PRODUCT MONOGRAPH

[Pr]MINT-EMTRICITABINE/TENOFOVIR
Emtricitabine and Tenofovir Tablets
(200 mg/300 mg)

Manufacturer's Standard

Antiretroviral Agent

(emtricitabine/tenofovir disoproxil fumarate)

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PART I. HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablet emtricitabine 200 mg/ tenofovir disoproxil fumarate 300 mg	pregelatinized starch, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, purified water, magnesium stearate. The film coating (Opadry II Blue - 32K505037) contains hypromellose, lactose monohydrate, titanium dioxide, triacetin, FD&C Blue#2.

MINT-EMTRICITABINE/TENOFOVIR tablets are a fixed-dose combination containing emtricitabine and tenofovir disoproxil fumarate (DF).

INDICATIONS AND CLINICAL USE

Treatment of HIV-1 Infection

MINT-EMTRICITABINE/TENOFOVIR is indicated in combination with other antiretroviral agents (such as non- nucleoside reverse transcriptase inhibitors or protease inhibitors) for the treatment of HIV-1 infection in adults.

Additional important information regarding the use of MINT-EMTRICITABINE/TENOFOVIR for the treatment of HIV-1 infection:

- It is not recommended that MINT-EMTRICITABINE/TENOFOVIR be used as a component of a triple nucleoside regimen.

- MINT-EMTRICITABINE/TENOFOVIR should not be coadministered with ATRIPLA® (efavirenz, emtricitabine and tenofovir disoproxil fumarate), COMPLERA® (emtricitabine, rilpivirine and tenofovir disoproxil fumarate), DESCOVY® (emtricitabine and tenofovir alafenamide), EMTRIVA (emtricitabine), GENVOYA® (elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide), ODEFSEY™ (emtricitabine, rilpivirine and tenofovir alafenamide), STRIBILD® (elvitegravir, cobicistat, emtricitabine and tenofovir disoproxil fumarate), VEMLIDY™ (tenofovir alafenamide), or VIREAD (tenofovir disoproxil fumarate) or lamivudine-containing products (see **WARNINGS AND PRECAUTIONS**).

- In treatment-experienced patients, the use of MINT-EMTRICITABINE/TENOFOVIR should be guided by laboratory testing and treatment history (see **VIROLOGY**).

Pre-Exposure Prophylaxis (PrEP) of HIV-1 Infection

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

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 (see **WARNINGS AND PRECAUTIONS**).

- 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 (see **WARNINGS AND PRECAUTIONS**).

- 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 (see **WARNINGS AND PRECAUTIONS**); and

- screen for HIV-1 infection at least once every 3 months while taking MINT-EMTRICITABINE/TENOFOVIR for PrEP.

Additional training and educational materials for healthcare professionals and consumers on MINT-EMTRICITABINE/TENOFOVIR for PrEP are accessible on the MINT-EMTRICITABINE/TENOFOVIR website (www.emtricitabine-tenofovir.com).

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 (see **CLINICAL TRIALS**).

Geriatrics (>65 years of age)

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

Pediatrics (<18 years of age)

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. For a complete listing, see the **DOSAGE FORMS**, **COMPOSITION AND PACKAGING** section of the Product Monograph.

MINT-EMTRICITABINE/TENOFOVIR is contraindicated for use as PrEP in individuals with unknown or positive 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 DF, a component of MINT-EMTRICITABINE/ TENOFOVIR, alone or in combination with other antiretrovirals (see **WARNINGS AND PRECAUTIONS**).

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

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 (see **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 emtricitabine and tenofovir DF during clinical practice (see **WARNINGS AND PRECAUTIONS**).

- **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 (see **WARNINGS AND PRECAUTIONS**).

General

MINT-EMTRICITABINE/TENOFOVIR should be used in the treatment of HIV-1 infected patients only in combination with other antiretroviral agents.

MINT-EMTRICITABINE/TENOFOVIR is a fixed-dose combination of emtricitabine and tenofovir DF. MINT-EMTRICITABINE/TENOFOVIR should not be coadministered with other products containing tenofovir DF or emtricitabine (ATRIPLA, COMPLERA, DESCOVY, EMTRIVA, GENVOYA, ODEFSEY, STRIBILD, or VIREAD), or with medicinal products containing tenofovir alafenamide (DESCOVY, GENVOYA, ODEFSEY, and VEMLIDY). Due to similarities between emtricitabine and lamivudine, MINT-EMTRICITABINE/TENOFOVIR should not be coadministered with other drugs containing lamivudine (Combivir®, 3TC®, Heptovir®, Kivexa®, Triumeq®, or Trizivir®).

MINT-EMTRICITABINE/TENOFOVIR should not be administered with adefovir dipivoxil (HEPSERA®).

Clinical studies in HIV-infected patients have demonstrated that certain regimens that only contain three nucleoside reverse transcriptase inhibitors (NRTI) are generally less effective than triple drug regimens containing two NRTIs in combination with either a non-nucleoside reverse transcriptase inhibitor or a HIV-1 protease inhibitor. In particular, early virological failure and high rates of resistance mutations have been reported. Triple nucleoside regimens should therefore be used with caution. Patients on a therapy utilizing a triple nucleoside-only regimen should be carefully monitored and considered for treatment modification.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Emtricitabine: In long-term oral carcinogenicity studies of emtricitabine, no drug-related increase in tumor incidence was 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).

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

Emtricitabine 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 DF: Tenofovir DF did not show any carcinogenic potential in a long-term oral carcinogenicity study in rats. A long-term oral carcinogenicity study in mice showed a low incidence of duodenal tumors, considered likely related to high local concentrations in the gastrointestinal tract at the high dose of 600 mg/kg/day. Liver adenomas were also seen at the high dose in female mice. The mechanism of tumor formation in mice and potential relevance for humans are uncertain.

Tenofovir DF 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, tenofovir DF was negative at doses up to 2000 mg/kg when administered orally to male mice.

There were no effects on fertility, mating performance or early embryonic development when tenofovir DF was administered at 600 mg/kg/day to male rats for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats. A dose of 600 mg/kg/day is equivalent to 19 times the human dose based on body surface area comparisons.

Drug Interactions

Use with Certain HCV Regimens

Tenofovir exposure is increased when MINT-EMTRICITABINE/TENOFOVIR is coadministered with HARVONI® (ledipasvir/sofosbuvir), EPCLUSA® (sofosbuvir/velpatasvir), or VOSEVI™ (sofosbuvir/velpatasvir/voxilaprevir). Patients receiving MINT-EMTRICITABINE/TENOFOVIR concomitantly with HARVONI, EPCLUSA or VOSEVI,

particularly those at increased risk for renal dysfunction, should be monitored for tenofovir DF-associated adverse reactions (see **DRUG INTERACTIONS**).

Use with Didanosine

Pharmacokinetic studies have shown that coadministration of didanosine and tenofovir DF results in 40-60% increase in C_{max} and AUC of didanosine (see Table 8). The mechanism of this interaction is unknown. Increases in didanosine concentrations of this magnitude could potentiate didanosine-associated adverse events, including pancreatitis, lactic acidosis, and neuropathy. In addition, suppression of CD4 counts has been observed in patients receiving tenofovir DF with didanosine at a dose of 400 mg daily (see **DRUG INTERACTIONS**).

Endocrine and Metabolism

Serum Lipids and Blood Glucose

Serum lipid and blood glucose levels may increase during antiretroviral therapy. Disease control and lifestyle 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.

Hepatic/Biliary/Pancreatic

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogs, including tenofovir DF, a component of MINT-EMTRICITABINE/TENOFOVIR, alone or in combination with other antiretrovirals in the treatment of HIV infection. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with MINT-EMTRICITABINE/TENOFOVIR should be suspended in any patient 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).

Hepatic Impairment

Tenofovir and tenofovir disoproxil are not metabolized by liver enzymes. Clinically relevant pharmacokinetic changes in patients with hepatic impairment are not observed. Therefore, no dose adjustment is required in patients with hepatic impairment. Emtricitabine has not been evaluated in patients with hepatic impairment; however, emtricitabine has not been shown to be metabolized by liver enzymes, so the impact of liver impairment is likely to be limited. The safety and efficacy of emtricitabine and tenofovir DF has not been established or specifically studied in patients with underlying liver disorders.

Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy

for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Hepatitis B Virus Infection

It is recommended that all patients be tested for the presence of hepatitis B virus (HBV) before initiating MINT-EMTRICITABINE/TENOFOVIR. MINT-EMTRICITABINE/TENOFOVIR is not approved for the treatment of chronic HBV infection and the safety and efficacy of emtricitabine and tenofovir DF tablets have not been established in patients infected with HBV. Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HBV and HIV after the discontinuation of emtricitabine and tenofovir DF tablets. In some patients infected with HBV and treated with emtricitabine, the exacerbations of hepatitis B were associated with liver decompensation and liver failure. Hepatic function should be closely monitored 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. In patients with advanced liver disease or cirrhosis, post-treatment exacerbation of hepatitis may lead to hepatic decompensation. Therefore, in these patients, discontinuation of treatment without initiation of alternative anti-hepatitis B therapy is not recommended.

Pancreatitis

Pancreatitis has occurred during therapy with combination regimens that included tenofovir DF. Caution should be used when administering nucleoside analogues (including MINT-EMTRICITABINE/TENOFOVIR) to patients with a history of pancreatitis or risk factors for the development of pancreatitis. Therapy should be suspended in patients with suspected pancreatitis.

Immune

Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome has been reported in HIV-1 infected patients treated with combination antiretroviral therapy, including the components of MINT-EMTRICITABINE/TENOFOVIR. During the initial phase of combination antiretroviral treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infections, cytomegalovirus, *Pneumocystis jiroveci* pneumonia (PCP), and tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the reported time to onset is more variable, and these events can occur many months after initiation of treatment.

Musculoskeletal

Bone Effects

Bone Mineral Density

In a clinical trial in treatment-naive HIV-1 infected adults through 144 weeks, decreases from baseline in bone mineral density (BMD) were seen at the lumbar spine and hip in both tenofovir DF and stavudine treatment arms of the study; significantly greater decreases were seen in the lumbar spine measurement in the tenofovir DF group relative to the stavudine group. Clinically relevant fractures were reported in both treatment groups. Increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide) were observed, suggesting increased bone turnover. Except for bone specific alkaline phosphatase, these changes resulted in values that remained within the normal range. These decreases in BMD and increases in biochemical markers of bone metabolism were also seen in the PrEP trials in HIV-1 uninfected individuals. The effects of tenofovir DF-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 patients who have a history of pathologic bone fracture or are at risk for osteopenia or osteoporosis. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial. If bone abnormalities are suspected then appropriate consultation should be obtained.

Mineralization Defects

Cases of hypophosphatemic osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in the extremities and which may contribute to fractures, have been reported in association with the use of tenofovir DF (see **ADVERSE REACTIONS, Post Market Adverse Drug Reactions**). Arthralgias 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 products containing tenofovir DF. Serum phosphate should be monitored in these patients.

Renal

Nephrotoxicity

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 in association with the use of tenofovir DF in clinical practice. The majority of these cases occurred in patients with underlying systemic or renal

disease, or in patients taking nephrotoxic agents; however, some cases occurred in patients without identified risk factors. 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. It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with MINT-EMTRICITABINE/TENOFOVIR. 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 of MINT-EMTRICITABINE/TENOFOVIR, and periodically during MINT-EMTRICITABINE/TENOFOVIR therapy (see **ADVERSE REACTIONS, Post Market Adverse Drug Reactions and DRUG INTERACTIONS**).

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 MINT-EMTRICITABINE/TENOFOVIR, 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 MINT-EMTRICITABINE/TENOFOVIR 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 MINT-EMTRICITABINE/TENOFOVIR should also be considered in case of progressive decline of renal function when no other cause has been identified (see **ADVERSE REACTIONS**).

MINT-EMTRICITABINE/TENOFOVIR should be avoided with concurrent or recent use of a nephrotoxic agent [eg, cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir, aminoglycosides, high-dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs)]. 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 DF. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction (see **DRUG INTERACTIONS**).

Renal Impairment

Treatment of HIV-1 infection

Dosing interval adjustment of MINT-EMTRICITABINE/TENOFOVIR 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 using these guidelines, and so the potential benefit of MINT-EMTRICITABINE/TENOFOVIR should be assessed against the potential risk of renal toxicity. MINT-EMTRICITABINE/TENOFOVIR should not be administered to patients with creatinine clearance <30 mL/min or patients requiring hemodialysis (see **DOSAGE AND ADMINISTRATION**).

Pre-exposure Prophylaxis of HIV-1 infection

MINT-EMTRICITABINE/TENOFOVIR for a PrEP indication should not be used in HIV-1

uninfected individuals with creatinine clearance below 60 mL/min.

If a decrease in creatinine clearance is observed in uninfected individuals while using MINT-EMTRICITABINE/TENOFOVIR for PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use (see **DOSAGE AND ADMINISTRATION**).

Special Populations

Pregnant Women

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to ART (antiretroviral therapy) including MINT-EMTRICITABINE/TENOFOVIR, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 800-258-4263.

Emtricitabine and tenofovir DF has been evaluated in a limited number of women during pregnancy and postpartum. Available human and animal data suggest that emtricitabine and tenofovir DF does not increase the risk of major birth defects overall compared to the background rate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, MINT-EMTRICITABINE/TENOFOVIR 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 MINT-EMTRICITABINE/TENOFOVIR for a PrEP indication, careful consideration should be given to whether use of MINT-EMTRICITABINE/TENOFOVIR should be continued, taking into account the potential increased risk of HIV-1 infection during pregnancy.

As of July 2015, the APR has received prospective reports of 1984 and 2608 exposures to emtricitabine- and tenofovir-containing regimens, respectively in the first trimester: and 949 and 1258 exposures, respectively, in second/third trimester, respectively. Birth defects

occurred in 47 of 1984 (2.4%) live births for emtricitabine-containing regimens and 60 of 2608 (2.3%) live births for tenofovir-containing regimens (first trimester exposure); and 20 of 949 (2.1%) live births for emtricitabine-containing regimens and 26 of 1258 (2.1%) live

births for tenofovir containing regimens (second/third trimester exposure). Among pregnant women in the U.S. reference population, the background rate of birth defects is 2.7%. There was no association between emtricitabine or tenofovir and overall birth defects observed in the APR.

Emtricitabine: The incidence of fetal variations and malformations was not increased in embryo-fetal toxicity studies performed with emtricitabine in mice at exposures (AUC) approximately 60-fold higher and in rabbits at approximately 120-fold higher than human exposures at the recommended daily dose.

Tenofovir DF: Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir. Reduced pup body weights, survival and delay in sexual maturation was observed in a peri- and postnatal toxicity study in rats at the

maternally toxic doses of 450 and 600 mg/kg (approximately 14 and 19 times the human dose based on body surface area comparisons).

Nursing Women

HIV-infected mothers should not breastfeed their infants to avoid risking postnatal transmission of HIV to the infant.

In humans, samples of breast milk obtained from five HIV-1 infected mothers show that tenofovir is secreted in human milk at low levels (estimated neonatal concentrations 128 to 266 times lower than the tenofovir IC_{50}). Tenofovir-associated risks, including the risk of developing viral resistance to tenofovir, in infants breastfed by mothers being treated with tenofovir DF are unknown.

Samples of breast milk obtained from five HIV-1 infected mothers show that emtricitabine is secreted in human milk at estimated neonatal concentrations 3 to 12 times higher than the emtricitabine IC_{50} but 3 to 12 times lower than the C_{min} achieved from oral administration of emtricitabine. Breast-feeding infants whose mothers are being treated with emtricitabine may be at risk for developing viral resistance to emtricitabine. Other emtricitabine-associated risks in infants breastfed by mothers being treated with emtricitabine are unknown.

