2022

Informational materials: Dual prevention pill

Population Council

What is the dual prevention pill (DPP)?

- The DPP is a single daily capsule to prevent HIV and unintended pregnancy.
- Each **DPP capsule** contains 2 tablets: Truvada for oral pre-exposure prophylaxis (PrEP) and Zinnia F, an oral contraceptive pill (OC) for pregnancy prevention. Each OC tablet contains ethinyl estradiol 30mcg/levonorgestrel 150mcg.
- Each PrEP tablet contains 2 drugs: 200 mg emtricitabine (FTC) and 300 mg tenofovir disoproxil fumarate (TDF).
- The **DPP regimen** contains 21 DPP capsules and 7 capsules with Truvada only.

Who can take the DPP?

The DPP is for women who are not pregnant, are HIV-negative, and who feel they are at risk of getting HIV.

What does the DPP look like?

- The DPP comes in a box with a 28-day supply of capsules.
- Each box contains 4 pouches, 1 for each week in the month.
- Each pouch contains a blister strip of 7 capsules.
- Pouches 1–3 have 21 pink and white DPP capsules (PrEP+OC) to use on Days 1–21.
- Pouch 4 has 7 white capsules with PrEP only to be used on Days 22–28.

How do I take the DPP?

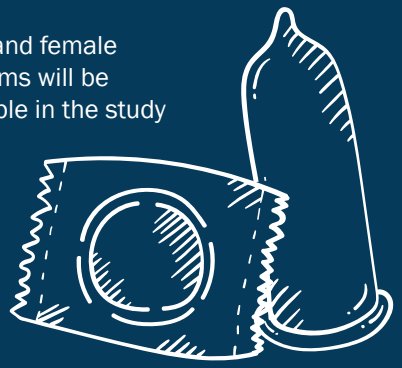
- Take one capsule per day at the same time each day.
- Set an alarm to remind yourself to take the tablet or find any method that would help you not to miss a dose.
- Use the pouches in order, starting with Pouch #1.
- Take the capsules in order, starting with Capsule #1.
- **Do not open a pouch until you are ready to take the first capsule in that pouch.**

What if I miss a dose of the DPP?

- If you miss a taking a capsule—whether it is a pink and white DPP capsule or a white PrEP capsule—take it as soon as you remember, even if it means taking 2 capsules in one day (in a 24-hour period). Then, continue taking the DPP once daily.
- Do not take more than 2 capsules in a day.
- Any missed capsules can increase your risk of getting HIV and unintended pregnancy.
- If you miss **2 or more doses** of the DPP, one after the other, call the study staff right away; use a back-up (condoms) until you can go to the study clinic.

Do I need to use condoms when using the DPP?

- It takes 7 days for the DPP to start working to prevent HIV and pregnancy. So, either abstain from sex or use a condom until you have been using the DPP for at least 7 days.
- The DPP does not prevent STIs, so we recommend using condoms to prevent STIs.
- Male and female condoms will be available in the study clinic.



How do I store the DPP?

- The DPP should be stored below 30°C (in a cool, dry place), away from sunlight.
- The pouches do not need to be kept in the box; if it is easier to store the pouches separately, you may do that. But remember to use the pouches in order of the numbers on the pouch (1, 2, 3, 4).
- After opening the pouch, you can take out the blister strip and carry it with you.
- Bring all leftover DPP capsules (including any missed doses) to your next study clinic visit.

What side effects should I expect?

Most common side effects expected (from PrEP and OC components) are:

Headache, nausea, breakthrough bleeding/ spotting, breast tenderness, abdominal pain, bloating, weight decrease, dark spots on skin

When should I go to the clinic?

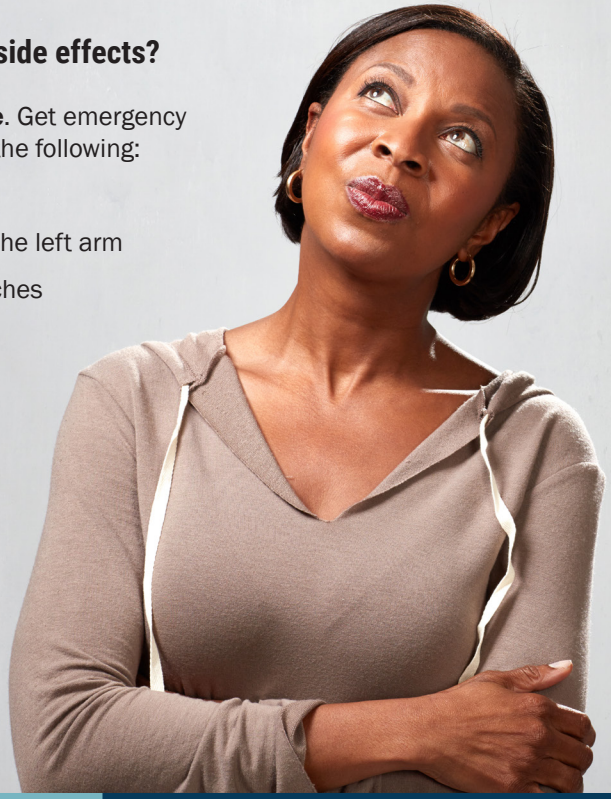
Come to the study clinic if you have any of these symptoms:

- Vomiting, nausea, or diarrhea that persists for more than 48 hours
- Unusual vaginal spotting or bleeding (not related to menses)
- Sudden skin rash

What should I do if I have severe side effects?

