For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Tenofovir Disoproxil Fumarate & Emtricitabine Tablets IP

Tenvir-EM

WARNINGS: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B, AND RISK OF DRUG RESISTANCE WITH USE OF TENOFOVIR DF/EMTRICITABINE FOR PRE-EXPOSURE PROPHYLAXIS (PrEP) IN UNDIAGNOSED EARLY HIV-1 INFECTION

SEVERE ACUTE EXACERBATIONS OF HEPATITIS B (HBV) HAVE BEEN REPORTED IN HBV-INFECTED PATIENTS WHO HAVE DISCONTINUED TENOFOVIR DF/EMTRICITABINE. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN HBV-INFECTED PATIENTS WHO DISCONTINUE TENOFOVIR DF/EMTRICITABINE. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS AND PRECAUTIONS)

TENOFOVIR DISOPROXIL FUMARATE/EMTRICITABINE USED FOR HIV-1 PrEP MUST ONLY BE PRESCRIBED TO INDIVIDUALS CONFIRMED TO BE HIV-NEGATIVE IMMEDIATELY PRIOR TO INITIATING AND PERIODICALLY (AT LEAST EVERY 3 MONTHS) DURING USE. DRUG-RESISTANT HIV-1 VARIANTS HAVE BEEN IDENTIFIED WITH USE OF TENOFOVIR DISOPROXIL FUMARATE/EMTRICITABINE FOR A PrEP INDICATION FOLLOWING UNDETECTED ACUTE HIV-1 INFECTION. DO NOT INITIATE TENOFOVIR DISOPROXIL FUMARATE/EMTRICITABINE FOR A PrEP IF SIGNS OR SYMPTOMS OF ACUTE HIV-1 INFECTION ARE PRESENT UNLESS NEGATIVE INFECTION STATUS IS CONFIRMED (SEE WARNINGS AND PRECAUTIONS).

COMPOSITION

TENVIR-EM

Each film-coated tablet contains:
Tenofovir Disoproxil
Fumarate IP ..... 300 mg
Emtricitabine IP ..... 200 mg
Colour: Lake Indigo Carmine

DOSAGE FORM

Oral, fixed-dose tablet

PHARMACOLOGY

Pharmacodynamics

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 polymerase alpha, beta, epsilon and mitochondrial DNA polymerase gamma.

Tenofovir disoproxil fumarate (Tenofovir DF)

Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 RT by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases alpha, beta, and mitochondrial DNA polymerase gamma.

Pharmacokinetics

One Tenofovir DF/Emtricitabine 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 1. Following oral administration of emtricitabine, emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1–2 hours post-dose. Less than 4 % of emtricitabine binds to human plasma proteins in vitro and the binding is independent of concentration over the range of 0.02-200 µg/mL. Following administration of radiolabelled 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 Disoproxil Fumarate

The pharmacokinetic properties of tenofovir disoproxil fumarate are summarized in Table 1. Following oral administration of Tenofovir DF, maximum tenofovir serum concentrations are achieved in 1.0 ± 0.4 hour. Less than 0.7 % of tenofovir binds to human plasma proteins in vitro and the binding is independent of concentration over the range of 0.01–25 µg/mL. Approximately 70–80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of Tenofovir DF, the terminal elimination half-life of tenofovir is approximately 17 hours.

Table 1: Single Dose Pharmacokinetic Parameters for Emtricitabine and Tenofovir in Adults[a]

	Emtricitabine	Tenofovir
Fasted oral bioavailability[b] (%)	92 (83.1-106.4)	25 (NC-45.0)
Plasma terminal elimination half-life[b] (hr)	10 (7.4-18.0)	17 (12.0-25.7)
C_{max}[c] (µg/mL)	1.8 ± 0.72[d]	0.30 ± 0.09
AUC[c] (µg·hr/mL)	10.0 ± 3.12[d]	2.29 ± 0.69
CL/F[c] (mL/min)	302 ± 94	1043 ± 115
CL_{renal}[c] (mL/min)	213 ± 89	243 ± 33

[a] NC = Not calculated
[b] Median (range)
[c] Mean (± SD)
[d] Data presented as steady state values.

Effects of Food on Oral Absorption

Tenofovir Disoproxil Fumarate/Emtricitabine may be administered with or without food. Administration of tenofovir disoproxil fumarate/emtricitabine following a high fat meal (784 kcal; 49 grams of fat) or a light meal (373 kcal; 8 grams of fat) delayed the time of tenofovir C_{max} by approximately 0.75 hour. The mean increases in tenofovir AUC and C_{max} were approximately 35% and 15%, respectively, when administered with a high fat or light meal, compared to administration in the fasted state. In previous safety and efficacy trials, Tenofovir DF was taken under fed conditions. Emtricitabine systemic exposures (AUC and C_{max}) were unaffected when tenofovir disoproxil fumarate/emtricitabine was administered with either a high fat or a light meal.

