PrMINT-EMTRICITABINE/TENOFOVIR for a Pre-exposure Prophylaxis (PrEP) Indication

Healthcare Provider Training

Pre-exposure Prophylaxis (PrEP) Indication

MINT-EMTRICITABINE/TENOFOVIR (emtricitabine/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 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.

Factors to Help Identify Individuals at High Risk

- Has a partner 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

When Prescribing MINT-EMTRICITABINE/TENOFOVIR for a PrEP Indication, Healthcare Providers MUST:

- Prescribe MINT-EMTRICITABINE/TENOFOVIR as part of a comprehensive prevention strategy because MINT-EMTRICITABINE/TENOFOVIR is not always effective in preventing the acquisition of HIV-1 infection
- Counsel all uninfected individuals to strictly adhere to the recommended daily MINT-EMTRICITABINE/TENOFOVIR dosing schedule because the effectiveness of MINT-EMTRICITABINE/TENOFOVIR in reducing the risk of acquiring HIV-1 infection is strongly correlated with adherence as demonstrated by measurable drug levels in clinical trials
- Confirm a negative HIV-1 test immediately prior to initiating MINT-EMTRICITABINE/TENOFOVIR for a PrEP indication. If clinical signs or symptoms consistent with acute viral infection are present or 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

- While using MINT-EMTRICITABINE/TENOFOVIR for a PrEP indication, HIV-1 screening tests should be repeated at least once 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 infection, including acute or primary HIV-1 infection

BOXED WARNING

- 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 MINT-EMTRICITABINE/TENOFOVIR, **alone or in combination with other antiretrovirals.**
- MINT-EMTRICITABINE/TENOFOVIR is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of emtricitabine and tenofovir DF 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 who have discontinued emtricitabine and tenofovir DF. 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 HIV and discontinue MINT-EMTRICITABINE/TENOFOVIR. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

BOXED WARNING

- Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia) has been reported with the use of MINT-EMTRICITABINE/TENOFOVIR during clinical practice.
- MINT-EMTRICITABINE/TENOFOVIR 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 for a PrEP indication following undetected acute HIV-1 infection. Do not initiate MINT-EMTRICITABINE/TENOFOVIR for a PrEP indication if signs or symptoms of acute HIV infection are present unless negative infection status is confirmed.

How does MINT-EMTRICITABINE/ TENOFOVIR for PrEP work?

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 is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate 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.

How does MINT-EMTRICITABINE/ TENOFOVIR for PrEP work?

Because MINT-EMTRICITABINE/TENOFOVIR is not always effective in preventing the acquisition of HIV-1 infection, MINT-EMTRICITABINE/TENOFOVIR for a PrEP indication must be used in combination with a comprehensive prevention strategy that includes safer sex practices, such as regular and correct condom use, regular HIV testing for themselves (and their sexual partners), and other proven HIV prevention methods to safely and effectively reduce the risk of acquiring HIV-1 infection

- MINT-EMTRICITABINE/TENOFOVIR for a PrEP indication must only be prescribed to uninfected individuals at high risk who are confirmed to be HIV negative
- Uninfected individuals who are prescribed MINT-EMTRICITABINE/ TENOFOVIR for a PrEP indication should not miss any doses. Missing doses may increase the risk of acquiring HIV-1 infection

Key Findings of the Emtricitabine and Tenofovir DF for a PrEP Indication Studies: The iPrEx Trial

The iPrEx Study was a randomized, double-blind, placebo-controlled, multinational clinical trial that included 2499 HIV-seronegative men or transgender women who have sex with men and with evidence of high-risk behaviour for HIV-1 infection. Subjects were randomly assigned to receive emtricitabine and tenofovir DF for PrEP (n=1251), or placebo (n=1248) once daily. Subjects received monthly HIV-1 testing, counseling, condoms, and management of other sexually transmitted infections. 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 study drugs. The primary outcome measure for the study was the incidence of documented HIV seroconversion.

Key Findings of the Emtricitabine and Tenofovir DF for a PrEP Indication Studies: The iPrEx Trial

In one clinical trial of emtricitabine and tenofovir DF for a PrEP indication, emtricitabine and tenofovir DF was shown to reduce the risk of HIV-1 acquisition by 42% vs placebo (p=0.002) for high risk men who have sex with men who also received comprehensive prevention services, including monthly HIV-1 testing, condom provision, counseling, and management of other sexually transmitted infections

- 95% Confidence Interval (18% to 60%)
- 4237 person-years of follow up (2124 emtricitabine and tenofovir DF; 2113 placebo)
- 131 emergent HIV-1 seroconversions were reported
  - 83 seroconversions occurred in subjects randomized to placebo
  - 48 seroconversions occurred in subjects in the emtricitabine and tenofovir DF for PrEP group

Key Findings of the Emtricitabine and Tenofovir DF for a PrEP Indication Studies: The iPrEx Trial

- 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.