Severe side effects are **extremely rare**. Get emergency medical care if you experience any of the following:

- Unusual pain or swelling in the leg
- Chest pain which may spread into the left arm
- Unusual, persistent, severe headaches
- Sudden difficulty breathing
- Coughing up blood
- Sudden partial or complete loss of vision, seeing double, or dizziness
- Sudden weakness/numbness on 1 side of body/1 part of body
- Problems with movement
- Severe abdominal pain



What medications are not allowed when using the DPP?

While taking the DPP, do not use:

- Any birth control methods with hormones, other than the ones provided in the study (such as **Triphasil or Nordette** [**Levonogestrel/Oestrogen**] and **Depo-Provera** [**Medoxyprogestrone**])
- Use of any HIV medications (such as **Tenofovir, Lamivudine, Efavirenz and Lopinavir/ Ritonavir**)
- Rifampicin
- Rifabutin
- Any antiepileptics (such as **Lamotrigine, Sodium Valproate and Valproic Acid**)
- Hepatitis C treatments (**Ledipasvir/sofosbuvir**)

You can use other prescription or over-the-counter medications.

Who do I call if I have a problem?

Dr Nkosiphile Ndlovu
Wits RHI
7 Esselen Street, Hillbrow
Johannesburg
+27 11 358 5471
+27 84 722 5877

OR

Visit the clinic between 08:00 and 16:30 weekdays

Research Centre Contact Number:
+27 67 072 7010

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)**

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

Indications and Usage	
HIV-1 Pre-Exposure Prophylaxis (PrEP) (1.2)	06/2020
Dosage and Administration	
HIV-1 Screening for Individuals Receiving TRUVADA for HIV-1 PrEP (2.2)	06/2020
Warnings and Precautions	
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 (5.2)	06/2020
Immune Reconstitution Syndrome (5.4)	06/2020

----------**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: 06/2020

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	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.

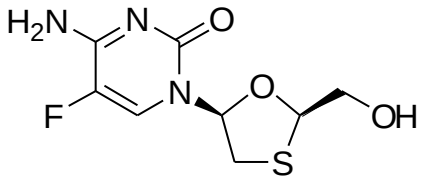
Tenofovir Disoproxil Fumarate: Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of TDF, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

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.

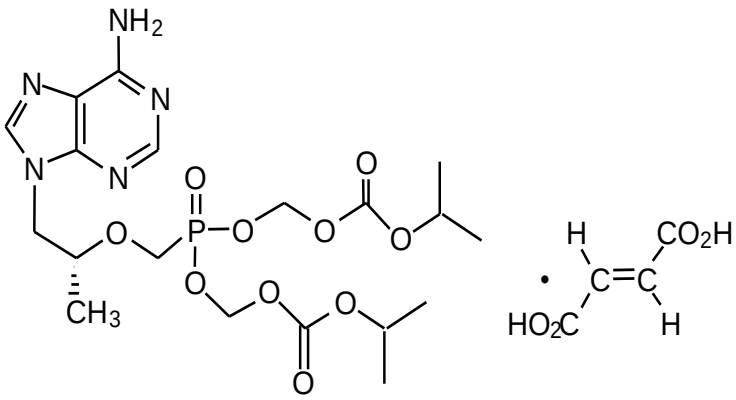
Emtricitabine: The chemical name of FTC is 5-fluoro-1-(2*R*,5*S*)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. FTC is the (-) enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5-position.

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-033

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-033
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: June 2020

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Zinnia F*

ethinylestradiol/levonorgestrel 30µg/150 µg coated tablets

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, health care provider or pharmacist
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, health care provider or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. WHAT ZINNIA F IS AND WHAT IT IS USED FOR

Zinnia F is a low dose combined contraceptive pill that protects against pregnancy (here generally designated as 'Pill').

Zinnia F contains 28 tablets per card.

The active tablets (21 white tablets) contain a small amount of two female sex hormones, a progestogen (levonorgestrel) and an estrogen (ethinylestradiol). The active tablet is generally designated as the "Pill".

The other tablets (7 brown tablets) are hormone-free.