Special Populations

Race

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

Tenofovir Disoproxil Fumarate: There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations following the administration of tenofovir disoproxil fumarate.

Gender

Emtricitabine and Tenofovir Disoproxil Fumarate: Emtricitabine and tenofovir pharmacokinetics are similar in male and female subjects.

Geriatric Patients

Pharmacokinetics of emtricitabine and tenofovir has not been fully evaluated in the elderly (65 years of age and older).

Patients with Impaired Renal Function

The pharmacokinetics of emtricitabine and tenofovir are altered in subjects with renal impairment (see **WARNINGS AND PRECAUTIONS**). In adult subjects with creatinine clearance <50 mL/min, C_{ss}, and $AUC_{0-\infty}$ of emtricitabine and tenofovir were increased. No data are available to make dose recommendations in pediatric patients with renal impairment.

Patients with Hepatic Impairment

The pharmacokinetics of tenofovir following a 300 mg dose of tenofovir disoproxil fumarate 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 tenofovir disoproxil fumarate/emtricitabine or emtricitabine have not been studied in subjects with hepatic impairment; however, emtricitabine is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.

INDICATIONS

Treatment of HIV-1 Infection

TENVIR-EM, a combination of Tenofovir disoproxil fumarate and emtricitabine is indicated for the treatment of HIV-1 infection in adults.

HIV-1 Pre-Exposure Prophylaxis

TENVIR-EM is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk.
This indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1 infection and in heterosexual serodiscordant couples.

If clinical symptoms consistent with acute viral infection are present and recent (< 1MONTH) exposures are suspected, delay starting PrEP for at least one month and reconfirm HIV-1 status or use a test cleared by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection (see **WARNINGS AND PRECAUTIONS, USE IN SPECIFIC POPULATIONS**).

When considering **TENVIR-EM** for pre-exposure prophylaxis 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

Table 2: Summary of Guidance for PrEP Use

	Men Who Have Sex with Men	Heterosexual Women and Men	Injection Drug Users
Detecting substantial risk of acquiring HIV infection	HIV-positive sexual partner Recent bacterial STI High number of sex partners History of inconsistent or no condom use Commercial sex work	HIV-positive sexual partner Recent bacterial STI High number of sex partners History of inconsistent or no condom use Commercial sex work In high-prevalence area or network	HIV-positive injecting partner Sharing injection equipment Recent drug treatment (but currently injecting)
Clinically eligible	Documented negative HIV test result before prescribing PrEP No signs/symptoms of acute HIV infection Normal renal function; no contraindicated medications Documented hepatitis B virus infection and vaccination status		
Prescription	Daily, continuing, oral doses of TDF/FTC, ≤90-day supply		
Other services	Follow-up visits at least every 3 months to provide the following: HIV test, medication adherence counseling, behavioral risk reduction support, side effect assessment, STI symptom assessment At 3 months and every 6 months thereafter, assess renal function Every 6 months, test for bacterial STIs		
	Do oral/rectal STI testing	Assess pregnancy intent Pregnancy test every 3 months	Access to clean needles/syringes and drug treatment services

STI: sexually transmitted infection

When prescribing **TENVIR-EM** for pre-exposure prophylaxis, healthcare providers must:

- prescribe **TENVIR-EM** as part of a comprehensive prevention strategy because **TENVIR-EM** 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 **TENVIR-EM** dosing schedule because the effectiveness of **TENVIR-EM** 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 **TENVIR-EM** 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 the FDA 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 **TENVIR-EM** for PrEP.

DOSAGE AND ADMINISTRATION

Testing Prior to Initiation of TENVIR-EM for Treatment of HIV-1 Infection or for HIV-1 PrEP

- Prior to or when initiating **TENVIR-EM**, test patients for hepatitis B virus infection (see **WARNINGS AND PRECAUTIONS**).
- Prior to initiation and during use of **TENVIR-EM**, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus (see **WARNINGS AND PRECAUTIONS**).

HIV-1 Screening for Individuals Receiving TENVIR-EM for HIV-1 PrEP

- Screen all patients for HIV-1 infection before initiating **TENVIR-EM** for HIV-1 PrEP and at least once every 3 months while taking **TENVIR-EM** (see **INDICATIONS, CONTRAINDICATIONS AND WARNINGS AND PRECAUTIONS**).

Recommended Dose for Treatment of HIV-1 Infection in Adults

The recommended dose of **TENVIR-EM** in adults is one tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) once daily taken orally with or without food.

Recommended Dose for Pre-exposure Prophylaxis

The dose of **TENVIR-EM** in HIV-1 uninfected adults is one tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) once daily taken orally with or without food.

