1. NAME OF THE MEDICINAL PRODUCT

TAVIN – EM

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Emtricitabine 200 mg

Tenofovir Disoproxil Fumarate 300 mg

3. PHARMACEUTICAL FORM

Film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This product 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.

4.2 Posology and method of administration

One tablet to be taken orally once daily with or without food.

Renal impairment: Significantly increased drug exposures occurred when Emtricitabine or Tenofovir disoproxil fumarate were administered to patients with moderate to severe renal impairment. Patients with lowered creatinine clearance (30 to 49 ml/min) should receive one tablet every 48 hours. This product should not be prescribed for patients with reduced renal function (creatinine clearance less than 30 ml/min or requiring hemodialysis).

4.3 Contraindications

This product is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product.

4.4 Special warnings and precautions for use

Redistribution/accumulation of body fat, including central obesity and 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 is unknown. Lactic acidosis

and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including emtricitabine and tenofovir. Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. It is not recommended that this product be used as a component of a triple nucleoside regimen.
Emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Emtricitabine and tenofovir exposure may be markedly increased in patients with moderate or severe renal impairment. Consequently, a dose interval adjustment is required in patients with creatinine clearance between 30 and 49 ml/min. The safety and efficacy of Emtricitabine and tenofovir in patients with renal impairment have not been established. Careful monitoring for signs of toxicity, such as deterioration of renal function, and for changes in viral load is required in patients with pre-existing renal impairment once Emtricitabine and tenofovir has been started at prolonged dosing intervals. Emtricitabine and tenofovir is not recommended for patients with creatinine clearance < 30 ml/min or patients who require haemodialysis.

As the required dose modifications for emtricitabine and tenofovir disoproxil fumarate cannot be achieved with this product, it is not recommended for use in patients with moderate to severe renal impairment (creatinine clearance < 30 ml/min). Renal events, which may include hypophosphataemia, have been reported with the use of tenofovir disoproxil fumarate in clinical practice. Careful monitoring of renal function (serum creatinine and serum phosphate) is recommended before taking this product, every four weeks during the first year, and then every three months. In patients with a history of renal dysfunction or in patients who are at risk for renal dysfunction, consideration should be given to more frequent monitoring of renal function. Use of this product should be avoided with concurrent or recent use of a nephrotoxic medicinal product. This product should be avoided in antiretroviral-experienced patients with HIV-1 harbouring the K65R mutation.
In a 144-week controlled clinical study that compared tenofovir disoproxil fumarate with stavudine in combination with lamivudine and efavirenz in antiretroviral-naïve patients, small decreases in bone mineral density of the hip and spine were observed in both treatment groups. Decreases in bone mineral density of spine and changes in bone biomarkers from baseline were significantly greater in the tenofovir disoproxil fumarate treatment group at 144 weeks. Decreases in bone mineral density of hip were significantly greater in this group until 96 weeks. However, there was no increased risk of fractures or

evidence for clinically relevant bone abnormalities over 144 weeks. If bone abnormalities are suspected then appropriate consultation should be obtained.

Patients with HIV and hepatitis B or C virus co-infection: Patients with chronic hepatitis B or C treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. Physicians should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV). Exacerbations of hepatitis have been reported in patients after the discontinuation of emtricitabine or tenofovir disoproxil fumarate. This product is not recommended for the treatment of chronic HBV infection and the safety and efficacy of this product has not been established in patients coinfected with HBV and HIV-1.

Liver disease: The safety and efficacy of emtricitabine or tenofovir disoproxil fumarate have not been established in patients with significant underlying liver disorders. Based on minimal hepatic metabolism and the renal route of elimination for, it is unlikely that a dose adjustment would be required for this product in patients with hepatic impairment. Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Lactic acidosis: Lactic acidosis, usually associated with hepatic steatosis, has been reported with the use of nucleoside analogues. Early symptoms (symptomatic hyperlactataemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness). Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure or renal failure. Lactic acidosis generally occurred after a few or several months of treatment. It is recommended that treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactataemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.

Keep away from the reach of children.

4.5 Interaction with other medicinal products and other forms of interaction

Emtricitabine has been evaluated in healthy volunteers in combination with tenofovir disoproxil fumarate (TDF), zidovudine, indinavir, famciclovir, and stavudine. A 20% increase in plasma trough concentrations of emtricitabine occurred when it was

administered concurrently with tenofovir disoproxil fumarate. When emtricitabine was given concurrently with zidovudine, zidovudine's AUC and Cmax increased by 13% and 17% respectively. Because renal elimination of emtricitabine is through glomerular filtration and active tubular secretion, there may be competition for elimination with other compounds that are also renally eliminated. When administered with tenofovir disoproxil fumarate, the Cmax and AUC of buffered and enteric-coated didanosine increased significantly. Increases in didanosine concentrations of this magnitude could potentiate didanosine-associated adverse events, including pancreatitis and neuropathy. Coadministration of tenofovir disoproxil fumarate 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. Patients receiving atazanavir or lopinavir/ritonavir and tenofovir disoproxil fumarate should be monitored for tenofovirassociated adverse events. Tenofovir disoproxil fumarate should be discontinued in patients who develop tenofovir-associated adverse events. Tenofovir disoproxil fumarate decreases the AUC and Cmin of atazanavir. When coadministered with tenofovir disoproxil fumarate, it is recommended that atazanavir 300 mg be given with ritonavir 100 mg; atazanavir should not be coadministered with tenofovir disoproxil fumarate unless given with ritonavir. Atazanavir without ritonavir should not be coadministered with this product. Coadministration with other drugs that are eliminated by active tubular secretion, such as cidofovir, acyclovir, valacyclovir, ganciclovir, and valganciclovir, may increase serum concentrations of either tenofovir or the coadministered drug due to competition for this elimination pathway.