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE ZINNIA F

2.1 Do not take Zinnia F:

- if you are hypersensitive (allergic) to ethinylestradiol, levonorgestrel or any of the other components of Zinnia F,
- if you now have or have a history of venous blood clots (in deep veins or in lungs), whether you are on anticoagulant therapy or not,
- if you now have or have a history of arterial blood clots (e.g. heart attack) or diseases associated with the early stages of such blood clots in the arteries (such as tightness in the chest, so-called Angina pectoris, or sudden visual disturbances or muscle paralysis),
- if you have a known tendency to form blood clots or any other condition associated with clots, such as disease of heart valves or heart rhythm problems),
- if you have lupus, a disorder of the immunes system,

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

- if you have many risk factors for artery disease (such as older age, smoking, diabetes and high blood pressure),
- if you have had a stroke,
- if you smoke (also see 2.2.3 'The "Pill" and vascular disease'),
- if you suffer from high blood pressure above 160/100 mm Hg and it has not been satisfactorily treated,
- if you suffer from sugar diabetes (Diabetes mellitus) and your blood vessels have already been damaged as a result,
- if you have a history of migraines, which are accompanied by sensory, perceptual and/or motor disturbances (so-called aura),
- if you now have or have a history of pancreatic inflammation,
- if you now have or have a history of liver disorder, as long as liver function tests have not returned to normal,
- if you have acute hepatitis (liver inflammation) or a hepatitis flare: combined oral contraceptives should not be started during these; continuing use for those already taking combined oral contraceptives is usually possible.
- if you now have or have a history of liver tumors (benign or malignant),
- if you are now suspected of having or have a history of sex-steroid influenced cancer (e.g. of lining of the uterus or the breasts),
- if you have undiagnosed vaginal bleeding,
- if you miss menstruation, the cause of which has not been found.

Discontinue use immediately, if one of the above-mentioned diseases or conditions appears for the first time while taking Zinnia F.

2.2 Warnings and precautions

2.2.1 Stop taking Zinnia F immediately (in addition to conditions specified in section 2.1)

- if you suspect or know that you are pregnant,
- if there are signs that you have a blood clot, such as sudden sensation, perception or movement problems,
- if your blood pressure constantly rises to values above 140/90 mmHg (you can think of starting to take the 'Pill' again, as soon as your blood pressure values have returned to normal through antihypertensive therapy),
- if surgery is planned (at least 4 weeks in advance) and/or during longer periods of immobilization (also see 2.2.3 'The "Pill" and vascular disease'). You can think of starting to take the "Pill" again at least two weeks after complete remobilization.
- if migraine appears for the first time or worsens,
- if headaches occur unusually frequently, persistently or in unusual severity,
- if severe upper abdominal pain or swelling occurs,
- if your skin and the whites of your eyes turn yellow, your urine turns brown and your stool very light in color (so-called jaundice), or if your skin itches over your entire body,
- if you suffer from sugar diabetes (Diabetes mellitus) and your blood sugar count is suddenly increased,
- if you suffer from a condition called porphyria, occurring in episodes, and which recurs while using Zinnia F.

2.2.2 You require special medical monitoring

- if you smoke (especially if you are over age 35 and you smoke more than 15 cigarettes per day),
- if you are 40 years of age or older,
- if you are overweight,
- if you have a heart or kidney condition,
- if you are inclined to have inflamed superficial veins (phlebitis) or pronounced varicose veins,
- if you have circulatory problems in your hands and feet,
- if your blood pressure has been measured to be over 140/90 mmHg,

- if you suffer from migraine,
- if you suffer from depression,
- if you have epilepsy,
- if you have sugar diabetes (Diabetes mellitus) or if your body's ability to use glucose is reduced, (decreased glucose tolerance). It may be that the required dose of the drugs used to treat your diabetes will change while using Zinnia F.
- if you are known to have a disturbed lipid (fat) metabolism,
- if you are known to have sickle cell disease,
- if you have a movement disorder called chorea,
- if you have had a liver disorder,
- if you are known to have a gallbladder disorder,
- if you suffer from a benign tumor in the muscle layer of the uterus (uterine myoma),
- if you suffer from a chronic inflammatory bowel disease (Crohn's disease, ulcerative colitis),
- if you have a certain manifestation of deafness (otosclerosis),
- in the event of prolonged immobilization, e.g. following accidents (see 2.2.1),
- if you suffer from a certain disorder of the immune system, the so-called lupus,
- if you are known to have haemolytic-uremic syndrome (a disorder of blood and kidneys).

2.2.3 The 'Pill' and blood vessel disease

Using the 'Pill' gives an increased risk of blood clots. The additional risk is at its highest during the first year a woman ever uses the 'Pill'. This increased risk when using the 'Pill' is lower than the risk of clots developing during pregnancy, which is estimated at 60 cases per 100,000 pregnancies. In 1 - 2% of the cases, such clots result in death. The frequency of a clot, caused by 'Pills' containing the amounts in Zinnia F is about 20 cases in every 100,000 women who have been using the 'Pill' for one year.

In rare cases, clots can also occur in an artery, such as in heart vessels or the arteries that supply the brain, resulting in a heart attack or stroke. In very rare cases, clots can also occur in the blood vessels of the liver, intestines, kidneys or eyes.