Dose adjustment for Renal Impairment

Treatment of HIV-1 infection

Table 3 provides dosage interval adjustment for patients with renal impairment. No dosage adjustment is necessary for HIV-1 infected patients with mild renal impairment (creatinine clearance 50–80 mL/min). The safety and effectiveness of the dosing interval adjustment recommendations in patients with moderate renal impairment (creatinine clearance 30–49 mL/min) have not been clinically evaluated; therefore, clinical response to treatment and renal function should be closely monitored in these patients(see **WARNINGS AND PRECAUTIONS**).

Table 3: Dosage Adjustment for HIV-1 Infected Adult Patients with Altered Creatinine Clearance

	Creatinine Clearance (mL/min)[a]		
	≥ 50	30–49	<30 (including patients requiring hemodialysis)
Recommended Dosing Interval	Every 24 hours	Every 48 hours	**TENVIR-EM** should not be administered

[a] Calculated using ideal (lean) body weight

HIV-1 Pre-exposure Prophylaxis

TENVIR-EM for a HIV-1 PrEP is not recommended in HIV-1 uninfected individuals with estimated creatinine clearance below 60 mL/min (see **WARNINGS AND PRECAUTIONS**).

If a decrease in creatinine clearance is observed in uninfected individuals while using **TENVIR-EM** for HIV-1 PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use (see **WARNINGS AND PRECAUTIONS**).

CONTRAINDICATIONS

TENVIR-EM for HIV-1 pre-exposure prophylaxis is contraindicated in individuals with unknown or positive HIV-1 status (see **WARNINGS AND PRECAUTIONS**).

WARNINGS AND PRECAUTIONS

Drug Interactions

Drugs Affecting Renal Function

FTC 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; however, coadministration of tenofovir disoproxil fumarate/emtricitabine with drugs that are eliminated by active tubular secretion may increase concentrations of FTC, tenofovir, and/or the coadministered drug. Some examples include, but are not limited to, acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs (see **WARNINGS AND PRECAUTIONS**). Drugs that decrease renal function may increase concentrations of FTC and/or tenofovir.

Established and Significant Interactions

Table 4 provides a listing of established or clinically significant drug interactions. The drug interactions described are based on studies conducted with either tenofovir disoproxil fumarate/emtricitabine, the components of tenofovir disoproxil fumarate/emtricitabine (FTC and TDF) as individual agents and/or in combination, or are predicted drug interactions that may occur with tenofovir disoproxil fumarate/emtricitabine.

Table 4 Established and Significanta Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Trials

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
NRTI: **didanosine[c]**	↑ didanosine	Patients receiving tenofovir disoproxil fumarate/emtricitabine and didanosine should be monitored closely for didanosine-associated adverse reactions. Discontinue didanosine in patients who develop didanosine-associated adverse reactions. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis, and neuropathy. Suppression of CD4+ cell counts has been observed in patients receiving TDF with didanosine 400 mg daily. In patients weighing greater than 60 kg, reduce the didanosine dose to 250 mg when it is coadministered with tenofovir disoproxil fumarate/emtricitabine. Data are not available to recommend a dose adjustment of didanosine for adult or pediatric patients weighing less than 60 kg. When coadministered, tenofovir disoproxil fumarate/emtricitabine and didanosine may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat)
HIV-1 Protease Inhibitors: **atazanavir[c]** **lopinavir/ritonavir[c]** **atazanavir/ritonavir[c]** **darunavir/ritonavir[c]**	↓ atazanavir ↑ tenofovir	When coadministered with tenofovir disoproxil fumarate/emtricitabine, atazanavir 300 mg should be given with ritonavir 100 mg. Monitor patients receiving tenofovir disoproxil fumarate/emtricitabine concomitantly with lopinavir/ritonavir, ritonavir-boosted atazanavir, or ritonavir-boosted darunavir for TDF-associated adverse reactions. Discontinue tenofovir disoproxil fumarate/emtricitabine in patients who develop TDF associated adverse reactions
Hepatitis C Antiviral Agents: sofosbuvir/velpatasvir[c] **sofosbuvir/velpatasvir/voxilaprevir[c]** **ledipasvir/sofosbuvir[c]**	↑ tenofovir	Monitor patients receiving tenofovir disoproxil fumarate/emtricitabine concomitantly with sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir for adverse reactions associated with TDF. Monitor patients receiving tenofovir disoproxil fumarate/emtricitabine concomitantly with ledipasvir/sofosbuvir without an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination for adverse reactions associated with TDF. In patients receiving tenofovir disoproxil fumarate/emtricitabine concomitantly with ledipasvir/sofosbuvir and an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination, consider an alternative HCV or antiretroviral therapy, as the safety of increased tenofovir concentrations in this setting has not been established. If coadministration is necessary, monitor for adverse reactions associated with TDF.

