Important Safety Information About Teva-Emtricitabine/Tenofovir for a Pre-exposure Prophylaxis (PrEP) Indication

PrTEVA-Emtricitabine/Tenofovir

(Emtricitabine and Tenofovir Tablets)

200 mg / 300 mg

Antiretroviral Agent

Important Safety Information for pre-exposure prophylaxis PrEP

Guide for Prescribers

This material was developed by Teva Canada Limited,
as part of the risk minimization plan for Teva-Emtricitabine/Tenofovir.
This material is not intended for promotional use.

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About Teva-Emtricitabine/Tenofovir for a PrEP Indication in adults at high risk

Indication and Prescribing Considerations

Teva-Emtricitabine/Tenofovir (emtricitabine/tenofovir disoproxil fumarate), a combination of emtricitabine and tenofovir disoproxil fumarate, is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk. This indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1 infection and in heterosexual serodiscordant couples.

When considering Teva-Emtricitabine/Tenofovir for PrEP, the following factors may help to identify individuals at high risk:

- Has partner(s) known to be HIV-1 infected, or
- Engages in sexual activity within a high prevalence area or social network and one or more of the following:
  - Inconsistent or no condom use
  - Diagnosis of a sexually transmitted infection (STI)
  - Exchange of sex for commodities (such as money, food, shelter, or drugs)
  - Use of illicit drugs, alcohol dependence
  - Incarceration
  - Partner(s) of unknown HIV-1 status with any of the factors listed above

The following points must be considered when prescribing Teva-Emtricitabine/Tenofovir for a PrEP indication:

- Prescribe Teva-Emtricitabine/Tenofovir as part of a comprehensive prevention strategy because Teva-Emtricitabine/Tenofovir is not always effective in preventing the acquisition of HIV-1 infection
- Counsel all uninfected individuals to strictly adhere to their Teva-Emtricitabine/Tenofovir daily dosing schedule because the effectiveness of Teva-Emtricitabine/Tenofovir in reducing the risk of acquiring HIV-1 infection was strongly correlated with adherence as demonstrated by measurable drug levels in clinical trials
- Confirm a negative HIV-1 test immediately prior to initiating Teva-Emtricitabine/Tenofovir for a PrEP indication. If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting PrEP for at least 1 month and reconfirm HIV-1 status or use a test approved by Health Canada as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection
- Screen uninfected individuals for HIV-1 infection at least once every 3 months while taking Teva-Emtricitabine/Tenofovir for a PrEP indication

Dosage and Dose Adjustment

Pre-exposure Prophylaxis of HIV-1 infection:

- The dose of Teva-Emtricitabine/Tenofovir is one tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) once daily taken orally with or without food.
- Do not use Teva-Emtricitabine/Tenofovir for PrEP in HIV-1 uninfected individuals with creatinine clearance below 60 mL/min.
- No dose adjustment is required in patients with hepatic impairment.
- Dose selection for the elderly patients (>65 years of age) should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

See Product Monograph for complete dosing and safety information.

Risk for Resistance in Undetected Acute HIV-1 Infection

Use Teva-Emtricitabine/Tenofovir to reduce the risk of acquiring HIV-1 only in individuals confirmed to be HIV-negative prior to initiating PrEP and **re-confirmed routinely while taking PrEP**. HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only Teva-Emtricitabine/Tenofovir, **because Teva-Emtricitabine/Tenofovir alone does not constitute a complete treatment regimen for HIV-1**.

Drug-resistant HIV-1 variants have been identified with the use of emtricitabine and tenofovir disoproxil fumarate for a PrEP indication following undetected acute HIV-1 infection. Do not initiate Teva-Emtricitabine/Tenofovir for a PrEP indication if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed. Therefore, care should be taken to minimize drug exposure in HIV-infected individuals.

Prior to initiating Teva-Emtricitabine/Tenofovir for a PrEP indication, evaluate seronegative individuals for current or recent signs or symptoms consistent with acute viral infections including:

- Fever
- Fatigue
- Myalgia
- Skin rash

Ask about potential exposure events (e.g., unprotected, or condom broke during sex with an HIV-1 infected partner) that may have occurred within the last month.

It is recommended that negative HIV-1 status be reconfirmed on a regular basis (at least every 3 months) using HIV-1 screening tests while uninfected individuals are taking Teva-Emtricitabine/Tenofovir for a PrEP indication.

Important Safety Information About Teva-Emtricitabine/Tenofovir for a PrEP Indication

Contraindications

- Teva-Emtricitabine/Tenofovir for a PrEP indication is contraindicated in individuals with positive or unknown HIV-1 status

Warnings and Precautions
Serious Warnings and Precautions

Lactic Acidosis and Severe Hepatomegaly with Steatosis

- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate, a component of Teva-Emtricitabine/Tenofovir, alone or in combination with other antiretrovirals.