The following signs can point to a clot. If you notice any of these signs in yourself, stop taking the tablets immediately and see your doctor, at once:

- unusual pain or swelling in a leg,
- pain and tightness in the chest, possibly radiating into the left arm,
- sudden difficulty in breathing,
- heavy cough without a clear cause,
- unusual, strong or persistent headaches,
- sudden partial or complete loss of vision,
- seeing double,
- indistinct speech, problems with speaking or loss of speech,
- dizziness,
- collapse, possibly in connection with an epileptic seizure,
- sudden weakness or numbness on one side of the body or in one part of the body,
- problems with movement,
- severe abdominal pain.

The risk of clots increases:

- with increasing age,
- with a history of blood clots in close family members (parents or siblings) at a relatively early age,
- with prolonged immobilization, major surgery, surgery to the legs, or major trauma. In these situations it is advisable to discontinue use of the 'Pill' (at least four weeks in advance of elective surgery as well as in the event of prolonged immobilization) and not to resume until two weeks after complete remobilization. If Zinnia F was not discontinued in time, a prevention for clots should be considered.

- if you are clearly overweight (Body Mass Index over 30 kg/m^2),
- in the first three to four weeks following delivery or a miscarriage in the second trimester of pregnancy.

The risk of arterial occlusion increases with:
- smoking. With heavier smoking and increasing age, the risk further increases. It is advisable not to smoke, especially if you are over 35 and using hormones to prevent pregnancy. If you cannot stop smoking, you are advised to use other methods of contraception, especially if there are other risk factors.
- increasing age,
- the occurrence of blood clots in close family members (parents or siblings) at an early age,
- disturbances in lipid (fat) metabolism,
- high blood pressure,
- sugar diabetes (Diabetes mellitus),
- heart conditions (such as valve disease, irregular beats),
- obesity (body mass index over 30 kg/m^2),
- migraine, especially migraine with aura.

Further diseases with possible blood vessel involvement include lupus, (an immune system disorder) haemolytic-uremic syndrome (a blood disorder causing kidney damage) and chronic inflammatory bowel disease (Crohn's disease and ulcerative colitis).

The presence of a severe or multiple risk factor(s) for vein or artery clots may also constitute a reason not to use Zinnia F.

The increased risk of blood clots just after giving birth must be considered.

2.2.4 The 'Pill' and cancer

Some studies have indicated that long-term use of combined oral contraceptives represents a risk factor with respect to developing cervical cancer in women, whose cervix is infected with a certain sexually transmitted virus (human papillomavirus). It has not yet been established, however, to which extent this finding is attributable to other factors (e.g., differences in the number of sex partners or in the use of barrier contraceptives).

There is a slightly increased risk of having breast cancer diagnosed in women who are currently using the 'Pill' as compared to women of the same age who do not use the 'Pill' for contraception. This excess risk gradually disappears after cessation of the 'Pill', and during the course of 10 years, there is no difference between previous 'Pill' users and other women of the same age. Because breast cancer is rare in women under 40 years of age, the excess number of cases in current and recent users of the 'Pill' is small in relation to the overall risk of breast cancer.

In very rare cases, benign, but nonetheless dangerous, liver tumors can occur, which can rupture causing severe internal bleeding. In case of severe upper abdominal pain, please contact your doctor immediately. Studies have suggested an increased risk of developing liver-cell cancer with long-term use of the 'Pill'; this type of cancer is, however, very rare.

2.2.5 Other conditions

High blood pressure
An increase in blood pressure has been reported in women taking the 'Pill'. This occurs more frequently in older users and with continued use. The frequency of high blood pressure increases with the content of the progestogen. If you have already contracted any disorders due to high blood pressure, or if you suffer from certain kidney disorders, it is advisable for you to use another method of contraception (see also 2.1 'Do not take Zinnia F, 2.2.1 'Stop taking Zinnia F immediately' and 2.2.2 'You require special medical monitoring').

Pigmentation spots
Yellowish-brown pigment spots may occasionally occur, especially in women with a history of chloasma gravidarum. It is therefore advisable for women with this tendency not to expose themselves directly to the sun or ultraviolet radiation (e.g. on sunbeds) while taking the 'Pill'.

Hereditary angioedema
If you suffer from hereditary angioedema (a severe allergic condition), medicinal products containing estrogens, may worsen the condition. You should immediately consult your doctor if you notice you have symptoms such as swelling of the face, tongue and/or throat and/or difficulty swallowing or skin rash combined with breathing problems.

Irregular bleeding
With all 'Pills', irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. If this irregular bleeding still occurs after three months or reappears after several months of regular cycles, please see your doctor.

It is possible that in some women withdrawal bleeding may not occur during the hormone free period (brown tablets). If you have taken Zinnia F according to the directions described in Section 3 'How to take Zinnia F ', it is unlikely that you are pregnant. However, if you have not taken the 'Pill' according to these directions prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before Zinnia F use is continued.