[a] This table is not all inclusive
[c] Indicates that a drug-drug interaction trial was conducted

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate a component of tenofovir disoproxil fumarate/emtricitabine, alone or in combination with other antiretrovirals. Treatment with tenofovir disoproxil fumarate/emtricitabine should be suspended in any patient or uninfected individual who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Severe Acute Exacerbation of Hepatitis B in Patients with HBV Infection All patients should be tested for the presence of chronic hepatitis B virus (HBV) before or when initiating tenofovir disoproxil fumarate/emtricitabine (see **DOSAGE AND ADMINISTRATION**).

Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in HBV-infected patients who have discontinued emtricitabine/tenofovir disoproxil fumarate. Patients infected with HBV who discontinue tenofovir disoproxil fumarate/emtricitabine should be closely monitored with both clinical and laboratory follow up for at least several months after stopping treatment . If appropriate, initiation of anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis, since posttreatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure. HBV-uninfected individuals should be offered vaccination.

New Onset or Worsening of Renal Impairment

Emtricitabine and tenofovir are principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir disoproxil fumarate (see **UNDESIRABLE EFFECTS**).

Prior to initiation and during use of tenofovir disoproxil fumarate/emtricitabine, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus.

Tenofovir Disoproxil Fumarate/emtricitabine should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs)) (see **WARNINGS AND PRECAUTIONS-Drug Interactions**). Cases of acute renal failure after initiation of high dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on tenofovir disoproxil fumarate. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.

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.

Treatment of HIV-1 infection

Dosing interval adjustment of tenofovir disoproxil fumarate/emtricitabine and close monitoring of renal function are recommended in all patients with creatinine clearance 30–49 mL/min. (see **DOSAGE AND ADMINISTRATION**). No safety or efficacy data are available in patients with renal impairment who received tenofovir disoproxil fumarate and emtricitabine using these dosing guidelines, so the potential benefit of tenofovir/emtricitabine therapy should be assessed against the potential risk of renal toxicity. Tenofovir disoproxil fumarate/emtricitabine should not be administered to patients with creatinine clearance below 30 mL/min or patients requiring hemodialysis.

Pre-exposure Prophylaxis

Tenofovir disoproxil fumarate/emtricitabine for a PrEP indication should not be used if estimated creatinine clearance is less than 60 mL/min. If a decrease in estimated creatinine clearance is observed in uninfected individuals while using tenofovir disoproxil fumarate/emtricitabine for PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use (see **DOSAGE AND ADMINISTRATION**).

Bone effects with Tenofovir DF

Bone Mineral Density

In clinical trials in HIV-1 infected adults and in a clinical trial of HIV-1 uninfected individuals, tenofovir disoproxil fumarate was associated with slightly greater decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators (see **UNDESIRABLE EFFECTS** and Tenofovir Disoproxil Fumarate prescribing information). Serum parathyroid hormone levels and 1, 25 Vitamin D levels were also higher in subjects receiving tenofovir disoproxil fumarate.

The effects of tenofovir disoproxil fumarate -associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Assessment of BMD should be considered for adult patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial. If bone abnormalities are suspected then appropriate consultation should be obtained.

Mineralization Defects

Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of tenofovir disoproxil fumarate (see **UNDESIRABLE EFFECTS**). 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 disoproxil fumarate (see **WARNINGS AND PRECAUTIONS**).

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in HIV-1 infected patients treated with combination antiretroviral therapy, including tenofovir disoproxil fumarate/emtricitabine. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

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

Comprehensive Management to Reduce the Risk of Acquiring HIV-1

Use tenofovir disoproxil fumarate/emtricitabine for pre-exposure prophylaxis only as part of a comprehensive prevention strategy that includes other prevention measures, such as safer sex practices, because tenofovir disoproxil fumarate/emtricitabine is not always effective in preventing the acquisition of HIV-1.

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

Use tenofovir disoproxil fumarate/emtricitabine to reduce the risk of acquiring HIV-1 only in individuals confirmed to be HIV-negative. HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only tenofovir disoproxil fumarate/emtricitabine, because tenofovir disoproxil fumarate/emtricitabine 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.

- 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 tenofovir disoproxil fumarate/emtricitabine 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 status or use a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection.While using tenofovir disoproxil fumarate/ emtricitabine for a HIV-1 PrEP,HIV-1 screening tests should be repeated at least every 3 months and upon diagnosis of any sexually transmitted infections. Some individuals, such as adolescents, may benefit from more frequent visits and counseling.

If a screening test indicates possible HIV-1 infection, or if symptoms consistent with acute HIV-1 infection develop following a potential exposure event, convert the HIV-1 PrEP regimen to an HIV treatment regimen until negative infection status is confirmed using a test approved or cleared by the FDA as an aid in the diagnosis of HIV-1, including acute or primary HIV-1 infection.

