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

About Emtricitabine/ Tenofovir disoproxil Accord for a PrEP indication

INDICATION AND PRESCRIBING CONSIDERATIONS

Emtricitabine/ Tenofovir disoproxil Accord, a combination of emtricitabine and tenofovir disoproxil fumarate, is indicated in combination with safer sex practices for pre exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 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 in heterosexual serodiscordant couples.

The following factors may help to identify individuals at high risk:

- 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, alcohol dependence
- Incarceration
- Partner(s) of unknown HIV-1 status with any of the factors listed above

Key safety information regarding the use of emtricitabine/ tenofovir disoproxil for PrEP

- 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 PrEP 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
- 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 as part of a comprehensive prevention strategy because emtricitabine/ tenofovir disoproxil is not always effective in preventing the acquisition of HIV-1 infection
- Do not initiate (or re-initiate) emtricitabine/ tenofovir disoproxil for PrEP 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

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- 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

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:**
  - 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 for a PrEP indication for at least 1 month and reconfirm HIV-1 status
- **During use of emtricitabine/ tenofovir disoproxil 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 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. The time to onset of protection after commencing Emtricitabine/ tenofovir disoproxil 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 (e.g. 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 as demonstrated by measurable drug levels in blood.

- The recommended dose of emtricitabine/ tenofovir disoproxil is one tablet, once daily
- All uninfected individuals at high risk taking emtricitabine/ tenofovir disoproxil for a PrEP indication should be counselled to strictly adhere to the recommended dosing schedule to reduce the risk of acquiring HIV-1 infection

- 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 prescription of emtricitabine/ tenofovir disoproxil is supplied to the individual

New onset or worsening renal impairment
Renal failure, renal impairment, elevated creatinine, hypophosphatemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil, a component of emtricitabine/ tenofovir disoproxil.
- Assess estimated creatinine clearance (CrCl) in all individuals before prescribing emtricitabine/ tenofovir disoproxil
- In individuals without renal risk factors, renal function (CrCl and serum phosphate) should also be monitored after 2 to 4 weeks of use, after 3 months of use and every 3 to 6 months thereafter. 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 have been reported after initiation of high-dose or multiple nonsteroidal anti-inflammatory drugs (NSAIDs) in HIV-1-infected patients treated with tenofovir disoproxil fumarate and with risk factors for renal dysfunction.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**
- Emtricitabine/ tenofovir disoproxil should only be used in individuals with CrCl <80mL/min if the potential benefits are considered to outweight the potential risks
- If serum phosphate is <1.5 mg/dL (0.48 mmol/L) or CrCl is decreased to <60 mL/min in any individual receiving emtricitabine/ tenofovir disoproxil for PrEP, renal function should be reevaluated within 1 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 CrCl 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

There are no data on the long-term renal effects of emtricitabine/ tenofovir disoproxi when used for PrEP in uninfected adolescents. Moreover, the reversibility of renal toxicity after cessation of emtricitabine/ tenofovir disoproxi for PrEP cannot be fully ascertained

When using emtricitabine/tenofovir disoproxil for pre-exposure prophylaxis individuals should be reassessed at each visit 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
Not recommended for use in individuals under the age of 18 years with renal impairment disoproxil.

HBV infection:
- There is a risk of 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
- HBV-uninfected individuals should be offered vaccination
- Individuals infected with HBV who discontinue emtricitabine/ tenofovir disoproxil should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment
- **Bone effects:** Decreases in bone mineral density (BMD) and mineralization defects, including osteomalacia, have been seen in patients treated with tenofovir disoproxil fumarate. Consider assessment of BMD in Individuals with a history of pathologic fracture or other risk factors for osteoporosis or bone loss. Persistent or worsening bone pain, pain in extremities, fractures, and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in at-risk patients.

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 enrol 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.

Adolescents taking Emtricitabine/ Tenofovir disoproxil Accord for PrEP
Use of tenofovir disoproxil may cause a reduction in BMD. The effects of tenofovir disoproxil -associated changes in BMD on long-term bone health and future fracture risk are currently unknown.
If bone abnormalities are detected or suspected during use of emtricitabine/tenofovir disoproxil, consultation with an endocrinologist and/or nephrologist should be obtained.

Reporting adverse events
Suspected adverse reactions should be reported to the Health Products Regulatory Authority via HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

Adverse reactions can also be reported to Accord Healthcare Ireland Ltd. via E-mail: medinfo@accord-healthcare.com; Tel: +44 (0) 1271 385 257; or by completing the online form at www.accord-healthcare.ie/drug-reaction-report.
Further copies of the prescribers Guide may be obtained from Accord Healthcare Ireland Ltd, Euro House, Euro Business Park, Little Island, Cork, T45 K857, Ireland; www.accord-healthcare.ie/medical-information-form; Tel: (0)21 461 9040.