Prescriber Education Slide Deck v.2; January 24, 2025.

PrMylan-Emtricitabine/Tenofovir Disoproxil for a Pre-exposure Prophylaxis (PrEP) indication

Training for Healthcare Providers

Visit https://www.viatris.ca/en-ca/products/branded-specialty for more details about Mylan-Emtricitabine/Tenofovir Disoproxil educational materials.

Pre-exposure Prophylaxis (PrEP) Indication

Mylan-Emtricitabine/Tenofovir Disoproxil is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection 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.

Mylan-Emtricitabine/Tenofovir Disoproxil Product Monograph, Etobicoke ON: Mylan Pharmaceuticals ULC, October 2018.

Factors that may Help 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 sexually transmitted infections
  - Exchange of sex for commodities (such as money, food, shelter, or drugs)
  - Use of illicit drugs or alcohol dependence
  - Incarceration
  - Partner(s) of unknown HIV-1 status with any of the factors listed above

Mylan-Emtricitabine/Tenofovir Disoproxil Product Monograph, Etobicoke ON: Mylan Pharmaceuticals ULC, October 2018.

When prescribing Mylan-Emtricitabine/Tenofovir Disoproxil for PrEP, healthcare providers MUST

- Prescribe Mylan-Emtricitabine/Tenofovir Disoproxil as part of a comprehensive prevention strategy because Mylan-Emtricitabine/Tenofovir Disoproxil is not always effective in preventing the acquisition of HIV-1 infection
- Counsel all uninfected individuals to strictly adhere to the recommended daily Mylan-Emtricitabine/Tenofovir Disoproxil dosing schedule because the effectiveness of Mylan-Emtricitabine/Tenofovir Disoproxil 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 Mylan-Emtricitabine/Tenofovir Disoproxil 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 one 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 using Mylan-Emtricitabine/Tenofovir Disoproxil for PrEP

Mylan-Emtricitabine/Tenofovir Disoproxil Product Monograph, Etobicoke ON: Mylan Pharmaceuticals ULC, October 2018.

BOXED WARNING – Serious Warnings and Precautions (1/2)

- **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 (DF), a component of Mylan-Emtricitabine/Tenofovir Disoproxil tablets, **alone or in combination with other antiretrovirals**.

- **Post-Treatment Exacerbation of Hepatitis B**

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

Mylan-Emtricitabine/Tenofovir Disoproxil Product Monograph, Etobicoke ON: Mylan Pharmaceuticals ULC, October 2018.

BOXED WARNING – Serious Warnings and Precautions (2/2)

- **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 DF tablets during clinical practice.

- **Risk of Drug Resistance with Use of Mylan-Emtricitabine/Tenofovir Disoproxil for Pre-Exposure Prophylaxis (PrEP) in Undiagnosed Early HIV-1 Infection**

Mylan-Emtricitabine/Tenofovir Disoproxil used for a PrEP indication must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initial use and periodically (at least every 3 months) during use. Drug-resistant HIV-1 variants have been identified with the use of emtricitabine and tenofovir DF tablets for a PrEP indication following undetected acute HIV-1 infection. Do not initiate Mylan-Emtricitabine/Tenofovir Disoproxil for a PrEP indication if signs or symptoms of acute HIV infection are present unless negative infection status is confirmed.

Mylan-Emtricitabine/Tenofovir Disoproxil Product Monograph, Etobicoke ON: Mylan Pharmaceuticals ULC, October 2018.

Mechanism of Action

Emtricitabine, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 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.

Tenofovir disoproxil fumarate (DF) is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir DF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 RT by competing with the natural substrate deoxyadenosine 5′-triphosphate and, after incorporation into DNA, by DNA chain termination.

Mylan-Emtricitabine/Tenofovir Disoproxil Product Monograph, Etobicoke ON: Mylan Pharmaceuticals ULC, October 2018.

