TRUVADA should be suspended in any person who develops clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity *[see Warnings and Precautions (5.6)]*.

Drug Interactions

Advise individuals that TRUVADA may interact with many drugs; therefore, advise individuals to report to their healthcare provider the use of any other medication, including other HIV drugs and drugs for treatment of hepatitis C virus *[see Warnings and Precautions (5.7) and Drug Interactions (7)].*

Dosage Recommendations for Treatment of HIV-1 Infection

Inform HIV-1 infected patients that it is important to take TRUVADA with other antiretroviral drugs for the treatment of HIV-1 on a regular dosing schedule with or without food and to avoid missing doses as it can result in development of resistance.

Pregnancy Registry

Inform individuals using TRUVADA for HIV-1 treatment or HIV-1 PrEP that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant women exposed to TRUVADA *[see Use in Specific Populations (8.1)].*

Lactation

Instruct mothers not to breastfeed if they are taking TRUVADA for the treatment of HIV-1 infection or if acute HIV-1 infection is suspected in a mother taking TRUVADA for HIV-1 PrEP because of the risk of passing the HIV-1 virus to the baby. In HIV-uninfected women, the benefits and risks of TRUVADA while breastfeeding should be evaluated, including the risk of HIV-1 acquisition due to medication nonadherence and subsequent mother to child transmission *[see Use in Specific Populations (8.2)].*

Manufactured for and distributed by:

Gilead Sciences, Inc.
Foster City, CA 94404

21752-GS-035

Medication Guide
TRUVADA® (tru-VAH-dah)
(emtricitabine and tenofovir disoproxil fumarate)
tablets

Read this Medication Guide before you start taking TRUVADA 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 your treatment.

This Medication Guide provides information about **two different ways** that TRUVADA may be used. See the section **"What is TRUVADA?"** for detailed information about how TRUVADA may be used.

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

TRUVADA can cause serious side effects, including:

- **Worsening of hepatitis B virus infection (HBV). Your healthcare provider will test you for HBV before start or when you start treatment with TRUVADA. If you have HBV infection and take TRUVADA, your HBV may get worse (flare-up) if you stop taking TRUVADA. A "flare-up" is when your HBV infection suddenly returns in a worse way than before.**
  - Do not run out of TRUVADA. Refill your prescription or talk to your healthcare provider before your TRUVADA is all gone.
  - Do not stop taking TRUVADA without first talking to your healthcare provider.
  - If you stop taking TRUVADA, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your HBV infection, or give you a medicine to treat hepatitis B. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking TRUVADA.

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

Other important information for people who take TRUVADA to help reduce their risk of getting human immunodeficiency virus-1 (HIV-1) infection, also called pre-exposure prophylaxis or "PrEP":

Before taking TRUVADA to reduce your risk of getting HIV-1:

- **You must be HIV-1 negative to start TRUVADA. You must get tested to make sure that you do not already have HIV-1 infection.**
- **Do not take TRUVADA for HIV-1 PrEP unless you are confirmed to be HIV-1 negative.**
- Some HIV-1 tests can miss HIV-1 infection in a person who has recently become infected. If you have flu-like symptoms, you could have recently become infected with HIV-1. Tell your healthcare provider if you had a flu-like illness within the last month before starting TRUVADA or at any time while taking TRUVADA. Symptoms of new HIV-1 infection include:
  - tiredness
  - fever
  - joint or muscle aches
  - headache
  - sore throat
  - vomiting or diarrhea
  - rash
  - night sweats
  - enlarged lymph nodes in the neck or groin

While you are taking TRUVADA for HIV-1 PrEP:

- **TRUVADA does not prevent other sexually transmitted infections (STIs). Practice safer sex by using a latex or polyurethane condom to reduce the risk of getting STIs.**
- **You must stay HIV-negative to keep taking TRUVADA for HIV-1 PrEP.**
  - Know your HIV-1 status and the HIV-1 status of your partners.
  - Ask your partners with HIV-1 if they are taking anti-HIV-1 medicines and have an undetectable viral load. An undetectable viral load is when the amount of virus in the blood is too low to be measured in a lab test. To maintain an undetectable viral load, your partners must keep taking HIV-1 medicines every day. Your risk of getting HIV-1 is lower if your partners with HIV-1 are taking effective treatment.
  - Get tested for HIV-1 at least every 3 months or when your healthcare provider tells you.
  - Get tested for other STIs such as syphilis, chlamydia, and gonorrhea. These infections make it easier for HIV-1 to infect you.
  - If you think you were exposed to HIV-1, tell your healthcare provider right away. They may want to do more tests to be sure you are still HIV-1 negative.
  - Get information and support to help reduce sexual risk behaviors.
  - Do not miss any doses of TRUVADA. Missing doses increases your risk of getting HIV-1 infection.

- If you do become HIV-1 positive, you need more medicine than TRUVADA alone to treat HIV-1. TRUVADA by itself is not a complete treatment for HIV-1.

If you have HIV-1 and take only TRUVADA, over time your HIV-1 may become harder to treat.

What is TRUVADA?

TRUVADA is a prescription medicine that may be used in two different ways. TRUVADA is used:

- to treat HIV-1 infection when used with other anti-HIV-1 medicines in adults and children who weigh at least 37 pounds (at least 17 kg).
- for HIV-1 PrEP to reduce the risk of getting HIV-1 infection in adults and adolescents who weigh at least 77 pounds (at least 35 kg).

HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

TRUVADA contains the prescription medicines emtricitabine and tenofovir disoproxil fumarate.

It is not known if TRUVADA for treatment of HIV-1 infection is safe and effective in children who weigh less than 37 pounds (17 kg).

It is not known if TRUVADA is safe and effective in reducing the risk of HIV-1 infection in people who weigh less than 77 pounds (35 kg).

For people taking TRUVADA for HIV-1 PrEP:

Do not take TRUVADA for HIV-1 PrEP if:

- **you already have HIV-1 infection.** If you are HIV-1 positive, you need to take other medicines with TRUVADA to treat HIV-1. TRUVADA by itself is not a complete treatment for HIV-1.
- **you do not know your HIV-1 infection status.** You may already be HIV-1 positive. You need to take other HIV-1 medicines with TRUVADA to treat HIV-1.

TRUVADA can only help reduce your risk of getting HIV-1 **before** you are infected.

What should I tell my healthcare provider before taking TRUVADA?

Before taking TRUVADA, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems, including HBV infection
- have kidney problems or receive kidney dialysis treatment
- have bone problems
- are pregnant or plan to become pregnant. It is not known if TRUVADA can harm your unborn baby. Tell your healthcare provider if you become pregnant during treatment with TRUVADA.

  Pregnancy Registry: There is a pregnancy registry for people who take TRUVADA during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk with your healthcare provider about how you can take part in this registry.
- are breastfeeding or plan to breastfeed. TRUVADA can pass to your baby in your breast milk.
  - Do not breastfeed if you have HIV-1 or if you think you have recently become infected with HIV-1 because of the risk of passing HIV-1 to your baby.
  - If you take TRUVADA for HIV-1 PrEP, talk with 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 may interact with TRUVADA. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

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

How should I take TRUVADA?

