1. NAME OF THE MEDICINAL PRODUCT

TAVIN-EM Tenofovir Disoproxil Fumarate and Emtricitabine Film Coated Tablets (300mg/200mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate,which is equivalent to 245 mg of tenofovir disoproxil.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral, film-coated tablets
White to off white, modified capsule shaped, film-coated tablets, debossed with “EM” on one side “144” on the other side of the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of HIV-1 infection:

TAVIN-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.
The following points should be considered when initiating therapy with Emtricitabine and Tenofovir disoproxil fumarate for the treatment of HIV-1 infection:

- It is not recommended that TAVIN-EM be used as a component of a triple nucleoside regimen.
- Emtricitabine and Tenofovir disoproxil fumarate should not be co-administered with lamivudine + tenofovir DF + Efavirenz, emtricitabine, tenofovir DF or lamivudine-containing products.

In treatment experienced patients, the use of TAVIN-EM should be guided by laboratory testing and treatment history.

Pre-exposure prophylaxis (PrEP):

Emtricitabine/Tenofovir Disoproxil is indicated in combination with safer sex practices for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in adults at high risk.When prescribing TAVIN-EM for PrEP, healthcare providers must:

- prescribe TAVIN-EM as part of a comprehensive prevention strategy because emtricitabine/tenofovir disoproxil is not always effective in preventing the acquisition of HIV-1 infection.
- counsel all uninfected individuals to strictly adhere to the recommended TAVIN-EM dosing schedulebecause the effectiveness of emtricitabine/tenofovir disoproxil in reducing the risk of acquiring HIV-1was strongly correlated with adherence as demonstrated by measurable drug levels in clinical trials.
- confirm a negative HIV-1 test immediately prior to initiating TAVIN-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, including acute or primary HIV-1 infection; and - screen for HIV-1 infection at least once every 3 months while taking emtricitabine/tenofovir disoproxil for PrEP.

4.2 Posology and method of administration

Treatment of HIV-1 infection:

The dosage of TAVIN-EM is one tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir DF) once daily taken orally with or without food.

Dose adjustment for renal impairment

Significantly increased drug exposures occurred when emtricitabine or tenofovir DF were administered to patients with moderate to severe renal impairment. Therefore, the dosing interval of TAVIN-EM should be adjusted in patients with baseline creatinine clearance of 30-49 mL/min using the recommendations in table below. 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.

No dose adjustment is necessary for patients with mild renal impairment (creatinine clearance of 50– 80 mL/min). Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients with mild renal impairment.

Dosage Adjustment for 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	TAVIN-EM should not be administered

a Calculated using ideal (lean) body weight

Pre-exposure prophylaxis (PrEP):

This indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1infection and in heterosexual serodiscordant couples.

Posology

Prevention of HIV in adults: One tablet, once daily.

Adults with renal impairment

Routine monitoring of calculated creatinine clearance and serum phosporus should be performed in patients with mild renal impairment.

TAVIN-EM should only be used in individuals with creatinine clearance (CrCl) < 80 mL/min if potential benefits are considered to outweigh the potential risks. See Table 1.

Table 1: Dosing recommendations in adults with renal impairment

	Pre-exposure prophylaxis
Mild renal impairment (CrCl 50-80mL/min)	Limited data from clinical studies support once daily dosing in HIV-1 uninfected individuals with CrCl 60-80 mL/min. Use is not recommended in HIV-1 uninfected individuals with CrCl < 60 mL/min as it has not been studied in this population
Moderate renal impairment (CrCl 30-49 mL/min)	Not recommended for use in this population.
Severe renal impairment (CrCl < 30 mL/min) and haemodialysis patients.	Not recommended for use in this population.

Method of administration

Taken orally with or without food.

4.3 Contraindications

TAVIN-EM is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product.
Use for pre-exposure prophylaxis in individuals with unknown or positive HIV-1 status.

4.4 Special warnings and precautions for use

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.

TAVIN-EM IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF TAVIN-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 DF. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE TAVIN-EM AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED.

Overall HIV-1 infection prevention strategy
Emtricitabine/Tenofovir Disoproxil is not always effective in preventing the acquisition of HIV. The time to onset of protection after commencing emtricitabine/tenofovir disoproxil is unknown.

Emtricitabine/Tenofovir Disoproxil should only be used for pre-exposure prophylaxis as part of an overall HIV-1 infection prevention strategy including the use of other HIV-1 prevention measures (e.g., consistent and correct condom use, knowledge of HIV-1 status, regular testing for other sexually transmitted infections).