Comprehensive HIV-1 Infection Prevention Strategy

Use Mylan-Emtricitabine/Tenofovir Disoproxil for PrEP only as part of a comprehensive prevention strategy that includes other prevention measures, such as safer sex practices, because Mylan-Emtricitabine/Tenofovir Disoproxil is not always effective in preventing the acquisition of HIV-1

- Counsel uninfected individuals about safer sex practices that include consistent and correct use of condoms, knowledge of their HIV-1 status and that of their partner(s), and regular testing for other sexually transmitted infections that can facilitate HIV-1 transmission (such as syphilis and gonorrhea).
- Inform uninfected individuals about and support their efforts in reducing sexual risk behavior.

Key Findings from Clinical Trials for a PrEP indication The iPrEx Study

The primary outcome measure for the study was the incidence of documented HIV-1 seroconversion.

Table 21. Study Demographics and Trial Design of iPrEx Trial

Study No.	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (N=2499)	Mean Age (Range)	Gender
CO-US-104-0288 iPrEx)	Randomized, double-blind, placebo-controlled multinational study in men and transgender women who have sex with men and with evidence of high risk behavior for HIV-1 infection Arm 1: emtricitabine and tenofovir DF tablets Arm 2: placebo	Arm 1: emtricitabine and tenofovir DF tablet taken orally QD Arm 2: Placebo tablet taken orally QD Duration of treatment was variable. Subjects remained on treatment until the target number of seroconversion events was identified and the last enrolled study subject completed 48 weeks of treatment. Subjects were followed for at least 8 weeks follow up. HBsAg reactive subjects were followed for hepatic flares for 24 weeks after study drug discontinuation. Subjects who HIV-1 seroconverted during study were followed through at least 24 weeks after the last dose of	Randomized: 1251 – emtricitabine and tenofovir DF tablets 1248 –placebo Race: Asian – 5% Black – 9% White – 18% Hispanic/Latino – 72%	27 (18 to 67 years)	Male: 100% subjects born male 29 (1%) report current identity as female

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Key Findings from Clinical Trials for a PrEP indication The iPrEx Study

Table 23 **iPrEx Study: Relative Risk Reduction Through End-of-Treatment Cutoff (Primary Analysis; mITT Analysis[a])**

	Placebo	Emtricitabine and tenofovir DF tablets	P-value[b]
End of Treatment[c]			
mITT Analysis	**N=1217**	**N=1224**	0.002
Person-Years follow-up[d]	2113	2124	
Number of HIV-1 Infections (Seroconversions)	83	48	
Relative Risk Reduction (2-sided 95% CI)	42% (18%, 60%)		

Abbreviation: CI = confidence interval
a Modified Intent-to-Treat (mITT) analysis excludes subjects who do not have follow-up HIV test and who were infected at enrollment
b p-values by log rank test
c End of treatment is defined as the next post-treatment visit after this date (approximately one month). This analysis excludes post-treatment stop seroconversions.
d Time to first evidence of seroconversion for those with event

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Key Findings from Clinical Trials for a PrEP indication The iPrEx Study

In a post hoc case control study of plasma and intracellular drug levels in about 10% of clinical trial subjects, risk reduction appeared to be the greatest in subjects with detectable intracellular tenofovir. Efficacy was therefore strongly correlated with adherence.

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Key Findings from Clinical Trials for a PrEP indication The PrEP Study

Table 22 Study Demographics and Trial Design of Partners PrEP Trial

Study No.	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (N=4758)	Mean Age (Range)	Gender
CO-US-104-0380 (Partners PrEP)	Randomized, double-blind, placebo-controlled 3-arm trial conducted in serodiscordant heterosexual couples in Kenya and Uganda	Arm 1: Tenofovir DF tablet taken orally QD Arm 2: emtricitabine and tenofovir DF tablet taken orally QD Arm 3: Matched Placebo tablets, taken orally QD. Duration of study drug treatment was variable. Subjects received the assigned study drugs once daily for a minimum of 24 months up to a maximum	Randomized: 1589 –TDF 1583 – emtricitabine and tenofovir DF tablets 1586 – placebo	33–34	Female: 38% Male 62%