- Take TRUVADA exactly as your healthcare provider tells you to take it. If you take TRUVADA to treat HIV-1 infection, you need to take other HIV-1 medicines. Your healthcare provider will tell you what medicines to take and how to take them.
- Take TRUVADA 1 time each day with or without food.
- Children who take TRUVADA are prescribed a lower strength tablet than adults. Children should swallow the TRUVADA tablet**.** Tell your healthcare provider if your child cannot swallow the tablet, because they may need a different HIV-1 medicine.
  - Your healthcare provider will change the dose of TRUVADA as needed based on your child's weight.
- Do not change your dose or stop taking TRUVADA without first talking with your healthcare provider. Stay under a

healthcare provider's care when taking TRUVADA. Do not miss a dose of TRUVADA.

- If you take too much TRUVADA, call your healthcare provider or go to the nearest hospital emergency room right away.
- When your TRUVADA supply starts to run low, get more from your healthcare provider or pharmacy.
  - If you are taking TRUVADA for treatment of HIV-1, the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to TRUVADA and become harder to treat.
  - If you are taking TRUVADA for HIV-1 PrEP, missing doses increases your risk of getting HIV-1 infection.

What are the possible side effects of TRUVADA?

TRUVADA may cause serious side effects, including:

- **See "What is the most important information I should know about TRUVADA?"**
- **New or worse kidney problems**, **including kidney failure.** Your healthcare provider should do blood and urine tests to check your kidneys before you start and during treatment with TRUVADA. Your healthcare provider may tell you to take TRUVADA less often, or to stop taking TRUVADA if you get new or worse kidney problems.
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when taking medicines to treat HIV-1 infection. 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 any new symptoms after starting your HIV-1 medicine.
- **Bone problems** can happen in some people who take TRUVADA. Bone problems include bone pain, or softening or thinning of bones, which may lead to fractures. Your healthcare provider may need to do tests to check your bones.
- **Too much lactic acid in your blood (lactic acidosis).** Too much lactic acid is a serious but rare medical emergency that can lead to death. Tell your healthcare provider right away if you get these symptoms: weakness or being more tired than usual, unusual muscle pain, being short of breath or fast breathing, stomach pain with nausea and vomiting, cold or blue hands and feet, feel dizzy or lightheaded, or a fast or abnormal heartbeat.
- **Severe liver problems.** In rare cases, severe liver problems can happen that can lead to death. Tell your healthcare provider right away if you get these symptoms: skin or the white part of your eyes turns yellow, dark "tea-colored" urine, light-colored stools, loss of appetite for several days or longer, nausea, or stomach-area pain.

The most common side effects of TRUVADA for treatment of HIV-1 include:

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

Common side effects in people who take TRUVADA for HIV-1 PrEP include:

- headache
- stomach-area (abdomen) pain
- decreased weight

These are not all the possible side effects of TRUVADA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TRUVADA?

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

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

General information about TRUVADA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TRUVADA for a condition for which it was not prescribed. Do not give TRUVADA to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about TRUVADA that is written for health professionals.

What are the ingredients in TRUVADA?

Active ingredients: emtricitabine and tenofovir disoproxil fumarate.

Inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch (gluten free). The 200 mg/300 mg strength tablets are coated with Opadry II Blue Y-30-10701, which contains FD&C Blue #2 aluminum lake, hypromellose 2910, lactose monohydrate, titanium dioxide, and triacetin. The 167 mg/250 mg, 133 mg/200 mg, and 100 mg/150 mg strength tablets are coated with Opadry II Blue, which contains FD&C Blue #2 aluminum lake, hypromellose 2910, lactose monohydrate, titanium dioxide, and triacetin.

Manufactured for and distributed by:
Gilead Sciences, Inc.
Foster City, CA 94404

21752-GS-035
For more information, call 1-800-445-3235 or go to www.TRUVADA.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 04/2024

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21752Orig1s060

RISK ASSESSMENT AND RISK MITIGATION REVIEW(S)

Risk Evaluation and Mitigation Strategy (REMS) Memorandum
REMS Modification: Release of REMS Requirement

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF ANTIMICROBIAL PRODUCTS
DIVISION OF ANTIVIRAL PRODUCTS

NDA:	21752
PRODUCT:	TRUVADA® (emtricitabine and tenofovir disoproxil fumarate) tablets
APPLICANT:	Gilead Sciences, Inc.
FROM:	Poonam Mishra, MD, MPH Deputy Director for Safety
DATE:	June 28, 2019

A Risk Evaluation and Mitigation Strategy (REMS) for Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg, FTC/TDF) for a pre-exposure prophylaxis (PrEP) indication was approved on July 16, 2012, to ensure the benefits of the drug outweigh the risks of human immunodeficiency virus-1 (HIV-1) acquisition and development of resistance if FTC/TDF is initiated or continued in the setting of unrecognized HIV-1 infection. A Single Shared System (SSS) REMS for FTC/TDF products was approved on June 8, 2017, and the most recent modification to the SSS REMS was approved on May 15, 2018. The SSS REMS consists of elements to assure safe use (ETASU) and a timetable for submission of REMS assessments.

On March 27, 2019, Gilead Sciences, Inc. submitted a proposed Major REMS Modification that includes a request for release from the SSS REMS requirement for FTC/TDF for HIV-1 PrEP.

After consultations between the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE), we have determined that the Applicant submitted an adequate rationale to support the proposed modifications described above. In addition, we have determined that the REMS is no longer necessary to ensure the benefits of the drug outweigh its risks for the following reasons:

The main safety concern identified in the premarket setting for Truvada was the risk of initiation of PrEP in the setting of undiagnosed HIV-1 infection or continued use following HIV-1 seroconversion, which may lead to the development of drug-resistant HIV-1 variants. In July 2012, at the time of the approval of the PrEP indication, there was limited awareness of PrEP among the general public or health care providers and no educational materials for a PrEP indication were available. A REMS was considered necessary to ensure the benefits of Truvada for the PrEP indication outweighed the risks of HIV-1 seroconversion and the development of drug resistance.

Since the approval, however, many public educational resources and treatment guidelines regarding PrEP have become widely available, including those through Department of Health and Human Services (DHHS) entities such as the Centers for Disease Control and Prevention (CDC), as well as state and local departments of health. REMS assessments have generally demonstrated an acceptable knowledge of the key risk messages associated with Truvada use for HIV-1 PrEP among both prescribers and HIV-1 uninfected individuals taking Truvada for HIV-1 PrEP (PrEP users).

Therefore, because the elements to assure safe use are no longer necessary to ensure the benefits of the drug outweigh the risks, a REMS is no longer required for emtricitabine/tenofovir disoproxil fumarate tablets, for PrEP.