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 MINT-EMTRICITABINE/TENOFOVIR**, whether they are taking MINT-EMTRICITABINE/TENOFOVIR for treatment or to reduce the risk of acquiring HIV-1.

Pediatrics (<18 years of age)

Safety and effectiveness in pediatric patients have not been established.

Geriatrics (>65 years of age)

Clinical studies of emtricitabine or tenofovir DF 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.

PrEP to Reduce the Risk of Acquiring HIV-1 Infection

Comprehensive HIV-1 Infection Prevention Strategy

Use 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 is not always effective in preventing the acquisition of HIV-1 (see **CLINICAL TRIALS**).

- 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.

Risk of Resistance

Use 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 treatment regimen for HIV-1 treatment**; therefore, care should be taken to minimize drug exposure in HIV-infected individuals (see **VIROLOGY: Resistance**).

- 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 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.

- 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 MINT-EMTRICITABINE/TENOFOVIR 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 MINT-EMTRICITABINE/TENOFOVIR dosing schedule. The effectiveness of MINT-EMTRICITABINE/TENOFOVIR in reducing the risk of acquiring HIV- 1 is strongly correlated with adherence as demonstrated by measurable drug levels in clinical trials (see **CLINICAL TRIALS).**

Additional training and educational materials for healthcare professionals and consumers on MINT-EMTRICITABINE/TENOFOVIR for PrEP are accessible on the MINT-EMTRICITABINE/TENOFOVIR website (www.emtricitabine-tenofovir.com).

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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

Emtricitabine and tenofovir DF tablets: Four hundred and forty-seven HIV-1 infected patients have received combination therapy with emtricitabine or tenofovir DF with either a non-nucleoside reverse transcriptase inhibitor or protease inhibitor for 48 weeks in ongoing clinical studies. Study 934 - Treatment Emergent Adverse Events: Assessment of adverse reactions is based on data from Study 934 in which 511 antiretroviral-naïve patients received either emtricitabine + tenofovir DF administered in combination with efavirenz (N=257) or Combivir® (lamivudine/zidovudine) administered in combination with efavirenz (N=254). Adverse events observed in this study were generally consistent with those seen in other studies in treatment experienced or treatment-naïve patients (Table 1).

Table 1. Selected Treatment-Emergent Adverse Events (Grades 2–4) Reported in ≥3% in Any Treatment Group in Study 934 (0–48 Weeks)

	Emtricitabine +Tenofovir disoproxil fumarate + EFV	AZT/3TC+EFV
	N=257	N=254
Blood and Lymphatic System Disorders		
Anemia	<1%	5%
Gastrointestinal Disorder		
Diarrhea	7%	4%
Nausea	8%	6%
Vomiting	1%	4%
General Disorders and Administration Site Condition		
Fatigue	7%	6%
Infections and Infestations		
Sinusitis	4%	2%
Upper respiratory tract infections	3%	3%
Nasopharyngitis	3%	1%
Nervous System Disorders		
Somnolence	3%	2%
Headache	5%	4%
Dizziness	8%	7%
Psychiatric Disorders		
Depression	4%	7%
Insomnia	4%	5%
Abnormal dreams	4%	3%
Skin and Subcutaneous Tissue Disorders		
Rash	5%	4%

Patients who received treatment up to 144 weeks in Study 934 reported adverse events similar in nature and severity to those reported in the first 48 weeks.

Through 48 weeks, 7 patients in the emtricitabine + tenofovir DF group and 5 patients in the lamivudine/zidovudine group experienced a new CDC Class C event (10 and 6 patients, respectively, through 144 weeks). Renal safety assessed by laboratory abnormalities was similar in the two groups and no patient discontinued study drug due to renal events.

At Weeks 48 and 144, total limb fat (as measured by dual-energy x-ray absorptiometry) was significantly less in a subgroup of patients in the lamivudine/zidovudine group compared to the tenofovir/emtricitabine subgroup (see Table 2).

Table 2. Study 934 Total Limb Fat at Week 48 and 144 (Dual-Energy X-Ray Absorptiometry)

	Emtricitabine + Tenofovir disoproxil fumarate + EFV	AZT/3TC +EFV
Week 48[1]	**N=51**	**N=49**
Total Limb Fat (kg) (Mean ± S.D.)	8.9 ±5.4	6.9 ±3.9
Week 144[2]	**N=145**	**N=124**
Total Limb Fat (kg) (Mean ± S.D.)	9.2 ±5.4	6.5 ±4.3

[1]P=0.03 for the comparison between arms

[2]P<0.001 for the comparison between arms

Laboratory Abnormalities: Laboratory Abnormalities observed in this study were generally consistent with those seen in other studies (Table 3).

Table 3. Grade 3/4 Laboratory Abnormalities Reported in ≥1% in Any Treatment Group in Study 934 (0–48 Weeks)

	Emtricitabine + Tenofovir disoproxil fumarate +EFV N=257	AZT/3TC+EFV N=254
Any ≥ Grade 3 Laboratory Abnormality	25%	22%
Fasting Cholesterol (>240 mg/dL)	15%	17%
Creatine Kinase (M: >990 U/L) (F: >845 U/L)	7%	6%
Serum Amylase (>175U/L)	7%	3%
Alkaline Phosphatase (>550 U/L)	1%	0%
AST (M: >180 U/L) (F: >170 U/L)	3%	2%
ALT (M: >215 U/L) (F: >170 U/L)	2%	2%

	Emtricitabine + Tenofovir disoproxil fumarate +EFV N=257	AZT/3TC+EFV N=254
Hemoglobin (<8.0 mg/dL)	0%	3%
Hyperglycemia (>250 mg/dl)	1%	1%
Hematuria (>75 RBC/HPF)	2%	2%
Neutrophil (>750/mm^3)	3%	4%
Fasting Triglycerides (>750 mg/dL)	4%	2%

Laboratory abnormalities in patients who received treatment up to 144 weeks in Study 934 were consistent with those observed in the first 48 weeks of treatment.

In addition to the events described above for Study 934, other adverse events that occurred in at least 3-5% of patients receiving emtricitabine or tenofovir DF with other antiretroviral agents in clinical trials include: anorexia, anxiety, arthralgia, asthenia, increased cough, depressive disorders, dyspepsia, fever, flatulence, myalgia, pain, abdominal pain, back pain, chest pain, paresthesia, peripheral neuropathy (including peripheral neuritis and neuropathy), pneumonia, rhinitis and rash event (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash and allergic reaction), sweating and weight loss.

Skin discoloration has been reported with higher frequency among emtricitabine treated patients. Skin discoloration mainly manifested by hyperpigmentation on the palms and/or soles was generally mild and asymptomatic and of little clinical significance. The mechanism is unknown.

In addition to the laboratory abnormalities described above for Study 934, Grade 3/4 elevations of bilirubin (>2.5 x ULN), pancreatic amylase (>2.0 x ULN), serum glucose (<40 or >250 mg/dL), serum lipase (>2.0 x ULN), and urine glucose (≥3+) occurred in up to 3% of patients treated with emtricitabine or tenofovir DF with other antiretroviral agents in clinical trials.

For more information, please consult the emtricitabine and tenofovir DF Product Monographs.

In Study 903 through 144 weeks, decreases from baseline in bone mineral density (BMD) were seen at the lumbar spine and hip in both arms of the study. At Week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in patients in the tenofovir DF group compared with patients in the stavudine group (see Table 4). In both groups, the majority of the reduction in BMD occurred in the first 24–48 weeks of the study and this reduction was sustained through Week 144. Twenty-eight percent of tenofovir DF-treated patients vs. 21% of the stavudine-treated patients lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 patients in the tenofovir DF group and 6 patients in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide) in the tenofovir DF group relative to the stavudine group, suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in the tenofovir DF group. Except for

bone specific alkaline phosphatase, these changes resulted in values that remained within the normal range. The effects of tenofovir DF-associated changes in BMD and biochemical markers on long- term bone health and future fracture risk are unknown.

Table 4 Changes in Bone Mineral Density Study 903

	Mean Percent Change (±SD) to Week 144 in BMD	
	Tenofovir DF + 3TC+ EFV	**d4T + 3TC +EFV**
Lumbar Spine	–2.2% ± 3.9	–1.0% ± 4.6
Hip	–2.8% ± 3.5	–2.4% ± 4.5

Adverse Reactions from Clinical Trials Experience in HIV-1 Uninfected Adult Subjects (PrEP)

No new adverse reactions to emtricitabine and tenofovir DF were identified from two randomized placebo- controlled clinical trials (iPrEx, Partners PrEP) in which 2830 HIV-1 uninfected adults received emtricitabine and tenofovir DF tablets once daily for pre-exposure prophylaxis. Subjects were followed for a median of 71 weeks and 87 weeks, respectively. These trials enrolled HIV-negative individuals ranging in age from 18 to 67 years. The iPrEx trial enrolled only men or transgender women of Hispanic/Latino (72%), White (18%), Black (9%) and Asian (5%) race. The Partners PrEP trial enrolled both men (61−64% across treatment groups) and women in Kenya and Uganda. Table 5 provides a list of all adverse events that occurred ≥2% of subjects 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%	-	-
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%	-	-

a. Not reported or reported below 2%.

Laboratory Abnormalities: Table 6 provides a list of laboratory abnormalities observed in both PrEP trials. Six subjects in the TDF-containing arms of the Partners PrEP trial discontinued participation in the study due to an increase in blood creatinine compared with no discontinuations in the placebo group. One subject in the emtricitabine and tenofovir DF arm of the iPrEx trial discontinued from the study due to an increase in blood creatinine and another due to low phosphorus.

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

	Grade[b]	iPrEx Trial		Partners PrEP Trial	
		FTC/TDF N=1251	Placebo N=1248	FTC/TDF N=1579	Placebo N=1584
Creatinine	1 (1.1-1.3 X ULN)	27 (2%)	21 (2%)	18 (1%)	12 (<1%)
	2-4 (> 1.4 x ULN)	5 (<1%)	3 (<1%)	2 (<1%)	1 (<1%)
Phosphorus	1 (2.5 - <LLN mg/dL)	81 (7%)	110 (9%)	NR[a]	NR[a]
	2-4 (<2.0 mg/dL)	123 (10%)	101 (8%)	140 (9%)	136 (9%)
AST	1 (1.25-<2.5 x ULN)	175 (14%)	175 (14%)	20 (1%)	25 (2%)
	2-4 (> 2.6 x ULN)	57 (5%)	61 (5%)	10 (<1%)	4 (<1%)
ALT	1 (1.25-<2.5 x ULN)	178 (14%)	194 (16%)	21 (1%)	13 (<1%)
	2-4 (> 2.6 x ULN)	84 (7%)	82 (7%)	4 (<1%)	6 (<1%)
Hemoglobin	1 (8.5 - 10 mg/dL)	49 (4%)	62 (5%)	56 (4%)	39 (2%)
	2-4 (<9.4 mg/dL)	13 (1%)	19 (2%)	28 (2%)	39 (2%)
Neutrophils	1 (1000-1300/mm^3)	23 (2%)	25 (2%)	208 (13%)	163 (10%)
	2-4 (<750/mm^3)	7 (<1%)	7 (<1%)	73 (5%)	56 (3%)

a. Grade 1 phosphorus was not reported for the Partners PrEP trial.
b. Grading is per DAIDS criteria.

In addition to the laboratory abnormalities described above, Grade 1 proteinuria (1+) occurred in 6% of subjects receiving emtricitabine and tenofovir DF in the iPrEx trial. Grade 2-3 proteinuria (2-4+) and glycosuria (3+) occurred in less than 1% of subjects treated with emtricitabine and tenofovir DF in the iPrEx trial and Partners PrEP trial.

In clinical trials of HIV-1 uninfected individuals, decreases in BMD were observed. In the iPrEx trial, a sub study 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 emtricitabine and tenofovir DF group compared with the placebo group, which returned toward baseline after discontinuation of treatment. Thirteen percent of subjects receiving emtricitabine and tenofovir DF vs. 6% of subjects receiving placebo lost at least 5% of BMD at the spine during treatment. Bone fractures were reported in 1.7% of the emtricitabine and tenofovir DF group compared with 1.4% in the placebo group. No correlation between BMD and fractures was noted. The Partners PrEP trial found similar fracture rates between treatment and placebo groups (0.8% and 0.6%, respectively). No BMD evaluations were conducted during this trial (see **CLINICAL TRIALS**).

Post Market Adverse Drug Reactions

Emtricitabine: The following adverse experiences have been reported in post-marketing experience without regard to causality. Because these events are voluntarily reported from a population of unknown size, estimates of frequency cannot be made. These events have been considered possible adverse reactions due to a combination of their seriousness, frequency of reporting or potential causal relationship with treatment.

Blood and lymphatic system disorders:	Thrombocytopenia
Gastrointestinal disorders:	Pancreatitis
General disorders and administrative site conditions:	Pyrexia
Metabolism and nutrition disorders:	Lactic acidosis

Tenofovir DF: The following adverse reactions have been identified during post-approval use of tenofovir DF. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been considered possible adverse reactions due to a combination of their seriousness, frequency of reporting or potential causal relationship with tenofovir DF.

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
Blood and lymphatic system disorders:	Thrombocytopenia
Hepatobiliary disorders:	Hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT, GGT)
Skin and Subcutaneous Tissue Disorders:	Rash
Musculoskeletal and Connective Tissue Disorders:	Rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing 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 (manifested as bone pain and infrequently contributing to fractures), hypokalemia, muscular weakness, myopathy, hypophosphatemia.

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.

Emtricitabine and Tenofovir DF: In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy an inflammatory reaction to infectious pathogens (active or inactive) may arise **(**see **WARNINGS AND PRECAUTIONS)**.

In HIV infected patients coinfected with HBV, clinical and laboratory evidence of exacerbations of hepatitis has occurred after discontinuation of treatment (see **WARNINGS AND PRECAUTIONS**).

DRUG INTERACTIONS

Overview

Drug interaction studies have been conducted with either emtricitabine and tenofovir DF tablets, or the components of emtricitabine and tenofovir DF as individual agents and/or in combination.

The steady state pharmacokinetics of emtricitabine and tenofovir were unaffected when emtricitabine and tenofovir DF were administered together versus each agent dosed alone (see Table 9 and Table 10).

In vitro and clinical pharmacokinetic drug-drug interaction studies have shown that the potential for CYP450 mediated interactions involving emtricitabine and tenofovir with other medicinal products is low.

Drug-Drug Interactions

Established and Other Potentially Significant Drug Interactions

The drug interactions described are based on studies conducted with the individual agents of emtricitabine and tenofovir DF and/or in combination or are potential drug interactions that may occur with MINT-EMTRICITABINE/TENOFOVIR.

