EDUCATIONAL GUIDE FOR PRESCRIBING PHYSICIANS ON PRE-EXPOSURE PROPHYLAXIS (PrEP)

EMTRICITABINA/TENOFOVIR DISOPROXIL

Emtricitabine/Tenofovir disoproxil is indicated, in combination with safe sex practices, as pre-exposure prophylaxis (PrEP) to reduce the risk of acquiring HIV-1 infection sexually in high-risk adults and adolescents. This indication is based on clinical trials with men who have sex with men (MSM) at high risk of HIV-1 infection and with men and women of serodiscordant heterosexual couples.

Version 1, agreed with INFARMED, I.P. on 05-2024 - Approved by Malta Medicines Authority on 06.Jan.2026

Important safety information regarding the use of Emtricitabine/Tenofovir disoproxil for PrEP:

- This medicine should only be used to reduce the risk of acquiring the HIV-1 in subjects whose HIV status is negative prior to initiation of treatment with emtricitabine/tenofovir disoproxil as prophylaxis pre-exposure. HIV-negative status should be reconfirmed at regular intervals (e.g. at least every 3 months) during Emtricitabine/Tenofovir disoproxil PrEP administration using a combined antigen/antibody test.
- The emergence of resistance mutations for HIV-1 occurred in individuals with undetectable HIV-1 infection who were only on Emtricitabine/Tenofovir disoproxil treatment.
- This medicine should only be used as part of an overall prevention strategy as it is not always effective in preventing the acquisition of HIV-1 infection.
- Do not start (or restart) prescribing this medicine as pre-exposure prophylaxis if signs or symptoms of acute HIV infection are detected, unless HIV status negative has been confirmed.
- Advise individuals not infected with HIV-1 to strictly adhere to the dosing schedule of this medicinal product.
- Do not prescribe this medicine to uninfected adults with creatinine clearance (CrCl) values < 60 ml/min and use it only in individuals with CrCl <80 ml/min if you believe that the potential benefits outweigh the potential risks.
- Kidney function should be monitored regularly while using this PrEP medicine.

Additional important information about using Emtricitabine/Tenofovir disoproxil for PrEP in adolescents:

- The use of Emtricitabine/Tenofovir disoproxil for PrEP in adolescents needs to be carefully considered on a case-by-case basis, taking into account the individual's ability and understanding of the need for adherence for Emtricitabine/Tenofovir disoproxil to be effective as PrEP and the risk of acquiring other sexually transmitted infections.
- Adherence in adolescents and young adults was found to be lower than adherence in older adults and no data are available on the use of Emtricitabine/Tenofovir disoproxil for PrEP in adolescent girls. A "Pre-Exposure Prophylaxis (PrEP) At-Risk Card" is available to facilitate adherence in adolescents as well as adults.
- At each visit, individuals should be reassessed to see if they are still at high risk of HIV-1 infection. The risk of HIV-1 infection should be weighed against the potential renal and bone effects of long-term use of emtricitabine/tenofovir disoproxil.
- Emtricitabine/Tenofovir disoproxil should not be used in adolescents with renal impairment (CrCl <90 ml/min/1.73m^2).

Factors that help identify individuals who are at high risk of HIV-1:

- Existence of partner(s) who you know to be infected with HIV-1 or
- Involvement in sexual activities, within a community or social network of greater prevalence, and with one or more of the following situations:
    - No use of condoms or inconsistent use
    - The diagnosis of Sexually Transmitted Infection (STI)
    - Engaging in transactional sex (exchange for money, food, housing, or drugs)
    - Use of illicit drugs or alcohol dependence
    - Incarceration
    - Partner(s) of unknown HIV-1 HIV status along with one of the factors listed above

Risk of developing resistance to drugs to treat HIV-1 in HIV-1 infected and undiagnosed individuals:

- The use of Emtricitabine/Tenofovir disoproxil for PrEP is contraindicated for individuals with unknown or positive HIV-1 status.