Regulatory Context for Truvada REMS for PrEP Indication

Truvada is a fixed-dose combination tablet of two antiretroviral drugs (FTC and TDF, both HIV-1 nucleoside analog reverse transcriptase inhibitors), which was approved on August 2, 2004, for the treatment of HIV-1 infection in combination with other antiretroviral drugs. On July 16, 2012, a supplemental new drug application (sNDA 21752/S-030) was approved to add a new indication for the use of Truvada (FTC 200mg/TDF 300 mg) for PrEP, in combination with safer sex practices, to reduce the risk of sexually-acquired HIV-1 infection in adults at high risk; a REMS was required as part of this approval. The REMS for Truvada does not apply to use of Truvada in combination with other antiretroviral agents for the treatment of HIV-1 infection. On May 15, 2018, Truvada received a supplemental approval (S-055) to expand the PrEP indication to include adolescents weighing at least 35 kg who are at risk of HIV-1 acquisition.

As noted in the Clinical Review by Dr. Peter Miele archived on July 13, 2012, approval of the sNDA for FTC/TDF for PrEP was based on review of the efficacy and safety data from two large, prospective, randomized, double-blind, placebo-controlled Phase 3 clinical trials. The iPrEx trial enrolled 2,499 HIV-seronegative men or transgender women who have sex with men (MSM) and with evidence of high-risk behavior for HIV-1 acquisition (with 3,891 person-years [PY] of follow-up) and the Partners PrEP trial enrolled 4,747 HIV-1 uninfected individuals in stable heterosexual HIV-1 serodiscordant relationships (with 7,830 PY of follow-up). Both trials demonstrated superiority of once-daily oral FTC/TDF over placebo in preventing sexually-acquired HIV-1 infection when offered as part of a comprehensive prevention strategy that included monthly HIV-1 testing, risk reduction counseling, provision of condoms, and treatment of any sexually transmitted infections. In these populations and trial settings, FTC/TDF reduced the risk of HIV-1 infection by 42% (95% CI 18-60%) relative to placebo in the iPrEx trial in the modified intent-to-treat analysis, and by 75% (95% CI 54-86%) relative to placebo in the Partners PrEP trial. In both trials, efficacy was strongly correlated with adherence to the daily dosage regimen, as demonstrated by post-hoc subgroup analyses using measured drug levels in blood samples. Risk reduction was substantially higher (~90%) in subjects with detectable drug concentrations relative to non-adherent subjects with no detectable drug levels. These trials also demonstrated the potential for development of drug-resistant HIV-1 variants. Resistance (mainly to the FTC component of Truvada) was detected among 10 trial participants randomized to active drug with undiagnosed, early HIV-1 infection at baseline. Development of drug-resistant HIV-1 variants may limit treatment options for the infected individual and increase the risk of transmission of drug-resistant virus to other individuals.

In accordance with section 505-1 of the FDCA, at the time of the approval of the PrEP indication in 2012, FDA determined that a REMS was necessary for Truvada for a PrEP indication to ensure the benefits of the drug outweigh the risks of HIV-1 acquisition and development of resistance if Truvada is initiated or continued in the setting of unrecognized HIV-1 infection. At that time, the REMS consisted of a Medication Guide, ETASU and a timetable for submission of REMS assessments.

As part of the Major REMS Modification (S-050) approved on February 25, 2016, the Medication Guide was eliminated as an element of the Truvada REMS. Please refer to the DRISK review

archived on February 15, 2016, for details. In reviewing the proposed modification, FDA determined that it was no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of Truvada outweigh its risks.

Single Shared System (SSS) REMS for FTC/TDF Products

A SSS REMS for FTC/TDF products was approved on June 8, 2017, that was to become applicable on the date of full approval of the first abbreviated new drug application (ANDA) referencing Truvada.

The FTC/TDF SSS REMS consists of Prescriber Training (ETASU A), which requires the sponsor to make training to healthcare providers available; however, the need for training is not linked to distribution or dispensing.

The goals of the REMS for FTC/TDF for a PrEP indication are:

To inform and educate prescribers and uninfected adults and adolescents at risk of acquiring HIV-1 infection about:

- The importance of strict adherence to the recommended dosing regimen
- The importance of regular monitoring of HIV-1 serostatus to avoid continuing to take emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, if seroconversion has occurred, to reduce the risk of development of resistant HIV-1 variants
- The fact that emtricitabine/tenofovir disoproxil fumarate for a PrEP indication must be considered as only part of a comprehensive prevention strategy to reduce the risk of HIV-1 infection and that other preventive measures should also be used

Review of periodic REMS assessment reports has been done by DRISK. Please refer to the REMS assessment reviews for detailed assessment. The most recent 76-Month (5^{th}) Truvada REMS assessment bridging report was submitted on December 4, 2018 and the REMS assessment review was archived on May 01, 2019.

Release of REMS Requirement

On March 27, 2019, Gilead Sciences, Inc. submitted a proposed Major REMS Modification that includes a request for release from the single shared system REMS requirement for FTC-TDF for a PrEP indication.

In their rationale, Gilead notes that several resources are widely available in the public domain, independent of the components of the REMS, that provide comprehensive PrEP education, with an emphasis on adherence and HIV-1 serostaus monitoring. Since the initial approval, the large number of education and awareness efforts by the public health departments at the federal, state and local levels, medical professional societies (e.g. International Antiviral Society-USA www.iasusa.org), scientific and academic community, and community-based organizations has led to increasing awareness for both health care providers and PrEP users with regard to the appropriate use of Truvada for PrEP.

Of note, there are many educational resources available on the CDC website, such as resources for clinicians, materials for patients, and training for clinicians available under Prescribe HIV

Prevention.[1] In addition, comprehensive guidelines for prescribing PrEP have been published by the CDC in "A Clinical Practice Guideline" [2], including a "Clinical Providers' Supplement".[3] The latter contains additional tools for clinicians providing PrEP, such as a patient/provider checklist, patient information sheets, provider information sheets, a risk incidence assessment, and supplemental counseling information. The DHHS website AIDS*info* has information on PrEP under HIV Prevention with a link to CDC resources.[4] In addition, multiple state and local health authorities, such as New York State[5], New York City Department of Health and Mental Hygiene[6], and San Francisco Department of Public Health Population Health Division, have information for patients and have issued guidance for health care providers on the safe use of PrEP. A comprehensive resource, "PrEP Education for Youth-Serving Primary Care Providers Toolkit"[7], has been made available by the Sexuality Information and Education Council of the United States (SIECUS), which focuses on delivering PrEP care to youth at high risk of HIV acquisition.

Please refer to the OSE/Division of Risk Management (DRISK) REMS review archived on June 27, 2019 for a comprehensive review of the REMS regulatory history, including REMS assessments, REMS modifications, and review of the rationale provided by the Applicant to support the proposed release of the REMS requirements. In addition, DRISK consulted the OSE's Division of Pharmacovigilance (DPV) and the Division of Epidemiology (DEPI) in preparation for a REMS Oversight Committee (ROC) meeting. Please refer to DPV review dated May 1, 2019, which provides an evaluation of the FDA Adverse Event reporting System (FAERS) database for reports of HIV seroconversion among individuals using Truvada for the PrEP indication. The DEPI-II review archived on April 9, 2019, provides a literature review of the incidence of HIV-1 seroconversion and the risk of drug resistance with use of Truvada for PrEP. This review also examined the association between adherence to daily FTC/TDF for PrEP and the risk of HIV seroconversion and the development of drug-resistant virus.