Post-Treatment Exacerbation of Hepatitis B

- Teva-Emtricitabine/Tenofovir is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of emtricitabine and tenofovir disoproxil fumarate tablets have not been established in patients co-infected with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients co-infected with HBV and HIV and have discontinued Teva-Emtricitabine/Tenofovir. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are infected with HBV and discontinue Teva-Emtricitabine/Tenofovir. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Nephrotoxicity

- Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia) has been reported with the use of emtricitabine and tenofovir disoproxil fumarate during clinical practice.

Warnings and Precautions

Comprehensive management to reduce the risk of acquiring HIV-1 infection

Teva-Emtricitabine/Tenofovir for a PrEP indication should be used only as part of a comprehensive prevention strategy that includes other prevention measures, such as safer sex practices, because Teva-Emtricitabine/Tenofovir is not always effective in preventing the acquisition of HIV-1.

- Counsel uninfected individuals at high risk about safer sex practices, including:
  - Using condoms consistently and correctly
  - Knowing their HIV-1 status and that of their partner(s)
  - Being regularly tested for other sexually transmitted infections that can facilitate HIV-1 transmission (such as syphilis and gonorrhea)
- Inform uninfected individuals at high risk about and support their efforts to reduce sexual risk behavior
- Use Teva-Emtricitabine/Tenofovir to reduce the risk of acquiring HIV-1 only in individuals confirmed to be HIV-1 negative. HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only Teva-Emtricitabine/Tenofovir **because Teva-Emtricitabine/Tenofovir alone does not constitute a complete treatment regimen for HIV-1 infection**, therefore care should be taken to minimize drug exposure in HIV-infected individuals:
  - Confirm a negative HIV-1 test immediately prior to initiating Teva-Emtricitabine/Tenofovir for a PrEP indication. Many HIV-1 tests, such as rapid tests, detect anti-HIV antibodies and may not identify HIV-1 during the acute stage of infection. Prior to initiating Teva-Emtricitabine/Tenofovir for a PrEP indication, evaluate seronegative individuals for current or recent signs or symptoms consistent with acute viral infections (e.g., fever, fatigue, myalgia, skin rash, etc.) and ask about potential exposure events (e.g., unprotected sex, or condom broke during sex with an HIV-1 infected partner) that may have occurred within the last month.
  - If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting Teva-Emtricitabine/Tenofovir for a PrEP indication for at least 1 month and reconfirm HIV-1 status or use a test approved by Health Canada as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection.
  - Screen for HIV-1 infection at least once every 3 months while taking Teva-Emtricitabine/Tenofovir for a PrEP indication.

- If symptoms consistent with acute HIV-1 infection develop following a potential exposure event, Teva-Emtricitabine/Tenofovir for a PrEP indication should be discontinued until negative infection status is confirmed using a test approved by Health Canada as an aid in the diagnosis of HIV-1, including acute or primary HIV-1 infection.
- Evaluate for signs or symptoms of acute HIV-1 infection prior to prescribing and during treatment with Teva-Emtricitabine/Tenofovir for a PrEP indication.
- Counsel all uninfected individuals to strictly adhere to a daily dosing schedule for Teva-Emtricitabine/Tenofovir. The effectiveness of Teva-Emtricitabine/Tenofovir in reducing the risk of acquiring HIV-1 was strongly correlated with adherence as demonstrated by measurable drug levels in clinical trials.

General Warnings

- **Renal impairment:** Can include cases of acute renal failure and Fanconi syndrome. It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with Teva-Emtricitabine/Tenofovir.
- In patients at risk of renal dysfunction including patients who have previously experienced renal events while receiving HEPSERA (adefovir dipivoxil), it is recommended that calculated creatinine clearance, serum phosphorus, urine glucose and urine protein be assessed prior to initiation of Teva-Emtricitabine/Tenofovir and periodically during Teva-Emtricitabine/Tenofovir therapy.
- Teva-Emtricitabine/Tenofovir should be avoided with concurrent or recent use of nephrotoxic drugs. Cases of acute renal failure after initiation of high dose or multiple NSAIDs have been reported in HIV-1 infected patients with risk factors for renal dysfunction who appeared stable on tenofovir disoproxil fumarate. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.
    - **Teva-Emtricitabine/Tenofovir for PrEP has not been studied and should not be used in HIV-1 uninfected individuals with estimated creatinine clearance below 60 mL/min. If a decrease in CrCl is observed in uninfected individuals while using Teva-Emtricitabine/Tenofovir for a PrEP indication, evaluate potential causes and reassess potential risks and benefits of continued use**
- **HBV infection:** It is recommended that all patients be tested for the presence of HBV before initiating Teva-Emtricitabine/Tenofovir
- **Serum Lipids and Blood Glucose:** Serum lipid and blood glucose levels may increase during antiretroviral therapy. Disease control and life style changes may also be contributing factors. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders and blood glucose elevations should be managed as clinically appropriate.
- **Coadministration with other products:** Do not use Teva-Emtricitabine/Tenofovir with drugs containing emtricitabine or tenofovir disoproxil fumarate, with drugs containing lamivudine, or with adefovir dipivoxil
- **Bone effects:** Decreases in bone mineral density (BMD) and mineralization defects, including osteomalacia, have been seen in patients treated with tenofovir disoproxil fumarate. Assessment of BMD should be considered for patients who have a history of pathologic bone fracture or are at risk for osteopenia or osteoporosis. Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in at-risk patients

