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

Tenofovir Disoproxil Fumarate & Emtricitabine Tablets

Tenvor-EM

WARNING
LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGS ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE WARNINGS).
TENVOR-EM IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF **TENVOR-EM** HAVE NOT BEEN ESTABLISHED IN PATIENTS CO-INFECTED WITH HBV AND HIV. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO HAVE DISCONTINUED EMTRICITABINE OR TENOFOVIR DISOPROXIL FUMARATE. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE **TENVOR-EM** AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS).

Composition
Each film-coated tablet contains
Tenofovir Disoproxil Fumarate…… 300 mg
Emtricitabine …….. 200mg

Colour: Lake Indigo Carmine
Dosage forms
Oral, fixed-dose tablet

Pharmacology
Pharmacodynamics
***Tenofovir disoproxil fumarate*:** 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 reverse transcriptase 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 and mitochondrial DNA polymerase

***Emtricitabine*:** Emtricitabine, a synthetic nucleoside analog of cytosine, is phosphorylated by cellular enzymes to form emtricitabine 5′-triphosphate. Emtricitabine 5′-triphosphate inhibits the activity of the HIV-1 reverse transcriptase 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 α, β, ε and mitochondrial DNA polymerase γ

Pharmacokinetics in Adults
***Tenofovir disoproxil fumarate*:** The pharmacokinetic properties of tenofovir disoproxil fumarate are summarized in Table 1. Following oral administration of tenofovir disoproxil fumarate, 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 g/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 disoproxil fumarate, the terminal elimination half-life of tenofovir is approximately 17 hours.

***Emtricitabine*:** The pharmacokinetic properties of emtricitabine are summarized in Table 1. Following oral administration, 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 g/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.

Table 1: Single dose pharmacokinetic parameters for emtricitabine and tenofovir in adults[1]

	Emtricitabine	Tenofovir
Fasted oral bioavailability[2] (%)	92 (83.1-106.4)	25 (NC45.0)
Plasma Terminal Elimination Half-Life [2] (hr)	10 (7.4-18.0)	17 (12.0-25.7)
C_{max} [3] (µg/mL)	1.8 ± 0.72 [4]	0.30 ± 0.09
AUC [3] (µg·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.		

Indications
TENVOR-EM 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.

Dose and method of administration
The dose of **TENVOR-EM** 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
Significantly increased drug exposures occurred when emtricitabine or tenofovir disoproxil fumarate were administered to patients with moderate to severe renal impairment. Therefore, the dosing interval of **TENVOR-EM** should be adjusted in patients with baseline creatinine clearance 30-49 mL/min using the recommendations in Table 2. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated; therefore, clinical response to treatment and renal function should be closely monitored in these patients.

Table 2: Dosage Adjustment for Patients with Altered Creatinine Clearance

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

[a] Calculated using ideal (lean) body weight

Use in special populations
Pediatric Use
Safety and effectiveness in pediatric patients have not been established.
Geriatric Use

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

Contraindications
TENVOR-EM is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product.

Warnings and Precautions
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 alone or in combination with other antiretrovirals. 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 **TENVOR-EM** 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).

Patients with HIV and Hepatitis B Virus Coinfection
It is recommended that all patients with HIV be tested for the presence of hepatitis B virus (HBV) before initiating antiretroviral therapy. **TENVOR-EM** is not indicated for the treatment of chronic HBV infection and the safety and efficacy of emtricitabine and tenofovir disoproxil fumarate have not been established in patients co-infected with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients after the discontinuation of emtricitabine and tenofovir disoproxil fumarate. Hepatic function should be closely monitored with both clinical and laboratory follow up for at least several months in patients who discontinue **TENVOR-EM** and are co-infected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Renal Impairment
Emtricitabine and tenofovir are principally eliminated by the kidney. Dosing interval adjustment of **TENVOR-EM** is recommended in all patients with creatinine clearance 30-49 mL/min, **TENVOR-EM** should not be administered to patients with creatine clearance < 30 mL/min or patients requiring hemodialysis.