In conclusion, REMS assessments have generally demonstrated acceptable knowledge of the key risk messages associated with Truvada use for HIV-1 PrEP among both prescribers and PrEP users. It is unclear what level of impact the REMS program had in disseminating the pertinent information related to Truvada use for PrEP taking into consideration the other publicly available educational resources. For instance, it is unknown what percentage of health care providers obtained their knowledge from the REMS program versus other publicly available resources (e.g., CDC). Based on cumulative postmarketing data, including data obtained as required by postmarketing requirements (PMR 1906-2 and 1906-3), HIV-1 seroconversion rates have been consistently low (≤1%), and reported cases of drug resistance have been rare – most are consistent with transmitted drug-resistant variants in non-adherent individuals or initiation of PrEP during acute HIV-1 infection.

The OSE and DAVP review teams presented the available evidence to support the proposal for a REMS release at the ROC meeting held on April 3, 2019. The committee, which consists of senior level management from the Offices of New Drugs, Surveillance and Epidemiology, and Regulatory Policy, is in agreement with the DRISK-DAVP recommendations to release the REMS requirements

[1] https://www.cdc.gov/actagainstaids/campaigns/prescribe-hiv-prevention/index.html
[2] https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf
[3] https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-provider-supplement-2017.pdf
[4] https://aidsinfo.nih.gov/understanding-hiv-aids/fact-sheets/20/85/pre-exposure-prophylaxis--prep-
[5] https://www.hivguidelines.org/prep-for-prevention/
[6] https://www1.nyc.gov/site/doh/providers/health-topics/pre-exposure-prophylaxis-provider-faq.page
[7] https://siecus.org/resources/prep-education-for-youth-serving-primary-care-providers-toolkit/

for FTC/TDF products for a PrEP indication. Please refer to the Meeting Minutes on the ROC SharePoint site for details.

The currently approved US Prescribing Information (USPI) and Medication Guide for Truvada adequately communicate the relevant information to ensure the safe and effective use of FTC/TDF for the PrEP indication throughout different sections of the labeling as appropriate (e.g. Boxed Warning, Indications and Usage, Warning and Precautions, Use in Specific Populations, Patient Counseling Information, and Medication Guide).[8] The approved labeling is adequate to address the serious risk of initiation of PrEP in the setting of undiagnosed HIV-1 infection or continued use following HIV-1 seroconversion, which may lead to the development of drug resistance. The labeling emphasizes:

- Use of Truvada for HIV-1 PrEP as part of a comprehensive prevention strategy that includes other preventive measures, such as safer sex practices
- Strict adherence to the recommended dosing schedule to reduce the risk of acquiring HIV-1 infection
- Screening of all individuals for HIV-1 infection before initiating Truvada for HIV-1 PrEP to confirm HIV-1 negative status
- Periodic HIV-1 screening tests during PrEP use to avoid use of Truvada alone if seroconversion has occurred, because Truvada alone does not constitute a complete regimen for HIV-1 treatment

Regulatory Action

FDA has determined that because elements to assure safe use are no longer necessary to ensure the benefits of the FTC/TDF for PrEP outweigh the risks, a REMS is no longer required. The approved Truvada USPI and Medication Guide are adequate to address the serious risk of initiation of PrEP in the setting of undiagnosed HIV-1 infection or continued use following HIV-1 seroconversion. Approval of the proposed REMS modification to release single shared system REMS requirement for FTC/TDF for HIV-1 PrEP is recommended.

[8] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021752s055lbl.pdf
Online resources accessed on May 29, 2019.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

RISK EVALUATION AND MITIGATION STRATEGY (REMS) MODIFICATION REVIEW

Date:	June 26, 2019
Reviewer(s)	Till Olickal, Ph.D., Pharm.D., Division of Risk Management (DRISK)
Team Leader	Elizabeth Everhart, MSN, RN, ACNP
Division Director:	Cynthia LaCivita, Pharm.D.
Subject:	Rationale for a modification to release the REMS
Therapeutic class:	Nucleoside Analog HIV-1 Reverse Transcriptase Inhibitor
Dosage forms:	200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate - fixed-dose combination oral tablet
Dosing Regimen:	One tablet (200 mg FTC / 300 mg TDF) once daily
Review Division	Division of Antiviral Products (DAVP) Office of Generic Drugs (OGD)
Applications Type/Number:	See Table 3 in Appendix
Action Date:	September 23, 2019
OSE RCM #:	2019-689

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EXECUTIVE SUMMARY

The purpose of this review is to evaluate if the single, shared system (SSS) risk evaluation and mitigation strategy (REMS) for emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) for an HIV-1 pre-exposure prophylaxis (PrEP) is still necessary to ensure the benefits outweigh the risks.

Truvada (FTC/TDF) for the PrEP indication for the prevention of HIV-1 infection in adults who are at high risk for acquiring HIV-1 was approved with a REMS on July 16, 2012. The identified risks associated with the use of Truvada for the PrEP indication were breakthrough HIV-1 infection and the development of resistant HIV-1 variants when antiretroviral prophylaxis is not used appropriately. The Truvada REMS only applied to the PrEP indication, not to the indication for the treatment of patients already infected with HIV-1.

On June 8, 2017 the Truvada REMS was modified to the SSS REMS for FTC/TDF to include approved abbreviated new drug applications (ANDAs). The goals are the same as the Truvada REMS and consists of the same elements to assure safe use (ETASU) and a timetable for submission of assessments.

The goals of the FTC/TDFREMS for PrEP are:

To inform and educate prescribers and uninfected adults and adolescents at high risk for acquiring HIV-1 infection about:

- The importance of strict adherence to the recommended dosing regimen.
- The importance of regular monitoring of HIV-1 serostatus to avoid continuing to take FTC/TDF for a PrEP indication, if seroconversion has occurred, to reduce the risk of development of resistant HIV-1 variants.
- The fact that FTC/TDF for a PrEP indication must be considered as only part of a comprehensive prevention strategy to reduce the risk of HIV-1 infection and that other preventive measures should also be used.

Gilead Sciences, Inc. (Gilead), the applicant for the reference listed drug (RLD) Truvada, submitted a proposed modification to the REMS to request elimination of the REMS with the rationale that REMS assessments have demonstrated that the REMS goals have been met; further, survey results and other data show that both healthcare providers and individuals taking PrEP are well-educated on its use and have a high level of awareness on its risks.