Risk of resistance with undetected HIV-1 infection:
Emtricitabine/Tenofovir Disoproxil should only be used to reduce the risk of acquiring HIV-1 in individuals confirmed to be HIV negative. Individuals should be re-confirmed to be HIV-negative at frequent intervals (e.g., at least every 3 months) using a combined antigen/antibody test while taking emtricitabine/tenofovir disoproxil for pre-exposure prophylaxis.

Emtricitabine/Tenofovir Disoproxil alone does not constitute a complete regimen for the treatment of HIV-1 and HIV-1 resistance mutations have emerged in individuals with undetected HIV-1 infection who are only taking emtricitabine/tenofovir disoproxil.

If clinical symptoms consistent with acute viral infection are present and recent (< 1 month) exposures to HIV-1 are suspected, use of emtricitabine/tenofovir disoproxil should be delayed for at least one month and HIV-1 status reconfirmed before starting Emtricitabine/Tenofovir Disoproxil for pre- exposure prophylaxis.
Importance of adherence:
The effectiveness of emtricitabine/tenofovir disoproxil in reducing the risk of acquiring HIV-1 is strongly correlated with adherence as demonstrated by measurable drug levels in blood.

HIV-1 uninfected individuals should be counselled at frequent intervals to strictly adhere to the recommended Emtricitabine/Tenofovir Disoproxil daily dosing schedule.

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. 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 TAVIN-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, HBV and HCV Co-infection
The efficacy and safety of tenofovir disoproxil fumarate-emtricitabine has not been thoroughly studied in the treatment of HIV-HBV co-infection. Several studies have indicated that discontinuation of tenofovir disoproxil fumarate-emtricitabine in HBV infected patients may result in severe and acute exacerbation or flare up of the hepatitis. Liver function tests should be monitored for at least several months in HIV/HBV co-infected patients who are suspended from treatment with tenofovir disoproxil fumarate-emtricitabine. Because of the risk of HIV resistance with two drug therapy, if co-infected patients require treatment, other agents such as adefovir or pegylated interferon should be used.

The safety and efficacy of Emtricitabine/Tenofovir Disoproxil for pre-exposure prophylaxis in patients with HBV or Hepatitis C Virus (HCV) infection has not been established.

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 DF.

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with tenofovir disoproxil fumarate and emtricitabine. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment.

Emtricitabine and tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic agent.

For the treatment of HIV-1 infection, dosing interval adjustment of TAVIN-EM and close monitoring of renal function are recommended in all patients with creatinine clearance 30-49 mL/min. No safety or efficacy data are available in patients with renal impairment who received tenofovir DF and emtricitabine using these dosing guidelines, so the potential benefit of Emtricitabine and tenofovir disoproxil fumarate therapy should be assessed against the potential risk of renal toxicity. Emtricitabine and tenofovir disoproxil fumarate should not be administered to patients with creatine clearance <30 mL/ min or patients requiring hemodialysis.

Renal management in pre-exposure prophylaxis:

Emtricitabine/Tenofovir Disoproxil has not been studied in HIV-1 uninfected individuals with creatinine clearance < 60 mL/min and is therefore not recommended for use in this population. If serum phosphate is < 1.5 mg/dL (0.48 mmol/L) or creatinine clearance is decreased to < 60 mL/min in any individual receiving emtricitabine/tenofovir disoproxil for pre-exposure prophylaxis, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations. Consideration should be given to interrupting use of emtricitabine/tenofovir disoproxil in individuals with creatinine clearance decreased to < 60 mL/min or decreases in serum phosphate to < 1.0 mg/dL (0.32 mmol/L). Interrupting use of emtricitabine/tenofovir disoproxil should also be considered in case of progressive decline of renal function when no other cause has been identified.

Decreases in Bone Mineral Density

Subclinical renal phosphate wasting could possibly contribute to a decrease in bone mineral density that was reported in a study conducted among treatment naïve patients who were treated with tenofovir disoproxil fumarate in reference to a published trial report. A decrease in bone mineral density at the lumbar spine and hip, especially between weeks 24 and 48, was evident but was non-progressive through 288 weeks. Thus, monitoring of bone mineral density should be considered in patients with history of, or risk factors for, pathologic fractures. To the knowledge of the authors, no study has examined the benefit of calcium and vitamin D supplementation or bisphosponates in this setting.

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.