After discontinuing the 'Pill', it can take some time to return to a normal cycle.

2.2.6 Reduced efficacy

The contraceptive effect can be reduced by forgetting to take the 'Pill', vomiting, gastrointestinal disturbances with diarrhoea or by some other medicines taken at the same time.

If Zinnia F and products containing St. John's wort are taken at the same time, it is advisable to use an additional barrier contraceptive (see Section 2.3, "Other medicines and Zinnia F").

2.2.7 Medical consultation / examination

Before you use Zinnia F, your doctor will ask you detailed questions about your medical history and that of your close relatives. A thorough general medical checkup and a gynaecological examination, including an examination of the breast and a cervical smear, will be conducted. Pregnancy has to be ruled out. These examinations should be repeated regularly while you are taking the 'Pill'. Please tell your doctor whether you smoke and whether you are taking other medicines.

Zinnia F does not protect you against HIV infection or other sexually transmitted diseases. Among other safe sex practices consistent and correct use of condoms, male or female, is critical for prevention of HIV transmission.

Folic-acid deficiency can interfere with the development of the brain and spinal cord (neural tube defects) in the unborn child. If you stop taking Zinnia F because you want to become pregnant, you are advised to adhere to a diet rich in folic acid (vegetables, fruit, wholegrain products), and to take an additional 0.4 milligrams of folic acid daily. It should be taken four weeks prior to the planned conception and continued up to week 12 of pregnancy. Any woman, who has already been pregnant with a child who had a neural tube (spinal cord) defect, should take 4 milligrams or 5 milligrams of folic acid daily over the same period. You are advised to heed the contraindications and warnings contained in the patient information leaflet of folic acid preparations.

2.3 Other medicines and Zinnia F

Talk to your doctor, health care provider or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

2.3.1 Interactions between Zinnia F and other medicinal products can cause it to lose its contraceptive efficacy and/or can result in breakthrough bleeding.

The following medicinal products can reduce the effect of Zinnia F:
- drugs, that increase intestinal motility (e.g. metoclopramide),
- drugs used in treating epilepsy such as phenytoin, barbiturates, barbexaclone, primidone, carbamazepine, oxcarbazepine, topiramate and felbamate,
- some antibiotics for the treatment of tuberculosis (e.g. rifampicin, rifabutin), certain others against bacterial infections (e.g. ampicillin, tetracycline) or fungal infections (e.g. griseofulvin),
- certain drugs for the treatment of HIV infection (e.g. ritonavir, nevirapine, efavirenz),
- modafinil (agent for the treatment of narcolepsy, a nervous system disorder),
- herbal products that contain St. John's wort (*Hypericum perforatum*).

If you are being treated with any of the drugs specified above, you are advised to use a barrier contraceptive (e.g. condom) in addition to Zinnia F. You are advised not only to use these additional methods of contraception during concomitant use with some of the drugs specified above, but for another seven to 28 days, depending upon the drug. If you have questions, ask your doctor or pharmacist.

If the use of these drugs extends beyond the last active tablet in the current blister pack, then you should skip the seven hormone free tablets and start taking the active tablets from the next pack of Zinnia F.

If long-term treatment with any of the drugs specified above is necessary, it is preferable to choose a non-hormonal method of contraception.

2.3.2 Interactions between Zinnia F and other drugs can also cause more numerous and more pronounced side effects.

The following medicinal products can impair the tolerance of Zinnia F:
- paracetamol (acetaminophen), a drug to relieve pain and fever),
- ascorbic acid (vitamin C)
- atorvastatin (a drug for lowering blood fat),
- troleandomycin (an antibiotic),
- imidazole, antifungal drugs (such as fluconazole),
- indinavir (an HIV drug).

2.3.3 Zinnia F and other 'Pills' can also affect the metabolism of other drugs.

Zinnia F can impair the efficacy or tolerability of the following drugs:
- cyclosporine (drug used to suppress the immune system),
- theophylline (a drug used for the treatment of asthma),
- glucocorticoids (e.g. cortisone),
- benzodiazepines (tranquilizers, such as diazepam, lorazepam),
- lamotrigine (a drug used for the treatment of epilepsy),
- clofibrate (a drug for lowering the blood fat),
- paracetamol (acetaminophen, a drug to relieve pain and fever),
- morphine (a narcotic pain killer).

Please, also follow the patient information leaflets of the other prescribed products.

If you are diabetic (if you have sugar diabetes) your required dose of blood-sugar lowering medicine (e.g. insulin) can change.

2.3.4 Laboratory tests

Use of the 'Pill' may influence the results of certain laboratory tests, including the results of liver, thyroid, adrenal gland and kidney function testing, as well as certain blood protein levels, e.g., proteins, which affect blood fat usage, carbohydrate usage, and clotting.

2.4. Pregnancy and breast-feeding.

Zinnia F should not be used during pregnancy. You should not be pregnant when starting Zinnia F. If pregnancy occurs during treatment with Zinnia F, further intake should be stopped, and you should see your doctor.