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Key Findings from Clinical Trials for a PrEP indication The PrEP Study

Table 24 **Partners PrEP Study: Relative Risk Reduction and HIV-1 Seroincidence for Partner Subjects (Primary Analysis; mITT Analysis[a])**

	emtricitabine and emtricitabine and tenofovir DF tablets	tenofovir	Placebo	Total
mITT Analysis	N=1576	N=1579	N=1578	N=4733
Person-years of follow-up[b]	2616	2604	2607	7827
Number of HIV-1 Infections (Seroconversions)	13	17	52	82
HIV-1 incidence, per 100 person-years	0.50	0.65	1.99	1.05
Relative Risk Reduction (2-sided 95% CI)	75% (55-87%)	67% (44-81%)		
p-value[c]	<0.0001	<0.0001		

a Modified Intent-to-Treat (mITT) analysis excludes subjects who were infected at enrollment
b Time to first evidence of seroconversion for those with event
c p-values using Cox's proportional hazards model for the active study drug relative to placebo

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Key Findings from Clinical Trials for a PrEP indication The PrEP Study

In a post-hoc case control study of plasma drug levels in about 10% of study subjects, risk reduction was most pronounced in subjects with detectable plasma tenofovir. Efficacy was therefore strongly correlated with adherence.

Mylan-Emtricitabine/Tenofovir Disoproxil Product Monograph, Etobicoke ON: Mylan Pharmaceuticals ULC, October 2018.

Important Safety Information

Comprehensive HIV-1 Infection Prevention Strategy

Prescribe Mylan-Emtricitabine/Tenofovir Disoproxil for PrEP only as part of a comprehensive prevention strategy that includes other prevention measures, such as safer sex practices, because Mylan-Emtricitabine/Tenofovir Disoproxil for a PrEP indication is not always effective in preventing the acquisition of HIV-1 infection

- Counsel uninfected individuals about safer sex practices that include consistent and correct use of condoms, knowledge of their HIV-1 status and that of their partner(s), and regular testing for other sexually transmitted infections that can facilitate HIV-1 transmission (such as syphilis and gonorrhea)
- Inform uninfected individuals about prevention strategy and support their efforts in reducing sexual risk behavior

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Important Safety Information

Risk of Resistance (1/2)

Prescribe Mylan-Emtricitabine/Tenofovir Disoproxil 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 Mylan-Emtricitabine/Tenofovir Disoproxil, **because Mylan-Emtricitabine/Tenofovir Disoproxil alone does not constitute a complete regimen for HIV-1 treatment**; therefore, care should be taken to minimize drug exposure in HIV-infected individuals

- 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 Mylan-Emtricitabine/Tenofovir Disoproxil for a PrEP indication, evaluate seronegative individuals for current or recent signs and symptoms consistent with acute viral infections (e.g., fever, fatigue, myalgia, skin rash, etc.) and 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.

Important Safety Information

Risk of Resistance (2/2)

- If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting PrEP for at least one month and reconfirm HIV-1 negative 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.
- While using Mylan-Emtricitabine/Tenofovir Disoproxil for a PrEP indication, HIV-1 screening tests should be repeated at least every 3 months. If symptoms consistent with acute HIV-1 infection develop following a potential exposure event, PrEP 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.

Counsel uninfected individuals to strictly adhere to the recommended Mylan-Emtricitabine/Tenofovir Disoproxil dosing schedule. The effectiveness of emtricitabine and tenofovir DF tablets in reducing the risk of acquiring HIV-1 infection is strongly correlated with adherence as demonstrated by measurable drug levels in clinical trials.

Mylan-Emtricitabine/Tenofovir Disoproxil Product Monograph, Etobicoke ON: Mylan Pharmaceuticals ULC, October 2018.