Key Findings of the Emtricitabine and tenTfovir DF for a PrEP Indication Studies: The Partners PrEP Trial

The Partners PrEP Study was a randomized, double-blind, placebo-controlled, 3-arm study that included 4758 HIV-serodiscordant heterosexual couples from Kenya and Uganda. Uninfected individuals were randomly assigned to receive emtricitabine and tenofovir DF for PrEP (n=1583), VIREAD (tenofovir disoproxil fumarate) (n=1589), or placebo (n=1586) once daily, with monthly follow-up for 24-36 months. All subjects received monthly HIV-1 testing, evaluation of adherence, assessment of sexual behavior, and safety evaluations.

Key Findings of Emtricitabine and Tenofovir DF for a PrEP Indication Studies: The Partners PrEP Trial

In another clinical study of emtricitabine and tenofovir DF for a PrEP indication, emtricitabine and tenofovir DF was shown to reduce HIV-1 acquisition by 75% in uninfected individuals in stable heterosexual serodiscordant relationships who also received comprehensive prevention services, including monthly HIV testing, evaluation of adherence, assessment of sexual behavior, and safety evaluations

- 95% Confidence Interval (55% to 87%)
- 7827 person-years of follow up (2616 emtricitabine and tenofovir DF; 2604 VIREAD®; 2607 placebo)
- 82 emergent HIV-1 seroconversions were reported
  - 52 seroconversions occurred in partner subjects randomized to placebo
  - 17 seroconversions occurred in partner subjects in the VIREAD group
  - 13 seroconversions occurred in partner subjects in the emtricitabine and tenofovir DF for PrEP group

Key Findings of Emtricitabine and Tenofovir DF for a PrEP Indication Studies: The Partners PrEP Trial

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

Important Safety Information: Comprehensive Management to Reduce the Risk of Acquiring HIV-1

Prescribe MINT-EMTRICITABINE/TENOFOVIR for PrEP only as part of a comprehensive prevention strategy that includes other prevention measures, such as safer sex practices, because MINT-EMTRICITABINE/TENOFOVIR 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 and support their efforts in reducing sexual risk behavior

Important Safety Information: Comprehensive Management to Reduce the Risk of Acquiring HIV-1 Infection

Prescribe MINT-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 MINT-EMTRICITABINE/TENOFOVIR, because MINT-EMTRICITABINE/TENOFOVIR 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 MINT-EMTRICITABINE/TENOFOVIR 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: Comprehensive Management to Reduce the Risk of Acquiring HIV-1 Infection

Confirm a negative HIV-1 test immediately prior to initiating MINT-EMTRICITABINE/TENOFOVIR for a PrEP indication. If clinical signs or symptoms consistent with acute viral infection are present or 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

Important Safety Information: Comprehensive Management to Reduce the Risk of Acquiring HIV-1 Infection

While using MINT-EMTRICITABINE/TENOFOVIR for a PrEP indication, HIV-1 screening tests should be repeated at least once 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 infection, including acute or primary HIV-1 infection

Counsel uninfected individuals to strictly adhere to the recommended daily MINT-EMTRICITABINE/TENOFOVIR dosing schedule. The effectiveness of emtricitabine and tenofovir DF for a PrEP indication in reducing the risk of acquiring HIV-1 infection **was** strongly correlated with adherence **as demonstrated by** measurable drug levels **in clinical trials.**

Important Safety Information: Additional Warnings and Precautions

New Onset or Worsening Renal Impairment

- Can include acute renal failure and Fanconi syndrome
- Assess estimated creatinine clearance (CrCl) before prescribing MINT-EMTRICITABINE/TENOFOVIR and periodically during treatment with MINT-EMTRICITABINE/TENOFOVIR
- In patients at risk of renal dysfunction, monitor estimated CrCl, serum phosphorus, urine glucose and urine protein before prescribing MINT-EMTRICITABINE/TENOFOVIR and periodically while MINT-EMTRICITABINE/TENOFOVIR is being used

Important Safety Information: Additional Warnings and Precautions

New Onset or Worsening Renal Impairment

- Avoid administering MINT-EMTRICITABINE/TENOFOVIR with concurrent or recent use of nephrotoxic drugs. **There have been 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**
- Emtricitabine and Tenofovir DF for PrEP has not been studied in HIV-1 uninfected individuals with creatinine clearance below 60 mL/min.
  - If a decrease in estimated CrCl is observed in uninfected individuals while using MINT-EMTRICITABINE/TENOFOVIR for a PrEP indication, evaluate potential causes and re-assess potential risks and benefits of continued use