Counsel uninfected individuals to strictly adhere to the recommended tenofovir disoproxil fumarate/emtricitabine dosing schedule. The effectiveness of tenofovir disoproxil fumarate/emtricitabine in reducing the risk of acquiring HIV-1 is strongly correlated with adherence as demonstrated by measurable drug levels in clinical trials.

Risk of Adverse Reactions Due to Drug Interactions

The concomitant use of tenofovir disoproxil fumarate/emtricitabine and other drugs may result in known or potentially significant drug interactions, some of which may lead to possible clinically significant adverse reactions from greater exposures of concomitant drugs (see **WARNINGS AND PRECAUTIONS -Drug Interactions**).

See Table 4 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with tenofovir disoproxil fumarate/emtricitabine; review concomitant medications during therapy with tenofovir disoproxil fumarate/emtricitabine; and monitor for adverse reactions associated with the concomitant drugs.

Pregnancy

Risk Summary

Data on the use of tenofovir disoproxil fumarate/emtricitabine during pregnancy from observational studies have shown no increased risk of major birth defects. Available data from the APR show no increase in the overall risk of major birth defects with first trimester exposure for emtricitabine (FTC) (2.3%) or tenofovir disoproxil fumarate (TDF) (2.1%) compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) *(see Data)*. The rate of miscarriage for individual drugs is not reported in the APR. In the U.S. general population, the estimated background risk of miscarriage in clinically recognized pregnancies is 15–20%.

In animal reproduction studies, no adverse developmental effects were observed when the components of tenofovir disoproxil fumarate/emtricitabine were administered separately at doses/exposures ≥60 (FTC), ≥14 (TDF) and 2.7 (tenofovir) times those of the recommended daily dose of tenofovir disoproxil fumarate/emtricitabine.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

HIV-1 PrEP: Published studies indicate an increased risk of HIV-1 infection during pregnancy and an increased risk of mother to child transmission during acute HIV-1 infection. In women at risk of acquiring HIV-1, consideration should be given to methods to prevent acquisition of HIV, including continuing or initiating tenofovir disoproxil fumarate/ emtricitabine for HIV-1 PrEP, during pregnancy.

Data

Human Data

Tenofovir disoproxil fumarate/emtricitabine *for HIV-1 PrEP*: In an observational study based on prospective reports to the APR, 78 HIV-seronegative women exposed to tenofovir disoproxil fumarate/emtricitabine during pregnancy delivered live-born infants with no major malformations. All except for one were first trimester exposures, and the median duration of exposure was 10.5 weeks. There were no new safety findings in the women receiving tenofovir disoproxil fumarate/ emtricitabine for HIV-1 PrEP compared with HIV-1 infected women treated with other antiretroviral medications.

Emtricitabine: Based on prospective reports to the APR of 3,749 exposures to FTC-containing regimens during pregnancy resulting in live births (including 2,614 exposed in the first trimester and 1,135 exposed in the second/third trimester), there was no increase in overall major birth defects with FTC compared with the background birth defect rate of 2.7% in a U.S. reference population of the MACDP. The prevalence of major birth defects in live births was 2.3% (95% CI: 1.8% to 2.9%) with first trimester exposure to FTC-containing regimens and 2.1% (95% CI: 1.4% to 3.1%) with the second/third trimester exposure to FTC-containing regimens.

Tenofovir Disoproxil Fumarate: Based on prospective reports from the APR of 4,817 exposures to TDF-containing regimens during pregnancy resulting in live births (including 3,342 exposed in the first trimester and 1,475 exposed in the second/third trimester), there was no increase in overall major birth defects with TDF compared with the background birth defect rate of 2.7% in a U.S. reference population of the MACDP. The prevalence of major birth defects in live births was 2.3% (95% CI: 1.8% to 2.8%) with first trimester exposure to TDF-containing regimens, and 2.1% (95% CI: 1.4% to 3.0%) with the second/third trimester exposure to TDF-containing regimens. Methodologic limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates women and infants from a limited geographic area, and does not include outcomes for births that occurred at <20 weeks gestation.

Additionally, published observational studies on emtricitabine and tenofovir exposure in pregnancy have not shown an increased risk for major malformations.

Animal Data

Emtricitabine

FTC was administered orally to pregnant mice (at 0, 250, 500, or 1,000 mg/kg/day), and rabbits (at 0, 100, 300, or 1,000 mg/kg/day) through organogenesis (on gestation days 6 through 15, and 7 through 19, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with FTC in mice at exposures (AUC) approximately 60 times higher and in rabbits at approximately 120 times higher than human exposures at the recommended daily dose. In a pre/postnatal development study in mice, FTC was administered orally at doses up to 1,000 mg/kg/day; no significant adverse effects directly related to drug were observed in the offspring exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 60 times higher than human exposures at the recommended daily dose.