DRISK and DVAP determined that a REMS is no longer necessary to ensure the benefits outweigh the risks for FTC/TDF for the PrEP indication. In support of this determination, the divisions noted that since the PrEP approval, non-REMS educational programs (e.g., CDC and local health departments, HHS initiative) and clinical guidelines for PrEP have become readily available and support greater awareness, education, and knowledge of PrEP among healthcare professionals (HCPs), PrEP users, and public health communities. These materials and

guidelines convey the importance of strict adherence to the recommended dosing schedule, importance of regular monitoring of HIV-1 serostatus to avoid continuing to take FTC/TDF for PrEP if seroconversion has occurred, and that FTC/TDF for PrEP must be considered as only part of a comprehensive prevention strategy to reduce the risk of HIV-1 infection and that other preventive measures should also be used. Further, the number of seroconversions among PrEP users has been consistently low since the approval. In addition, REMS assessments have generally indicated that prescriber and patient survey respondents were knowledgeable about the risks associated with PrEP use. The REMS Oversight Committee (ROC) concurred with the divisions' determination that the REMS is no longer necessary to ensure the benefits outweigh the risks. Product labeling, which includes a Boxed Warning and Medication Guide will be used to communicate the key messages that FTC/TDF should be considered as part of a comprehensive management to reduce the risk of acquiring HIV-1, that FTC/TDF for PrEP must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiating and periodically (at least every 3 months) during use, and that uninfected individuals should be counseled to strictly adhere to the recommended FTC/TDF dosing schedule.

DRSK recommends that the SSS REMS for FTC/TDF for the PrEP indication be released.

1. INTRODUCTION

The purpose of this review is to determine if the REMS for FTC/TDF as PrEP is still necessary to ensure the benefits outweigh the risks. This evaluation takes into consideration the greater public awareness of PrEP and its increased uptake and use, since the time the REMS was first approved, the consistently low number of seroconversions among PrEP users, the available non-REMS educational programs by the Centers for Disease Control and Prevention (CDC) and local health departments, as well as the Department of Health and Human Services (HHS) initiative, the updated 2017 clinical guidelines for PrEP by the CDC, , and the results of the five REMS assessment reports submitted by Gilead.

1.1 PRODUCT BACKGROUND

The RLD for this product is Truvada (NDA 21752), a combination of emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) as a fixed-dose, oral tablet. Both emtricitabine and tenofovir disoproxil fumarate are nucleoside analog HIV-1 reverse transcriptase inhibitors. Truvada was initially approved on August 2, 2004, in combination with other antiretroviral agents (such as nonnucleoside reverse transcriptase inhibitors or protease inhibitors) for the treatment of HIV-1 infected in adults. Truvada is currently available as 100 mg/150 mg, 133 mg/200 mg, 167 mg/250 mg and 200 mg/300 mg tablets for the treatment of HIV-1 infection. Truvada for the PrEP indication (200 mg/300 mg tablets) was approved with a REMS on July 16, 2012 for the prevention of HIV-1 infection in adults at risk for acquiring HIV-1. Truvada is marketed by Gilead Sciences, Inc.

The FTC/TDF SSS REMS was approved on June 8, 2017. On May 15, 2018 Truvada (NDA 21752/S-055) received approval to expand the PrEP indication to include adolescents weighing at least 35 kg who are at risk of HIV-1 infection.[1] The SSS REMS was subsequently modified on July 24, 2018 to align all members of the SSS REMS to include the changes from the REMS

modification approved by the RLD. The SSS REMS only applies to the PrEP indication, not to the indication for the treatment of patients already infected with HIV-1. FTC/TDF is the only antiretroviral therapy currently approved in the U.S. for a PrEP indication.

1.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 21752, ANDAs 206436, 90894, 90513 and 209721 relevant to this review:

- 07/16/2012: Truvada was approved for the PrEP indication with a REMS.
- 06/08/2017: FTC/TDF SSS REMS approved along with the approval of Teva (ANDA 90894).
- 09/21/2017: The FTC/TDF SSS REMS was revised.
- 12/08/2017: The FTC/TDF SSS REMS was modified, based on modifications to change the graphics for the SSS REMS educational materials and removal of Truvada brand from the REMS.
- 01/26/2018: ANDA 90513 (Aurobindo) was approved and joined the SSS REMS.
- 04/09/2018: ANDA 206436 (Mylan) was approved and joined the SSS REMS.
- 05/15/2018: Truvada NDA 21752/S-055 was approved expanding the PrEP indication to include adolescents weighing at least 35 kg who are at risk of HIV-1 acquisition.
- 07/18/2018: FDA received the original application for ANDA 212114.
- 07/24/2018: The FTC/TDF SSS REMS was modified to align all members of the SSS REMS to include the changes from the REMS modification approved by Truvada, the RLD on May 15, 2018 to expand the indication of PrEP to include adolescents weighing at least 35 kg who are at risk of HIV-1 infection.
- 08/22/2018: ANDA 209721 (Amneal) was approved and joined the FTC/TDF SSS REMS.
- 03/27/2019: Gilead submitted prior approval supplement 60, requesting elimination of the FTC/TDF SSS REMS
- 04/3/2019: REMS Oversight Committee (ROC) meeting[a] was held to discuss releasing the FTC/TDF SSS REMS. The ROC unanimously concurred with DRISK/DAVP recommendation that the REMS is no longer necessary to ensure the benefits outweigh the risk associated with FTC/TDF for PrEP.

2. EMTRICITABINE/TENOFOVIR DISOPROXIL FUMARATE (FTC/TDF) SSS REMS

The current approved FTC/TDF SSS REMS (dated July 24, 2018) consists of ETASU and a timetable for submission of assessments.

[a] As per the 21st Century Review process, all REMS with elements to assure safe use (ETASU) are discussed at the REMS Oversight Committee (ROC) which consists of senior level management from the Office of New Drugs, Surveillance and Epidemiology, and the Office of Regulatory Policy.

2.1 REMS GOALS

The goals of the FTC/TDF SSS REMS for PrEP are:

To inform and educate prescribers and uninfected adults and adolescents at high risk for acquiring HIV-1 infection about:

- The importance of strict adherence to the recommended dosing regimen
- The importance of regular monitoring of HIV-1 serostatus to avoid continuing to take FTC/TDF for a PrEP indication, if seroconversion has occurred, to reduce the risk of development of resistant HIV-1 variants
- The fact that FTC/TDF for a PrEP indication must be considered as only part of a comprehensive prevention strategy to reduce the risk of HIV-1 infection and that other preventive measures should also be used

2.2 ELEMENTS TO ASSURE SAFE USE

The FTC/TDF SSS REMS for the PrEP indication requires that the FTC/TDF applicants covered by the REMS must provide training to healthcare providers who prescribe FTC/TDF for PrEP.

The training includes the following educational materials: Training Guide for Healthcare Providers, Healthcare Provider Education Slide Deck, Important Safety Information-for Healthcare Providers, Important Safety Information for Adults Who Don't have HIV, Agreement Form for Initiating emtricitabine/tenofovir disoproxil fumarate for Pre-exposure Prophylaxis (PrEP), Checklist for Prescribers, Safety Information Fact Sheet for Prescribers, and Important Safety Information for Adolescents Who Don't have HIV. The training must be available online or in a hardcopy format by mail.