Important Safety Information: Additional Warnings and Precautions

Bone effects

- Decreases in bone mineral density (BMD) and mineralization defects, including osteomalacia, have been seen in patients treated with tenofovir disoproxil fumarate. Consider assessment of BMD in individuals with a history of pathologic fracture or other risk factors for osteoporosis or bone loss
- 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: Additional Warnings and Precautions

Redistribution/accumulation of body fat

- Observed in patients receiving antiretroviral therapy for treatment of HIV-1 infection

HBV Infection

- It is recommended that all individuals be tested for the presence of chronic HBV before initiating MINT-EMTRICITABINE/TENOFOVIR
- HBV-uninfected individuals should be offered vaccination

Coadministration with other products

- Do not use MINT-EMTRICITABINE/TENOFOVIR with drugs containing emtricitabine or tenofovir disoproxil fumarate, with drugs containing lamivudine, or with adefovir dipivoxil

Important Safety Information:

Use of MINT-EMTRICITABINE/ TENOFOVIR for a PrEP Indication in Specific Populations

Pregnancy

- There are no adequate and well-controlled trials in pregnant women
- MINT-EMTRICITABINE/TENOFOVIR should be used in pregnancy only if clearly needed
- If an uninfected individual becomes pregnant while taking MINT-EMTRICITABINE/TENOFOVIR for a PrEP indication, careful consideration should be given to whether the use of MINT-EMTRICITABINE/TENOFOVIR should be continued, taking into account the potential increased risk of HIV infection during pregnancy*
- A pregnancy registry is available. Enroll pregnant women taking MINT-EMTRICITABINE/TENOFOVIR for a PrEP indication by calling 1-800-258-4263

*Gray RH, *et al.* Lancet 2005;366(9492):1182-1188

Important Safety Information: Use of MINT-EMTRICITABINE/ TENOFOVIR for a PrEP Indication in Specific Populations

Nursing Mothers

- The components of MINT-EMTRICITABINE/TENOFOVIR are excreted in breast milk. Because the risks to the infant are not known, **mothers taking MINT-EMTRICITABINE/TENOFOVIR for a PrEP indication should be instructed not to breastfeed**. If an uninfected individual acquires HIV-1 infection, it is recommended that she not breastfeed to avoid risking postnatal transmission of HIV-1 infection

Pediatrics

- Emtricitabine and Tenofovir DF for a PrEP indication is based on trials in adults. Safety and effectiveness in pediatric patients have not been established.

See Product Monograph for complete safety information

Important Safety Information: Confirming and Regularly Reconfirming Negative HIV-1 Status

MINT-EMTRICITABINE/TENOFOVIR should be used to reduce the risk of acquiring HIV-1 infection only in individuals confirmed to be HIV-1 negative

- A negative HIV-1 status should be confirmed before prescribing MINT-EMTRICITABINE/TENOFOVIR for a PrEP indication
- Individuals should be regularly tested (at least once every 3 months) while taking MINT-EMTRICITABINE/TENOFOVIR for a PrEP indication to reconfirm that they are HIV-1 negative
- 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

Important Safety Information: Confirming and Regularly Reconfirming Negative HIV-1 Status

Potential for Resistance in Undetected Acute HIV-1 Infection

- It is important to be alert to the signs of potential acute HIV-1 infection when prescribing MINT-EMTRICITABINE/TENOFOVIR for a PrEP indication. These include fever, headache, fatigue, arthralgia, vomiting, myalgia, diarrhea, pharyngitis, rash, night sweats, and cervical and inguinal adenopathy
- HIV-1 resistance mutations may emerge in individuals with undetected HIV-1 infection who are taking MINT-EMTRICITABINE/TENOFOVIR for a PrEP indication
  - Although MINT-EMTRICITABINE/TENOFOVIR is active against HIV-1, MINT-EMTRICITABINE/TENOFOVIR alone does not constitute a complete treatment regimen for HIV-1 infection
  - HIV-1 infected patients taking MINT-EMTRICITABINE/TENOFOVIR must take it with other antiretroviral agents to fully suppress virus replication and avoid the development of resistance

Important Safety Information: Drug Interactions and Common Adverse Events

Drug Interactions

- Coadministration with drug that reduce renal function or compete for active tubular secretion may increase concentrations of tenofovir
  - For further details about MINT-EMTRICITABINE/TENOFOVIR drug interactions, please see the Product Monograph for MINT-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	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%.