- Use this medicine to reduce the risk of acquiring HIV-1 infection only in people with confirmed HIV-1 negative status. Emtricitabine/Tenofovir disoproxil alone is not a complete regimen for the treatment of HIV-1 infection, and resistance mutations for HIV-1 have emerged in individuals with undetectable HIV-1 infection who were only on Emtricitabine/Tenofovir disoproxil treatment.

- **Prior to initiation of treatment with Emtricitabine/Tenofovir disoproxil for PrEP:**
  o Confirm negative HIV status using a combined antigen/antibody test.
  o In the presence of clinical symptomatology consistent with acute viral infection, and if recent exposure (< 1 month) to HIV-1 is suspected, the start of PrEP should be postponed for at least one month and HIV-1 status should be reconfirmed.

- **During treatment with Emtricitabine/Tenofovir disoproxil for PrEP:**
  o Perform screening tests for HIV-1 infection at regular intervals (e.g. at least every 3 months) using a combined antigen/antibody test.
  o If symptoms consistent with acute HIV-1 infection develop after an event with potential exposure, use of this medicinal product should be discontinued until negative HIV status has been confirmed.

Use emtricitabine/tenofovir disoproxil for PrEP only as part of an overall strategy for prevention

Emtricitabine/tenofovir disoproxil for PrEP should only be used as part of an overall strategy

for prevention of HIV-1 infection, including the use of other HIV-1 prevention measures, such as safe sex practices, as the use of emtricitabine/tenofovir disoproxil is not always effective in preventing the acquisition of HIV-1 infection. The time to onset of protection after starting the drug is unknown.

- **Advise high-risk uninfected individuals about safe sex practices, including:**
  - o Use condoms consistently and correctly
  - o Know your HIV-1 status and that of your partner(s)
  - o Regularly test for other STIs that may facilitate HIV-1 transmission (e.g., syphilis and gonorrhea).

Importance of strict adherence to the recommended dosage regimen

The effectiveness of Emtricitabine/Tenofovir disoproxil as PrEP in reducing the risk of acquiring HIV-1 is strongly correlated with adherence, as demonstrated by measurable levels of the drug in the blood.

- The recommended dosage in adults and adolescents aged 12 to 18 years, who weigh at least 35 kg, is one tablet, once a day.
- All high-risk, uninfected individuals taking this PrEP drug should be advised to strictly adhere to the recommended dosing schedule to reduce the risk of acquiring HIV-1 infection. It is also recommended that individuals add a reminder on their mobile phone or any other device that alerts them to when it is time to take Emtricitabine/Tenofovir disoproxil.
- All high-risk, uninfected individuals taking this PrEP medication should be provided with an "Educational Guide for Individuals at Risk" about Pre-Exposure Prophylaxis (PrEP)" and a "Pre-Exposure Prophylaxis (PrEP) Card for At-Risk Individuals" before starting treatment.

Emtricitabine/Tenofovir disoproxil related renal toxicity

Cases of renal failure, renal impairment, elevated creatinine, hypophosphatemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil.

- Before prescribing this drug, evaluate the estimated ClCr values in all individuals.
- In individuals without risk factors for kidney disease, it is recommended that renal function (creatinine clearance and serum phosphate) be monitored after two to four weeks of use, after three months of use, and then at intervals of three to six months. In patients at risk of renal impairment, more frequent monitoring of renal function is required.
- The use of this medicinal product should be avoided concomitantly with

nephrotoxic medicinal products or shortly after use. If concomitant use is unavoidable, renal function should be monitored weekly.

- Cases of acute renal failure have been reported following initiation of high doses of nonsteroidal anti-inflammatory drugs (NSAIDs), or concomitant use of different NSAIDs, in HIV-1 infected patients treated with tenofovir and with risk factors for renal dysfunction; for these patients, consider alternatives to NSAIDs. If emtricitabine/tenofovir disoproxil is co-administered with an NSAID, renal function should be closely monitored.

