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

Emtricitabine/Tenofovir disoproxil Krka (emtricitabine/tenofovir disoproxil succinate) 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 and adolescents 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 Krka for PrEP

- HIV-1 resistance mutations have emerged in individuals with undetected HIV-1 infection who were only taking Emtricitabine/Tenofovir disoproxil Krka
- Emtricitabine/Tenofovir disoproxil Krka 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 Krka for pre-exposure prophylaxis and re-confirmed at frequent intervals (e.g. at least every 3 months) while taking Emtricitabine/Tenofovir disoproxil Krka for PrEP, using a combined antigen/antibody test
- Emtricitabine/Tenofovir disoproxil Krka should only be used as part of a comprehensive prevention strategy because Emtricitabine/Tenofovir disoproxil Krka is not always effective in preventing the acquisition of HIV-1 infection
- Do not initiate (or re-initiate) Emtricitabine/Tenofovir disoproxil Krka 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 Krka dosing schedule
- Do not prescribe Emtricitabine/Tenofovir disoproxil Krka to uninfected individuals with an estimated creatinine clearance (CrCl) below 60 mL/min and only use in adults with CrCl <80/mL/min if potential benefits outweigh the risks. Renal function should be regularly monitored while taking Emtricitabine/Tenofovir disoproxil Krka for PrEP

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

- The use of Emtricitabine/Tenofovir disoproxil Krka 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 Krka for PrEP to be effective, 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 Krka
- Emtricitabine/Tenofovir disoproxil Krka should not be used in adolescents with renal impairment (i.e. CrCl <90mL/min/1.73m²).

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 Krka for a PrEP indication is contraindicated in individuals with unknown or HIV-1-positive status.

- Use Emtricitabine/Tenofovir disoproxil Krka to reduce the risk of acquiring HIV-1 infection only in individuals confirmed to be HIV-1 negative. Emtricitabine/Tenofovir disoproxil Krka 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 Krka

- **Before starting Emtricitabine/Tenofovir disoproxil Krka 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 Krka for a PrEP indication for at least 1 month and reconfirm HIV-1 status

- **During use of Emtricitabine/Tenofovir disoproxil Krka 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 Krka should be discontinued until negative infection status is confirmed

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

Emtricitabine/Tenofovir disoproxil Krka 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 Krka is not always effective in preventing the acquisition of HIV-1 infection. The time to onset of protection after commencing Emtricitabine/Tenofovir disoproxil Krka 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 Krka for a PrEP indication in reducing the risk of acquiring HIV-1 infection is strongly correlated with adherence and measurable drug levels.

- The recommended dose of Emtricitabine/Tenofovir disoproxil Krka in adults and adolescents aged 12 years and older, weighing at least 35kg, is one table, once daily
- All uninfected individuals at high risk taking Emtricitabine/Tenofovir disoproxil Krka 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
- All uninfected individuals at high risk taking Emtricitabine/Tenofovir disoproxil Krka for a PrEP indication should be supplied with a PrEP educational brochure prior to initiation of treatment and and a PrEP reminder card when each new supply of Emtricitabine/Tenofovir disoproxil Krka is supplied to the individual

Emtricitabine/Tenofovir disoproxil Krka 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, a component of Emtricitabine/Tenofovir disoproxil Krka.

- Assess estimated creatinine clearance (CrCl) in all patients before prescribing Emtricitabine/Tenofovir disoproxil Krka
- 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, a more frequent monitoring of renal function is required
- Avoid administering Emtricitabine/Tenofovir disoproxil Krka with concurrent or recent use of nephrotoxic drugs. If concomitant use of Emtricitabine/Tenofovir disoproxil Krka 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 Krka is co-administered with an NSAID, renal function should be monitored adequately

Adults taking Emtricitabine/Tenofovir disoproxil Krka for PrEP:

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

Adolescents taking Emtricitabine/Tenofovir disoproxil Krka for PrEP:

- **Emtricitabine/Tenofovir disoproxil Krka should not be used in adolescents with renal impairment (CrCl <90mL/min/1.73m^2)**
- There are no data on the long-term renal effects of Emtricitabine/Tenofovir disoproxil Krka when used for PrEP in uninfected adolescents. Moreover, the reversibility of renal toxicity after cessation of Emtricitabine/Tenofovir disoproxil Krka for PrEP cannot be fully ascertained
- At each visit the individual should be reassessed to ascertain whether they remain at high risk for 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 Krka
- 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 Krka should also be considered in case of progressive decline of renal function when no other cause has been identified

Bone effects

Adults taking Emtricitabine/Tenofovir disoproxil Krka for PrEP:

- Small decreases in bone mineral density (BMD) have been seen in uninfected individuals receiving Emtricitabine/Tenofovir disoproxil Krka
  - If bone abnormalities are suspected then appropriate consultation should be obtained

Adolescents taking Emtricitabine/Tenofovir disoproxil Krka for PrEP:

- 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. 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 disoproxil Krka
  - 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 Krka. As a result, it is recommended that:

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

Use of Emtricitabine/Tenofovir disoproxil Krka 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 Krka 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.

For more information about Emtricitabine/Tenofovir disoproxil Krka and its indication for PrEP, please refer to the Summary of Product Characteristics.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the patient information leaflet. You can also report side effects directly via the national reporting system: *HPRA Pharmacovigilance, Earlsfort Terrace, IRL-Dublin 2; Tel: +3531 6764971; Fax: +3531 6762517. Website: www.hpra.ie; Email: medsafety@hpra.ie* Any suspected adverse reactions can also be reported to Krka, d. d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto; Tel: +386 7 331 21 11 and +386 1 47 51 100; Website: www.krka.si; Email: pharmacovigilance@krka.biz.