Do not use Zinnia F during the first 6 months of breast-feeding, since milk production may be reduced and small quantities of the active substance can pass into breast milk. You should use a non-hormonal method of contraception, if you are breastfeeding.

Ask your doctor or pharmacist for advice before taking any medicine.

2.5 Driving and using machines

No special precautionary measures are necessary.

2.6 Zinnia F contains lactose and sucrose.

Each active tablet of this medicinal product contains lactose and sucrose (sugar) while the hormone free tablets contains sucrose. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product.

2.7 Zinnia F contains methylparaben and propylparaben.

Each hormone free tablet contains methylparaben and propylparaben**.** These may cause allergic reactions (possibly delayed).

3. HOW TO TAKE ZINNIA F

Always take Zinnia F exactly as your doctor or health care provider told you. You should check with your doctor, health care provider or pharmacist if you are not sure.

The usual dose is: One tablet of Zinnia F daily.

3.1 How to take Zinnia F

Each blister card contains 21 active tablets (white) and 7 hormone-free tablets (brown). Take one tablet daily until the blister card is empty. Start with the next blister pack on the following day without any pause.

You should take the 'Pill' whole (do not chew) with some liquid, if necessary.

You must take the 'Pill' each day at about the same time in the sequence indicated on the blister pack for 28 consecutive days. After you have taken all the 21 active tablets (white), take the hormone free tablets (brown) the next seven days. Generally the withdrawal bleeding will start during these 7 days. This usually begins 2 to 3 days after taking the last active tablet and can persist until you start taking tablets from the next blister pack.

3.2 When to start taking Zinnia F

<u>If you did not take a contraceptive 'Pill' last month:</u>

Start with the white active tablets in your blister card. You may start taking Zinnia F on day 1 of your natural cycle, i.e. the first day of your menstrual bleeding. If you begin taking the tablets on any other day, an additional barrier contraceptive should be used during the first seven days of taking the 'Pill'.

If you are switching to Zinnia F from another 'Pill' (with two hormonal active substances), or from a vaginal ring or a patch:

- if you have been taking a 'Pill' with a tablet-free interval once a month following your last 'Pill' containing an active substance, start taking Zinnia F on the day following your tablet-free interval.
- if you have been taking a 'Pill' that comes in a calendar pack containing placebo tablets along with the 'Pills' containing active substances, start taking Zinnia F on the day following your last placebo.
- if you have been using a vaginal ring or a patch, start taking Zinnia F on the day following the usual ring-free, or patch-free interval.

If you are switching to Zinnia F from a 'Pill', that contains only one hormone (progestogen), a so-called mini pill:
You can discontinue the 'mini pill' on any day. Start taking Zinnia F on the following day. During the first seven days, you should use an additional barrier contraceptive (e.g. condom).

If you are switching to Zinnia F from an injectable product (so-called 'three-month injection'), from an implant or an intrauterine device:
Start taking Zinnia F at the time you would normally get the next injection or on the day the implant or intrauterine device is removed. Use an additional barrier contraceptive during the first seven days.

If you have just had a baby and are not breastfeeding:
Do not start taking the product any earlier than 21days after delivery. A longer period of up to 42 days should be allowed in any woman having risk factors for blood clots (See section 2.2.3, The "Pill" and blood vessel disease).

If you begin to take the tablets later, you should use an additional barrier contraceptive during the first seven days. If you have already had sexual intercourse, pregnancy must be ruled out, or you must wait for your first menstrual bleed before starting to take Zinnia F. See also section 2.4 'Pregnancy and breastfeeding'.

If you have just had a miscarriage or an abortion:
You may take Zinnia F immediately.

3.3 Duration of use

Zinnia F can be taken for as long as a hormonal method of contraception is desired and there are no significant health risks (see 2.1 'Do not take Zinnia F' and 2.2.1 'Stop taking Zinnia F immediately'). Regarding check-ups see 2.2.7 'Medical consultation / examination.'

3.4 If you take more Zinnia F than you should

Possible signs of an overdose are nausea, vomiting (usually after 12 to 24 hours, sometimes continuing for several days), chest tightness, giddiness, abdominal pain, sleepiness / tiredness, vaginal bleeding. If you have taken large quantities, consult a doctor so that the symptoms can be treated.

3.5 If you forget to take Zinnia F

- If you are less than 12 hours late in taking one active tablet, the contraceptive effect of Zinnia F is not reduced. You should take the missed tablet as soon as possible, and then take the subsequent 'Pills' at your usual time.

- If you are more than 12 hours late in taking one of the active tablets, the contraceptive effect is no longer fully ensured. If no bleeding appears during the seven day hormone free period (brown tablets) after having taken the 21 white active tablets , you could be pregnant. In this case, you must see your doctor before starting a new blister pack.

There are generally two things to bear in mind:
1. You must never stop taking the 'Pill' for more than seven days.
2. In order to build up sufficient contraceptive protection, you should take the 'Pill' without interruption for seven days.