Important Safety Information

Warnings and Precautions

Nephrotoxicity (1/2)

- Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia) has been reported in association with the use of tenofovir DF in clinical practice
- Assess creatinine clearance (CrCl) in all patients prior to initiating therapy and as clinically appropriate during therapy with Mylan-Emtricitabine/Tenofovir Disoproxil
- In patients at risk of renal dysfunction, including patients who have previously experienced renal events while receiving HEPSERA, it is recommended that calculated creatinine clearance, serum phosphorus, urine glucose, and urine protein be assessed prior to initiation, and periodically during Mylan-Emtricitabine/Tenofovir Disoproxil therapy
- If serum phosphate is < 1.5 mg/dl (0.48 mmol/l) or creatinine clearance is decreased to < 50 ml/min in any patient receiving Mylan-Emtricitabine/Tenofovir Disoproxil tablets, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations. Consideration should also be given to interrupting treatment with Mylan-Emtricitabine/Tenofovir Disoproxil tablets in patients with creatinine clearance decreased to < 50 ml/min or decreases in serum phosphate to < 1.0 mg/dl (0.32 mmol/l). Interrupting treatment with Mylan-Emtricitabine/Tenofovir Disoproxil should also be considered in case of progressive decline of renal function when no other cause has been identified.

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Important Safety Information

Warnings and Precautions

Nephrotoxicity (2/2)

- Avoid administering Mylan-Emtricitabine/Tenofovir Disoproxil with concurrent or recent use of nephrotoxic agents, [eg, cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir, aminoglycosides, high-dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs)]. **There have been three post marketing reports of acute renal failure in patients on concomitant NSAIDS therapy where a relationship to tenofovir DF could not be excluded. These events mostly occurred in medically complex patients, where underlying disease processes confound interpretation** Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.

Renal Impairment

- ***Treatment of HIV-1 infection***
  - Dosing interval adjustment of Mylan-Emtricitabine/Tenofovir Disoproxil and close monitoring of renal function are recommended in all patients with creatinine clearance 30-49 mL/min. No safety and efficacy data are available in patients with renal dysfunction who received emtricitabine and tenofovir DF tablets using these guidelines, and so the potential benefit of Mylan-Emtricitabine/Tenofovir Disoproxil should be assessed against the potential risk of renal toxicity. Mylan-Emtricitabine/Tenofovir Disoproxil should not be administered to patients with creatinine clearance <30 mL/min or patients requiring hemodialysis.
- ***Pre-exposure Prophylaxis of HIV-1 infection***
  - Mylan-Emtricitabine/Tenofovir Disoproxil for a PrEP indication should not be used in HIV-1 uninfected individuals with creatinine clearance below 60 mL/min
    - No dose adjustment of Mylan-Emtricitabine/Tenofovir Disoproxil for PrEP tablets is necessary with mild renal impairment patients (creatinine clearance 50-80 mL/min)
    - If a decrease in estimated CrCl is observed in uninfected individuals while using Mylan-Emtricitabine/Tenofovir Disoproxil for a PrEP indication, evaluate potential causes and re-assess potential risks and benefits of continued use

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Important Safety Information

Warnings and Precautions

Bone effects

- Assessment of bone mineral density (BMD) should be considered for patients who have a history of pathologic bone fracture or are at risk for osteopenia or osteoporosis. If bone abnormalities are suspected then appropriate consultation should be obtained.
- Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing tenofovir DF. Serum phosphate should be monitored in these patients.

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Important Safety Information

Warnings and Precautions

Serum Lipids and Blood Glucose

- Serum lipids 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.