Table 7. Established and Other Potentially Significant[a] Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Antiretroviral Agents:		
Didanosine	↑ didanosine	Pharmacokinetic studies have shown that coadministration of didanosine and tenofovir DF results in 40-60% increase in C_{max} and AUC of didanosine (see Table 8). The mechanism of this interaction is unknown. **Increases in didanosine concentrations of this magnitude could potentiate didanosine-associated adverse events, including pancreatitis, lactic acidosis, and neuropathy.** In addition, suppression of CD4 counts has been observed in patients receiving tenofovir DF with didanosine at a dose of 400 mg daily. A reduced dose of Videx EC® (ddI-EC) is recommended when coadministered with MINT-EMTRICITABINE/TENOFOVIR. When coadministered with MINT-EMTRICITABINE/ TENOFOVIR, the Videx EC® Product Monograph recommends a reduced dose of 250 mg ddI-EC for HIV infected adults with body weight ≥60 kg and creatinine clearance ≥60 mL/min. For patients with body weight <60 kg, and creatinine clearance ≥60 mL/min, the recommended dose of ddI-EC is 200 mg. Data are not available to recommend a dose adjustment for patients with creatinine clearance <60mL/min or for the buffered tablet formulation of didanosine (Videx®). Caution should be used when coadministering reduced-dose didanosine, tenofovir, and an NNRTI in treatment-naïve patients with high viral loads at baseline since such use has been associated with reports of a high rate of virologic failure and emergence of resistance at an early stage. All patients receiving tenofovir DF and didanosine concomitantly should be closely monitored for didanosine-related adverse events and clinical response.
Atazanavir/ritonavir Darunavir/ritonavir Lopinavir/ritonavir	↑ tenofovir	Atazanavir/ritonavir, darunavir/ritonavir and lopinavir/ritonavir have been shown to increase tenofovir concentrations (see Table 11). The mechanism of this interaction is unknown. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders. Patients receiving atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir and MINT-EMTRICITABINE/TENOFOVIR should be monitored for MINT-EMTRICITABINE/TENOFOVIR-associated adverse events.
Atazanavir	↓ atazanavir	Tenofovir decreases atazanavir concentrations (see Table 12). Although safety and efficacy data are limited, it is recommended that atazanavir, without ritonavir, should not be coadministered with MINT-EMTRICITABINE/TENOFOVIR. The recommended regimen is atazanavir 300 mg given with ritonavir 100 mg when used in combination with MINT-EMTRICITABINE/TENOFOVIR (all as a single daily dose with food).

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Hepatitis C Virus Antiviral Agents:		
Ledipasvir/sofosbuvir Sofosbuvir/velpatasvir Sofosbuvir/velpatasvir/ voxilaprevir	↑ tenofovir	Coadministration of tenofovir DF and HARVONI (ledipasvir/sofosbuvir), EPCLUSA (sofosbuvir/velpatasvir), or VOSEVI (sofosbuvir/velpatasvir/voxilaprevir) has been shown to increase tenofovir exposure (see Table 11). Patients receiving a regimen containing tenofovir DF concomitantly with HARVONI, EPCLUSA, or VOSEVI should be monitored for adverse reactions associated with tenofovir DF (see **WARNINGS AND PRECAUTIONS, Drug Interactions**).

a This table is not all inclusive.
b ↑ = increase, ↓ = decrease

Drugs Affecting Renal Function

Emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No drug-drug interactions due to competition for renal excretion have been observed. Since emtricitabine and tenofovir are primarily eliminated by the kidneys, coadministration of MINT-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. Some examples include, but are not limited to cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir, aminoglycosides and high-dose or multiple NSAIDs.

MINT-EMTRICITABINE/TENOFOVIR should not be administered with HEPSERA (adefovir dipivoxil) (see **WARNINGS AND PRECAUTIONS, General**).

Drugs without Clinically Significant Interactions with MINT-EMTRICITABINE/ TENOFOVIR

No clinically significant drug interactions have been observed between emtricitabine and famciclovir, indinavir, zidovudine, stavudine, tenofovir DF, sofosbuvir, edipasvir/sofosbuvir, sofosbuvir/velpatasvir, and sofosbuvir/velpatasvir/voxilaprevir (see Table 9 and Table 10). Similarly, no clinically significant drug interactions have been observed between tenofovir DF and abacavir, efavirenz, emtricitabine, entecavir, indinavir, lamivudine, methadone, nelfinavir, oral contraceptives, ribavirin, saquinavir/ritonavir, sofosbuvir and tacrolimus in studies conducted in healthy volunteers (see Table 11 and Table 12).

Assessment of Drug Interactions

Drug-drug interaction studies were conducted with either emtricitabine and tenofovir DF, or the components of emtricitabine or tenofovir DF as individual agents and/or in combination.

The effects of didanosine in the presence of tenofovir are shown in Table 8.

The effects of coadministered drugs on the exposure of emtricitabine are shown in Table 9. The effects of emtricitabine on the exposure of coadministered drugs are shown in Table 10.

The effects of coadministered drugs on the exposure of tenofovir DF are shown in Table 11. The effects of tenofovir DF on the exposure of coadministered drugs are shown in Table 12

Table 8 Drug Interactions: Pharmacokinetic Parameters for Didanosine in the Presence of Tenofovir

Didanosine[1] Dose (mg)/ Method of Administration2	Tenofovir Method of Administration[2]	N	% Difference (90% CI) vs. Didanosine 400 mg Alone, Fasted[3]	
			C_{max}	AUC
Buffered tablets				
400 once daily[4] × 7 days	Fasted 1 hour after didanosine	14	↑ 27 (↑ 8 to ↑ 46)	↑ 43 (↑ 30 to ↑ 57)
Enteric coated capsules				
400 once, fasted	With food, 2 hr after didanosine	26	↑ 48 (↑ 25 to ↑ 76)	↑ 48 (↑ 31 to ↑ 67)
400 once, with food	Simultaneously with didanosine	26	↑ 64 (↑ 41 to ↑ 89)	↑ 60 (↑ 44 to ↑ 79)
250 once, fasted	With food, 2 hr after didanosine	28	↓ 10 (↓ 22 to ↑ 3)	0 (↓ 11 to ↑ 12)
250 once, fasted	Simultaneously with didanosine	28	↓ 8 (↓ 19 to ↑ 5)	↑ 14 (0 to ↑ 31)
250 once, with food	Simultaneously with didanosine	28	↓ 29 (↓ 39 to ↓ 18)	↓ 11 (↓ 23 to ↑ 2)

1. See **PRECAUTIONS** regarding use of didanosine with tenofovir DF.
2. Administration with food was with a light meal (~373 kcal, 20% fat).
3. Increase = ↑; Decrease = ↓
4. Includes 4 subjects weighing <60 kg receiving ddI 250 mg.

Table 9 Drug Interactions: Changes in Pharmacokinetic Parameters for Emtricitabine in the Presence of the Coadministered Drug[1]

Coadministered Drug	Dose of Coadministered Drug (mg)	Emtricitabine Dose (mg)	N	% Change of Emtricitabine Pharmacokinetic Parameters [2] (90% CI)		
				C_{max}	AUC	C_{min}
Tenofovir DF	300 once daily × 7 days	200 once daily × 7 days	17	↓ 4 (↓ 13 to ↑ 6)	↑ 7 (0 to ↑4)	↑ 20 (↑ 12 to ↑ 29)
Zidovudine	300 twice daily × 7 days	200 once daily × 7 days	27	↓ 3 (↓ 10 to ↑ 4)	↓ 3 (↓ 7 to ↑ 1)	↓ 4 (↓ 12 to ↑ 4)
Indinavir	800 × 1	200 × 1	12	↓ 8 (↓ 18 to ↑ 4)	↑ 1 (↓ 6 to ↑ 9)	NC
Famciclovir	500 × 1	200 × 1	12	↓ 10 (↓ 20 to ↑ 1)	↓ 8 (↓ 14 to ↓ 1)	NC
Stavudine	40 × 1	200 × 1	6	↑ 4 (↓ 6 to ↑ 16)	↑ 2 (↓ 6 to ↑ 11)	NC

1. All interaction studies conducted in healthy volunteers.
2. ↑ = Increase; ↓ = Decrease; NC= Not Calculated

Table 10 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Emtricitabine[1]

Coadministered Drug	Dose of Coadministered Drug (mg)	Emtricitabine Dose (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters [2] (90% CI)		
				C_{max}	AUC	C_{min}
Tenofovir DF	300 once daily × 7 days	200 once daily × 7 days	17	↑ 3 (↓ 5 to ↑ 11)	0 (↓ 8 to ↑ 9)	↑ 2 (↓ 8 to ↑ 13)
Zidovudine	300 twice daily × 7 days	200 once daily × 7 days	27	↑ 17 (0 to ↑ 38)	↑ 13 (↑ 5 to ↑ 20)	↓ 2 (↓ 11 to ↑ 9)
Indinavir	800 × 1	200 × 1	12	↓ 2 (↓ 16 to ↑ 13)	↑ 2 (↓ 11 to ↑ 17)	NC
Famciclovir	500 × 1	200 × 1	12	↓ 7 (↓ 22 to ↑ 11)	↓ 9 (↓ 17 to ↓ 1)	NC
Stavudine	40 × 1	200 × 1	6	↑ 5 (↓ 5 to ↑ 16)	↑ 9 (↓ 17 to ↑ 44)	NC

1. All interaction studies conducted in healthy volunteers.
2. ↑ = Increase; ↓ = Decrease; NC=Not Calculated

Table 11 Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir[1] in the Presence of the Coadministered Drug

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters[2] (90% CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 single dose	8	↓ 8 (↓ 24 to ↑ 12)	↑ 4 (↓ 14 to ↑ 26)	NC
Atazanavir[3]	400 once daily × 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Atazanavir/ Ritonavir[3]	300/100 once daily	12	↑ 34 (↑ 20 to ↑ 51)	↑ 37 (↑ 30 to ↑ 45)	↑ 29 (↑ 21 to ↑ 36)
Darunavir/ Ritonavir[4]	300/100 twice daily	12	↑ 24 (↑ 8 to ↑ 42)	↑ 22 (↑ 10 to ↑ 35)	↑ 37 (↑ 19 to ↑ 57)
Didanosine (enteric-coated)	400 single dose	25	↓ 2 (↓ 7 to ↑ 4)	↑ 2 (↓ 2 to ↑ 5)	NC
Didanosine (buffered)	250 or 400 once daily × 7 days[5]	14	↑ 1 (↓ 12 to ↑ 14)	↓ 5 (↓ 14 to ↑ 4)	↓ 22 (↓ 36 to ↓ 7)
Efavirenz	600 once daily × 14 days	29	↑ 7 (↓ 4 to ↑ 17)	↓ 2 (↓ 8 to ↑ 3)	↑ 2 (↓ 9 to ↑ 12)
Emtricitabine	200 once daily × 7 days	17	↑ 3 (↓ 5 to ↑ 11)	0 (↓ 8 to ↑ 9)	↑ 2 (↓ 8 to ↑ 13)
Entecavir	1 mg once daily × 10 days	28	NA	NA	NA
Indinavir	800 three times daily × 7 days	13	↑ 14 (↓ 3 to ↑ 31)	↑ 7 (↓ 5 to ↑ 19)	↑ 8 (↓ 7 to ↑ 22)
Lamivudine	150 twice daily × 7 days	15	↑ 2 (↓ 4 to ↑ 9)	↓ 3 (↓ 15 to ↑ 10)	↓ 8 (↓ 33 to ↑ 18)
Ledipasvir/ Sofosbuvir[6, 7]	90/400 once daily x10 days	24	↑ 47 (↑ 37 to ↑ 58)	↑ 35 (↑ 29 to ↑ 42)	↑ 47 (↑ 38 to ↑ 57)
Ledipasvir/ Sofosbuvir[6, 8]		23	↑ 64 (↑ 54 to ↑ 74)	↑ 50 (↑ 42 to ↑ 59)	↑ 59 (↑ 49 to ↑ 70)
Ledipasvir/ Sofosbuvir[9]		15	↑ 79 (↑ 56 to ↑ 104)	↑ 98 (↑ 77 to ↑ 123)	↑ 163 (↑ 132 to ↑ 197)
Ledipasvir/ Sofosbuvir[10]		14	↑32 (↑25 to ↑ 39	↑ 40 (↑ 31 to ↑ 50)	↑ 91 (↑ 74 to ↑ 110)
Ledipasvir/ Sofosbuvir[11]		29	↑ 61 (↑ 51 to ↑ 72)	↑ 65 (↑ 59 to ↑ 71)	↑ 115 (↑ 105 to ↑ 126)
Lopinavir/ Ritonavir	400/100 twice daily 14 days	24	↓ 33 (↓ 17 to ↑ 49)	↑ 32 (↑ 25 to ↑ 40)	↑ 28 (↑ 7 to ↑ 49)

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters[2] (90% CI)		
			C_{max}	AUC	C_{min}
Nelfinavir	1250 twice daily 14 days	29	↓2 (↓ 9 to ↑ 5)	↑1 (↓ 5 to ↑ 7)	↑ 9 (↑ 2 to ↑ 17)
Saquinavir/Ritonavir	1000/100 twice daily × 14 days	35	↑ 15 (↑ 7 to ↑ 22)	↑ 14 (↑ 9 to ↑ 19)	↑23 (↑ 16 to ↑ 30)
Sofosbuvir[12]	400 single dose	16	↑ 25 (↑ 8 to ↑ 45)	↓ 2 (↓ 9 to ↑ 5)	↓ 1 (↓ 9 to ↑ 7)
Sofosbuvir/ Velpatasvir[13]	400/100 once daily	24	↑ 55 (↑43 to ↑ 68)	↑ 30 (↑ 24 to ↑ 36)	↑ 39 (↑ 31 to ↑ 48)
Sofosbuvir/ Velpatasvir[14]		29	↑ 55 (↑ 45 to ↑ 66)	↑ 39 (↑ 33 to ↑ 44)	↑ 52 (↑ 45 to ↑ 59)
Sofosbuvir/ Velpatasvir[15]		15	↑ 77 (↑ 53 to ↑104)	↑ 81 (↑ 68 to ↑ 94)	↑ 121 (↑ 100 to ↑ 143)
Sofosbuvir/ Velpatasvir[16]		24	↑ 44 (↑ 33 to ↑ 55)	↑ 40 (↑ 34 to ↑ 46)	↑ 84 (↑ 76 to ↑ 92)
Sofosbuvir/ Velpatasvir[17]		24	↑ 36 (↑ 25 to ↑ 47)	↑ 35 (↑ 29 to ↑ 42)	↑ 45 (↑ 39 to ↑ 51)
Sofosbuvir/ Velpatasvir[18]		30	↑ 46 (↑ 39 to ↑ 54)	↑ 40 (↑ 34 to ↑ 45)	↑ 70 (↑ 61 to ↑ 79)
Sofosbuvir/ Velpatasvir/ Voxilaprevir[19]	400/100/100 + 100 voxilaprevir[20] 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)	↑ 6 (↓ 1 to ↑ 13)	↑ 11 (↑ 4 to ↑ 18)
Tipranavir/Ritonavir[21]	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)

1. Patients received tenofovir 300 mg once daily.
2. Increase = ↑; Decrease = ↓; NC = Not Calculated; NA = Not Available
3. Reyataz® Prescribing Information (Bristol-Myers Squibb)
4. Prezista® Prescribing Information
5. weight <60kg: 250 mg, ≥60 kg more: 400 mg
6. Data generated from simultaneous dosing with HARVONI (ledipasvir/sofosbuvir). Staggered administration (12 hours apart) provided similar results.
7. Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine and tenofovir DF coadministered with HARVONI.
8. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine and tenofovir DF coadministered with HARVONI.
9. Study conducted with ATRIPLA (efavirenz/emtricitabine/tenofovir DF) coadministered with HARVONI.
10. Study conducted with COMPLERA (emtricitabine/rilpivirine/tenofovir DF) coadministered with HARVONI.
11. Study conducted with emtricitabine/tenofovir DF + dolutegravir coadministered with HARVONI.
12. Study conducted with ATRIPLA coadministered with SOVALDI® (sofosbuvir).
13. Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine and tenofovir DF coadministered with EPCLUSA (sofosbuvir/velpatasvir).
14. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine and tenofovir DF

coadministered with EPCLUSA.