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 disoproxil fumarate (see Post Marketing Experience). 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.

TENVOR-EM should be avoided with concurrent or recent use of a nephrotoxic agent. Patients at risk for, or with a history of, renal dysfunction and patients receiving concomitant nephrotoxic agents should be carefully monitored for changes in serum creatinine and phosphorus.

Bone effects
***Tenofovir disoproxil fumarte*:** In study 903 through 48 weeks, decreases from baseline in bone mineral density (BMD) were seen at the lumbar spine and hip in both arms of the study. At 48 weeks, percent decreases in BMD from baseline (mean ± SD) were greater in patients receiving TDF + lamivudine + efavirenz (spine, -3.3% ± 3.9; hip, -3.2% ± 3.6) compared with patients receiving stavudine + lamivudine + efavirenz (spine, -2.0% ± 3.5; hip, -1.8% ± 3.3). In addition, there were significant increases in levels of four 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 were also higher in tenofovir DF group relative to the stavudine group. Except for bone specific alkaline phosphatase, these changes resulted in values that remained within the normal range. There was one bone fracture reported in the tenofovir DF group compared with four in the stavudine group; no pathologic fractures were identified over 48 weeks of study treatment. The clinical significance of the changes in BMD and biochemical markers is unknown and follow-up is continuing to assess long-term impact.

Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at substantial risk for osteopenia. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be considered for HIV-associated osteopenia or osteoporosis. If bone abnormalities are suspected then appropriate consultation should be obtained.

Fat Redistribution
Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement and “cushingoid appearance” have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Immune Reconstitution Syndrome
Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including emtricitabine and tenofovir. 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.

Pregnancy
Pregnancy Category B:
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 disoproxil fumarate: 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.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, **TENVOR-EM** should be used during pregnancy only if clearly needed.

Lactation
It is recommended that HIV-infected women do not breast feed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that tenofovir is secreted in milk. It is not known whether tenofovir is excreted in human milk. It is not known whether emtricitabine is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving TENVOR-EM**.

Drug Interactions
***Tenofovir disoproxil fumarate*:** When tenofovir disoproxil fumarate was administered with didanosine the C_{max} and AUC of didanosine administered as either the buffered or enteric-coated formulation increased significantly. The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse events, including pancreatitis, and neuropathy. In adults weighing > 60 kg, the didanosine dose should be reduced to 250 mg when it is co-administered with **TENVOR-EM**. data are not available to recommend a dose adjustment of didanosine for patients weighing < 60 kg. When co-administered, **TENVOR-EM** and didanosine enteric coated capsules may be taken under fasted conditions or with a light meal (< 400 kcal, 20% fat). Co-administration of didanosine buffered tablet formulation with **TENVOR-EM** should be under fasted conditions. Co-administration of **TENVOR-EM** and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse events. Didanosine should be discontinued in patients who develop didanosine-associated adverse events.

Atazanavir and lopinavir/ritonavir have been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown.
Patients receiving atazanavir and lopinavir/ritonavir and TENVOR-EM should be monitored for TENVOR-EM-associated adverse events. TENVOR-EM should be discontinued in patients who develop such undesirable effects.

Tenofovir decreases the AUC and C_{min} of atazanavir. When coadministered with **TENVOR-EM**, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Atazanavir without ritonavir should not be coadministered with **TENVOR-EM**.

No drug interaction studies have been conducted using the fixed-dose combination tablet of tenofovir DF and emtricitabine tablets.

***Emtricitabine and tenofovir disoproxil fumarate*:** The steady state pharmacokinetics of emtricitabine and tenofovir were unaffected when emtricitabine and tenofovir disoproxil fumarate were administered together versus each agent dosed alone.

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

Emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Co-administration of **TENVOR-EM** 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 adefovir dipivoxil, cidofovir, acyclovir, valacyclovir, ganciclovir and valganciclovir.