Important Safety Information

Common Adverse Reactions with Teva-Emtricitabine/Tenofovir

Selected adverse events (all grades) reported in ≥ 2% of uninfected individuals in any treatment group in the iPrEx and Partners PrEP studies:

	iPrEx Trial		Partners PrEP Trial	
	FTC/TDF N=1251 (in %)	Placebo N=1248 (in %)	FTC/TDF N=1579 (in %)	Placebo N=1584 (in %)
Gastrointestinal Disorder				
Diarrhea	7	8	2	3
Abdominal pain	4	2	-*	-
Infections and Infestations				
Pharyngitis	13	16	-	-
Urethritis	5	7	-	-
Urinary tract infection	2	2	5	7
Syphilis	6	5	-	-
Secondary syphilis	6	4	-	-
Anogenital warts	2	3	-	-
Musculoskeletal and Connective Tissue Disorders				
Back pain	5	5	-	-
Nervous Systems Disorders				
Headache	7	6	-	-
Psychiatric Disorders				
Depression	6	7	-	-
Anxiety	3	3	-	-
Reproductive System and Breast Disorders				
Genital ulceration	2	2	2	2
Investigations				
Weight decreased	3	2	-	-

* Not reported or reported below 2%

Use of Teva-Emtricitabine/Tenofovir for a PrEP Indication in Special Populations

- **Pregnant Women** Emtricitabine and tenofovir disoproxil fumarate tablets have been evaluated in a limited number of women during pregnancy and postpartum. Teva-Emtricitabine/Tenofovir should be used during pregnancy only if the potential benefits outweigh the potential risks to the fetus. If an uninfected individual becomes pregnant while taking Teva-Emtricitabine/Tenofovir for a PrEP indication, careful consideration should be given to whether use of Teva-Emtricitabine/Tenofovir should be continued, taking into account the potential increased risk of HIV-1 infection during pregnancy
    - A pregnancy registry is available. Enroll women taking Teva-Emtricitabine/Tenofovir for a PrEP indication by calling 1-800-258-4263
- **Nursing Women:** The components of Teva-Emtricitabine/Tenofovir (emtricitabine/tenofovir disoproxil fumarate) are excreted in breast milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving emtricitabine and tenofovir disoproxil fumarate tablets whether they are taking Teva-Emtricitabine/Tenofovir for treatment or to reduce the risk of acquiring HIV-1.** If an uninfected individual acquires HIV-1 infection, it is recommended that she not breastfeed to avoid risking postnatal transmission of HIV to the infant.
- **Pediatrics:** Safety and effectiveness in pediatric patients have not been established.

Teva-Emtricitabine/Tenofovir Drug Interactions

- Since emtricitabine and tenofovir are primarily eliminated by the kidneys, coadministration of Teva-Emtricitabine/Tenofovir with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of emtricitabine, tenofovir, and/or other renally eliminated drugs

For further details about Teva-Emtricitabine/Tenofovir drug interactions, please consult the Product Monograph for Teva-Emtricitabine/Tenofovir.

Use the **Checklist for Prescribers: Initiation of Teva-Emtricitabine/Tenofovir for Pre-exposure Prophylaxis (PrEP) and the Agreement Form for Initiating Teva-Emtricitabine/Tenofovir for Pre-exposure Prophylaxis (PrEP)** to help manage and counsel individuals about the safe use of Teva-Emtricitabine/Tenofovir for a PrEP indication.

Medical Information and Reporting Instructions

For healthcare professionals with specific questions about Teva-Emtricitabine/Tenofovir, please contact us at:

MedInfo
Medical Affairs
Teva Canada Innovation
1080 Beaver Hall Hill, Suite 1200
Montreal (Quebec) H2Z 1S8
Call toll-free at 1 855 223-6838
Email: TCIMedical.Affairs@tevapharm.com

You can report any suspected side effects associated with the use of Teva-Emtricitabine/Tenofovir to:

- **Teva Canada Limited** at 1-800-268-4127 option 3 (English), 1-877-777-9117 (French), Telefax: 1-416-335-4472; or
- **Health Canada by:**
  - Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
  - Calling toll-free at 1-866-234-2345.

Teva-Emtricitabine/Tenofovir is indicated in combination with safer sex practices for PrEP to reduce the risk of sexually acquired HIV-1 infection in adults at high risk.

Consult the product monograph at https://www.tevacanada.com/globalassets/canada-ph2/product-monographs/emtricitabine-tenofovir-tabs-200mg-300mg-teva-pm-apr11_2019-full-indication-wis-eng.pdf for contraindications, warnings, precautions, adverse reactions, interactions, dosing and conditions of clinical use.

This document is also available for download at: https://www.tevacanada.com/en/canada/our-products/product-page/emtricitabinetenofovir-02399059

The product monograph is also available by calling Teva Canada at 1 855 223-6838.

Reference: 1. Teva-Emtricitabine/Tenofovir Product Monograph. Teva Canada Limited. April 11, 2019.