15. Study conducted with ATRIPLA (efavirenz/emtricitabine/tenofovir DF) coadministered with EPCLUSA.
16. Study conducted with COMPLERA (emtricitabine/rilpivirine/tenofovir DF) coadministered with EPCLUSA.
17. Study conducted with STRIBILD (elvitegravir/cobicistat/emtricitabine/tenofovir DF) coadministered with EPCLUSA.
18. Administered as raltegravir + emtricitabine and tenofovir DF coadministered with EPCLUSA.
19. Comparison based on exposures when administered as darunavir + ritonavir + emtricitabine and tenofovir DF coadministered with VOSEVI.
20. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.
21. Aptivus® Prescribing Information.

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[1] (90% CI)		
			C_{max}	AUC	C_{min}
Abacavir[2]	300 single dose	8	↑ 12 (↓ 1 to ↑ 26)	↑ 11 (↑ 4 to ↑ 19)	NC
Atazanavir[3]	400 once daily × 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
Atazanavir[3]	Atazanavir/Ritonavir 300/100 once daily × 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓ 25[7] (↓ 42 to ↓ 3)	↓ 23[7] (↓ 46 to ↑ 10)
Darunavir[4]	Darunavir/Ritonavir 300/100 once daily	12	↑ 16 (↓ 6 to ↑ 42)	↑ 21 (↓ 5 to ↑ 54)	↑ 24 (↓ 10 to ↑ 69)
Didanosine[2] (enteric-coated)	250 once, simultaneously with tenofovir DF and a light meal[5]	33	↓29[6] (↓39 to ↓18)	↓ 11 (↓ 23 to ↑ 2)[6]	NC
Efavirenz[2]	600 once daily × 14 days	30	↓ 4 (↓ 9 to ↑ 1)	↓ 3 (↓ 7 to 0)	↓ 7 (↓ 13 to ↓1)
Emtricitabine[2]	200 once daily × 7 days	17	↓ 4 (↓ 13 to ↑ 6)	↑ 7 (0 to ↑ 4)	↑ 20 (↑ 12 to ↑ 29
Entecavir[2]	1 mg once daily × 10 days	28	NA	↑ 13 (↑ 11 to ↑ 15)	NA
Indinavir[2]	800 three times daily × 7 days	12	↓ 6 (↓ 23 to ↑ 10)	↓ 2 (↓ 12 to ↑ 8)	↑ 43 (↓ 45 to ↑ 130)
Lamivudine[2]	150 twice daily × 7 days	15	↓ 29 (↓ 39 to ↓ 19)	↓ 10 (↓ 17 to ↓ 3)	↑ 17 (↑ 3 to ↑ 32)
Lopinavir[2]	Lopinavir/Ritonavir 400/100 twice daily × 14 days	24	↓ 14 (↓ 23 to ↓ 4)	↓ 12 (↓ 20 to ↓ 5)	↓ 11 (↓ 22 to ↑ 1)
Ritonavir			↓ 24 (↓ 46 to ↓ 3)	↓ 22 (↓ 34 to ↓ 9)	↓ 15 (↓ 32 to ↑ 2)
Ledipasvir	Ledipasvir/Sofosbuvir 90/400 once daily[13,14]	24	↑ 68 (↑ 54 to ↑ 84)	↑ 96 (↑ 74 to ↑ 121)	↑ 118 (↑ 91 to ↑ 150)
Sofosbuvir			↑1 (↓ 12 to ↑ 15)	↑ 11 (↑ 2 to ↑ 21)	NC
GS-331007[12]			↑17 (↑ 12 to ↑ 23)	↑ 31 (↑ 25 to ↑ 36)	↑ 42 (↑ 34 to ↑ 49)

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters[1] (90% CI)		
			C_{max}	AUC	C_{min}
Ledipasvir	Ledipasvir/Sofosbuvir 90/400 once daily[13,15]	23	↑11 (↓ 1 to ↑ 24)	↑ 12 (0 to ↑ 25)	↑ 17 (↑ 4 to ↑ 31)
Sofosbuvir			↓ 37 (↓ 48 to ↓ 25)	↓ 27 (↓ 35 to ↓ 18)	NC
GS-331007[12]			↑ 10 (↑ 4 to ↑ 16)	↑ 20 (↑ 16 to ↑ 24)	↑ 26 (↑ 20 to ↑ 32)
Ledipasvir	Ledipasvir/Sofosbuvir 90/400 once daily[16]	15	↓ 34 (↓ 41 to ↓ 25)	↓ 34 (↓ 41 to ↓ 25)	↓ 34 (↓ 43 to ↓ 24)
Sofosbuvir			↑ 3 (↓ 13 to ↑ 23)	↓ 6 (↓ 19 to ↑ 10)	NC
GS-331007[12]			↓ 14 (↓ 24 to ↓ 4)	↓ 10 (↓ 17 to ↓ 3)	↑ 7 (↑ 2 to ↑13)
Ledipasvir	Ledipasvir/Sofosbuvir 90/400 once daily[17]	14	↑ 1 (↓ 5 to ↑ 7)	↑ 8 (↑ 2 to ↑ 15)	↑ 16 (↑ 8 to ↑ 25)
Sofosbuvir			↑ 5 (↓ 7 to ↑ 20)	↑ 10 (↑ 1 to ↑ 21)	NC
GS-331007[12]			↑ 6 (↑ 1 to ↑ 11)	↑ 15 (↑ 11 to ↑ 19)	↑ 18 (↑ 13 to ↑ 23)
Sofosbuvir	Sofosbuvir/Velpatasvir 400/100 once daily[18]	24	↑ 12 (↓ 3 to ↑ 29)	↑ 22 (↑ 12 to ↑ 33)	NC
GS-331007[12]			↑ 21 (↑ 12 to ↑ 29)	↑ 32 (↑ 27 to ↑ 36)	↑ 42 (↑ 37 to ↑ 49)
Velpatasvir			↑ 55 (↑ 41 to ↑ 71)	↑ 142 (↑ 123 to ↑ 164)	↑ 301 (↑ 257 to ↑ 350)
Sofosbuvir	Sofosbuvir/Velpatasvir 400/100 once daily[19]	29	↓ 38 (↓ 46 to ↓ 29)	↓ 28 (↓ 34 to ↓ 20)	NC
GS-331007[12]			↑ 4 (↓ 1 to ↑ 8)	↑ 13 (↑ 8 to ↑ 18)	↑ 13 (↑ 6 to ↑ 19)
Velpatasvir			↓ 24 (↓ 35 to ↓ 11)	↓ 16 (↓ 28 to ↓ 2)	↑ 1 (↓ 13 to ↑ 18)
Sofosbuvir	Sofosbuvir/Velpatasvir 400/100 once daily[20]	14	↑ 38 (↑ 14 to ↑ 67)	↓ 3 (↓ 17 to ↑ 14)	NC
GS-331007[12]			↓ 14 (↓ 20 to ↓ 7)	↓ 10 (↓ 15 to ↓ 4)	↑ 1 (↓ 5 to ↑ 7)
Velpatasvir			↓ 47 (↓ 57 to ↓ 36)	↓ 53 (↓ 61 to ↓ 43)	↓ 57 (↓ 64 to ↓ 48)

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters[1] (90% CI)		
			C_{max}	AUC	C_{min}
Sofosbuvir	Sofosbuvir/Velpatasvir 400/100 once daily[21]	24	↑ 9 (↓ 5 to ↑ 25)	↑ 16 (↑ 9 to ↑ 24)	NC
GS-331007[12]			↓ 4 (↓ 10 to ↑ 1)	↑ 4 (0 to ↑ 7)	↑ 12 (↑ 7 to ↑ 17)
Velpatasvir			↓ 4 (↓ 15 to ↑ 10)	↓ 1 (↓ 12 to ↑ 11)	↑ 2 (↓ 9 to ↑ 15)
Sofosbuvir	Sofosbuvir/Velpatasvir 400/100 once daily[22]	24	↑ 1 (↓ 15 to ↑ 19)	↑ 24 (↑ 13 to ↑ 37)	NC
GS-331007[12]			↑ 13 (↑ 7 to ↑ 18)	↑ 35 (↑ 30 to ↑ 40	↑ 45 (↑ 38 to ↑ 52)
Velpatasvir			↑ 5 (↓ 7 to ↑ 19)	↑ 19 (↑ 7 to ↑ 34)	↑ 37 (↑ 22 to ↑ 54)
Sofosbuvir	Sofosbuvir/Velpatasvir 400/100 once daily[23]	30	↑ 9 (↓ 3 to ↑ 23)	↑ 16 (↑ 7 to ↑ 25)	NC
GS-331007[12]			↓ 5 (↓ 9 to ↓ 2)	↑ 3 (0 to ↑ 6)	↑ 8 (↑ 4 to ↑ 13)
Velpatasvir			↓ 3 (↓ 13 to ↑ 8)	↓ 2 (↓ 12 to ↑ 10)	↓ 3 (↓ 13 to ↑ 7)
Sofosbuvir	400/100/100 + 100 voxilaprevir[24] once daily	29	↓ 30[25] (↓ 38 to ↓ 22)	↓ 22[25] (↓ 27 to ↓ 17)	NA
GS-331007[12]			↑ 6[25] (↑ 1 to ↑ 10)	↑ 15[25] (↑ 12 to ↑ 19)	NA
Velpatasvir			↓ 22[25] (↓ 27 to ↓ 16)	↓ 5[24] (↓ 12 to ↑ 2)	↑ 16[25] (↑ 7 to ↑ 26)
Voxilaprevir			↑ 72[25] (↑ 51 to ↑ 97)	↑ 143[25] (↑ 115 to ↑ 175)	↑ 300[25] (↑ 244 to ↑ 365)
Methadone[8]	40-110 once daily × 14 days[9]	13	↑ 5 (↓ 3 to ↑ 14)	↑ 5 (↓ 2 to ↑ 13)	↑ 6 (↓ 3 to ↑ 15)
Nelfinavir[2]	1250 twice daily × 14 days	29	↓8 (↓ 15 to ↓ 1)	↓7 (↓ 15 to ↑ 2)	↑ 1 (↓ 15 to ↑ 19)
M8 metabolite			↓ 8 (↓ 16 to 0)	↓ 7 (↓ 17 to ↑ 5)	↓ 2 (↓ 16 to ↑ 15)
Norgestimate	Ethinyl Estradiol/ Norgestimate (Ortho-Tricyclen®) Once daily × 7 days	20	↓ 6 (↓ 13 to ↑ 1)	↓ 5 (↓ 9 to ↓ 1)	↓ 4 (↓ 8 to ↑ 1)
Ethinylestradiol[10]			↓ 6 (↓ 12 to 0)	↓ 4 (↓ 9 to ↑ 1)	↓ 2 (↓ 9 to ↑ 6)
Ribavirin	600 single dose	22	↓ 5 (↓ 11 to ↑ 1)	↑ 12 (↑ 6 to ↑ 17)	NC

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters[1] (90% CI)		
			C_{max}	AUC	C_{min}
Saquinavir	1000/100 twice daily ×14 days	32	↑ 22 (↑ 6 to ↑ 41)	↑ 29[11] (↑12 to ↑48)	↑ 47[11] (↑ 23 to↑ 76)
Ritonavir			↑ 10 (↓ 5 to ↑ 28)	↑ 11 (0 to ↑ 22)	↑ 23 (↑ 3 to ↑ 46)
Sofosbuvir	Sofosbuvir 400 single dose[26]	16	↓ 19 (↓ 40 to ↑10)	↓ 6 (↓ 24 to ↑16)	NC
GS-331007[12]			↓ 23 (↓ 30 to ↓ 16)	↓ 16 (↓ 24 to ↓ 8)	NC
Tacrolimus	0.05 mg/kg twice daily × 7 days	21	↑ 3 (↓ 3 to ↑ 9)	↑ 4 (↓ 3 to ↑ 11)	↑ 10 (↑ 2 to ↑ 17)
Tipranavir[27]	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)

1. Increase = ↑; Decrease = ↓; NC = Not Calculated; NA = Not Available
2. Study conducted with tenofovir DF.
3. Reyataz Prescribing Information (Bristol-Myers Squibb)
4. Prezista Prescribing Information.
5. 373 kcal, 8.2 g fat
6. Compared with didanosine (enteric-coated) 400 mg administered alone under fasting conditions.
7. In HIV-infected patients, addition of tenofovir DF 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.
8. R-(active), S-and total methadone exposures were equivalent when dosed alone or with tenofovir DF.
9. Individual subjects were maintained on their stable methadone dose. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported.
10. Ethinyl estradiol and 17-deacetyl norgestimate (pharmacologically active metabolite) exposures were equivalent when dosed alone or with tenofovir DF.
11. Increases in AUC and C_{min} are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir DF and ritonavir-boosted saquinavir are coadministered.
12. The predominant circulating nucleoside metabolite of sofosbuvir.
13. Data generated from simultaneous dosing with HARVONI (ledipasvir/sofosbuvir). Staggered administration (12 hours apart) provided similar results.
14. Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine and tenofovir DF coadministered with HARVONI.
15. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine and tenofovir DF coadministered with HARVONI.
16. Study conducted with ATRIPLA (efavirenz/emtricitabine/tenofovir DF) coadministered with HARVONI.
17. Study conducted with COMPLERA (emtricitabine/rilpivirine/tenofovir) coadministered with HARVONI.
18. Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine and tenofovir DF coadministered with EPCLUSA (sofosbuvir/velpatasvir).
19. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine and tenofovir DF coadministered with EPCLUSA.
20. Study conducted with ATRIPLA (efavirenz/emtricitabine/tenofovir DF) coadministered with EPCLUSA.

21. Study conducted with COMPLERA (emtricitabine/rilpivirine/tenofovir DF) coadministered with EPCLUSA.
22. Study conducted with STRIBILD (elvitegravir/cobicistat/emtricitabine/tenofovir DF) coadministered with EPCLUSA.
23. Comparison based on exposures when administered as raltegravir + emtricitabine and tenofovir DF coadministered with EPCLUSA.
24. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.
25. Comparison based on exposures when administered as darunavir + ritonavir + emtricitabine and tenofovir DF coadministered with VOSEVI.
26. Study conducted with ATRIPLA coadministered with SOVALDI.
27. Aptivus Prescribing Information

Drug-Food Interactions

MINT-EMTRICITABINE/TENOFOVIR can be taken with or without food. Compared to fasted administration, dosing of emtricitabine and tenofovir DF following a either a high fat meal or a light meal increased the mean AUC and C_{max} of tenofovir by 35% and 15%, respectively, without affecting emtricitabine exposures **(**see **ACTIONS AND CLINICAL PHARMACOLOGY, Effect of Food on Absorption)**.

Drug-Herb Interactions

Interactions of emtricitabine and tenofovir DF with herbs have not been established.

Drug-Laboratory Interactions

Interactions of emtricitabine and tenofovir DF with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose Treatment of HIV-1 Infection

The dose of MINT-EMTRICITABINE/TENOFOVIR is one tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir DF) once daily taken orally with or without food.

Pre-exposure Prophylaxis of HIV-1 Infection

The dose of MINT-EMTRICITABINE/TENOFOVIR is one tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir DF) once daily taken orally with or without food.

Special Populations

Dose Adjustment for Renal Impairment

Treatment of HIV-1 Infection

Significantly increased drug exposures occurred when emtricitabine or tenofovir DF were

administered to patients with moderate to severe renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency**). Therefore, the dosing interval of MINT-EMTRICITABINE/TENOFOVIR should be adjusted in HIV-1 infected adult patients with baseline creatinine clearance 30–49 mL/min using the recommendations in Table 13. These dosing interval recommendations are based on modeling of single-dose pharmacokinetic data in non-HIV infected subjects with varying degrees of renal impairment, including end-stage renal disease requiring hemodialysis. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated in moderate to severe renal impairment, therefore, clinical response to treatment and renal function should be closely monitored in these patients.

