Important Safety Information for Prescribers About Emtricitabine/ Tenofovir Disoproxil for a Pre-exposure Prophylaxis (PrEP) Indication

Emtricitabine/Tenofovir disoproxil is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection 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 on men and women in heterosexual serodiscordant couples.

Key Safety Information Regarding the Use of Emtricitabine/Tenofovir Disoproxil for PrEP:

- HIV-1 resistance mutations have emerged in individuals with undetected HIV-1 infection who were only taking Emtricitabine/ Tenofovir disoproxil.
- Emtricitabine/Tenofovir disoproxil should only be used to reduce the risk of acquiring HIV-1 in individuals confirmed to be HIV-negative prior to initiating Emtricitabine/Tenofovir disoproxil for pre-exposure prophylaxis and re-confirmed at frequent intervals (e.g. at least every 3 months) while taking Emtricitabine/Tenofovir disoproxil for PrEP, using a combined antigen/antibody test.
- Do not initiate (or re-initiate) Emtricitabine/Tenofovir disoproxil for pre-exposure prophylaxis if signs or symptoms of acute HIV infection are present unless negative infection status is confirmed.
- Counsel HIV-1 uninfected individuals to strictly adhere to the recommended Emtricitabine/Tenofovir disoproxil dosing schedule.
- Do not prescribe Emtricitabine/Tenofovir disoproxil to uninfected individuals with an estimated creatinine clearance (CrCl) below 60 mL/min and only use emtricitabine/ tenofovir disoproxil in individuals with CrCl <80 mL/min if the potential benefits are considered to outweigh the potential risks. Renal function should be regularly monitored while taking Emtricitabine/Tenofovir disoproxil for PrEP.

Factors to help identify individuals at high risk of acquiring HIV-1:

- 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:
  - o Inconsistent or no condom use
  - o Diagnosis of a sexually transmitted infection (STI)
  - o Exchange of sex for commodities (such as money, food, shelter, or drugs)
  - o Use of illicit drugs or alcohol dependence
  - o Incarceration
  - o Partner(s) of unknown HIV-1 status with any of the factors listed above

Risk of Development of HIV-1 Drug Resistance in Undiagnosed HIV-1–Infected Individuals

Emtricitabine/Tenofovir disoproxil for a PrEP indication is contraindicated in individuals with unknown or HIV-1–positive status

- Use Emtricitabine/Tenofovir disoproxil to reduce the risk of acquiring HIV-1 infection only in individuals confirmed to be HIV-1 negative. Emtricitabine/Tenofovir disoproxil alone does not constitute a complete treatment regimen for HIV-1 infection and HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only Emtricitabine/Tenofovir disoproxil.
- Before starting Emtricitabine/Tenofovir disoproxil for PrEP:
  - o Confirm a negative HIV-1 test, using a combined antigen/antibody test.
  - o If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting Emtricitabine/Tenofovir disoproxil for a PrEP indication for at least 1 month and reconfirm HIV-1 status.
- During use of Emtricitabine/Tenofovir disoproxil for PrEP:
  - o Screen for HIV-1 infection at frequent intervals (e.g. at least every 3 months) using a combined antigen/antibody test.
  - o If symptoms consistent with acute HIV-1 infection develop following a potential exposure event, Emtricitabine/Tenofovir disoproxil should be discontinued until negative infection status is confirmed.

Only Use Emtricitabine/Tenofovir Disoproxil for PrEP as Part of a Comprehensive Prevention Strategy

Emtricitabine/Tenofovir disoproxil for a PrEP indication should be used only as part of an overall HIV-1 infection prevention strategy including the use of other HIV-1 infection prevention measures, such as safer sex practices, because Emtricitabine/Tenofovir disoproxil is not always effective in preventing the acquisition of HIV-1 infection.

- Counsel uninfected individuals at high risk about safer sex practices, including:
  - o Using condoms consistently and correctly
  - o Knowing their HIV-1 status and that of their partner(s)
  - o Being regularly tested for other sexually transmitted infections that can facilitate HIV- 1 transmission (eg, syphilis and gonorrhoea).