<u>You missed one 'Pill' in week 1:</u>
Take the missed 'Pill' as soon as possible, even if this means taking two 'Pills' at the same time. Then continue taking the tablets as usual. However, an additional barrier contraceptive (e.g. condom) should be used for the next seven days. If you had sexual intercourse in the week prior to the missed 'Pill', you are at risk of being pregnant. The likelihood of becoming pregnant is greater, the closer the missed 'Pill' is to the period when the brown hormone-free tablets were taken.

<u>You missed one 'Pill' in week 2:</u>
Take the missed 'Pill' as soon as possible, even if this means taking two 'Pills' at the same time. Then, take the subsequent 'Pills' again at your usual time. Provided you took Zinnia F regularly on the seven days preceding the missed 'Pill', then the contraceptive effect of the 'Pill' is ensured, and you do not have to use any additional contraceptive measures. If this was not the case or if you missed more than one 'Pill', then you are advised to use an additional barrier contraceptive (e.g. condom) for seven days.

<u>You missed one 'Pill' in week 3:</u>
Due to the upcoming seven-day hormone free tablet interval, contraceptive protection is no longer fully assured. You can, however, sustain the contraceptive effect by adjusting your tablet-taking schedule. By following one of the two procedures described below, it is not necessary to use additional contraceptive measures, although this is only true if you took the tablets correctly on the seven days preceding the first missed 'Pill.'(If this is not the case, you should proceed as described above, "You Missed one 'Pill' in week 1." You should also use an additional barrier contraceptive (e.g. condom) for the next seven days.

You can choose between two options:

1. Take the missed 'Pill' as soon as possible, even if this means taking two 'Pills' at the same time. Then, take the subsequent 'Pills' again at your usual time. Skip the seven brown hormone free tablets and start taking "Pills"(white tablets) from the next blister pack right away. Withdrawal bleeding will probably not occur until you have used up the active tablets in the second blister pack, but there may be spotting and breakthrough bleeding while you are taking the second pack.

Or

2. You can immediately start the brown hormone free tablets (you also have to count the day you missed the 'Pill' as if it were a hormone-free pill day). Start taking the tablets from the next blister pack right away. If you wish to start taking the next blister pack on your accustomed day of the week, you can take fewer hormone free tablets accordingly.
   Please bear in mind that the maximum time between your last white tablet from the previous blister and the first white tablet of the current blister should not exceed 7 days.

<u>If you have missed more than one active tablet from the current blister pack:</u>
If you miss more than one active tablets of Zinnia F from the current blister pack, contraceptive protection is no longer certain.

The likelihood of becoming pregnant is all the greater, the more 'Pills' you missed and the closer this is to the period when the brown tablets were taken. It is advisable for you to use an additional barrier contraceptive (e.g. condom) until your next regular withdrawal bleed. If no bleeding occurs during the hormone free period (brown tablets) , you could be pregnant. In this event, you must see your doctor before starting a new blister pack.

What has to be considered if you suffer from vomiting or diarrhoea

If you have digestive problems, such as vomiting or diarrhoea, occurring within the first four hours after taking the white active tablets, the active substances might not have been completely absorbed. In such cases, follow the instructions that apply to when you miss a 'Pill' and you notice it within 12 hours. If you do not wish to deviate from your tablet-taking rhythm, you will have to take the replacement tablet from another blister pack. If your gastrointestinal complaints continue for several days or recur, you or your partner should use an additional barrier contraceptive (e.g. diaphragm, condom), and you should inform your doctor.

What has to be considered if you wish to change the timing of the withdrawal bleed

To postpone withdrawal bleeding, you should continue taking the active tablets from the next pack of Zinnia F right away, skipping the brown tablets. Withdrawal bleeding can be delayed for as long as desired by taking the tablets continuously, though evidence for this is limited beyond 2 years. If you do this, you may experience increased breakthrough bleeding or spotting. Following a subsequent regular seven-day use of the brown tablets, you can continue to take the white active tablets as usual.

3.6 If you stop taking Zinnia F

If you wish to stop taking Zinnia F, ask your doctor or pharmacist.

If you have any further questions on the use of this medicine, ask your doctor, health care provider or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Zinnia F can cause side effects, although not everybody gets them.

The most common side effects, which may affect more than 1 in 10 people associated with taking the 'Pill' containing the active substances, ethinylestradiol and levonorgestrel, are headaches (including migraine), spotting and intermenstrual bleeding.