No dose adjustment of MINT-EMTRICITABINE/TENOFOVIR is necessary with mild renal impairment patients (creatinine clearance 50-80 mL/min). Routine monitoring of calculated creatinine clearance, serum phosphorus, urine glucose, and urine protein should be performed for patients with mild renal impairment (creatinine clearance 50−80 mL/min) **(**see **WARNINGS AND PRECAUTIONS)**.

Table 13 Dosage Adjustment for HIV-1 Infected Adult Patients with Altered Creatinine Clearance

	Creatinine Clearance (mL/min)[1]		
	≥50	**30–49**	**<30 (Including Patients Requiring Hemodialysis)**
Recommended Dosing Interval	Every 24 hours	Every 48 hours	MINT-EMTRICITABINE/TENOFOVIR should not be administered.

1. Calculated using ideal (lean) body weight.

Pre-exposure Prophylaxis of HIV-1 Infection

Do not use MINT-EMTRICITABINE/TENOFOVIR for PrEP in HIV-1 uninfected individuals with creatinine clearance below 60 mL/min (see **WARNINGS AND PRECAUTIONS**).

No dose adjustment of MINT-EMTRICITABINE/TENOFOVIR is necessary with mild renal impairment patients (creatinine clearance 50-80 mL/min). Routine monitoring of calculated creatinine clearance, serum phosphorus, urine glucose and urine protein should be performed in all individuals with mild renal impairment. If a decrease in calculated creatinine clearance is observed in uninfected individuals while using MINT-EMTRICITABINE/TENOFOVIR for PrEP, evaluate potential causes and re- assess potential risks and benefits of continued use (see **WARNINGS AND PRECAUTIONS**).

Hepatic Impairment

No dose adjustment is required in patients with hepatic impairment (see **WARNINGS AND PRECAUTIONS**).

Geriatrics (>65 years of age)

Clinical studies of emtricitabine or tenofovir DF 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.

Missed Dose

If a patient misses a dose within 12 hours of the regularly scheduled time, but then remembers it that same day, the patient should take the missed dose with food as soon as possible and resume their normal dosing schedule. If a patient misses a dose of MINT-EMTRICITABINE/TENOFOVIR by more than 12 hours and it is almost time for their next dose, the patient should not take the missed dose and simply resume the usual dosing schedule. The patient should not take more than 1 dose of MINT-EMTRICITABINE/TENOFOVIR in a day and should not take 2 doses of MINT-EMTRICITABINE/TENOFOVIR at the same time to make up for missing a dose.

Uninfected individuals who miss doses are at greater risk of acquiring HIV-1 than those who do not miss doses (see **WARNINGS AND PRECAUTIONS)**.

OVERDOSAGE

For management of a suspected drug overdose, please contact your regional Poison Control Centre.

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

Emtricitabine*:* Limited clinical experience is available at doses higher than the therapeutic dose of emtricitabine. In one clinical pharmacology study single doses of emtricitabine 1200 mg were administered to 11 patients. No severe adverse reactions were reported. The effects of higher doses are not known.

Hemodialysis treatment removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min); however, a single treatment does not significantly affect emtricitabine C_{max} or AUC. It is not known whether emtricitabine can be removed by peritoneal dialysis.

Tenofovir DF: Limited clinical experience at doses higher than the therapeutic dose of tenofovir DF 300 mg is available. In one study, 600 mg tenofovir DF was administered to 8 patients orally for 28 days. No severe adverse reactions were reported. The effects of higher doses are not known.

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of tenofovir DF, a four-hour hemodialysis session

removed approximately 10% of the administered tenofovir dose.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

MINT-EMTRICITABINE/TENOFOVIR is a fixed-dose combination of antiviral drugs, emtricitabine and tenofovir DF (see **VIROLOGY**).

Pharmacokinetics

Emtricitabine and tenofovir DF: One emtricitabine and tenofovir DF Tablet was bioequivalent to one emtricitabine Capsule (200 mg) plus one tenofovir DF Tablet (300 mg) following single-dose administration to fasting healthy subjects (N=39).

Emtricitabine: The pharmacokinetic properties of emtricitabine are summarized in Table 14. Following oral administration of emtricitabine, emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1–2 hours post-dose. In vitro binding of emtricitabine to human plasma proteins is <4% and is independent of concentration over the range of 0.02– 200 μg/mL. Following administration of radiolabelled emtricitabine, approximately 86% is recovered in the urine and 13% is recovered as metabolites. The metabolites of emtricitabine 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 emtricitabine, the plasma emtricitabine half-life is approximately 10 hours.

Tenofovir DF: The pharmacokinetic properties of tenofovir DF are summarized in Table 14. Following oral administration of tenofovir DF, maximum tenofovir serum concentrations are achieved in 1.0 ± 0.4 hour. In vitro binding of tenofovir to human plasma proteins is <0.7% and 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 tenofovir DF, the terminal elimination half-life of tenofovir is approximately 17 hours.

Table 14 Single Dose Pharmacokinetic Parameters for Emtricitabine and Tenofovir in Adults

	Emtricitabine	Tenofovir
Fasted Oral Bioavailability[2] (%)	92 (83.1–106.4)	25 (NC–45.0)[1]
Plasma Terminal Elimination Half-Life[2] (hr)	10 (7.4–18.0)	17 (12.0–25.7)
C_{max}[3] (mcg/mL)	1.8 ± 0.72[4]	0.30 ± 0.09
AUC[3] (mcg·hr/mL)	10.0 ± 3.12[4]	2.29 ± 0.69
CL/F[3] (mL/min)	302 ± 94	1043 ± 115
CL_{renal}[3] (mL/min)	213 ± 89	243 ± 33

1. NC = Not calculated
2. Median (range)
3. Mean ± SD
4. Data presented as steady state values.

Effects of Food on Oral Absorption

MINT-EMTRICITABINE/TENOFOVIR may be administered with or without food. Administration of emtricitabine and tenofovir DF tablets 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 studies, tenofovir DF was taken under fed conditions.
Emtricitabine systemic exposures (AUC and C_{max}) were unaffected when emtricitabine and tenofovir DF was administered with either a high fat or a light meal.

Special Populations and Conditions

Pediatrics and Geriatrics

Pharmacokinetics of emtricitabine and tenofovir have not been fully evaluated in children (<18 years) or in the elderly (>65 years).

Race

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

Tenofovir DF*:* There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations.

Gender

Emtricitabine and tenofovir DF: Emtricitabine and tenofovir pharmacokinetics are similar in male and female patients.

Hepatic Insufficiency

The pharmacokinetics of tenofovir following a 300 mg single dose of tenofovir DF 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 emtricitabine and tenofovir DF or emtricitabine have not been studied in patients with hepatic impairment; however, emtricitabine has not been shown to be significantly metabolized by liver enzymes, so the impact of liver impairment is likely to be limited.

Renal Insufficiency

The pharmacokinetics of emtricitabine and tenofovir are altered in patients with renal insufficiency. In patients with creatinine clearance <50 mL/min, C_{max} and $AUC_{0-\infty}$ of emtricitabine and tenofovir were increased (see **WARNINGS, Nephrotoxicity**).

It is recommended that the dosing interval for MINT-EMTRICITABINE/TENOFOVIR be modified in HIV-1 infected patients with creatinine clearance 30–49 mL/min. MINT-EMTRICITABINE/TENOFOVIR should not be used in HIV-1 infected patients with creatinine clearance <30 mL/min and in patients with end-stage renal disease requiring dialysis **(**see **DOSAGE AND ADMINISTRATION)**.

MINT-EMTRICITABINE/TENOFOVIR for PrEP has not been studied and should not be used in HIV-1 uninfected individuals with creatinine clearance below 60 mL/min. **(**see **DOSAGE AND ADMINISTRATION)**.

STORAGE AND STABILITY

Store between 15–30 °C .

- Keep container tightly closed
- Dispense only in original container
- Do not use if seal over bottle opening is broken or missing.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

MINT-EMTRICITABINE/TENOFOVIR is available as tablets. Each tablet contains 200 mg of

emtricitabine and 300 mg of tenofovir DF (which is equivalent to 245 mg of tenofovir disoproxil), as active ingredients. The tablets also include the following inactive ingredients: pregelatinized starch, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, purified water and magnesium stearate. The film coating (Opadry II Blue -32K505037) contains hypromellose, lactose monohydrate, titanium dioxide, triacetin, FD&C Blue#2.

The tablets are blue, capsule shaped, film coated tablets debossed with 'H' on one side and '124' on the other side.
Each bottle contains 30 tablets and a desiccant (silica gel canister) and is closed with a child-resistant closure.

PART II. SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Emtricitabine:

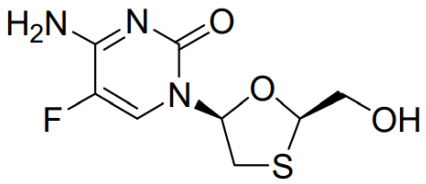
Common Name: emtricitabine (USAN)

Chemical Name: 5-fluoro-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine

Empirical Formula: $C_8H_{10}FN_3O_3S$

Molecular Weight: 247.25 g/mol

Structural Formula:



Physicochemical Properties:

Physical Description: Emtricitabine is a white to off-white powder.

Solubility: Sparingly soluble in water and in methanol, practically insoluble in methylene chloride.

Log P:	0.43
pKa:	2.65
pH:	5.3

Tenofovir DF:

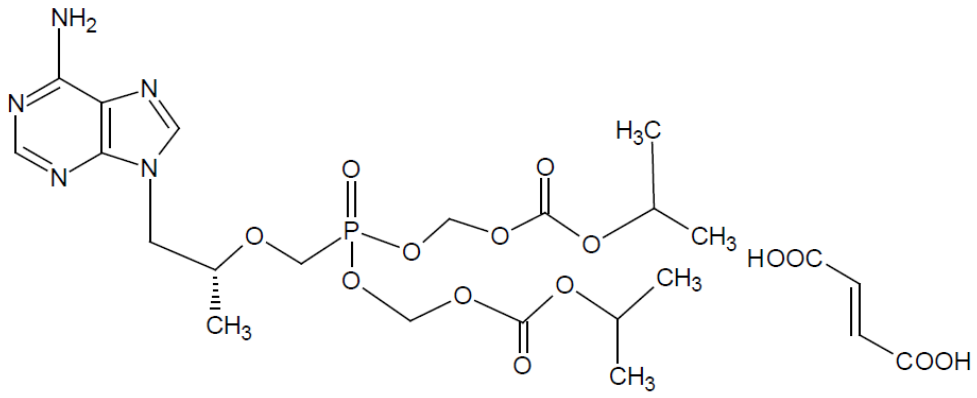
Common Name: tenofovir disoproxil fumarate (USAN)

Chemical Name: 9-[(R)-2-[[bis[[(isopropoxycarbonyl)oxy]methoxy]phosphinyl]-methoxy]propyl]adenine fumarate (1:1)

Empirical Formula: $C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$

Molecular Weight: 635.52 g/mol

Structural Formula:



Physicochemical Properties:

Physical Description: Tenofovir disoproxil fumarate is a white to off-white crystalline powder.

Solubility: Sparingly soluble in methanol and in ethanol.

Log P, pKa & pH: Sample is slightly soluble in water, hence log P, pKa and pH values are not determined.

CLINICAL TRIALS

Comparative Bioavailability Studies

A randomized, double-blind, balanced, two-treatment, two sequence, two-period, single-dose, crossover oral bioequivalence study of MINT-EMTRICITABINE/TENOFOVIR 200 mg/300 mg tablets (Mint Pharmaceuticals Inc.) and PrTRUVADA® 200 mg/300 mg tablets (Gilead Sciences Canada, Inc.) was conducted in healthy, adult, Asian, male subjects under fasting conditions. The comparative bioavailability data from the 41 subjects that were included in the statistical analysis of the parent compound, Emtricitabine, and free Tenofovir are presented in the following tables.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Emtricitabine (1x 200 mg Emtricitabine / 300 mg Tenofovir Disoproxil Fumarate) From measured data Geometric Mean Arithmetic Mean (CV%)				
Pharmacokinetic Parameter	TEST[1]	REFERENCE[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng•h/mL)	11296.92 11546.54 (20.88)	11107.08 11300.38 (17.85)	101.8	97.1 - 106.6
AUC_I (ng•h/mL)	11611.02 11850.37 (20.26)	11399.13 11592.54 (17.59)	101.9	97.5 - 106.5
C_{max} (ng/mL)	2172.16 2227.44 (22.27)	2196.17 2249.60 (21.29)	98.9	92.5 - 105.8
T_{max} [3] (h)	1.33 (0.67 - 3.50)	1.50 (0.50 - 4.00)		
$T_{½}$ [4] (h)	7.53 (41.78)	7.13 (38.47)		

[1]MINT-EMTRICITABINE/TENOFOVIR (Emtricitabine/Tenofovir Disoproxil Fumarate) Tablets, 200 mg/300 mg (Mint Pharmaceuticals Inc.)
[2] PrTRUVADA® (Emtricitabine/Tenofovir Disoproxil Fumarate) Tablets, 200 mg/300 mg (Gilead Sciences Canada, Inc.)
[3]Expressed as the median (range) only
[4]Expressed as the arithmetic mean (CV%) only

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Tenofovir (1x 200 mg Emtricitabine / 300 mg Tenofovir Disoproxil Fumarate) From measured data Geometric Mean Arithmetic Mean (CV%)				
Pharmacokinetic Parameter	TEST[1]	REFERENCE[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng•h/mL)	2245.81 2335.17 (28.08)	2185.89 2256.36 (25.56)	102.7	97.1 - 108.6
AUC_I (ng•h/mL)	2424.38 2507.93 (26.32)	2348.02 2413.69 (23.95)	103.2	97.9 - 108.7
C_{max} (ng/mL)	299.39 312.30 (28.67)	299.43 310.08 (25.96)	100.0	93.8 - 106.5
T_{max} [3] (h)	1.00 (0.50 - 2.00)	0.85 (0.50 - 2.67)		
$T_{½}$ [4] (h)	17.95 (16.33)	17.02 (14.21)		

[1]MINT-EMTRICITABINE/TENOFOVIR (Emtricitabine/Tenofovir Disoproxil Fumarate) Tablets, 200 mg/300 mg (Mint Pharmaceuticals Inc.)
[2] [Pr]TRUVADA® (Emtricitabine/Tenofovir Disoproxil Fumarate) Tablets, 200 mg/300 mg (Gilead Sciences Canada, Inc.)
[3]Expressed as the median (range) only
[4]Expressed as the arithmetic mean (CV%) only

Clinical Studies in Patients with HIV-1 Infection

Study Demographics and Trial Design Description of Clinical Studies

For safety and efficacy studies using emtricitabine or tenofovir DF in combination with other antiretroviral agents, also consult the Product Monograph for these products.

Clinical Study 934 supports the use of emtricitabine and tenofovir DF tablets for the treatment of HIV-1 infection. Additional data in support of the use of emtricitabine and tenofovir DF are derived from Study 903, in which lamivudine and tenofovir DF were used in combination in treatment-naïve adults, and clinical Study 303 in which emtricitabine and lamivudine demonstrated comparable efficacy, safety and resistance patterns as part of multidrug regimens (see Table 19 and Table 20).