Early Virologic Failure

Caution when using triple nucleoside reverse transcriptase inhibitor (NRTI) therapy. Clinical studies have demonstrated that such treatments are generally less effective than triple drug regimens containing 2 NRTIs in combination with either a non–nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor; early virologic failure and high rates of resistance substitutions have been reported. Patients receiving triple NRTI therapy should be carefully monitored and considered for treatment modification.

4.5 Interaction with other medicinal products and other forms of interaction

Any medications that reduce renal function may increase concentration of emtricitabine and tenofovirdisoproxil fumarate. No drug interactions with clinical consequences are known for emtricitabine. Co- administration of tenofovir disoproxil fumarate with certain protease inhibitors, including atazanavir,lopinavir/ritonavir, and darunavir (TMC-114)/ritonavir results in increased plasma levels of tenofovir disoproxil fumarate and, in the case of atazanavir and lopinavir/ritonavir, reduced protease inhibitor troughs. While no dose adjustment is recommended when tenofovir disoproxil fumarate is used withthese drugs, in cases where baseline protease resistance mutations have modestly raised the concentration of the drug required to inhibit the virus, this effect of tenofovir disoproxil fumarate could be significant. Atazanavir should always be ritonavir boosted (atazanavir 300 mg should be boosted with ritonavir 100 mg) when used with tenofovir disoproxil fumarate.

Tenofovir disoproxil fumarate should be used very cautiously with didanosine due to increased rates of adverse reactions including peripheral neuropathy and pancreatitis. This is likely a result of a drug interaction resulting in a 40%–50% increase in plasma didanosine levels and/or intracellular drug interactions. In addition, use of tenofovir disoproxil fumarate with didanosine has also been associated with paradoxical CD4 declines or less than robust CD4 increases in some, but not all studies. These results are reminiscent of those seen in studies combining didanosine with hydroxyurea. If co- administration of didanosine and tenofovir disoproxil fumarate is necessary, didanosine dose should be adjusted and patients should be closely monitored for didanosine- related adverse reactions. The recommended didanosine dose for patients weighing >60 kg in this setting is 250 mg; however, thereis no adequate information for patients weighing below 60 kg.

Patients with Renal Impairment

Because both tenofovir disoproxil fumarate and emtricitabine are excreted via the kidneys, modification of tenofovir disoproxil fumarate dosage and special caution is necessary when treating patients with renal impairments.

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy Category B:

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

Lactation

Tenofovir disoproxil fumarate-Emtricitabine is excreted in breast milk and should not be used while nursing. The Centres for Disease Control and Prevention recommend that HIV-infected women do not breast feed their infants to avoid risking postnatal transmission of HIV.

4.7 Effects on ability to drive and use machines

Unknown

4.8 Undesirable effects

The most frequently reported adverse reactions considered possibly or probably related to emtricitabine and/or tenofovir disoproxil fumarate were nausea and diarrhoea.
Laboratory abnormalities such as elevated creatine kinase, triglycerides, neutropenia, and amylase have been reported.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Emtricitabine is an NRTI that is converted intracellularly to its active metabolite, emtricitabine 5'- triphosphate. Tenofovir DF is an ester prodrug of the NRTI, tenofovir. The prodrug is hydrolysed intracellularly to tenofovir, which is then converted to the active metabolite, tenofovir diphosphate. The active metabolites of the drugs compete with deoxycytidine 5'-triphosphate (emtricitabine 5'- triphosphate) or deoxyadenosine 5'-triphosphate (tenofovir diphosphate) for incorporation into HIV DNA, thereby terminating viral DNA chain growth and inhibiting the activity of the viral reverse transcriptase.

5.2 Pharmacokinetic properties

Absorption

The median bioavailability of emtricitabine in fasted patients following a single oral dose is 92%. The median bioavailability of tenofovir in fasted patients following a single oral dose is 25%.

Distribution

Protein binding of emtricitabine is less than 4%; and of tenofovir, is less than 0.7% (plasma) and 7.2% (serum).

Metabolism and Elimination

Emtricitabine undergoes limited metabolism and is primarily excreted by the kidneys. The median terminal elimination half-lives of emtricitabine and tenofovir were 15.5 and 17.6 hours when healthy volunteers received a single dose of co-formulated emtricitabine/tenofovir DF 200mg/300mg on two separate occasions.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose
Croscarmellose sodium
Pregelatinized starch
Magnesium Stearate
Isopropyl alcohol
Opadry AMB white 80W68912
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to the expiry date on the labels/ outer carton.

6.4 Special precautions for storage

Store below 30°C in a tightly closed container.

6.5 Nature and contents of container

30 tablets in HDPE Container.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Manufacturer

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