Tenofovir Disoproxil Fumarate

TDF was administered orally to pregnant rats (at 0, 50, 150, or 450 mg/kg/day) and rabbits (at 0, 30, 100, or 300 mg/kg/ day) through organogenesis (on gestation days 7 through 17, and 6 through 18, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with TDF in rats at doses up to 14 times the human dose based on body surface area comparisons and in rabbits at doses up to 19 times the human dose based on body surface area comparisons. In a pre/postnatal development study in rats, TDF was administered orally through lactation at doses up to 600 mg/kg/day; no adverse effects were observed in the offspring at tenofovir exposures of approximately 2.7 times higher than human exposures at the recommended daily dose of tenofovir disoproxil fumarate/emtricitabine.

Lactation

Risk Summary

Based on published data, FTC and tenofovir have been shown to be present in human breast milk *(see Data)*. It is not known if the components of tenofovir disoproxil fumarate/emtricitabine affect milk production or have effects on the breastfed child.

Treatment of HIV-1 Infection:

The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV-1. Because of the potential for: (1) HIV transmission (in HIV-negative infants); (2) developing viral resistance (in HIV-positive infants); and (3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are taking tenofovir disoproxil fumarate/ emtricitabine for the treatment of HIV-1.

HIV-1 PrEP:

In HIV-uninfected women, the developmental and health benefits of breastfeeding and the mother's clinical need for tenofovir disoproxil fumarate/emtricitabine for HIV-1 PrEP should be considered along with any potential adverse effects on the breastfed child from tenofovir disoproxil fumarate/emtricitabine and the risk of HIV-1 acquisition due to nonadherence and subsequent mother to child transmission.

Women should not breastfeed if acute HIV-1 infection is suspected because of the risk of HIV-1 transmission to the infant.

Data

HIV-1 PrEP: In a study of 50 breastfeeding women who received tenofovir disoproxil fumarate/emtricitabine for HIV-1 PrEP between 1 and 24 weeks postpartum (median 13 weeks), after 7 days of treatment, tenofovir was undetectable but FTC was detectable in the plasma of most infants. In these infants, the average FTC plasma concentration was less than 1% of the FTC Cmax observed in HIV-infected infants (up to 3 months of age) receiving the therapeutic dose of FTC (3 mg/kg/day). There were no serious adverse events. Two infants (4%) had an adverse event of mild diarrhea which resolved.

Pediatric Use

Treatment of HIV-1 Infection

No pediatric clinical trial was conducted to evaluate the safety and efficacy of tenofovir disoproxil fumarate/emtricitabine. Data from previously conducted trials with the individual drug products, emtricitabine and tenofovir disoproxil fumarate, were relied upon to support dosing recommendations for tenofovir disoproxil fumarate/emtricitabine. For additional information, consult the prescribing information for Emtricitabine and Tenofovir disoproxil fumarate.

Tenofovir disoproxil fumarate/emtricitabine should only be administered to HIV-1 infected pediatric patients with body weight greater than or equal to 17 kg and who are able to swallow a whole tablet. Because it is a fixed-dose combination tablet, tenofovir disoproxil fumarate/emtricitabine cannot be adjusted for patients of lower weight. Tenofovir disoproxil fumarate/emtricitabine has not been evaluated for use in pediatric patients weighing less than 17 kg.

HIV-1 PrEP

The safety and effectiveness of tenofovir disoproxil fumarate/emtricitabine for HIV-1 PrEP in at-risk adolescents weighing at least 35 kg is supported by data from adequate and well-controlled studies of tenofovir disoproxil fumarate/emtricitabine for HIV-1 PrEP in adults with additional data from safety and pharmacokinetic studies in previously conducted trials with the individual drug products, FTC and TDF, in HIV-1 infected adults and pediatric subjects (see **DOSAGE AND ADMINISTRATION, UNDESIRABLE EFFECTS**).

Safety, adherence, and resistance were evaluated in a single-arm, open-label clinical trial (ATN113) in which 67 HIV-1 uninfected at-risk adolescent men who have sex with men received tenofovir disoproxil fumarate/emtricitabine once daily for HIV-1 PrEP. The mean age of subjects was 17 years (range 15 to 18 years); 46% were Hispanic, 52% Black, and 37% White. The safety profile of tenofovir disoproxil fumarate/emtricitabine in ATN113 was similar to that observed in the adult HIV-1 PrEP trials (see **UNDESIRABLE EFFECTS**).

In the ATN113 trial, HIV-1 seroconversion occurred in 3 subjects. Tenofovir diphosphate levels in dried blood spot assays indicate that these subjects had poor adherence. No tenofovir-or FTC-associated HIV-1 resistance substitutions were detected in virus isolated from the 3 subjects who seroconverted.