Table 15 Study 934 Emtricitabine + Tenofovir DF + Efavirenz Compared with Lamivudine/Zidovudine +Efavirenz

Study Number	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (N=511)	Mean Age	Gender
GS-01-934	Randomized, open-label, parallel, multicenter, active controlled study. **Arm 1**: emtricitabine+ tenofovir DF+ efavirenz **Arm 2**: lamivudine/ zidovudine + efavirenz	**Arm 1**[1]: efavirenz 600 mg once daily for oral administration, emtricitabine 200 mg once and tenofovir DF 300 mg once daily **Arm 2**: efavirenz 600 mg once daily for oral administration and Combivir (lamivudine/ zidovudine) 150/300 mg twice daily. 144 weeks	Antiretroviral naïve patients (HIV-1 RNA > 10,000 copies/mL) (N=511)	Mean 38 years (18–80)	Male : 86% Female: 14%

[1]From weeks 96 to 144 of the study, patients received emtricitabine and tenofovir DF with efavirenz in place of emtricitabine + tenofovir DF

Data through 144 weeks are reported for Study 934, a randomized, open-label, active controlled multicenter study comparing emtricitabine + tenofovir administered in combination with efavirenz versus lamivudine/zidovudine administered in combination with efavirenz in 511 antiretroviral-naïve patients. From weeks 96 to 144 of the study, patients randomized to emtricitabine + tenofovir received emtricitabine and tenofovir DF with efavirenz in place of emtricitabine + tenofovir. Patients 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 2–1191) and median baseline plasma HIV-1RNA was 5.01 log_{10} copies/mL (range 3.56–6.54). Patients were stratified by baseline CD4 count (< or ≥200 cells/mm^3); 41% had CD4 cell counts <200 cells/mm^3 and 51% of patients had baseline viral loads >100,000 copies/mL.

Emtricitabine:

Table 16 Study 303: Emtricitabine QD + Stable Background Therapy (SBT) Compared to Lamivudine BID + SBT

Study No.	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (N=440)	Mean Age (Range)	Gender
FTC-303	Randomized (2:1), open-label, active-controlled switch study. **Arm 1**: emtricitabine + (d4T or ZDV + PI or NNRTI) **Arm 2**: lamivudine + (d4T or ZDV + PI or NNRTI)	**Arm 1**: emtricitabine 200 mg capsules orally, QD + (d4T or ZDV + PI or NNRTI) for 48 weeks **Arm 2**: lamivudine 150 mg tablet orally, BID + (d4T or ZDV + PI or NNRTI) for 48 weeks	Stable treatment-experienced (HIV-1 RNA <400 copies/mL) (N=440)	42 years (22–80)	Male: 86% Female: 14%

Study 303 was a 48-week, open-label, active-controlled multicenter study comparing emtricitabine (200 mg QD) to lamivudine, in combination with stavudine or zidovudine and a protease inhibitor or NNRTI in 440 patients who were on a lamivudine-containing triple-antiretroviral drug regimen for at least 12 weeks prior to study entry and had HIV-1 RNA ≤400 copies/mL.

Patients were randomized 1:2 to continue therapy with lamivudine (150 mg BID) or to switch to emtricitabine (200 mg QD). All patients were maintained on their stable background regimen. Patients had a mean age of 42 years (range 22–80), 86% were male, 64% Caucasian, 21% African-American and 13% Hispanic. Patients had a mean baseline CD4 cell count of 527 cells/mm^3 (range 37–1909), and a median baseline plasma HIV RNA of 1.7 log_{10} copies/mL (range 1.7–4.0). The median duration of prior antiretroviral therapy was 27.6 months.

Tenofovir DF:

Table 17 Study 903: Tenofovir DF + Lamivudine + Efavirenz Compared with Stavudine + Lamivudine + Efavirenz

Study No.	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (N=600)	Mean Age (Range)	Gender
GS-99-903	Randomized (1:1), double-blind, active-controlled, equivalence study. **Arm 1:** tenofovir DF + lamivudine + efavirenz **Arm 2:** stavudine + lamivudine + efavirenz	**Arm 1:** tenofovir DF 300 mg tablets QD, stavudine placebo capsules BID, lamivudine 150 mg tablets BID, efavirenz 600 mg QD **Arm 2:** tenofovir DF placebo tablets QD, stavudine[1] capsules 40/30 mg BID, lamivudine 150 mg tablets BID, efavirenz 600 mg QD All for oral (PO) administration for 144 weeks double-blind phase followed by 192-week open-label phase. (Nevirapine 200 mg BID could replace efavirenz in the event of efavirenz-associated central nervous system toxicity or rash.)	Treatment-naive (HIV-1 RNA >5,000 copies/mL) (N=600)	36 years (18–64)	Male: 74% Female: 26%

1. Stavudine/placebo capsules 20/15 mg BID as need for dose reduction.

Study 903 is a double-blind, active-controlled multicenter study comparing tenofovir DF (300 mg QD) administered in combination with lamivudine and efavirenz versus stavudine, lamivudine, and efavirenz in 600 antiretroviral-naïve patients. Patients had a mean age of 36 years (range 18–64), 74% were male, 64% were Caucasian and 20% were Black. The mean baseline CD4 cell count was 279 cells/mm^3 (range 3–956) and median baseline plasma HIV-1 RNA was 77,600 copies/mL (range 417–5,130,000). Patients were stratified by baseline HIV-1 RNA and CD4 count. Forty-three percent of patients had baseline viral loads >100,000 copies/mL and 39% had CD4 cell counts <200 cells/mm^3.

Study Results Emtricitabine and Tenofovir DF

Study 934: Emtricitabine + Tenofovir + Efavirenz Compared with Lamivudine/Zidovudine + Efavirenz

Treatment outcomes through 48 and 144 weeks for those patients who did not have efavirenz resistance at baseline are presented in Table 18.

Table 18 Outcomes of Randomized Treatment at Weeks 48 and 144 (Study 934)

Outcome	At Week 48		At Week 144[1]	
	Emtricitabine+ Tenofovir DF +EFV	3TC+AZT +EFV	Emtricitabine+ Tenofovir DF+ EFV	3TC/AZT +EFV
	(N=244)	(N=243)	(N=227)	(N=229)
Responder[2]	84%	73%	71%	58%
Virologic failure[3]	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[4]	10%	14%	20%	22%

1. Patients who were responders at Week 48 or Week 96 but did not consent to continue study after Week 48 or Week 96 were excluded from analysis.
2. Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Week 48.
3. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48.
4. Includes lost to follow-up, patient withdrawal, non-compliance, protocol violation and other reasons.

In this study, emtricitabine + tenofovir DF in combination with efavirenz demonstrated statistically significant superiority to lamivudine/zidovudine in combination with efavirenz in achieving and maintaining HIV-1 RNA <400 copies/mL through 48 weeks and 144 weeks (Table 18). The difference in the percentages of responders, stratified by baseline CD4 cell count (< or ≥200 cells/mm^3), between the emtricitabine + tenofovir DF group and the

lamivudine/zidovudine group was 11.4%, and the 95% CI was 4.3% to 18.6% (p=0.002) at Week 48 and was 13% at Week 144, 95% CI = 4% to 22% (p=0.004). Through 48 weeks of therapy, 80% and 70% of patients in the emtricitabine + tenofovir DF and the lamivudine/zidovudine arms, respectively, achieved and maintained HIV-1 RNA <50 copies/mL (64% and 56%, respectively, through Week 144). The difference in the percentages of responders stratified by baseline CD4 cell count (< or ≥200 cells/mm^3) between the emtricitabine + tenofovir DF group and the lamivudine/zidovudine group was 9.1%, and the 95% CI was 1.6% to 16.6% (p=0.021) at Week 48 and was 8% at Week 144, 95% CI = −1% to 17% (p=0.082). The mean increase from baseline in CD4 cell count was 190 cells/mm^3 for the emtricitabine + tenofovir + efavirenz arm, and 158 cells/mm^3 for the lamivudine/zidovudine + efavirenz arm (p=0.002) at Week 48 (312

and 271 cells/mm^3, respectively, at Week 144, p=0.089).

The difference in the proportion of patients who achieved and maintained HIV-1 RNA <400 copies/mL through 48 weeks largely results from the higher number of discontinuations due to adverse events and other reasons in the zidovudine/lamivudine group in this open label study.

Emtricitabine:

Study 303: Emtricitabine QD + Stable Background Therapy (SBT) Compared to Lamivudine BID + SBT

Treatment outcomes through 48 weeks are presented in Table 19.

Table 19 Outcomes of Randomized Treatment at Week 48 (Study 303)

Outcome at Week 48	Emtricitabine + ZDV/d4T + NNRTI/PI (N=294)	Lamivudine + ZDV/d4T + NNRTI/PI (N=146)
Responder[1]	77% (67%)	82% (72%)
Virologic Failure[2]	7%	8%
Death	0%	<1%
Study Discontinuation Due to Adverse Event	4%	0%
Study Discontinuation For Other Reasons[3]	12%	10%

1. Patients achieved and maintained confirmed HIV RNA <400 copies/mL (<50 copies/mL) through Week 48.
2. Includes patients who failed to achieve virologic suppression or rebounded after achieving virologic suppression.
3. Includes lost to follow-up, patient withdrawal, non-compliance, protocol violation and other reasons.

The mean increase from baseline in CD4 cell count was 29 cells/mm^3 for the emtricitabine arm and 61 cells/mm^3 for the lamivudine arm. Through 48 weeks, in the emtricitabine group 2 patients (0.7%) experienced a new CDC Class C event, compared to 2 patients (1.4%) in the lamivudine group.

Tenofovir DF:

Study 903: Tenofovir DF + Lamivudine + Efavirenz Compared with Stavudine + Lamivudine + Efavirenz

Treatment outcomes at Week 48 and Week 144 are presented in Table 20 below.

Table 20 Outcomes of Randomized Treatment (Study 903)

Outcomes	At Week 48		At Week 144	
	Tenofovir DF + 3TC + EFV (N=299)	Stavudine + 3TC + EFV (N=301)	Tenofovir DF + 3TC + EFV (N=299)	Stavudine + 3TC + EFV (N=301)
	%	%	%	%
Responder[1]	79% (76%)	82% (79%)	68% (62%)	62% (58%)
Virologic failure[2]	6%	4%	10%	8%
Rebound	5%	3%	8%	7%
Never suppressed	0%	1%	0%	0%
Added an antiretroviral agent	1%	1%	2%	1%
Death	<1%	1%	<1%	2%
Discontinued due to adverse event	6%	6%	8%	13%
Discontinued for other reasons[3]	8%	7%	14%	15%

1. Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL (<50 copies/mL) at Weeks 48 and 144.
2. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48 and 144.
3. Includes lost to follow-up, patient's withdrawal, noncompliance, protocol violation and other reasons.

Through 48 weeks, the mean increase from baseline in CD4 cell count was 169 cells/mm^3 for the tenofovir DF arm and 167 cells/mm^3 for the stavudine arm. Eight patients in the tenofovir DF group and six patients in the stavudine group experienced a new CDC Class C event.

Through 144 weeks, the mean increase from baseline in CD4 cell count was 263 cells/mm^3 for the tenofovir DF arm and 283 cells/mm^3 for the stavudine arm. Eleven patients in the tenofovir DF group and nine patients in the stavudine group experienced a new CDC Class C event.

Clinical Studies in HIV-1 Uninfected Subjects

The iPrEx study and Partners PrEP study support the use of emtricitabine and tenofovir DF to help reduce the risk of acquiring HIV-1.

iPrEx Trial

The study demographics and trial design for the iPrEx Trial are summarized in Table 21.

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 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 study drugs	Randomized: 1251 – emtricitabine and tenofovir DF 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

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-1 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.

Partners PrEP Study

The demographics and trial design for the Partners PrEP study are summarized in Table 22.

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 of 36 months.	Randomized: 1589 –TDF 1583 – emtricitabine and tenofovir DF 1586 – placebo	33–34	Female: 38% Male 62%

All 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).

Study Results iPrEx Study

Subjects were followed for 4237 person-years. The primary outcome measure for the study was the incidence of documented HIV-1 seroconversion. The results of the iPrEx study are summarized below in Table 23.

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

	Placebo	Emtricitabine and tenofovir DF	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

Risk reduction was found to be higher (53%; 95% CI: 34% to 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 emtricitabine and tenofovir DF 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 the greatest in subjects with detectable intracellular tenofovir. Efficacy was therefore strongly correlated with adherence.

Partners PrEP Study

The efficacy analyses results of the Partner's PrEP study are summarized in Table 24 below.

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

	Emtricitabine and tenofovir DF	Tenofovir DF	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

Two of the 13 seroconversions in the emtricitabine and tenofovir DF arm and 3 of the 52 seroconversions in the placebo arm occurred in women during treatment interruptions for pregnancy. 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.

VIROLOGY (MICROBIOLOGY)

Mechanism of Action

Emtricitabine: 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. Emtricitabine 5′-triphosphate is a weak inhibitor of mammalian DNA polymerases α, β, ε and mitochondrial DNA polymerase γ.

Tenofovir DF: Tenofovir 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. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Antiviral Activity

Emtricitabine and tenofovir DF: In combination studies evaluating the in vitro antiviral activity of emtricitabine and tenofovir together, synergistic antiviral effects were observed. Additive to synergistic effects were observed in combination studies with protease inhibitors, integrase strand transfer inhibitors, and with nucleoside and non-nucleoside analogue inhibitors of HIV-1 reverse transcriptase.

Emtricitabine: The in vitro antiviral activity of emtricitabine against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The IC_{50} values for emtricitabine were in the range of 0.0013–0.64 μM (0.0003–0.158 μg/mL). In drug combination studies of emtricitabine with nucleoside reverse transcriptase inhibitors (abacavir, lamivudine, stavudine, zalcitabine, or zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, or nevirapine), protease inhibitors (amprenavir, nelfinavir, ritonavir, or saquinavir), and with integrase strand transfer inhibitors, additive to synergistic effects were observed. Most of these drug combinations have not been studied in humans. Emtricitabine displayed antiviral activity in vitro against HIV-1 clades A, B, C, D, E, F, and G (IC_{50} values ranged from 0.007–0.075 μM) and showed strain specific activity against HIV-2 (IC_{50} values ranged from 0.007–1.5 μM).

Tenofovir DF: The in vitro 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 IC_{50} (50% inhibitory concentration) values for tenofovir were in the range of 0.04–8.5 μM. In drug combination studies of tenofovir with integrase strand transfer inhibitors, nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, or zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, or nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, or saquinavir), additive to synergistic effects were observed. Most of these drug combinations have not been studied in humans. Tenofovir displayed antiviral activity in vitro against HIV-1 clades A, B, C, D, E, F, G, and O (IC_{50} values ranged from 0.5–2.2 μM).

Prophylactic Activity in a Nonhuman Primate Model of HIV Transmission

Emtricitabine and tenofovir DF*:* The prophylactic activity of the combination of daily oral emtricitabine and tenofovir DF 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 emtricitabine and tenofovir DF 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 DF: HIV-1 isolates with reduced susceptibility to the combination of emtricitabine and tenofovir have been selected in vitro. 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 HIV-1 reverse transcriptase has been selected by tenofovir and results in reduced susceptibility to tenofovir.

In Study 934 (emtricitabine + tenofovir DF + efavirenz compared with lamivudine/zidovudine + efavirenz), resistance analysis was performed on HIV isolates from all patients with >400 copies/mL of HIV-1 RNA at Week 144 or early discontinuation. Genotypic resistance to efavirenz, predominantly the K103N mutation, was the most common form of resistance that developed. Resistance to efavirenz occurred in 13/19 (68%) analyzed patients in the emtricitabine + tenofovir group and in 21/29 (72%) analyzed patients in the lamivudine/zidovudine group. The M184V mutation, associated with resistance to emtricitabine and lamivudine, was observed in 2/19 (11%) analyzed patients in the emtricitabine + tenofovir DF group and in 10/29 (34%) analyzed patients in the lamivudine/zidovudine group.

In treatment-naïve patients treated with emtricitabine + tenofovir DF + efavirenz, none of the HIV isolates from 19 patients analyzed for resistance showed reduced susceptibility to tenofovir or the presence of the K65R or K70E mutation.