System Organ Class	Frequency of side effects			
	Common (may affect up to 1 in 10 people)	Uncommon (may affect up to 1 in 100 people)	Rare (may affect up to 1 in 1,000 people)	Very rare (may affect up to 1 in 10,000 people)
Infections	vaginal inflammation, including mycosis (Candidiasis)			
Immune system disorders		hives	allergic reactions	painful swelling of the skin and mucous membrane (angioedema), very severe

System Organ Class	Frequency of side effects			
	Common (may affect up to 1 in 10 people)	Uncommon (may affect up to 1 in 100 people)	Rare (may affect up to 1 in 1,000 people)	Very rare (may affect up to 1 in 10,000 people)
				allergic reactions with breathing and circulatory symptoms
Metabolism and nutrition disorders		changes of appetite (increase or decrease)	decreased ability to metabolize glucose (glucose intolerance)	
Psychiatric disorders	mood swings including depression; changes of the sex drive (libido)			
Nervous system disorders	nervousness; giddiness, dizziness			
Eye disorders	visual disturbances		contact lens intolerance	
Gastrointestinal disorders	nausea, vomiting, abdominal pain	diarrhoea, abdominal cramps, flatulence		
Hepatobiliary disorders			jaundice caused by cholestasis	
System Organ Class	Frequency of side effects			
	Common (may affect up to 1 in 10 people)	Uncommon (may affect up to 1 in 100 people)	Rare (may affect up to 1 in 1,000 people)	Very rare (may affect up to 1 in 10,000 people)
Skin and subcutaneous tissue disorders	acne	rash, yellowish-brown skin spots (chloasma) possibly persisting, increased body and facial hair, hair loss	red nodules (Erythema nodosum) severe skin rash (Erythema multiforme)	
Reproductive system and breast disorders	breast pain, breast tenderness, breast hypertrophy, breast discharge, painful menstrual bleeding, changes in the			

System Organ Class	Frequency of side effects			
	Common (may affect up to 1 in 10 people)	Uncommon (may affect up to 1 in 100 people)	Rare (may affect up to 1 in 1,000 people)	Very rare (may affect up to 1 in 10,000 people)
	strength of menstrual bleeding, increased vaginal discharge, missed menstrual bleeding			
General disorders	fluid retention in tissue			
Investigations	weight changes (increase or decrease)	blood pressure increase, changes in blood lipid levels	reduction of the folic acid levels in blood	

As regards other severe side effects, such as the formation of blood clots, see 2.2.3 ‘The “Pill” and vascular disease’, or with respect to hepatic tumors, breast and cervical cancer, see 2.2.4 ‘The “Pill” and cancer’.

Moreover, the following side effects have been reported in connection with using the ‘Pill’: The frequency of these reactions cannot be calculated from the reports.
- optic neuritis (can cause partial or complete loss of vision),
- worsening of varicose veins,
- pancreatitis with a currently existing, severe lipid (fat) metabolism disturbance,
- gall bladder disorder, including gall stones,
- a blood disorder resulting in kidney damage (haemolytic-uremic syndrome),
- herpes, which can occur during pregnancy (Herpes gestationis),
- a kind of deafness (otosclerosis),
- deterioration of lupus, an immune disorder,
- deterioration of a blood disorder called porphyria,
- deterioration of body movement diseases called “chorea”,
- deterioration of depression,
- deterioration of chronic inflammatory bowel disease (Crohn's disease and ulcerative colitis).

If you get any side effects, talk to your doctor, health care provider or pharmacist. This includes any possible side effects not listed in this leaflet.

5. HOW TO STORE ZINNIA F

Keep this medicine out of the sight and reach of children.

Store below 30^{o}C. Protect from light.

Do not use this medicine after the expiry date which is stated on the label after {EXP}. The expiry date refers to the last day of that month.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Zinnia F contains:

The active substances in the active tablets are 30 micrograms of ethinylestradiol and 150 micrograms of levonorgestrel.

The other ingredients are:

White active tablets (21 per blister)
Core tablet: Lactose monohydrate, magnesium stearate, maize starch, povidone and talc.
Coating: Calcium carbonate, carnauba wax, glycerol, macrogol, povidone, sucrose, talc and titanium dioxide.

Brown hormone free tablets (7 per blister)
Core tablet: Ferrous fumarate, magnesium stearate, maize starch, methylparaben, polysorbate 80, propylparaben, sodium starch glycolate and talc.
Coating: Carnauba wax, gum acacia, red oxide of iron, shellac, sodium benzoate, sucrose, talc and titanium dioxide.

What Zinnia F looks like and contents of the pack:

Zinnia F active tablets are 21 white active tablets and 7 brown hormone free tablets.

A blister strip of Zinnia F tablets contains 21 white, circular, biconvex, sugar-coated tablets, and 7 brown, circular, biconvex, sugar coated tablets. Zinnia F tablets are provided in clear transparent PVC/PVdC-Alu blister cards in a carton, containing 1, 3, 6 blister cards of 28 tablets each.

Supplier and Manufacturer

Supplier

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Manufacturer

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Hormone free tablets

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Sarkhej, Near Matoda, Village
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For any information about this medicinal product, please contact the supplier.

This leaflet was last approved in May 2015. Section 6 updated in February 2017.

Detailed information on this medicine is available on the World Health Organization (WHO) web site: http://www.who.int/prequal/