This EM contains important safety information about Invented name (**Emtricitabine/ Tenofovir disoproxil Mylan**) and advice on risk minimisation.

This booklet was developed by MAH.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to: Medicines Authority at http://www.medicinesauthority.gov.mt/adrportal
Adverse reactions/events should also be reported to MAH at e-mail address or to the local representative of Viatris: V.J. Salomone Pharma Ltd., Upper Cross Road, Marsa MRS1542, Malta, Tel:+356 21 220 174 and 24h PV mobile +356 99644126

PrEP Educational Guide for Prescribers

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

Emtricitabine/Tenofovir disoproxil Mylan 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.

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

- Emtricitabine/ Tenofovir disoproxil Mylan should only be used to reduce the risk of acquiring HIV-1 in individuals confirmed to be HIV-negative priorto initiating Emtricitabine/ Tenofovir disoproxil Mylan for PrEP. HIV-negative status should be confirmed at frequent intervals (e.g. at least every 3 months) while taking Emtricitabine/tenofovir disoproxil Mylan for PrEP, using a combined antigen/antibody test.
- HIV-1 resistance mutations have emerged in individuals with undetected HIV-1 infection who were only taking Emtricitabine/tenofovir disoproxil Mylan.
- Do not initiate (or re-initiate) Emtricitabine/ Tenofovir disoproxil Mylan for PrEPif signs or symptoms of acute HIV infection are present unless negativeinfection status is confirmed.
- Counsel HIV-1 uninfected individuals to strictly adhere to the recommended Emtricitabine/ Tenofovir disoproxil Mylan dosing schedule.
- Do not prescribe Emtricitabine/ Tenofovir disoproxil Mylan to uninfected individuals with an estimated creatinine clearance (CrCl) below 60 mL/

min and only use Emtricitabine/ Tenofovir disoproxil Mylan in adults 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.

Important additional information for the use of Emtricitabine/ Tenofovir disoproxil Mylan for PrEP in adolescents:

- The use of Emtricitabine/ Tenofovir disoproxil Mylan for PrEP in adolescents has to be carefully considered on an individual basis, including considerations of competence, the individual's understanding of the need for adherence to Emtricitabine/tenofovir disoproxil Mylan for PrEP to beeffective, and the risk of acquiring other sexually transmitted infections
- Adherence in adolescents and young adults has been shown to be lower than in older adults and no data is available on the use of PrEP in female adolescents. A Reminder Card is available to support adherence in both adults and adolescents
- At each visit individuals should be reassessed to ascertain whether they remain at high risk of HIV-1 infection. The risk of HIV-1 infection should be balanced against the potential for renal and bone effects with long-term use of Emtricitabine/tenofovir disoproxil Mylan
- Emtricitabine/ Tenofovir disoproxil Mylan should not be used in adolescents with renal impairment (i.e. CrCl <90 mL/min/1.73m^2)

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:
  - Inconsistent or no condom use
  - Diagnosis of a sexually transmitted infection (STI)
  - 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

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

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

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

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

Emtricitabine/ Tenofovir disoproxil Mylan 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 Mylan is not always effective in preventing the acquisition of HIV-1 infection. The time to onset of protection after commencing Emtricitabine/ Tenofovir disoproxil Mylan is unknown.

- **Counsel uninfected individuals at high risk about safer sex practices,including:**
  - Using condoms consistently and correctly
  - Knowing their HIV-1 status and that of their partner(s)
  - 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 Mylan for a PrEP indicationin reducing the risk of acquiring HIV-1 infection is strongly correlated with adherence and measurable drug levels in blood.

- The recommended dose of Emtricitabine/ Tenofovir disoproxil Mylan in adults and adolescents aged 12 years and older, weighing at least 35kg, is one tablet, once daily All uninfected individuals at high risk taking Emtricitabine/ Tenofovir disoproxil Mylan 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. It is also recommended to individuals to add a reminder to their mobile phone or any other device thatcan alert them when it is time to take Emtricitabine/ Tenofovir disoproxil Mylan
- All uninfected individuals at high risk taking Emtricitabine/ Tenofovir disoproxil Mylan for a PrEP indication should be supplied with a PrEP educational guide prior to initiation of treatment and a PrEP remindercard when the medicine is supplied to the individual

Emtricitabine/ Tenofovir disoproxil Mylan related renal toxicity

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 before prescribing Emtricitabine/ Tenofovir disoproxil Mylan.
- 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 thereafter. In individuals at risk for renal impairment, more frequent monitoring of renal function is required.
- Avoid administering Emtricitabine/ Tenofovir disoproxil Mylan 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 have been reported after initiation of high dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) in HIV-1 infected patients treated with tenofovir and with risk factors for renal dysfunction.. If Emtricitabine/ Tenofovir disoproxil Mylan is co-administered with an NSAID, renal function should be monitored adequately.

Adults taking Emtricitabine/ Tenofovir disoproxil Mylan for PrEP:

- **Do not prescribe Emtricitabine/ Tenofovir disoproxil Mylan for PrEP to individuals with an estimated CrCl below 60 mL/min.**
- Emtricitabine/ Tenofovir disoproxil Mylan should only be used in individuals with CrCl <80mL/min if the potential benefits are considered to outweighthe potential risks
- 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 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 Mylan should also be considered in case of progressive decline of renal function when no other cause has been identified.

Adolescents taking Emtricitabine/ Tenofovir disoproxil Mylan for PrEP:

- Emtricitabine/ Tenofovir disoproxil Mylan should not be used in adolescents with renal impairment (i.e. CrCl <90 mL/min/1.73m2)
- There are no data on the long-term renal effects of Emtricitabine/ Tenofovir disoproxil Mylan when used for PrEP in uninfected adolescents. Moreover, the reversibility of renal toxicity after cessation of Emtricitabine/ Tenofovir disoproxil Mylan for PrEP cannot be fully ascertained
- At each visit the individual should be reassessed to ascertain whether they remain at high risk of HIV-1 infection. The risk of HIV-1 infection should be balanced against the potential risk for adverse renal effects with long-term use of Emtricitabine/ Tenofovir disoproxil Mylan
- If serum phosphate is <3.0 mg/dl (0.96 mmol/l), renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose
- If renal abnormalities are suspected or detected then consultation with a nephrologist should be obtained to consider interruption of treatment
- Interrupting Emtricitabine/ Tenofovir disoproxil Mylan should also be consideredin case of progressive decline of renal function when no other cause hasbeen identified

Bone effects

Adults taking Emtricitabine/ Tenofovir disoproxil Mylan for PrEP

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

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

Adolescents taking Emtricitabine/Tenofovir for PrEP:

- TDF may cause a reduction in BMD. The effects of TDF-associated changes in BMD on long-term bone health and future fracture risk are uncertain. At each visit the individual should be reassessed to ascertain whether they remain at high risk of HIV-1 infection. The risk of HIV-1 infection should be balanced against the potential risk for adverse bone effects with long-term use of Emtricitabine/Tenofovir
    - o If bone abnormalities are detected or suspected in adolescents, consultation with an endocrinologist and/or nephrologist 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 Mylan. As a result, it is recommended that:

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

Use of Emtricitabine/ Tenofovir disoproxil Mylan 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 Mylan** 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.

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