The training must be made available by the Applicants to prescribers; however, the completion of training by prescribers is not linked to distribution or dispensing of FTC/TDF.

In order to inform healthcare providers about the REMS program and to facilitate training and education, FTC/TDF REMS Applicants are required to disseminate to likely prescribers information (REMS letters and Safety Information Fact Sheet for Prescribers) about the potential and known safety risks associated with FTC/TDF for PrEP to healthcare providers and professional organizations representing the healthcare providers likely to prescribe FTC/TDF for PrEP. The Applicants must also make these materials available via link from the FTC/TDF SSS REMS Program Website.

2.3 TIMETABLE FOR SUBMISSION OF ASSESSMENTS

The FTC/TDF NDA Applicant must submit REMS Assessments to the FDA every 18 months from the date of initial approval of the SSS REMS (06/08/2017).

3. GILEAD'S RATIONALE FOR REMS ELIMINIATION

On March 27, 2019, Gilead, submitted a prior approval supplement requesting elimination of the REMS for FTC/TDF with the rationale that REMS assessments have demonstrated that the REMS goals have been met. Further, survey results and other data show that both healthcare providers and individuals taking PrEP are well-educated on its use and have a high level of awareness on its risks. In their rationale, they included information about the extensive increase in the use of PrEP and the accompanying educational programs now widely available in the community. They cite educational campaigns by public health authorities both within government and non-government entities, as well as by wider community-based organizations. In addition, they note that cumulative evidence indicates that the original safety concerns of lack of adherence, seroconversion, and development of resistance have not been borne out to the extent initially anticipated.[2]

Gilead's rationale for elimination of the REMS included that, since approval of the PrEP indication, leading US and international guidelines on PrEP have been issued to assist HCPs to optimally and safely use PrEP. Some of the guidelines and resources now available include publications from the following:

- IAS (International Antiviral Society)
- EACS (European AIDS Clinical Society)
- WHO (World Health Organization)
- Local health authorities as follows have all issued guidance on the safe use of PrEP:

    - SFDPH (San Francisco Department of Public Health)
    - NYCDOH (New York City Department of Health and Mental Hygiene)

The guidelines include instructions on counseling, adherence, HIV testing, sexually transmitted infections testing, and safety monitoring, each of which are consistent with the goals of the REMS. Gilead also noted the newly released draft recommendation statement from the U. S. Preventive Services Task Force (USPSTF) which states that clinicians should offer PrEP to those at high risk for HIV infection; this is in line with clinical guidelines. Recognizing that when taken as prescribed, PrEP is highly effective at preventing HIV among those at high risk, the Task Force concluded with "high certainty" that there is a "substantial net benefit" to use in this population, giving it an "A" recommendation. The Affordable Care Act requires all commercial payers and states expanding Medicaid to provide first dollar coverage (no co-pay or deductible) for "A" or "B" rated USPSTF recommendations. As such, by March 2020, commercial and federal insurance must pay for clinical management, medications, and services for anyone who qualifies for PrEP. This is important for PrEP users as it removes cost barriers; moreover, it is a validation of PrEP from a national authority specifically tasked with preventive services and care.

Gilead made note of numerous articles in peer reviewed journals, including articles in American Academy of Family Physicians[3] and Clinical Infectious Diseases[4,5] that advocate for the safe use of PrEP; websites, such as Up – To Date[6], offer many resources covering various aspects of PrEP for medical professionals, students, hospitals or institutions, group practices, and PrEP users or

caregivers. Other available resources for information regarding PrEP include nongovernmental advocacy and community – based organizations such as Planned Parenthood, PleasePrEPMe, PrEP Watch, and the Facebook group "PrEP Facts: Rethinking HIV Prevention and Sex". Each of these organizations has key websites with resources and guidelines for providers and potential PrEP users.[2]

In reviewing the submitted rationale for release of the FTC/TDF SSS REMS, DRISK agrees that prescribers and uninfected individuals generally understand key risk messages regarding PrEP use and that educational resources for PrEP use are readily available outside of the REMS. As concluded in the final Truvada for PrEP REMS Assessment Report submitted on December 4, 2018, the available information at this time suggests that prescriber survey respondents understand the important key messages regarding PrEP.. Similarly, available information suggests that uninfected individuals taking Truvada for a PrEP indication also have good understanding of the key messages.

4. INFORMATION THAT SUPPORTS ELMINATION OF THE REMS

4.1 PUBLIC AWARENESS OF PREP

In 2012, at the time of the PrEP approval, there were no educational materials for this indication and a REMS was considered necessary to ensure the benefits of FTC/TDF for PrEP indication outweighed the risks of HIV seroconversion and development of drug resistance. Since the approval, many public educational resources have become widely available, including those through various HHS entities such as CDC and the National Institutes of Health (NIH), as well as local departments of health.

The CDC issued guidelines for PrEP in 2014 and updated them in 2017.[7] The guidelines provide clear criteria for determining a person's HIV risk and indications for PrEP use. It recommends that patients receive HIV testing to confirm negative status before starting PrEP. The guidelines recommend regular monitoring of HIV infection status, side effects, adherence, and sexual or injection risk behaviors. The guidelines further underscore the importance of counseling about adherence to the PrEP regimen and HIV risk reduction, including encouraging condom use for additional protection. The 2017 guideline provides clinicians additional materials and tools for use when prescribing PrEP (e.g., patient counseling and information sheets, checklist for initiating PrEP).

The CDC also has multiple educational and other resources on its website, including a consumer information sheet called "PrEP 101". There are additional links that direct patients to a variety of educational tools such as the HIV Risk Reduction Tool, which contains materials focused on patients. There is also a continuing medical education (CME/CE) program for health care providers via Medscape, as well as other resources for clinicians such as PrEP FAQs and a CDC Fact Sheet available on the website.

Since the expansion of the indication to the adolescent population in May 2018, and the availability of the REMS Adolescent brochure, other resources are now also available for prescribers caring for at-risk adolescents. A 2018 publication from the Journal of Pediatric

Health Care details a new educational curriculum for providing PrEP to adolescents.[8] This paper outlines a curriculum with the goal of reaching adolescent providers unfamiliar with PrEP assessment, administration, and monitoring. An expert panel of seven made up of nursing and medical professionals and public health officials (three of whom were from CDC) reviewed the curriculum for content validity. A pilot implementation of the curriculum was conducted with staff from eight school-based health clinics located in New York City. Key domains identified as essential for inclusion in the curriculum were: "What is PrEP/PEP?", "Overview of PrEP Efficacy—Clinical Trials, PrEP Eligibility, Sexual History Taking in the PrEP Era", "Can Adolescents Access PrEP?", "How to conduct an Adolescent PrEP Medical Visit" and "Benefits and Insurance Navigation".