4.6 Pregnancy and lactation

Pregnancy Category B

This product 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 this product.

4.7 Effects on ability to drive and use machines

Not known. Dizziness has been reported during treatment with both emtricitabine and tenofovir disoproxil fumarate.

4.8 Undesirable effects

The most frequently reported adverse effects of emtricitabine are mild to moderate headache, nausea, diarrhea, and skin rash. Skin discoloration on palms and soles was reported with higher frequency in emtricitabine-treated patients than in controls, but the mechanism of skin discoloration is unknown. In some patients coinfected with HIV and hepatitis B, exacerbation of hepatitis has been reported after discontinuing treatment with emtricitabine. Treatment-emergent grade 3 or 4 laboratory abnormalities have been reported in at least 1% of patients receiving emtricitabine. These abnormalities include triglycerides greater than 750 mg/dl and creatine kinase over four times the upper limit of normal.

The most common adverse effects associated with tenofovir disoproxil fumarate are asthenia, diarrhea, nausea, and vomiting. Less common side effects of tenofovir disoproxil fumarate are hepatotoxicity, including lactic acidosis; abdominal pain; anorexia; and flatulence. Some side effects of tenofovir disoproxil fumarate occurring with undetermined incidence include allergic reaction, dyspnea, Fanconi's syndrome, hypophosphatemia, pancreatitis, proximal tubulopathy, renal failure or insufficiency, and acute tubular necrosis. Higher tenofovir concentrations could potentiate tenofovir disoproxil fumarate - associated adverse events, including renal disorders.

4.9 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. Hemodialysis treatment removes approximately 30% of the emtrictabine 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 disoproxil fumarate 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 disoproxil fumarate, a 4-hour haemodialysis session removed approximately 10% of the administered tenofovir dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.

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.

5.2 Pharmacokinetic properties

Emtricitabine is rapidly and extensively absorbed following oral administration, reaching peak plasma concentrations (Cmax) at 1 to 2 hours. The mean absolute bioavailability of emtricitabine is 93% following multiple doses of the drug. Emtricitabine is less than 4% bound to plasma proteins. Emtricitabine does not inhibit CYP450 enzymes. Biotransformation occurs through glucuronidation and oxidation. Following administration of 14C-emtricitabine, 86% of the dose was recovered in urine and 14% in feces. The plasma half-life of emtricitabine is approximately 10 hours. Renal clearance of the drug

exceeds estimated creatinine clearance, indicating elimination by both glomerular filtration and active tubular secretion.

Tenofovir: Oral bioavailability of tenofovir disoproxil fumarate in fasted patients is approximately 25%. Administration of tenofovir disoproxil fumarate with a high fat meal increases the oral bioavailability, with an increase in tenofovir area under the plasma concentration-time curve (AUC) of approximately 40% and an increase in maximum plasma concentration (Cmax) of approximately 14%. Food delays the time to tenofovir Cmax by approximately 1 hour. Following oral administration of a single 300 mg dose of tenofovir disoproxil fumarate to HIV infected patients in the fasted state Cmax is achieved in approximately 1 hour. The pharmacokinetics of tenofovir is dose proportional over a wide dose range and are not affected by repeat dosing. Binding of tenofovir to human plasma or serum proteins is less than 0.7% and 7.2%, respectively. After multiple oral doses of tenofovir disoproxil fumarate under fed conditions, approximately 32% of the administered dose is recovered in urine over 24 hours. Tenofovir is principally eliminated by the kidneys by a combination of glomerular filtration and active tubular secretion.

5.3 Preclinical safety data

Non-clinical data on emtricitabine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. Emtricitabine did not show any carcinogenic potential in long-term oral carcinogenicity studies in mice and rats.

Preclinical studies of tenofovir disoproxil fumarate showed target organ effects in gastrointestinal tract, kidney, bone and a decrease in serum phosphate concentration.

Combination of emtricitabine and tenofovir disoproxil fumarate, found no exacerbation of toxicological effects compared to the separate components.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

1) Microcrystalline Cellulose
2) Croscarmellose sodium
3) Pregelatinized starch
4) Magnesium Stearate

5) Isopropyl alcohol

6) Opadry AMB white 80W68912

7) Purified water

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at 20° to 25° C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F).

6.5 Nature and contents of container

30 tablets in a HDPE bottle.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

Emcure Pharmaceuticals Ltd.

8. MARKETING AUTHORISATION NUMBER(S)

Shall be provided when available.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not Applicable

10. DATE OF REVISION OF THE TEXT

25th March 2014.