<u>Adults</u> taking Emtricitabine/Tenofovir disoproxil for PrEP:

- **Do not prescribe the drug to individuals with an estimated CrCl of less than 60 ml/min.**
- This medicinal product should only be reused in individuals with CrCl <80 ml/min if it is considered that the potential benefits outweigh the potential risks.
- If serum phosphate is < 1.5 mg/dl (0.48 mmol/l) or Clcr decreases to values < 60 ml/min, renal function should be reassessed within one week, including determination of blood glucose and potassium concentrations and urine glucose.
- Discontinuation of treatment with emtricitabine/tenofovir disoproxil should be considered in subjects with a decrease in CrCl to values < 60 ml/min or a decrease in serum phosphate to levels < 1.0 mg/dl (0.32 mmol/l).
- Discontinuation of emtricitabine/tenofovir disoproxil should also be considered if progressive decline in renal function occurs in cases where no other cause has been identified.

<u>Adolescents</u> taking Emtricitabine/Tenofovir disoproxil for PrEP:

- The drug should not be used in adolescents with renal impairment (ClCr < 90 ml/min/1.73m^2).
- There are no data on the long-term renal effects of emtricitabine/tenofovir disoproxil when used for PrEP in uninfected adolescents. In addition, the reversibility of renal toxicity after cessation of the PrEP drug cannot be fully verified.
- At each visit, the individual should be reassessed to see if they are still at high risk of HIV-1 infection. The risk of HIV-1 infection should be weighed against the potential renal effects of long-term use of emtricitabine/tenofovir disoproxil.
- If serum phosphate is < 3.0 mg/dl (0.96 mmol/l), renal function should be reassessed within one week, including determination of blood glucose and potassium and urine glucose concentrations.
- If kidney abnormalities are suspected or detected, consultation with a nephrologist should be sought to consider stopping treatment.
- Discontinuation of treatment should be considered if progressive decline in renal function occurs in cases where no other cause has been identified.

Bone effects

Adults taking Emtricitabine/Tenofovir disoproxil for PrEP:

Small decreases in bone mineral density (BMD) have been reported in non-infected subjects taking emtricitabine/tenofovir disoproxil.

- If bone abnormalities are suspected, appropriate medical consultation should be sought.

Adolescents taking Emtricitabine/Tenofovir disoproxil for PrEP:

Tenofovir disoproxil may cause a decrease in BMD. There is uncertainty about the effects of changes in BMD associated with tenofovir disoproxil on long-term bone health and future risk of fractures. At each visit, the individual should be reassessed to see if they are still at high risk of HIV-1 infection. The risk of HIV-1 infection should be weighed against the potential bone effects of long-term use of emtricitabine/tenofovir disoproxil.

- If bone abnormalities are detected or suspected in adolescents, consultation with an endocrinologist and/or nephrologist should be sought.

HBV infection

There is a risk of severe acute exacerbations of hepatitis when hepatitis B-infected individuals discontinue treatment with emtricitabine/tenofovir disoproxil. As such, it is recommended that:

- all individuals are tested for the presence of chronic HBV before starting treatment with this medicine and routinely while using Emtricitabine/Tenofovir disoproxil for PrEP.
- current HIV treatment guidelines for the management of HIV infection in patients co-infected with hepatitis B virus (HBV) should be consulted.
- HBV-infected individuals who have discontinued treatment with this medicinal product are monitored with clinical and laboratory follow-up for at least several months after stopping therapy.

Use of Emtricitabine/Tenofovir disoproxil for PrEP in pregnancy

The balance between benefits and risks for women who may be pregnant or who wish to become pregnant should be evaluated. Prescribers are advised to include women exposed to Emtricitabine/Tenofovir disoproxil for PrEP during pregnancy in the *Antiretroviral pregnancy Registry,* in www.apregistry.com This study aims to detect any significant teratogenic effects related to antiretroviral drugs to which pregnant women are exposed.

Reporting of suspected undesirable effects

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 Generis: V.J. Salomone Pharma Ltd., Upper Cross Road, Marsa MRS1542, Malta, Tel:+356 21 220 174 and 24h PV mobile +356 99644126