No clinically significant drug interactions have been observed between emtricitabine and famciclovir, indinavir, stavudine and tenofovir disoproxil fumarate. Similarly, no clinically significant drug interactions have been observed between tenofovir disoproxil fumarate and abacavir, adefovir dipivoxil, ribavirin, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, methadone and oral contraceptives in studies conducted in healthy volunteers (see Tables 5 and 6).

TENVOR-EM is a fixed-dose combination of emtricitabine and tenofovir disoproxil fumarate. **TENVOR-EM** should not be co-administered with emtricitabine or tenofovir DF. Due to similarities between emtricitabine and lamivudine, **TENVOR-EM** should not be co-administered with other drugs containing lamivudine, including **Duovir, Lamivir, Lamivir-HBV, Duovir-N, Duovir-E Kit, Triomune, Odivir Kit and Lamivir-S.**

Table 3. Drug Interactions: Changes in Pharmacokinetic Parameters for Emtricitabine in the Presence of the Co-administered drug

Co-administered Drug	Dose of Co-administered Dose (mg)	Emtricitabine Drug Dose (mg)	N	% Change of Emtricitabine Pharmacokinetic Parameters[2] (90% CI)		
				C_{max}	AUC	C_{min}
Tenofovir DF	300 once daily x 7 days	200 once daily x 7 days	17	⇔	⇔	20 (↑12 to ↑29)
Indinavir	800 x 1	200 x 1	12	⇔	⇔	NA
Famciclovir	500 x 1	200 x 1	12	⇔	⇔	NA
Stavudine	40 x 1	200 x 1	6	⇔	⇔	NA
1. All interaction studies conducted in healthy volunteers 2. ↑ = Increase; ⇔ = No Effect; NA = Not Applicable						

Table 4. Drug Interactions: Changes in Pharmacokinetic Parameters for Co-administered Drug in the Presence of Emtricitabine[1]

Co-administered Drug	Dose of Co-administered Drug (mg)	Emtricitabine Dose (mg)	N	% Change of Emtricitabine Pharmacokinetic Parameters[2] (90% CI)		
				C_{max}	AUC	C_{min}
Tenofovir DF	300 once daily x 7 days	200 once daily x 7 days	17	⇔	⇔	⇔
Indinavir	800 x 1	200 x 1	12	⇔	⇔	NA
Famciclovir	500 x 1	200 x 1	12	⇔	⇔	NA
Stavudine	40 x 1	200 x 1	6	⇔	⇔	NA
1. Allinteraction studies conducted in healthy volunteers 2. ↑= Increase; ↓ = Decrease; ⇔ = No Effect; NA = Not Applicable						

Table 5. Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir[1] in the Presence of the Co-administered Drug

Co-administered Drug (mg)	Dose of Co-administered	N	% Change of Tenofovir Drug (mg) Pharmacokinetic parameters[2] (90% CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	⇔	⇔	NC
Adefovir dipivoxil	10 once	22	⇔	⇔	NC
Atazanavir	400 once daily x 14 days	33	↑14 (↑8 to ↑20)	↑24 (↑21 to ↑28	↑22 (↑15 to ↑30)
Didanosine (enteric-coated)	400 Once	25	⇔	⇔	⇔
Didanosine (buffered)	250 or 400 once daily x 7 days	14	⇔	⇔	⇔
Efavirenz	600 once daily x 14 days	29	⇔	⇔	⇔
Emtricitabine	200 once daily x 7 days	17	⇔	⇔	⇔
Indinavir	800 three times daily x 7 days	13	(↓3 to ↓33)	⇔	⇔
Lamivudine	150 twice daily x 7 days	15	⇔	⇔	⇔
Lopinavir/Ritonavir	400/100 twice daily x 14 days	24	⇔	↑32 (↑25 to ↑38)	↑51 ↑37 to↑66)
1. Patients received Tenofovir DF 300 mg once daily 2. Increase =↑Decrease = ↓ No Effect = ⇔; NC = Not Calculated					

Table 6. Drug Interactions: Changes in Pharmacokinetic Parameters for Co-administered Drug in the Presence of Tenofovir