Adherence to study drug, as demonstrated by tenofovir diphosphate levels in dried blood spot assays, declined markedly after Week 12 once subjects switched from monthly to quarterly visits, suggesting that adolescents may benefit from more frequent visits and counseling.

Geriatric Use

Clinical trials of emtricitabine, tenofovir disoproxil fumarate or tenofovir disoproxil fumarate/emtricitabine did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects.

Renal Impairment *Treatment of HIV-1 infection*

The dosing interval for tenofovir disoproxil fumarate/emtricitabine should be modified in HIV-infected adult patients with creatinine clearance of 30–49 mL/min. Tenofovir disoproxil fumarate/emtricitabine is not recommended in patients with estimated creatinine clearance below 30 mL/min and in patients with end-stage renal disease requiring dialysis. (see **DOSAGE AND ADMINISTRATION**).

HIV-1 PrEP Tenofovir disoproxil fumarate/emtricitabine for a HIV-1 PrEP indication is not recommended 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 tenofovir disoproxil fumarate/emtricitabine for HIV -1 PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use (see **DOSAGE AND ADMINISTRATION**).

UNDESIRABLE EFFECTS

The following are the adverse reactions:

- Severe Acute Exacerbations of Hepatitis B in Patients with HBV Infection (see **WARNINGS AND PRECAUTIONS**).
- New Onset or Worsening Renal Impairment (see **WARNINGS AND PRECAUTIONS**).
- Lactic Acidosis/Severe Hepatomegaly with Steatosis (see **WARNINGS AND PRECAUTIONS**).
- Bone Effects of Tenofovir DF (see **WARNINGS AND PRECAUTIONS**).
- Immune Reconstitution Syndrome (see **WARNINGS AND PRECAUTIONS**).

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice

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

Clinical Trials in Adult Subjects

In Study 934, 511 antiretroviral naïve subjects received either tenofovir disoproxil fumarate + emtricitabine administered in combination with efavirenz (N=257) or zidovudine/lamivudine administered in combination with efavirenz (N=254) for 144 weeks. The most common adverse reactions (incidence greater than or equal to 10%, any severity) included diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash. Table 5 provides the treatment-emergent adverse reactions (Grade 2-4) occurring in greater than or equal to 5% of subjects treated in any treatment group.

Skin discoloration, manifested by hyperpigmentation, occurred in 3% of subjects taking FTC+TDF, and was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

Table 5: Selected Treatment-Emergent Adverse Reactions[a] (Grades 2–4) Reported in ≥5% in Any Treatment Group in Study 934 (0–144 Weeks)

	FTC + TDF + EFV[b]	AZT/3TC + EFV
	N=257	N=254
Diarrhea Nausea Vomiting	9% 9% 2%	5% 7% 5%
Fatigue	9%	8%
Sinusitis Upper respiratory tract infections Nasopharyngitis	8% 8% 5%	4% 5% 3%
Headache Dizziness	6% 8%	5% 7%
Depression Insomnia	9% 5%	7% 7%
Rash event[c]	7%	9%

[a] Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.

[b] From Weeks 96 to 144 of the trial, subjects received tenofovir disoproxil fumarate/ emtricitabine with efavirenz in place of Tenofovir DF + Emtricitabine with efavirenz.

[c] Rash event includes rash, exfoliative rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, and rash vesicular.

Laboratory Abnormalities:

Laboratory abnormalities observed in this trial were generally consistent with those seen in other trials of tenofovir disoproxil fumarate and/or emtricitabine (Table 6).

Table 6: Significant Laboratory Abnormalities Reported in ≥1% of Subjects in Any Treatment Group in Study 934 (0–144 Weeks)

	FTC + TDF + EFV[a]	AZT/3TC + EFV
	N=257	N=254
Any ≥ Grade 3 Laboratory Abnormality	30%	26%
Fasting Cholesterol (>240mg/dL)	22%	24%
Creatinine Kinase (M: >990 U/L) (F: >845 U/L)	9%	7%
Serum Amylase (>175 U/L)	8%	4%
Alkaline Phosphatase (>550 U/L)	1%	0%
AST (M: >180 U/L) (F: >170 U/L)	3%	3%
ALT (M: >215 U/L) (F: >170 U/L)	2%	3%
Hemoglobin (<8.0 mg/dL)	0%	4%
Hyperglycemia (>250 mg/dL)	2%	1%
Hematuria (>75 RBC/HPF)	3%	2%
Glycosuria (≥ 3+)	< 1%	1%
Neutrophils (<750/mm³)	3%	5%
Fasting Triglycerides (>750 mg/dL)	4%	2%

[a] From Weeks 96 to 144 of the trial, subjects received tenofovir disoproxil fumarate + emtricitabine with efavirenz in place of Tenofovir DF + Emtricitabine with efavirenz.