In March 2016, the Sexuality Information and Education Council of the United States (SIECUS), convened an Expert Work Group, to address issues surrounding PrEP delivery and to develop an online resource to support primary care providers in offering PrEP to adolescents and young adults under age 25. SIECUS compiled some of the resources about PrEP and HIV that are already exist and developed new tools, such as the "PrEP Education for Youth- Serving Primary Care Providers Toolkit".[9]

In 2019, the HHS announced an initiative to address the ongoing HIV public health crisis, which includes substantial resources for training, including for PrEP, with the goals of first reducing the numbers of incident HIV infections in the United States by 75% within 5 years, and then by 90% within 10 years. This initiative will leverage critical scientific advances in HIV prevention, diagnosis, treatment, and care by coordinating the highly successful programs, resources, and infrastructure of the CDC, NIH, the Health Resources and Services Administration (HRSA), the Substance Abuse and Mental Health Services Administration (SAMHSA), and the Indian Health Service (IHS). The strategic initiative includes four pillars; resources for training in PrEP is one of the strategic pillars, the other strategic pillars are to diagnose all individuals with HIV as early as possible, treat HIV infection rapidly and effectively to achieve sustained viral suppression, and rapidly detect and respond to emerging clusters of HIV infection to further reduce new transmissions.[10]

4.2 Analysis of Safety Information

Seroconversion

In July 2017, FDA's Division of Epidemiology (DEPI) reviewed the drug utilization study report, which was submitted by the Gilead to fulfill postmarketing commitment (PMC) 2849-1. The study was conducted between January 2012 and September 2016. Based on the review, the PMC was fulfilled. Importantly, the study provided a basic understanding that a substantial number of people were being prescribed Truvada for PrEP during that time frame.[11]

Additional postmarketing risk assessments have confirmed that the risk of HIV seroconversion is strongly associated with adherence to a daily PrEP regimen. For instance, among3,328 PrEP users across 8 studies/demonstration projects, no seroconversions were observed among individuals estimated to be taking seven tablets per week; the HIV incidence among individuals estimated to be taking 4-7 tablets per week was also low at 0.14 per 100 PY.[12]

In April 2019, DEPI conducted a literature review of the incidence of HIV seroconversion and risk of viral resistance with the use of FTC/TDF for PrEP. Based on the review, the HIV seroconversion rate among HIV-negative individuals who initiated PrEP ranged from 0.0 to 6.4 per 100 PYs across a PMR study and nine additional studies conducted solely in the U.S. [13] The reviewer concluded that the absolute number of HIV seroconversion cases was low, at 18 total in the U.S. studies and 41 in the PMR study. It should be noted that seroconversion is inversely associated with adherence to FTC-TDF for PrEP. There were three cases of antiviral resistance described in the U.S. studies, with one case of resistance appearing to have been acquired during PrEP therapy.

The Division of Pharmacovigilance (DPV) II was consulted to conduct a postmarketing FAERS search to identify cases of seroconversion among persons using Truvada for PrEP. The reviewer concluded that 66 US cases of seroconversion while taking FTC/TDF for PrEP were reported in FAERS; of those, some degree of resistance was reported in 21/66 cases. The reviewer stated that the identified cases were limited by incomplete information and that the origin of resistant mutations could not be confirmed to be due to selective pressure or transmission of a resistant strain.[14]

Community studies have also shown high PrEP effectiveness in real-world settings. Within an integrated healthcare system in Northern California, a study identified no HIV infections during more than 5000 person-years of PrEP use, consistent with high levels of adherence. The study concluded that once-daily FTC/TDF for HIV PrEP has emerged as a primary tool for HIV prevention.[15,16] PrEP adherence was high in clinical practice, consistent with the lack of HIV seroconversions during PrEP use.[17]

Cumulative evidence indicates that the original concerns regarding adherence, seroconversion, and resistance addressed in the REMS are not, in fact, occurring at the frequency originally anticipated. More recently, in the DISCOVER trial (NCT02842086), the largest PrEP trial conducted to date, there were only 22 HIV infections in 8756 person-years of follow-up in participants at risk of HIV-1 receiving Descovy (emtricitabine/tenofovir alafenamide; FTC/TAF) or Truvada for PrEP. Moreover, only 2 of the 22 participants who became infected with HIV-1 had levels of tenofovir drug concentration in dry blood spots (DBS) considered to be protective. The rest of the infections were either suspected to be present at baseline (5 participants) or the result of low levels of tenofovir drug concentration in DBS (15 participants). Very low levels of resistance were observed in the DISCOVER trial; of 22 total infections, 4 participants had resistance to FTC and all four were suspected of having HIV infection prior to starting PrEP.**Error! Bookmark not defined.**[12,18]

4.3 Results of REMS Assessments

The REMS has been assessed five times at 12, 30, 48, 66 and 76 months. REMS Assessments have generally indicated that prescribers and patients survey respondents were knowledgeable about the risks associated with FTC/TDF for PrEP. The first goal about informing and educating prescribers, uninfected adults and adolescents about the importance of strict adherence to the dosing regimen and third goal, that PrEP must be considered as part of comprehensive

prevention strategy have been met. However, the second goal about the importance of regular monitoring of HIV-1 serostatus to avoid continuing to take FTC/TDF PrEP, if seroconversion has occurred was not consistently met. The threshold for knowledge is set at 80%; in the second goal's evaluation of prescriber respondents' understanding of the requirement for regular monitoring in the respective reports, the results were 70% at the 30th month, 80% at the 48th month, and 75% at the 66th month.[19] The following table (Table 1) summarizes the previous REMS assessments.

Table 1: Summary of previous REMS assessments [20, 21]

Assessment Reports	Meeting Goals	Key Findings
1-Year reviewed Oct. 3, 2013	Incomplete not Met	• Insufficient information to assess the REMS Surveys were not interpretable (10 UIs, 22 HCPs)
30-Month reviewed Aug. 25, 2015	Complete Partially Met	• 1st goal (strict adherence) met • 2nd goal (regular monitoring) not met • 3rd goal (Truvada for PrEP is only part of a comprehensive prevention strategy) met
48-Month reviewed Feb. 21, 2017	Complete Met	• All goals were met Over 80% of HCPs and UIs on the surveys were aware of the three goals
66-Month reviewed Jul 11, 2018	Complete Partially Met	• All objectives were met except 2nd objective 75% of prescriber respondents were aware that Truvada should not be started right away in an individual who presents with clinical symptoms of an acute viral infection
76-Month reviewed May 1, 2019	Complete Unable to determine	• Opened between September 23, 2017 and July 8, 2018 • Recruitment activities were terminated on March 29, 2018 • 15 HCP and 6 UI completed survey • Sample size not reached for both groups No conclusions drawn from survey

5. DISCUSSION

A discussion of whether the FTC/TDF SSS REMS was still necessary to ensure the benefits of the drug outweigh the risks occurred during review of the 76-month REMS Assessment Report and at the REMS Oversight Committee meeting.