Co-administered Drug (mg)	Dose of Co-administered	N	% Change of Co-Drug Pharmacokinetic[1] (90% CI) Drug (mg)		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	↑12 (↑1 to↑26)	⇔	NA
Adefovir dipivoxil	10 once	22			NA
Atazanavir	400 once daily x 14 days	34	↓21 (↓27 to↓14)	↓25 (↓30 to↓19)	↓40 (↓48 to ↓32)
(Atazanavir	Atazanavir/Ritonavir 300/100 once daily x 42 days	10	↓ 28 (↑50 to↓5)	↓25[2] (↓42 to↓ 3)[2]	↓23[2] ↓46 to ↑10)
Efavirenz	600 once daily x 14 days	30	⇔	⇔	⇔
Emtricitabine	200 once daily x 7 days	17	⇔	⇔	↑20 (↑12 to↑29)
Indinavir	800 three times daily x 7 days	12	↓11 (↑30 to↑12)	⇔	⇔
Lamivudine	150 twice daily x 7 days	15	↓24 (↓34 to↓12)	⇔	⇔
Lopinavir	Lopinavir/Ritonavir 400/100 twice daily x 14 days	24	⇔	⇔	⇔
Methadone[3]	40-110 once daily x 14 days[4]	13	⇔	⇔	⇔
Oral Contraceptives[5]	Ethinyl Estradiol/Norgestimate (Ortho-Tricyclen) Once daily x 7 days	20	⇔	⇔	⇔
Ribavirin	600 once	22	⇔	⇔	NA
Ritonavir	Lopinavir/Ritonavir 400/100 twice daily x 14 days	24			
1. Increase = ↑; Decrease = ↓; No Effect = ⇔; NA = Not Applicable 2. 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 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. 3. R-(active), S- and total methadone exposures were equivalent when dose alone or with Tenofovir DF 4. Individual subjects were maintained on their stable methadone dose. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms were reported 5. When dosed alone or with Tenofovir DF.					

Following multiple dosing to HIV-negative subjects receiving either chronic methadone maintenance therapy or oral contraceptives, or single doses of ribavirin, steady state tenofovir pharmacokinetics were similar to those observed in previous studies, indicating lack of clinically significant drug interactions between these agents and Tenofovir DF.

Co-administration of tenofovir disoproxil fumarate with didanosine results in changes in the pharmacokinetics of didanosine that may be of clinical significance. Table 7 summarizes the effects of tenofovir disoproxil fumarate on the pharmacokinetics of didanosine. Concomitant dosing of tenofovir disoproxil fumarate with didanosine buffered tablets or enteric-coated capsules significantly increases the C_{max} and AUC of didanosine. When didanosine 250 mg enteric-coated capsules were administered with tenofovir DF, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions. The mechanism of this interaction is unknown.

Table7: Drug interactions: Pharmacokinetic Parameters for Didanosine in the Presence of Tenofovir DF

Didanosine[1] Dose (mg) Method of Administration[2]	Tenofovir DF Method of Administration[2]	N		% Difference (90% CI) vs. Didanosine 400 mg Alone, Fasted[3]
			C_{max}	AUC
Buffered tablets				
400 once daily[4] x 7 days	Fasted 1 hour after didanosine	14	↑ 28 (↑11 to↑48)	↑44 (↑31 to↑ 59)
Enteric coated capsules				
400 once, fasted	With food, 2 hr after didanosine	26	↑48 (↑25 to↑76)	↑48 (↑31 to↑ 67)
400 once, fasted	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)	⇔
250 once, fasted	Simultaneously with didanosine	28	⇔	↑14 (0 to ↑31)
250 once, with food	Simultaneously with didanosine	28	↑60 (↑44 to↑79)	↓11 (↓23 to ↑2)
1. See PRECAUTIONS regarding use of didanosine with Tenofovir 2. Administration with food was with a light meal (~ 373 kcal, 20% fat) 3. Increase = ↑; Decrease = ↓; No Difference = ⇔ 4. Includes 4 subjects weighing < 60 kg receiving ddI 250 mg				