The Importance of Strict Adherence to the Recommended Dosing Regimen

The effectiveness of Emtricitabine/Tenofovir disoproxil for a PrEP indication in reducing the risk of acquiring HIV-1 infection is strongly correlated with adherence and measurable drug levels.

- All uninfected individuals at high risk taking Emtricitabine/Tenofovir disoproxil for a PrEP indication must be counselled to strictly adhere to the recommended daily dosing schedule to reduce the risk of acquiring HIV-1 infection.
- The recommended dose is one tablet, once daily
- All uninfected individuals at high risk taking emtricitabine/ tenofovir disoproxil for a PrEP indication should be supplied with a PrEP educational brochure prior to initiation of treatment and a PrEP reminder card when each new bottle is supplied to the individual

Emtricitabine/Tenofovir disoproxil related renal toxicity

Emtricitabine/ tenofovir disoproxil should only be used in individuals with CrCl <80mL/min if the potential benefits are considered to outweigh the potential risks. Renal failure, renal impairment, elevated creatinine, hypophosphatemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil.

• Assess estimated creatinine clearance (CrCl) in all patients prescribing Emtricitabine/Tenofovir disoproxil.

- In individuals without renal risk factors, renal function (creatinine clearance and serum phosphate) should also be monitored after two to four weeks of treatment, after three months of treatment and every three to six months. In individuals at risk for renal impairment, more frequent monitoring of renal function is required.
- Avoid administering Emtricitabine/Tenofovir disoproxil with concurrent or recent use of nephrotoxic drugs. If concomitant use of Emtricitabine/ Tenofovir disoproxil and nephrotoxic agents is unavoidable, renal function should be monitored weekly.
- Cases of acute renal failure, some requiring hospitalization and renal replacement therapy, have been reported after initiation of high dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) in patients with risk factors for renal dysfunction; consider alternatives to NSAIDs in these patients. If Emtricitabine/Tenofovir disoproxil is co-administered with an NSAID, renal function should be monitored adequately.
- **Do not prescribe Emtricitabine/Tenofovir Disoproxil for PrEP to individuals with an estimated CrCl below 60 mL/min.**
- 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 PrEP, renal function should be reevaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations.
- Consideration should be given to interrupting use of Emtrictabine/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.

Bone effects

Small decreases in bone mineral density (BMD) have been seen in uninfected individuals receiving Emtrictabine/Tenofovir disoproxil.

- If bone abnormalities are suspected then appropriate consultation should be obtained.

HBV infection

There is a risk of acute and severe acute exacerbation of hepatitis when individuals with hepatitis B infection stop taking Emtricitabine/ Tenofovir disoproxil. As a result, it is recommended that:

- all individuals be tested for the presence of current HBV before initiating Emtricitabine/Tenofovir disoproxil and routinely during the use of Emtricitabine/Tenofovir disoproxil for PrEP
- HBV-uninfected individuals should be offered vaccination
- individuals infected with HBV who discontinue Emtricitabine/Tenofovir disoproxil are closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment.

Use of Emtricitabine/tenofovir disoproxil for a PrEP indication in pregnancy

The balance of risks and benefits for women who may be pregnant or may want to become pregnant should be evaluated, if applicable. Prescribers are encouraged to enroll women exposed to emtricitabine/ tenofovir disoproxil for PrEP during pregnancy to the Antiretroviral Pregnancy Registry at www.apregistry.com. The Registry aims to detect any major teratogenic effects involving antiretroviral agents to which pregnant women are exposed.

Important Safety Information for Prescribers About Emtricitabine/ Tenofovir Disoproxil for a Pre-exposure Prophylaxis (PrEP) Indication

Reporting of side effects
Healthcare providers are asked to report any suspected adverse reactions. For any side effects please report to the Medicines Authority at http://www.medicinesauthority.gov.mt/adrportal or to the local representative of Mylan S.A.S. :
V.J. Salomone Pharma Ltd.,
Upper Cross Road,
Marsa MRS1542, Malta, Tel: +356 21 220 174 and 24h PV mobile +356 99644126.
By reporting side effects you can help provide more information on the safety of this medicine.

Further copies of this material can be requested from info.uk@mylan.co.uk