Hepatitis B Virus Infection

- It is recommended that all patients be tested for the presence of HBV before initiating Mylan-Emtricitabine/Tenofovir Disoproxil
- In patients with advanced liver disease or cirrhosis, post-treatment exacerbation of hepatitis may lead to hepatic decompensation. Therefore, discontinuation of emtricitabine and tenofovir DF treatment without initiation of alternative anti-hepatitis B therapy is not recommended

Drug Interactions

- Mylan-Emtricitabine/Tenofovir Disoproxil should not be co-administered with other drugs containing emtricitabine or tenofovir DF, lamivudine-containing products, or with adefovir dipivoxil

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Important Safety Information

Warnings and Precautions

Pregnant Women

- Emtricitabine and tenofovir DF tablets have been evaluated in a limited number of women during pregnancy and postpartum
- Mylan-Emtricitabine/Tenofovir Disoproxil should be used in pregnant women only if the potential benefits outweigh the potential risks to the fetus
- If an uninfected individual becomes pregnant while taking Mylan-Emtricitabine/Tenofovir Disoproxil for a PrEP indication, careful consideration should be given to whether the use of Mylan-Emtricitabine/Tenofovir Disoproxil should be continued, taking into account the potential increased risk of HIV infection during pregnancy
- Enroll pregnant women taking Mylan-Emtricitabine/Tenofovir Disoproxil for a PrEP indication into Antiretroviral Pregnancy Registry by calling 1-800-258-4263

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Important Safety Information

Warnings and Precautions

Nursing Women

- **HIV-infected mothers should not breastfeed their infants to avoid risking postnatal transmission of HIV to the infant.**
- **Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving Mylan-Emtricitabine/Tenofovir Disoproxil tablets, whether they are taking Mylan-Emtricitabine/Tenofovir Disoproxil for treatment or to reduce the risk of acquiring HIV-1 infection**

Pediatrics (<18 years of age)

- Safety and effectiveness in pediatric patients have not been established

Geriatrics (>65 years of age)

- Clinical studies of emtricitabine tablets or tenofovir DF tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

See Product Monograph for complete safety information.

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Important Safety Information

Warnings and Precautions

Risk of Resistance

Use Mylan-Emtricitabine/Tenofovir Disoproxil 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 Mylan-Emtricitabine/Tenofovir Disoproxil, **because Mylan-Emtricitabine/Tenofovir Disoproxil alone does not constitute a complete treatment regimen for HIV-1 treatment;** therefore, care should be taken to minimize drug exposure in HIV-infected individuals

- Prior to initiating Mylan-Emtricitabine/Tenofovir Disoproxil 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, or condom broke during sex with an HIV-1 infected partner) that may have occurred within the last month

Important Safety Information

Warnings and Precautions

Risk of Resistance

- If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting PrEP for at least one month and reconfirm HIV-1 negative 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
- While using Mylan-Emtricitabine/Tenofovir Disoproxil for a PrEP indication, HIV-1 screening tests should be repeated at least every 3 months
- If symptoms consistent with acute HIV-1 infection develop following a potential exposure event, PrEP 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
- Counsel uninfected individuals to strictly adhere to the recommended MylanEmtricitabine/Tenofovir Disoproxil dosing schedule. The effectiveness of emtricitabine and tenofovir DF tablets in reducing the risk of acquiring HIV-1 is strongly correlated with adherence as demonstrated by measurable drug levels in clinical trials.

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Important Safety Information

Drug interactions

- **Drugs Affecting Renal Function**

Coadministration of Mylan-Emtricitabine/Tenofovir Disoproxil with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of emtricitabine, tenofovir, and/or other renally eliminated drugs. Some examples include, but are not limited to cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir, aminoglycosides and high-dose or multiple NSAIDs.

- Do not use Mylan-Emtricitabine/Tenofovir Disoproxil with drugs containing emtricitabine or tenofovir disoproxil fumarate, or with medicinal products containing tenofovir alafenamide, or with drugs containing lamivudine, or with adefovir dipivoxil

For further details about Mylan-Emtricitabine/Tenofovir Disoproxil drug interactions, please see the Product Monograph for Mylan-Emtricitabine/Tenofovir Disoproxil

Mylan-Emtricitabine/Tenofovir Disoproxil Product Monograph, Etobicoke ON: Mylan Pharmaceuticals ULC, October 2018.