Undesirable Effects
Clinical trials

Tenofovir DF and Emtricitabine: Safety and efficacy studies using tenofovir DF and emtricitabine coformulated tablets or using emtricitabine and tenofovir DF in combination are ongoing. Two hundred eighty three HIV-1 infected patients have received combination therapy with emtricitabine and tenofovir DR with either a non-nucleoside reverse transcriptase inhibitor or protease inhibitor for 24 to 48 weeks in ongoing clinical studies. Based on these limited data, no new patterns of adverse events were identified and there was no increased frequency of established toxicities.

Emtricitabine: Adverse events that occurred in > 5% of patients receiving emtricitabine with other antiretroviral agents in clinical trials include abdominal pain, asthenia, headache, diarrhoea, nausea, vomiting, dizziness and rash event (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash and allergic reaction). Approximately 1% of patients discontinued participation in the clinical studies because of these adverse events.

Other adverse events reported include dyspepsia, arthralgia, myalgia, abnormal dreams, depressive disorder, insomnia, neuropathy, peripheral neuritis, paraesthesia, increased cough and rhinitis.
All adverse events reported include dyspepsia, arthralgia, myalgia, abnormal dreams, depressive disorder, insomnia, neuropathy, peripheral neuritis, paraesthesia, increased cough and rhinitis.

All adverse events were reported with similar frequency in emtricitabine and control treatment groups with the exception of skin discoloration, which was reported with higher frequency in the emtricitabine, treated group. Skin discoloration, manifested by hyperpigmentation on the palms and/or soles was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

Grade ¾ elevations of ALT and AST (> 5 x ULN), bilirubin (> 2.5 x ULN), creatine kinase (> 4 x ULN), decreased neutrophils (< 750/mm^3), pancreatic amylase (> 2.0 x ULN), serum amylase (> 2 x ULN), serum glucose (< 40 or > 250 mg/dL), serum lipase (> 2.0 x ULN) and triglycerides (> 750 mg/dL) have been reported to occur in 1-12% of patients receiving emtricitabine.

Tenofovir DF: Adverse events that occurred in > 5% of patients receiving TDF with other antiretroviral agents in clinical trials included: headache, nausea, diarrhoea, vomiting, rash event (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash and pustular rash), and depression. Less than 1% of patients continued participation in the clinical studies because of gastrointestinal adverse events.

Other adverse events include asthenia, pain, abdominal pain, back pain, chest pain, fever, flatulence, dizziness, dyspepsia, anorexia, arthralgia, insomnia, abnormal dreams, paraesthesia, peripheral neuropathy (including peripheral neuritis and neuropathy), pneumonia, sweating, myalgia and weight loss.

Grade ¾ elevations of ALT and AST (> 5 x ULN), creatine kinase (> 4 x ULN), serum amylase (> 2 x ULN), urine glucose (≥ 3+), serum glucose (> 250 mg/dL) and serum triglycerides (> 750 mg/dL), haematuria (> 100 RBC/HPF) and decreased neutrophils (< 750/mm^3) have been reported to occur in 2-12% of patients receiving TDF.

Post Marketing Experience

Emtricitabine: No additional events have been identified for inclusion in this section.
Tenofovir disoproxil fumarate: in addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of tenofovir DF. Because they are reported voluntarily form a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion because of a combination of their seriousness, frequency of reporting or potential causal connection to tenofovir DF.

Immune system disorders: Allergic reaction

Metabolism and nutrition disorders: Hypophosphataemia, lactic acidosis
Respiratory, thoracic, and mediastinal disorders: Dyspnoea

Gastrointestinal disorders: Abdominal pain, pancreatitis

Renal and urinary disorders: Renal insufficiency, renal failure, fanconi syndrome, proximal tubulopathy, proteinuria, increased creatinine, acute tubular necrosis.

Overdose
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.

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

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

Storage:
Store below 30°C.

Presentation :
Tenvor-EM Container of 30 tablets

Cipla

DI93 B