The following information is supportive that the FTC/TDF SSS REMS is no longer necessary to assure the benefits outweigh the risks.

- The increased uptake of PrEP, combined with the publication of clinical guidelines by multiple national and community public health entities have integrated the safety messages of the REMS into their resources and materials, have contributed to a greater awareness, education, and knowledge of PrEP among HCPs, PrEP users, and public health communities, since the time of the first REMS approval.

- The importance of strict adherence to the recommended dosing regimen, is comprehensively covered in CDC's clinical guidelines for PrEP in section 10, Supplemental Counseling Information – Medication Adherence.[7]

- The importance of regular monitoring of HIV-1 serostatus to avoid continuing to take FTC/TDF for PrEP, if seroconversion has occurred, to reduce the risk of development of resistant HIV-1 variants, is also extensively covered under the same section 10, Supplemental Counseling Information – Monitoring PrEP Patients.[7]

- The fact that FTC/TDF for a PrEP must be considered as only part of a comprehensive HIV prevention strategy, and that other preventive measures should also be used, is thoroughly covered in CDC's clinical guidelines for PrEP in section 11, Supplemental Counseling Information – HIV Risk Reduction. This section reinforces the need for consistent PrEP use together with other prevention methods (consistent condom use, discontinuing drug injection or never sharing injection equipment) which confer very high levels of protection.[7]

The clinical guidelines for PrEP stated that PrEP is a rapidly changing field of HIV prevention with several additional clinical trials and studies now underway or planned. Updates to these guidelines are anticipated as studies provide new information on PrEP efficacy, HIV testing, drug levels, adherence, longer term clinical safety, and changes in HIV risk behaviors associated with PrEP use in MSM, heterosexuals, injection drug users, and pregnant women; as well as information on the efficacy and safety of other antiretroviral medications, and other routes and schedules of medication delivery for PrEP.[7]

Table 2 provides a comparison of the REMS material, "Checklist for Prescribers" and. the "Patient/Provider Checklist" provided through the CDC. Key factors, including a discussion of safety risks, the importance of HIV-1 testing prior to the initiation of treatment, adherence, regular monitoring, comprehensive prevention strategy, practicing safer sex, knowledge of HIV-1 status, and screening for STIs are discussed in both checklists.

Table 2: Comparison of the REMS and CDC Checklist for Prescribers

REMS - Checklist for Prescribers	CDC – Patient/Provider Checklist
Discussion of known **safety risks** with use of emtricitabine/tenofovir disoproxil fumarate for HIV-1 PrEP with an uninfected adult or adolescent considering or taking emtricitabine/tenofovir disoproxil fumarate for HIV-1 PrEP	Yes, A medication fact sheet listing dosing instructions and side effects
Importance of HIV-1 **testing** immediately before first prescribing emtricitabine/tenofovir disoproxil fumarate for HIV-1 PrEP	Yes
Importance of **adherence** with taking a daily dose of emtricitabine/tenofovir disoproxil fumarate to lower the risk for getting HIV-1 infection	Yes
Importance of **regular monitoring** (at least every 3 months) of HIV-1 serostatus to avoid continuing to take emtricitabine/tenofovir disoproxil fumarate for HIV-1 PrEP if seroconversion has occurred, to reduce the development of resistant HIV-1 variants. Adolescents may benefit from more frequent visits and counseling	Yes, Limit refill periods to recommended intervals for repeat HIV testing (at least every 3 months)
Importance of taking emtricitabine/tenofovir disoproxil fumarate for HIV-1 PrEP as part of a **comprehensive prevention strategy**	Yes
Importance of **practicing safer sex** consistently and correctly to reduce the risk of HIV-1 infection	Yes
Importance for an adult or adolescent to know his/her **HIV-1 status** and that of their partner(s), if possible	Yes, partially; there is no discussion about partner(s)
Importance of **screening** for sexually transmitted infections (STIs) that can facilitate HIV-1 transmission (such as syphilis, chlamydia and gonorrhea)	Yes

In postmarketing risk assessments, reports of HIV seroconversions have been low and only a small number of cases were reported with resistant variants; these variants were considered to be most likely transmitted variants in non-adherent individuals or developed in the setting of unrecognized HIV infection at baseline.

Since the time of approval there has been improved understanding among prescribers and users of the clinical data supporting PrEP, as demonstrated by reports from real-world experience and the periodic REMS assessments. As previously described, several national guidelines have been published that address the indication of use, monitoring, and follow-up schedules associated with PrEP use.

At this time, there have been no newly identified or emerging safety issues concerning FTC/TDF that would require continued or new communications to healthcare providers or patients.

DRISK and DAVP have determined and the ROC has concurred that the SSS REMS for FTC/TDF is no longer necessary to ensure the benefits outweigh the risks. Therefore, DRISK recommends that the REMS be released.

Product labeling, which includes a Boxed Warning and Medication Guide, will continue to communicate that FTC/TDF is only part of a comprehensive management to reduce the risk of acquiring HIV-1, that it must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiating and periodically (at least every 3 months) during use, and that uninfected patients should be counseled to strictly adhere to the recommended dosing schedule.

6. CONCLUSION AND RECOMMENDATIONS

DRISK and DAVP have determined that the REMS is no longer necessary to ensure the benefits outweigh the risks for the following reasons:

- Educational materials and treatment guidelines are readily available outside of the REMS from sources such as CDC and other HHS entities, as well as local departments of health. These materials adequately convey the importance of strict adherence to the recommended PrEP dosing regimen, of regular monitoring of HIV-1 serostatus, and of the need for a comprehensive HIV prevention strategy, to include PrEP.

- The number of seroconversions among PrEP users has been consistently low; drug-resistant variants have been reported in only a small number of cases and most were consistent with transmitted variants or developed in the setting of undetected baseline infection.

- REMS assessments have demonstrated acceptable knowledge of the risks associated with PrEP in both prescribers and individuals.

- No new safety issues have been identified warranting continuation of the REMS.

Therefore, DRISK recommends that the REMS for FTC/TDF for the PrEP indication be released.

7. APPENDICES

7.1 Table 3: Application Type/Number and Applicant Name involved in Emtricitabine/Tenofovir Disoproxil Fumarate SSS REMS

Drug Name	Sponsor Name	Application Type and Number	Submission Date and number (eCTD Sequence)
Truvada (200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate	Gilead Sciences, Inc (Gilead)	NDA* 21752	March 27, 2019 (0698)
(200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate	Mylan Laboratories Ltd (Mylan)	ANDA** 206436	May 17, 2019 (0091)
(200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate	Teva Pharmaceuticals (Teva)	ANDA** 90894	May 17, 2019 (0084)
(200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate	Aurobindo Pharma Ltd. (Aurobindo)	ANDA** 90513	May 17, 2019 (0072)
(200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate	Amneal Pharmaceuticals Company GmBH (Amneal)	ANDA** 209721	May, 21, 2019 (0029)

* New drug application (NDA)
** Abbreviated new drug application (ANDA)

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/s/

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I concur.

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