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

Table 5. Selected Adverse Events (All Grades) Reported in ≥2% of Uninfected individuals in Any Treatment Group in the iPrEx Trial and Partners PrEP Trial

	iPrEx Trial		Partners PrEP Trial	
	FTC/TDF N=1251	Placebo N=1248	FTC/TDF N=1579	Placebo N=1584
Gastrointestinal Disorder				
Diarrhea	7%	8%	2%	3%
Abdominal pain	4%	2%	_[a]	-
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%	-	-

[a] Not reported or reported below 2%.

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

	iPrEx Trial		Partners PrEP Trial	
	FTC/TDF N=1251	Placebo N=1248	FTC/TDF N=1579	Placebo N=1584
Musculoskeletal and Connective Tissue Disorders				
Back pain	5%	5%	-	-
Nervous System Disorders				
Headache	7%	6%	-	-
Psychiatric Disorders				
Depression	6%	7%	-	-
Anxiety	3%	3%	-	-
Reproductive System and Breast				
Genital ulceration	2%	2%	2%	2%
Investigations				
Weight decreased	3%	2%	-	-

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Other Educational Materials

Prescriber-Patient Agreement Form for Initiating Mylan-Emtricitabine/Tenofovir Disoproxil for PrEP

- Developed for prescribers and patients to support discussion of appropriate use of Mylan-Emtricitabine/Tenofovir Disoproxil for a PrEP indication
- Form describes risk factors for uninfected individuals, safety risks associated with use of emtricitabine and tenofovir DF, details on comprehensive prevention strategy, prescriber's and patient's obligation to participate in education and counselling

Checklist for Prescribers: Initiation of Mylan-Emtricitabine/Tenofovir Disoproxil for PrEP

- Checklist for prescribers of key factors to consider before starting an uninfected individual on Mylan-Emtricitabine/Tenofovir Disoproxil for a PrEP indication
- Checklist items include confirming a negative HIV-1 testing, screening for signs or symptoms of acute HIV-1 infection, counselling on safety risks and importance of adherence, and other components of comprehensive prevention strategy

Educational Information about Mylan-Emtricitabine/Tenofovir Disoproxil to Reduce the Risk of Contracting HIV-1 Infection

- Brochure developed to help educate uninfected patients taking Mylan-Emtricitabine/Tenofovir Disoproxil for a PrEP indication

Copies are available online at the following website: https://www.viatris.ca/en-ca/products/branded-specialty

Mylan-Emtricitabine/Tenofovir Disoproxil Product Monograph, Etobicoke ON: Mylan Pharmaceuticals ULC, October 2018.

Indication and clinical use

Mylan-Emtricitabine/Tenofovir Disoproxil 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. When considering Mylan-Emtricitabine/Tenofovir Disoproxil 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 sexually transmitted infections
  - exchange of sex for commodities (such as money, food, shelter, or drugs)
  - use of illicit drugs or alcohol dependence
  - incarceration
  - partner(s) of unknown HIV-1 status with any of the factors listed above

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Indication and clinical use

When prescribing Mylan-Emtricitabine/Tenofovir Disoproxil for PrEP, healthcare providers must:

- prescribe Mylan-Emtricitabine/Tenofovir Disoproxil as part of a comprehensive prevention strategy because Mylan-Emtricitabine/Tenofovir Disoproxil is not always effective in preventing the acquisition of HIV-1 infection;
- counsel all uninfected individuals to strictly adhere to the recommended Mylan-Emtricitabine/Tenofovir Disoproxil dosing schedule because the effectiveness of Mylan-Emtricitabine/Tenofovir Disoproxil in reducing the risk of acquiring HIV-1 was strongly correlated with adherence as demonstrated by measurable drug levels in clinical trials;
- confirm a negative HIV-1 test immediately prior to initiating Mylan-Emtricitabine/Tenofovir Disoproxil 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 one 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; and
- screen for HIV-1 infection at least once every 3 months while taking Mylan-Emtricitabine/Tenofovir Disoproxil for PrEP.

Mylan-Emtricitabine/Tenofovir Disoproxil Product Monograph, Etobicoke ON: Mylan Pharmaceuticals ULC, October 2018.