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

Emtricitabine-resistant isolates of HIV have been recovered from some patients treated with emtricitabine alone or in combination with other antiretroviral agents. In a clinical study, viral isolates from 6/16 (37.5%) treatment-naïve patients with virologic failure showed >20-fold reduced susceptibility to emtricitabine. Genotypic analysis of these isolates showed that the resistance was due to M184V/I mutations in the HIV RT gene.

Tenofovir DF: 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 emtricitabine and lamivudine. Therefore, cross-resistance among these NRTIs may occur in patients whose virus harbors the K65R or K70E substitutions. HIV-1 isolates with reduced susceptibility to tenofovir have been selected in vitro. These viruses expressed a K65R mutation in RT and showed a 2–4 fold reduction in susceptibility to tenofovir.

Tenofovir-resistant isolates of HIV-1 have also been recovered from some patients treated with tenofovir DF in combination with certain antiretroviral agents. In treatment-naïve patients, 7/29 (24%) isolates from patients failing tenofovir DF + lamivudine + efavirenz at 48 weeks showed

>1.4 fold (median 3.4) reduced susceptibility in vitro to tenofovir.

In treatment-experienced patients, 14/304 (4.6%, studies 902 and 907) isolates from patients failing tenofovir DF at 96 weeks showed >1.4 fold (median 2.7) reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a mutation in the HIV-1 RT gene resulting in the K65R amino acid substitution.

iPrEx Trial: In a clinical study of HIV-1 seronegative subjects (**iPrEx Trial,** see **CLINICAL TRIALS**), no mutations associated with resistance to emtricitabine or tenofovir were detected at the time of seroconversion among 48 subjects in the emtricitabine and tenofovir DF 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 emtricitabine were observed in 3 of the 10 subjects (2 of 2 in the emtricitabine and tenofovir DF group and 1 of 8 in the placebo group). One of the two subjects in the emtricitabine and tenofovir DF 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 a clinical study of HIV-1 seronegative subjects (**Partners PrEP Trial,** see **CLINICAL TRIALS**), no variants expressing amino acid substitutions associated with resistance to emtricitabine or tenofovir were detected at the time of seroconversion among 12 subjects in the emtricitabine and tenofovir DF group, 15 subjects in the tenofovir DF 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 emtricitabine and tenofovir DF group, 5 in the tenofovir DF group, and 6 in the placebo group). One of the three subjects in the emtricitabine and tenofovir DF 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 tenofovir DF 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 tenofovir DF group, 1 in the emtricitabine and tenofovir DF 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 tenofovir or emtricitabine and may have been present in the infecting virus.

Cross-resistance

Emtricitabine and tenofovir DF: Cross-resistance among certain nucleoside reverse transcriptase inhibitors (NRTIs) has been recognized. The M184V/I and/or K65R or K70E substitutions selected in vitro by the combination of emtricitabine and tenofovir are also observed in some HIV-1 isolates from subjects failing treatment with tenofovir in combination with either lamivudine or emtricitabine, 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: Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine and zalcitabine but retained susceptibility in vitro to didanosine, stavudine, tenofovir, zidovudine,

and NNRTIs (delavirdine, efavirenz, and nevirapine). Isolates from heavily treatment-experienced patients containing the M184V/I amino acid substitution in the context of other NRTI resistance-associated substitutions may retain susceptibility to tenofovir. HIV-1 isolates containing the K65R substitution, selected in vivo by abacavir, didanosine, tenofovir, and zalcitabine, demonstrated reduced susceptibility to inhibition by emtricitabine. Viruses harboring mutations conferring reduced susceptibility to stavudine and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to emtricitabine. HIV-1 containing the K103N substitution associated with resistance to NNRTIs was susceptible to emtricitabine.

Tenofovir DF: HIV-1 isolates from patients (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.
Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the RT showed reduced susceptibility to tenofovir.

NON-CLINICAL TOXICOLOGY

Toxicology

Tenofovir and tenofovir DF 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 4 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.

Carcinogenesis

Emtricitabine: In long-term oral carcinogenicity studies of emtricitabine, no drug-related increase in tumor incidence was 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).

Tenofovir DF: Long-term oral carcinogenicity studies were conducted in mice and rats receiving tenofovir DF. At the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In the mouse study, (60/sex/group), one male and two female mice in the 600 mg/kg/day group (15 times the human systemic exposure at the recommended human dose of 300 mg/day) developed duodenal tumors. The mechanism underlying this effect is uncertain but may relate to high local drug concentrations in the gastrointestinal tract. No treatment-related tumors were seen in mice in the 100 or 300 mg/kg/day groups. In the rat study (60/sex/group) at doses of 30, 100, and 300 mg/kg/day (approximately 5 times human exposure), no treatment-

related increase in tumor incidence was observed.

Mutagenesis

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

Tenofovir DF: Tenofovir DF was negative in the in vitro bacterial mutation (Ames) assay (*Salmonella-Eschericia coli*/Mammalian-Microsome Reverse Mutation Assay) but positive in the in vitro mouse lymphoma assay (L5178Y TK +/- Forward Mutation Assay), with and without metabolic activation. Tenofovir DF was negative in the in vivo mouse micronucleus assay at plasma exposure levels of more than 10× the human exposure.

Impairment of Fertility

Emtricitabine: Emtricitabine 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 DF: Reproductive toxicity was evaluated in rats and rabbits. Tenofovir DF had no adverse effects on fertility or general reproductive performance in rats at doses up to 600 mg/kg/day. Tenofovir DF had no adverse effects on embryo-fetal development in rats at doses 450 mg/kg/day and in rabbits at doses up to 300 mg/kg/day. In a study of effects on peri- and postnatal development in rats, effects considered due to maternal toxicity (450– 600 mg/kg/day) were reduced survival and a slight delay in sexual maturation in the F1 generation. There were no adverse effects on growth, development, behavior, or reproductive parameters at non-maternally toxic doses (150 mg/kg/day).

Pregnancy

Emtricitabine: The incidence of fetal variations and malformations was not increased in embryofetal toxicity studies performed with emtricitabine in mice at exposures (AUC) approximately 60-fold higher and in rabbits at approximately 120-fold higher than human exposures at the recommended daily dose.

Tenofovir DF: Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir. Reduced pup body weights, survival and delay in sexual maturation was observed in a peri- and postnatal toxicity study in rats at the maternally toxic doses of 450 and 600 mg/kg (approximately 14 and 19 times the human dose based on body surface area comparisons).

Antiretroviral Pregnancy Registry
To monitor fetal outcomes of pregnant women exposed to ART (antiretroviral therapy) including MINT-EMTRICITABINE/TENOFOVIR an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 800–258–4263.

REFERENCES

1. Deeks SG, Barditch-Crovo P, Lietman PS, Hwang F, Cundy KC, Rooney JF, et al. Safety, pharmacokinetics, and antiretroviral activity of intravenous 9-[2-(R)-(phosphonomethoxy)propyl]adenine, a novel anti-human immunodeficiency virus (HIV) therapy, in HIV-infected adults. Antimicrob Agents Chemother 1998 Sep;42 (9):2380-4.

2. Barditch-Crovo P, Deeks SG, Collier A, Safrin S, Coakley DF, Miller M, et al. Phase I/II trial of the pharmacokinetics, safety, and antiretroviral activity of tenofovir disoproxil fumarate in HIV-1 infected adults. Antimicrob Agents Chemother 2001 Oct;45 (10):2733-9.

3. Schooley RT, Ruane P, Myers RA, Beall G, Lampiris H, Berger D, et al. Tenofovir DF in antiretroviral-experienced patients: results from a 48-week, randomized, double-blind study. AIDS 2002 Jun 14;16 (9):1257-63.

4. Margot NA, Isaacson E, McGowan I, Cheng AK, Schooley RT, Miller MD. Genotypic and phenotypic analyses of HIV-1 in antiretroviral-experienced patients treated with tenofovir DF. AIDS 2002 Jun 14;16 (9):1227-35.

5. Gallant, J.E., DeJesus, E., Arribas, J.R., Pozniak, A.L., Gazzard, B., Campo, R.E. et al. Tenofovir DF, Emtricitabine and Efavirenz versus Zidovudine, Lamivudine and Efavirenz for HIV. New Engl. J. Med. 2006 (354): 251-260.

6. EMEA Public Statement, Efficacy and safety concerns regarding the co-administration of tenofovir disoproxil fumarate (TDF, Viread) and didanosine (ddI, Videx), 2005. http://www.emea.eu.int/pdfs/human/press/pus/6233105en.pdf.

7. Podzamczer D, Ferrer E, Gatell JM, Niubo J, Dalmau D, Leon A, Knobel H, Polo C, Iniguez D, Ruiz I. Early virological failure with a combination of tenofovir, didanosine and efavirenz. Antiviral Therapy 2005; 10: 171-177.

8. Benaboud, S., et al. 2011. Concentrations of Tenofovir and Emtricitabine in Breast Milk of HIV-1 Infected Women in Abidjan, Côte d'Ivoire, in the ANRS 12109 TEmAA Study, Step 2. Antimicrob. Agents Chemother. 55: 1315-1317.

9. Baeten J, Donnell D, Ndase P, Mugo N, Campbell J, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med 2012;367 (5):399-410.

10. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men. N Engl J Med 2010;363 (27):2587-99.

11. Truvada® Product monograph, Gilead Sciences Canada Inc., Date of Revision: July 5, 2018; Control Number 215258.

PART III. CONSUMER INFORMATION

PrMINT-EMTRICITABINE/TENOFOVIR

Emtricitabine and Tenofovir Tablets

This leaflet is Part III of a three part "Product Monograph" published when MINT-EMTRICITABINE/ TENOFOVIR was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about MINT-EMTRICITABINE/TENOFOVIR. Contact your healthcare professional if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

MINT-EMTRICITABINE/TENOFOVIR is a type of medicine called an HIV (human immunodeficiency virus) nucleoside analog reverse transcriptase inhibitor (NRTI). MINT-EMTRICITABINE/TENOFOVIR contains 2 medicines, emtricitabine and tenofovir disoproxil fumarate, or tenofovir DF combined in one pill.

MINT-EMTRICITABINE/TENOFOVIR is used:

- **To treat HIV-1 Infection** when used with other anti-HIV medicines in adults.

OR

- **To help reduce the risk of getting HIV-1 infection** when used with safer sex practices in:
    - HIV-1 negative men who have sex with men, who are at high risk of getting infected with HIV-1 through sex.
    - Male-female sex partners when one partner has HIV-1 infection and the other does not.

  This is sometimes called Pre-Exposure Prophylaxis or PrEP.

- MINT-EMTRICITABINE/TENOFOVIR is for adults age 18 and older. MINT-EMTRICITABINE/TENOFOVIR is not indicated in children under age 18 or adults over age 65.

What it does:

- **Use of MINT-EMTRICITABINE/ TENOFOVIR to treat HIV-1 infection:**

When used with other HIV-1 medicines to treat HIV-1 infection, MINT-EMTRICITABINE/TENOFOVIR helps block HIV reverse transcriptase, a chemical in your body (enzyme) that is needed for HIV to multiply. MINT-EMTRICITABINE/TENOFOVIR lowers the amount of HIV in the blood (viral load). Lowering the amount of HIV in the blood lowers the chance of infections that happen when your immune system is weak (opportunistic infections).

HIV infection destroys CD4+ (T) cells, which are important to the immune system. The immune system helps fight infection. After a large number of T cells are destroyed, acquired immune deficiency syndrome (AIDS) develops. MINT-EMTRICITABINE/TENOFOVIR may also help to increase the number of T cells (CD4+ cells).

MINT-EMTRICITABINE/TENOFOVIR does not cure HIV-1 infection or AIDS. If you have HIV-1 infection, you must stay on continuous HIV therapy to control HIV infection and decrease HIV-related illnesses.
People taking MINT-EMTRICITABINE/TENOFOVIR may still get opportunistic infections or other conditions that happen with HIV infection.
Opportunistic infections are infections that develop because the immune system is weak. Some of these conditions are pneumonia, herpes virus infections, and *Mycobacterium avium* complex (MAC) infections.

- **Use of MINT-EMTRICITABINE/ TENOFOVIR to reduce the risk of HIV-1 infection (PrEP indication):**

When used with safer sex practices, MINT-EMTRICITABINE/TENOFOVIR may help to reduce the risk of getting HIV-1 infection:

- MINT-EMTRICITABINE/TENOFOVIR works better to reduce the risk of getting HIV-1 when the medicines are in your bloodstream **before** you are exposed to HIV-1.

It is very important that you see your healthcare professional regularly while taking MINT-EMTRICITABINE/ TENOFOVIR.

Considerations when MINT-EMTRICITABINE/TENOFOVIR is used for PrEP:

- Together with your healthcare professional, you need to decide whether MINT-EMTRICITABINE/TENOFOVIR is right for you.
- MINT-EMTRICITABINE/TENOFOVIR can only help reduce your risk of getting HIV-1 **before** you are infected.
- Do not take MINT-EMTRICITABINE/TENOFOVIR to help reduce your risk of getting HIV-1 if:
    - you already have HIV-1 infection. If you are HIV-1 positive, you need to take other medicines with MINT-EMTRICITABINE/TENOFOVIR to treat HIV-1. MINT-EMTRICITABINE/TENOFOVIR 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 MINT-EMTRICITABINE/TENOFOVIR to treat HIV-1.
- Your healthcare professional will run tests to determine that you are HIV- negative before starting PrEP treatment.

When it should not be used:

Do not use MINT-EMTRICITABINE/TENOFOVIR if:

- You are allergic (hypersensitive) to any of the ingredients

in this formulation (see: **What the medicinal ingredients are; What the nonmedicinal ingredients are**)

- Do not use MINT-EMTRICITABINE/TENOFOVIR to reduce the risk of getting HIV if you already have HIV or do not know your HIV status.

What the medicinal ingredients are:

emtricitabine
tenofovir disoproxil fumarate (tenofovir DF)

What the nonmedicinal ingredients are:
pregelatinized starch, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, purified water and magnesium stearate. The film coating (Opadry II Blue -32K505037) contains hypromellose, lactose monohydrate, titanium dioxide, triacetin, FD&C Blue#2.