Adverse Reactions from Clinical Trial Experience in Uninfected Adult Subjects Taking tenofovir disoproxil fumarate/emtricitabine for HIV-1 PrEP

Clinical Trials in Adult Subjects

The safety profile of tenofovir disoproxil fumarate/emtricitabine for HIV-1 PrEP was comparable to that observed in clinical trials of HIV-infected subjects based on two randomized placebo-controlled clinical trials (iPrEx, Partners PrEP) in which 2,830 HIV-1 uninfected adults received tenofovir disoproxil fumarate/emtricitabine once daily for HIV-1 PrEP. Subjects were followed for a median of 71 weeks and 87 weeks, respectively. Table 7 provides a list of selected adverse events that occurred in 2% or more of subjects in any treatment group in the iPrEx trial, with an incidence greater than placebo.

Laboratory Abnormalities: Table 8 provides a list of laboratory abnormalities observed in both 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 tenofovir disoproxil fumarate/ emtricitabine arm of the iPrEx trial discontinued from the study due to an increase in blood creatinine and another due to low phosphorous.

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

Table 7: Selected Adverse Events (All Grades) Reported in ≥2% in Any Treatment Group in the iPrEx Trial and Greater than Placebo

	FTC/TDF (N=1251)	Placebo (N=1248)
Headache	7%	6%
Abdominal pain	4%	2%
Weight decreased	3%	2%

a. Not reported or reported below 2%.

In the Partners PrEP trial, the frequency of adverse events in the tenofovir disoproxil fumarate/emtricitabine treatment group was generally either less than or the same as in the placebo group.

Table 8: Laboratory Abnormalities (Highest Toxicity Grade) Reported for Each Subject in the iPrEx Trial and Partners PrEP Trial

		iPrEx Trial		Partners PrEP trial	
	Grade 2-4	FTC/TDF N= 1251	Placebo N= 1248	FTC/TDF N= 1579	Placebo N= 1584
Creatinine					
	(> 1.4 x ULN)	<1%	<1%	<1%	<1%
Phosphorus					
	(<2.0 mg/dL)	10%	8%	9%	9%
AST					
	(> 2.6 x ULN)	5%	5%	<1%	<1%
ALT					
	(> 2.6 x ULN)	7%	7%	<1%	<1%
Hemoglobin					
	<9.4 mg/dL	1%	2%	2%	2%
Neutrophils					
	(<750/mm³)	<1%	<1%	5%	3%

[a] Grading is per DAIDS criteria.

Changes in Bone Mineral Density:

In clinical trials of HIV-1 uninfected individuals, decreases in BMD were observed. In the iPrEx trial, a substudy of 503 subjects found mean changes from baseline in BMD ranging from -0.4% to -1.0% across total hip, spine, femoral neck, and trochanter in the tenofovir disoproxil fumarate/emtricitabine group compared with the placebo group, which returned toward baseline after discontinuation of treatment. Thirteen percent of subjects receiving tenofovir disoproxil fumarate/ emtricitabine 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 tenofovir disoproxil fumarate/emtricitabine 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.

Postmarketing Experience:

The following adverse reactions have been identified during post approval use of tenofovir disoproxil fumarate. No additional adverse reactions have been identified during post approval use of emtricitabine. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causual relationship to drug exposure.

Immune system disorders: allergic reaction, including angioedema
Metabolism and nutrition disorders: lactic acidosis, hypokalemia, hypophosphatemia
Respiratory, thoracic, and mediastinal disorders: dyspnea
Gastrointestinal disorders: pancreatitis, increased amylase, abdominal pain
Hepatobiliary Disorders: hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT)
Skin and Subcutaneous Tissue Disorders: rash
Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy
Renal and Urinary disorders: acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria.
General Disorders and Administration Site Conditions: asthenia

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

If you experience any side effects, talk to your doctor or pharmacist or write to **drugsafety@cipla.com**. You can also report side effects directly via the national pharmacovigilance program of India by calling on **1800 180 3024**.

By reporting side effects you can help provide more information on the safety of this product.

OVERDOSAGE

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

Emtricitabine:

Hemodialysis treatment removes approximately 30% of the 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). It is not known whether emtricitabine can be removed by peritoneal dialysis.

Tenofovir Disoproxil Fumarate:

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of tenofovir disoproxil fumarate, a 4-hour haemodialysis session removed approximately 10% of the administered tenofovir dose.

SHELF- LIFE: See on pack.

STORAGE AND HANDLING INSTRUCTIONS: Store in a cool dry place.

PACKAGING INFORMATION:

TENVIR-EM tablets ..... Container of 30 tablets

Last updated: May 2018
Last reviewed: May 2018

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