Indication and clinical use

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.

Clinical studies of emtricitabine and tenofovir DF tablets, emtricitabine tablets or tenofovir DF tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Safety and effectiveness in pediatric patients have not been established.

Mylan-Emtricitabine/Tenofovir Disoproxil Product Monograph, Etobicoke ON: Mylan Pharmaceuticals ULC, October 2018.

Contraindications

Mylan-Emtricitabine/Tenofovir Disoproxil is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product.

Mylan-Emtricitabine/Tenofovir Disoproxil is contraindicated for use as PrEP in individuals with unknown or positive HIV- 1 status.

Mylan-Emtricitabine/Tenofovir Disoproxil Product Monograph, Etobicoke ON: Mylan Pharmaceuticals ULC, October 2018.

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 DF (VIREAD®), a component of Mylan-Emtricitabine/Tenofovir Disoproxil, alone or in combination with other antiretrovirals.

Post-Treatment Exacerbation of Hepatitis B: Mylan-Emtricitabine/Tenofovir Disoproxil is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of Mylan-Emtricitabine/Tenofovir Disoproxil have not been established in patients coinfected with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HBV and HIV and have discontinued Mylan-Emtricitabine/Tenofovir Disoproxil. 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 Mylan-Emtricitabine/Tenofovir Disoproxil. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Mylan-Emtricitabine/Tenofovir Disoproxil Product Monograph, Etobicoke ON: Mylan Pharmaceuticals ULC, October 2018.

Serious warnings and precautions

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 Mylan-Emtricitabine/Tenofovir Disoproxil during clinical practice.

Risk of Drug Resistance with Use of Mylan-Emtricitabine/Tenofovir Disoproxil for Pre-Exposure Prophylaxis (PrEP) in Undiagnosed Early HIV-1 Infection: Mylan-Emtricitabine/Tenofovir Disoproxil used for a PrEP indication must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initial use and periodically (at least every 3 months) during use. Drug-resistant HIV-1 variants have been identified with the use of Mylan-Emtricitabine/Tenofovir Disoproxil for a PrEP indication following undetected acute HIV-1 infection. Do not initiate Mylan-Emtricitabine/Tenofovir Disoproxil for a PrEP indication if signs or symptoms of acute HIV infection are present unless negative infection status is confirmed.

Mylan-Emtricitabine/Tenofovir Disoproxil Product Monograph, Etobicoke ON: Mylan Pharmaceuticals ULC, October 2018.

Other relevant warnings and precautions

- Serum lipids and blood glucose
- Hepatic Impairment including severe or potentially fatal hepatic adverse events in patients with chronic hepatitis B or C
- Pancreatitis
- Bone Effects (Bone Mineral Density and Mineralization Defects)
- Renal Impairment
- Mothers should be instructed **not to** breast-feed if they are receiving Mylan-Emtricitabine/Tenofovir Disoproxil tablets
- Mylan-Emtricitabine/Tenofovir Disoproxil should be used in pregnant women **only if** the potential benefits outweigh the potential risks to the fetus
- Mylan-Emtricitabine/Tenofovir Disoproxil should **not** be administered with adefovir dipivoxil, products containing tenofovir DF, or emtricibine, or with medicinal ingredients containing tenofovir alafenamide, or drugs containing lamivudine
- Caution when used with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir particularly in those at risk of renal dysfunction

Mylan-Emtricitabine/Tenofovir Disoproxil Product Monograph, Etobicoke ON: Mylan Pharmaceuticals ULC, October 2018.

For more information

Consult the Product Monograph at https://health-products.canada.ca/dpd-bdpp/index-eng.jsp for more information about conditions of clinical use, contraindications, warnings, precautions, adverse reactions, interactions and dosing.

The Product Monograph is also available by calling 1 844 596-9526.

Mylan-Emtricitabine/Tenofovir Disoproxil Product Monograph, Etobicoke ON: Mylan Pharmaceuticals ULC, October 2018.