What dosage forms it comes in:
MINT-EMTRICITABINE/TENOFOVIR is available as tablets. Each tablet contains 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate (which is equivalent to 245 mg of tenofovir disoproxil), as active ingredients. The tablets are blue, capsule shaped, film coated tablets debossed with 'H' on one side and '124' on the other side. Each bottle contains 30 tablets and a desiccant (silica gel canister) and is closed with a child-resistant closure.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- The most serious possible side effect is harm to the kidneys, including damage to kidney cells, kidney tissue inflammation and kidney failure. Your healthcare professional may monitor your kidney function before beginning and while receiving MINT-EMTRICITABINE/TENOFOVIR. Some patients treated with tenofovir DF (a component of MINT-EMTRICITABINE/TENOFOVIR) have had kidney problems. Your healthcare professional may need to perform additional blood tests if you have had kidney problems in the past or need to take another drug that can cause kidney problems.
- **If you are also infected with the Hepatitis B Virus, "flare-ups" of Hepatitis B Virus infection**, in which the disease suddenly returns in a worse way than before, can occur if you stop taking MINT-EMTRICITABINE/TENOFOVIR. Do not stop taking MINT-EMTRICITABINE/TENOFOVIR without your healthcare professional's advice. If you stop taking MINT-EMTRICITABINE/ TENOFOVIR, tell your healthcare professional immediately about any new, unusual or worsening symptoms that you notice after stopping treatment. After you stop taking MINT-EMTRICITABINE/TENOFOVIR, your healthcare professional will still need to check your health and take blood tests to check your liver for several months. MINT-EMTRICITABINE/TENOFOVIR is not approved for the treatment of Hepatitis B Virus infection.
- The class of medicines to which MINT-EMTRICITABINE/TENOFOVIR belongs (NRTIs) can cause a condition called lactic acidosis, together with an enlarged liver. Non-specific symptoms such as nausea, vomiting and stomach pain might indicate the development of lactic acidosis. This rare but serious side effect has occasionally been fatal. Lactic acidosis occurs more often in women, particularly if they are very overweight. You should consult your healthcare professional immediately if such symptoms occur while you are receiving MINT-EMTRICITABINE/ TENOFOVIR. The symptoms that may indicate lactic acidosis include feeling very weak, tired or uncomfortable; unusual or unexpected stomach discomfort; feeling cold; feeling dizzy or lightheaded; suddenly developing a slow or irregular heartbeat. If you notice these symptoms, stop taking MINT-EMTRICITABINE/TENOFOVIR and consult a healthcare professional immediately.
- Tenofovir DF caused harm to the bones of animals. Tenofovir DF reduced bone density in humans. If you notice bone pain, or suffer a bone fracture, or other bone problem, consult your healthcare professional. If you have bone problems, you may wish to discuss calcium and/or vitamin D supplements with your healthcare professionals.
- MINT-EMTRICITABINE/TENOFOVIR should only be used for the PrEP indication if you are HIV negative before and during treatment. Discuss with your healthcare professional if you have had a recent flu-like illness. Your healthcare professional will run tests to confirm that you are HIV negative before and during MINT-EMTRICITABINE/TENOFOVIR treatment.

Do NOT take MINT-EMTRICITABINE/ TENOFOVIR if:

- you are on other medications that may affect your kidneys and have not discussed this with your healthcare professional.
- you have or are at known risk for any type of bone disease or bone related problems and have not discussed this with your healthcare professional.
- you are allergic to MINT-EMTRICITABINE/ TENOFOVIR or any of its ingredients. The medicinal ingredients are emtricitabine and tenofovir DF **(**see: **What the nonmedicinal ingredients are)**.
- you are already taking 3TC® (lamivudine), ATRIPLA® (efavirenz/emtricitabine/tenofovir disoproxil fumarate), Combivir® (lamivudine/zidovudine), COMPLERA® (emtricitabine/rilpivirine/tenofovir disoproxil fumarate), DESCOVY® (emtricitabine and tenofovir alafenamide), EMTRIVA® (emtricitabine), GENVOYA® (elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide), Heptovir® (lamivudine), Kivexa® (abacavir sulfate and lamivudine),

STRIBILD® (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate), Triumeq® (abacavir sulfate/dolutegravir sodium/lamivudine), Trizivir® (abacavir sulfate/lamivudine/zidovudine), or VIREAD® (tenofovir disoproxil fumarate) because these medicines contain the same or similar active ingredients you are also taking HEPSERA® to treat your HBV infection

Changes in your immune system (Immune Reconstitution Inflammatory Syndrome) can happen when an HIV-1 infected person starts taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time, or you could develop an autoimmune disease in which your immune system reacts against your own body [e.g. Grave's disease (which affects the thyroid gland), Guillain-Barré syndrome (which affects the nervous system) or polymyositis (which affects the muscles)] and it may develop at any time, sometimes months later after the start of HIV therapy. Sometimes symptoms can be severe, so if you develop high temperature (fever), joint or muscle pain, redness, rash, swelling or fatigue, or any new symptoms, contact your healthcare professional right away.

Before taking MINT-EMTRICITABINE/ TENOFOVIR to reduce your risk of getting HIV-1 infection (PrEP indication):

- **You must get tested to be sure you are HIV-negative.** It is important that you also get tested at least every 3 months as recommended by your healthcare provider while taking MINT-EMTRICITABINE/ TENOFOVIR. **Do not take MINT-EMTRICITABINE/TENOFOVIR to reduce the risk of getting HIV (PrEP) unless you are confirmed to be HIV-negative.**
- Tell your healthcare provider if you have any of the following symptoms within the last month before you start taking MINT-EMTRICITABINE/TENOFOVIR or at any time while taking MINT-EMTRICITABINE/TENOFOVIR:
  - tiredness
  - fever
  - sweating a lot (especially at night)
  - rash
  - vomiting or diarrhea
  - joint or muscle aches
  - headache
  - sore throat
  - enlarged lymph nodes in the neck or groin

These may be signs of HIV infection and you may need to have a different kind of test to diagnose HIV. If you are already taking MINT-EMTRICITABINE/TENOFOVIR to prevent HIV-1 infection (PrEP), your healthcare provider may tell you to stop taking MINT-EMTRICITABINE/TENOFOVIR until an HIV test confirms that you do not have HIV-1 infection.

Just taking MINT-EMTRICITABINE/TENOFOVIR may not keep you from getting HIV. MINT-EMTRICITABINE/ TENOFOVIR does NOT always prevent HIV.

You must still practice safer sex at all times. Do not have any kind of sex without protection. Always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

You must also use other prevention methods to keep from getting HIV.

- Know your HIV-1 status and the HIV-1 status of your partners.
- While taking MINT-EMTRICITABINE/TENOFOVIR, get tested at least every 3 months for HIV, as recommended by your healthcare provider. Ask your partners to get tested.
- 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-negative.
- Get tested for other sexually transmitted infections such as syphilis and gonorrhea. These infections make it easier for HIV to infect you.
- Get information and support to help reduce risky sexual behavior.
- Have fewer sex partners.
- Do not miss any doses of MINT-EMTRICITABINE/ TENOFOVIR. Missing doses may increase your risk of getting HIV-1 infection.

BEFORE you use MINT-EMTRICITABINE/ TENOFOVIR (emtricitabine/tenofovir DF) talk to your healthcare professional:

If you are pregnant or planning to become pregnant: Pregnant mothers should not take MINT-EMTRICITABINE/TENOFOVIR unless specifically directed by the healthcare professional.

If you are a female who is taking MINT-EMTRICITABINE/ TENOFOVIR to prevent HIV infection (PrEP) and you become pregnant while taking MINT-EMTRICITABINE/TENOFOVIR, talk to your healthcare provider about whether you should continue taking MINT-EMTRICITABINE/TENOFOVIR.

Pregnancy Registry. There is a pregnancy registry for women who take antiviral medicines during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this Antiretroviral Pregnancy Registry.

If you are breastfeeding or planning to breastfeed: Do not breastfeed if you are taking MINT-EMTRICITABINE/ TENOFOVIR or have HIV. Emtricitabine and tenofovir DF, the two components of MINT-EMTRICITABINE/ TENOFOVIR, pass to your baby in your breast milk. You should not breastfeed because of the risk of passing HIV to your baby. Talk to your healthcare professional about the best way to feed your baby.

If you have other medical conditions: Let your healthcare professional know if you have other medical conditions, especially liver, bone and kidney problems.

If you are taking other medicines: Some medicines can interact when taken together, including prescription and non-prescription

medicines and dietary supplements **(**see **INTERACTIONS WITH THIS MEDICATION)**.

If you are taking didanosine: Taking didanosine and MINT-EMTRICITABINE/TENOFOVIR may cause serious reactions including lactic acidosis (too much acid in the blood), pancreatitis (inflamed pancreas) and nerve damage (neuropathy) **(**see **INTERACTIONS WITH THIS MEDICATION and SIDE EFFECTS AND WHAT TO DO ABOUT THEM)**.

MINT-EMTRICITABINE/TENOFOVIR should not be used with or soon after cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir, aminoglycosides, or nonsteroidal anti-inflammatory drugs (NSAIDS), due to potential harm to the kidneys.

It is a good idea to keep a complete list of all the medicines that you take. Make a new list when medicines are added or stopped. Give copies of this list to all of your healthcare providers every time you visit your healthcare professional or fill a prescription

Other Special Warnings:
Your blood sugar levels (glucose) or levels of fats (lipids) in your blood may increase with HIV treatment. Your doctor may order blood tests for you.

Additional training and educational materials for consumers and healthcare professionals on MINT-EMTRICITABINE/TENOFOVIR for PrEP are accessible on the MINT-EMTRICITABINE/TENOFOVIR website (www.emtricitabine-tenofovir.com).

INTERACTIONS WITH THIS MEDICATION

Let your healthcare professional know if you are taking these or any other medications:

- Drugs that contain didanosine (Videx®, Videx EC®). Tenofovir DF (a component of MINT-EMTRICITABINE/TENOFOVIR) may increase the amount of Videx in your blood. You may need to be followed more carefully if you are taking MINT-EMTRICITABINE/TENOFOVIR and Videx together. Also, the dose of didanosine may need to be reduced.
- Reyataz® (atazanavir sulfate), Kaletra® (lopinavir/ritonavir), Prezista® (darunavir), HARVONI® (ledipasvir/sofosbuvir), EPCLUSA® (sofosbuvir/velpatasvir) or VOSEVI™ (sofosbuvir/velpatasvir/voxilaprevir). These medicines may increase the amount of tenofovir DF (a component of MINT-EMTRICITABINE/TENOFOVIR) in your blood, which could result in more side effects. You may need to be followed more carefully if you are taking MINT-EMTRICITABINE/TENOFOVIR together with Reyataz, Kaletra, Prezista, HARVONI, EPCLUSA or VOSEVI. MINT-EMTRICITABINE/TENOFOVIR may decrease the amount of Reyataz in your blood. If you are taking MINT-EMTRICITABINE/TENOFOVIR and Reyataz together, you should also be taking Norvir® (ritonavir).
- Non-steroidal anti-inflammatory drugs.

PROPER USE OF THIS MEDICATION

Stay under a Healthcare professional's care when taking MINT-EMTRICITABINE/ TENOFOVIR. **Do not change your treatment or stop treatment without first talking with your healthcare professional**.

Take MINT-EMTRICITABINE/TENOFOVIR exactly as your healthcare professional prescribed it. Follow the directions from your healthcare professional, exactly as written on the label. Set up a dosing schedule and follow it carefully.

When used to treat HIV-1 infection, MINT-EMTRICITABINE/TENOFOVIR is always used with other HIV-1 medicines.

If you take MINT-EMTRICITABINE/TENOFOVIR to reduce your risk of getting HIV-1:

- you must also use other methods to reduce your risk of getting HIV.
- **take MINT-EMTRICITABINE/TENOFOVIR every day**, not just when you think you have been exposed to HIV-1.

Avoid doing things that can increase your risk of getting HIV infection or spreading HIV infection to other people:

- Do not re-use or share needles or other injection equipment.
- Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.
- Do not have any kind of sex without protection. Always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vagina secretions, or blood.

Ask your healthcare provider if you have any questions on how to prevent getting HIV infection or spreading HIV infection to other people.

When your MINT-EMTRICITABINE/TENOFOVIR supply starts to run low, get more from your healthcare professional. This is very important because 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 MINT-EMTRICITABINE/TENOFOVIR and become harder to treat.

Only take medicine that has been prescribed specifically for you. Do not give MINT-EMTRICITABINE/TENOFOVIR to others or take medicine prescribed for someone else.

Do not use if seal over bottle opening is broken or missing.

<u>Usual Adult Dose:</u>
For the treatment of HIV-1 infection:

- The usual dose of MINT-EMTRICITABINE/TENOFOVIR is one tablet orally (by mouth) once a day, in combination with other anti-HIV medicines.
- MINT-EMTRICITABINE/TENOFOVIR may be taken with or without a meal.

For prevention of HIV-1 infection (PrEP):

- The usual dose of MINT-EMTRICITABINE/ TENOFOVIR is one tablet orally (by mouth) once a day.
- MINT-EMTRICITABINE/TENOFOVIR may be taken with or without a meal

Overdose:

If you think you, or a person you are caring for, have taken too much MINT-EMTRICITABINE/TENOFOVIR, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

It is important that you do not miss any doses. If you miss a dose of MINT-EMTRICITABINE/TENOFOVIR and it is less than 12 hours from the time you usually take MINT-EMTRICITABINE/TENOFOVIR, then take the dose. If more than 12 hours has passed from the time you usually take MINT-EMTRICITABINE/ TENOFOVIR, then wait until the next scheduled daily dose. **Do not** take more than 1 dose of MINT-EMTRICITABINE/TENOFOVIR in a day. **Do not** take 2 doses at the same time. Call your healthcare professional if you are not sure what to do.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects of MINT-EMTRICITABINE/ TENOFOVIR are:

- Diarrhea
- Nausea
- Vomiting
- Dizziness
- Headache

Other side effects include:

- Stomach pain
- Indigestion
- Inflammation of the pancreas
- Sleeping problems
- Abnormal dreams
- Weakness
- Pain
- Shortness of breath
- Allergic reaction (including swelling of the face, lips, tongue or throat)
- Rash
- Flatulence (intestinal gas)
- Skin discoloration (small spots or freckles) may also happen with MINT-EMTRICITABINE/TENOFOVIR.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptoms/Effect		Talk with your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Rare	**Effect: Kidney problems** **Symptoms** • You may have increased or decreased urination as well as increased thirst • You may have swelling of your legs and feet • You may feel listless and tired		✓ ✓ ✓	
Rare	**Effect: Lactic acidosis** **Symptoms** • Feeling very weak or tired • Unusual muscle pain • Stomach pain with nausea and vomiting • Feeling cold, especially in arms and legs • Feeling dizzy or lightheaded • Fast or irregular heartbeat		✓ ✓ ✓ ✓ ✓ ✓	
Very Rare	**Effect: Hepatotoxicity (severe liver problems) with hepatomegaly (liver enlargement) and steatosis (fat in the liver)** **Symptoms** • Jaundice (skin or the white part of eyes turns yellow) • Urine turns dark • Bowel movements (stools) turn light in color • Loss of appetite for several days or longer • Feeling sick to your stomach (nausea) • Lower stomach pain		✓ ✓ ✓ ✓ ✓ ✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptoms/Effect		Talk with your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Very Rare	**Effect: Flare-ups of hepatitis B virus infection following drug discontinuation** **Symptoms** • Jaundice (skin or the white part of eyes turn yellow)		✓	
	• Urine turns dark		✓	
	• Bowel movements (stools) turn light in color		✓	
	• Loss of appetite for several days or longer		✓	
	• Feeling sick to your stomach (nausea)		✓	
	• Lower stomach pain		✓	

Lactic acidosis is a medical emergency and must be treated in the hospital. You may be more likely to get lactic acidosis or serious liver problems if you are very overweight (obese) or have been taking nucleoside analog medicines, like MINT-EMTRICITABINE/TENOFOVIR for a long time.

Muscle pain, muscle weakness, bone pain and softening of the bone (infrequently contributing to fractures) have also been reported.

There have been other side effects in patients taking emtricitabine or tenofovir DF. *This is not a complete list of side effects.* If you have questions about side effects, ask your healthcare professional. You should report any new or continuing symptoms to your healthcare professional right away. Your healthcare professional may be able to help you manage these side effects.

HOW TO STORE IT

- Keep MINT-EMTRICITABINE/TENOFOVIR and all other medications out of reach and sight of children.
- MINT-EMTRICITABINE/TENOFOVIR should be stored at 15-30 °C (59-86°F). It should remain stable until the expiration date printed on the label.
- Do not keep your medicines in places that are too hot or cold.
- Do not keep medicine that is out of date or that you no longer need. If you throw any medicines away, make sure that children will not find them.
- Keep MINT-EMTRICITABINE/TENOFOVIR in its original container and keep the container tightly closed.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about MINT-EMTRICITABINE/TENOFOVIR:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.mintpharmaceuticals.com), or by calling 1-877-398-9696.

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