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	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 Disorders				
Genital ulceration	2%	2%	2%	2%
Investigations				
Weight decreased	3%	2%	-	-

Additional Educational Materials

Agreement Form for Initiating MINT-EMTRICITABINE/TENOFOVIR for PrEP of Sexually Acquired HIV-1 Infection

- Designed for prescribers to use with uninfected individuals to facilitate discussion of appropriate use of MINT-EMTRICITABINE/TENOFOVIR for a PrEP indication
- Form covers safety risks associated with use of MINT-EMTRICITABINE/TENOFOVIR for a PrEP indication, the importance of adherence to the recommended daily dosing regimen, regular assessment of HIV-1 test results, and screening for sexually transmitted infections

Checklist for Prescribers: Initiation of MINT-EMTRICITABINE/TENOFOVIR for PrEP

- Checklist of key components for prescribers to consider before starting an uninfected individual on MINT-EMTRICITABINE/TENOFOVIR for a PrEP indication
- Checklist items include confirming a negative HIV-1 test result, screening for signs or symptoms of acute HIV-1 infection, counselling on safety risks and importance of adherence, and other components to ensure a comprehensive prevention strategy

Additional Educational Materials

Important Safety Information about MINT-EMTRICITABINE/TENOFOVIR for a PrEP Indication for Healthcare Providers

- Brochure for prescribers to use to educate uninfected individuals taking MINT-EMTRICITABINE/TENOFOVIR for a PrEP indication.

Important Safety Information about MINT-EMTRICITABINE/TENOFOVIR to Reduce the Risk of Getting Human Immunodeficiency Virus-1 (HIV-1) Infection for Uninfected Individuals

- Brochure to educate uninfected individuals taking MINT-EMTRICITABINE/TENOFOVIR for a PrEP indication.

Training Guide for Healthcare Providers

- Education for prescribers on important Safety Information about MINT-EMTRICITABINE/TENOFOVIR for a PrEP indication.

Copies are available online at the following website: www.emtricitabine-tenofovir.com

Indication and clinical use

MINT-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. When considering MINT-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 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

Indication and clinical use

When prescribing MINT-EMTRICITABINE/TENOFOVIR for PrEP, healthcare providers must:

- prescribe MINT-EMTRICITABINE/TENOFOVIR as part of a comprehensive prevention strategy because MINT-EMTRICITABINE/TENOFOVIR is not always effective in preventing the acquisition of HIV-1 infection;
- counsel all uninfected individuals to strictly adhere to the recommended MINT-EMTRICITABINE/TENOFOVIR dosing schedule because the effectiveness of MINT-EMTRICITABINE/TENOFOVIR 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 MINT-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 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 taking MINT-EMTRICITABINE/TENOFOVIR for PrEP.

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, EMTRIVA or VIREAD 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.

Contraindications

MINT-EMTRICITABINE/TENOFOVIR is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product.

MINT-EMTRICITABINE/TENOFOVIR is contraindicated for use as PrEP in individuals with unknown or positive HIV- 1 status.

Most 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 MINT-EMTRICITABINE/TENOFOVIR, alone or in combination with other antiretrovirals.

Post-Treatment Exacerbation of Hepatitis: MINT-EMTRICITABINE/TENOFOVIR is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of emtricitabine and tenofovir DF 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. 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 MINT-EMTRICITABINE/TENOFOVIR. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Most 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 MINT-EMTRICITABINE/TENOFOVIR during clinical practice.

Risk of Drug Resistance with Use of MINT-EMTRICITABINE/TENOFOVIR for Pre-Exposure Prophylaxis (PrEP) in Undiagnosed Early HIV-1 Infection: MINT-EMTRICITABINE/TENOFOVIR 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 for a PrEP indication following undetected acute HIV-1 infection. Do not initiate MINT-EMTRICITABINE/TENOFOVIR for a PrEP indication if signs or symptoms of acute HIV infection are present unless negative infection status is confirmed.

Other relevant warnings and precautions

- Fat Redistribution
- 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 MINT-EMTRICITABINE/TENOFOVIR
- Not recommended in pregnant women unless the potential benefit outweighs the potential risks to the fetus
- MINT-EMTRICITABINE/TENOFOVIR should not be administered with HEPSERA® (adefovir dipivoxil)
- Caution when used with HARVONI® particularly in those at risk of renal dysfunction

For More Information

Please consult the product monograph at www.mintpharmaceuticals.com for important information relating to adverse reactions, drug interactions, and dosing information which have not been discussed in this piece.

The product monograph is also available by calling 1-877-398-9696