APPROVED BY THE MINISTRY OF HEALTH ON APRIL 2024

Safety information brochure for the medical staff regarding the use of Emfovir S.K. 200/245 mg

Which contains Emtricitabine/Tenofovir Disoproxil fumarate, for the indication of pre-exposure prophylaxis (PrEP) treatment for human immunodeficiency virus (HIV-1)

החברה הישראלית לרפואת איידס

הוועד למלחמה באיידס
ISRAEL AIDS TASK FORCE

K.S. Kim International (SK-Pharma) Ltd. Yigal Alon 94, Tel-Aviv-Yafo, 6789139 Tel: 03-6114543

SK-PHARMA

APPROVED BY THE MINISTRY OF HEALTH ON APRIL 2024

This brochure was handed to you as a part of the Doctor's HIV Pre-exposure Prophylaxis (PrEP) training program

The program's goal is to train doctors in prescribing PrEP to individuals at risk of HIV-1 infection, monitor individuals taking the product, and help to prevent HIV-1 and other sexually transmitted diseases.
Emfovir S.K. 200/245 mg contains the active ingredients emtricitabine and tenofovir disoproxil and is indicated in combination with safer sex practices for HIV-1 PrEP to lower the risk of sexually acquired HIV-1 infection in adults at high risk.

The highlights are as follows:

- Emfovir S.K. 200/245 mg is to be used for PrEP indication to lower the risk of HIV-1 infection only in individuals who were checked for HIV-1 and were found negative before starting Emfovir S.K. 200/245 mg. During continued administration of Emfovir S.K. 200/245 mg, testing for HIV should occur at least every three months to ensure that the individual has remained HIV-1 negative.
- Emfovir S.K. 200/245 mg should be used only as part of a comprehensive prevention program, since the product is not always effective in preventing acquisition of HIV-1 infection.
- The prevention program for PrEP should include regular follow-up with individuals taking the product, in order to counsel on the importance of adherence to the recommended Emfovir S.K. 200/245 mg dosing schedule, and to encourage safer sexual conduct. Follow-up should be conducted by the prescribing physician in the lines of regular patient visits.
- The monitoring should include testing for HIV-1 infection, sexually transmitted diseases (including syphilis, chlamydia and gonorrhea), hepatitis B (HBV) and hepatitis C (HCV) infections, kidney function and urinary protein tests, and inquiry about side effects.
- Emfovir S.K. 200/245 mg alone does not constitute a complete regimen for the treatment of HIV-1 infection, and HIV-1 resistance mutations have emerged in individuals with undetected HIV-1 infection who are taking only Emtricitabine/ Tenofovir.
  Emfovir S.K. 200/245 mg should not be initiated or continued if signs and/or symptoms of acute HIV-1 infection arise. Initiation of Emfovir S.K. 200/245 mg for PrEP needs to be postponed by at least one month, until the individual's

negative HIV-1 status is confirmed. Treatment should be initiated only when a negative HIV-1 status is confirmed.

- Strict adherence to the recommended dosage regimen is essential. Individuals using Emfovir S.K. 200/245 mg for PrEP need to be instructed on the importance of taking Emfovir S.K. 200/245 mg at the recommended dosage, which is one tablet once a day, every day.
- Emfovir S.K. 200/245 mg is not recommended for individuals with kidney function of CrCl<60 ml/min.
- In case of an individual with kidney function of CrCl<80 ml/min, Emfovir S.K. 200/245 mg should be prescribed only if the benefits outweigh the risks. In this case, kidney function should be regularly monitored.

Emfovir S.K. 200/245 mg for PrEP is indicated in individuals who meet both criteria A and B:

(Criteria to assist with identification of individuals at high risk for HIV-1 infection)

A. Partners of HIV positive individuals not taking anti-retroviral treatment (ART) or with poor adherence to ART treatment

Or

Men having sex with men.

B. And at least one of the following:
   - Lack of use or inconsistent use of condoms in casual sex encounters.
   - Recently diagnosed with one or more sexually transmitted disease.
   - Using sex for financial profit.
   - Drug and alcohol use before or/and during sex without a condom.
   - Sex with a partner with unknown HIV status, that meets any of the criteria stated above.
   - or for whom it is unknown whether they meet any of the above criteria.

Open and non-judgmental discourse regarding sexual practices and sexual orientation

In order to improve communication and proper follow-up of individuals who would benefit from PrEP, it is important to have an open and non-judgmental discourse regarding sexual conduct, including between partners of the same sex.

The risk of HIV-1 resistance occurrence in individuals with undiagnosed HIV infection during administration of the product

- Emfovir S.K. 200/245 mg, in the indication of PrEP, is contraindicated in patients with a positive or unknown HIV-1 status.
- Emfovir S.K. 200/245 mg should be prescribed only to individuals that were tested and found negative.
- Emfovir S.K. 200/245 mg alone does not provide a full **treatment** regimen for HIV-1 infection. Resistant mutations of HIV-1 were discovered in undiagnosed individuals who have taken only Emtricitabine/Tenofovir, without additional anti-retroviral treatment. Therefore, there is a need to follow the administration and monitoring guidelines presented in this brochure and in Emfovir S.K. 200/245 mg prescribing information.

Before initiation of Emfovir S.K. 200/245 mg treatment for PrEP indication

- Negative HIV-1 status must be checked by using an antigen/antibody combination test.
- In case symptoms of acute viral infection arise, and there is a suspicion of HIV exposure in the last month, PrEP treatment initiation should be postponed for at least one month, until a negative HIV-1 status is re-ensured.
- The exclusive setting in which Emfovir S.K. 200/245 mg would be given, and the tests that will be required during its use, should be explained during individual's first clinic visit. Confirm individuals agreement to these requirements.

During Emfovir S.K. 200/245 mg use for the PrEP indication

- Negative HIV-1 status should be ensured in repeated tests at frequent intervals, of at least every three months.
- Also, tests for sexually transmitted diseases, HBV, HCV, kidney function, urinary protein, and inquiry about side effects should be performed. The frequency of the tests is presented in the table below.
- In case symptoms of acute viral infection arise, and there is a suspicion of HIV exposure, Emfovir S.K. 200/245 mg should be discontinued until negative HIV-1 status is confirmed.

Emfovir S.K. 200/245 mg must be used as part of a comprehensive prevention program

- Emfovir S.K. 200/245 mg alone is not a complete regimen for the treatment of HIV infection and does not protect against infection with other sexually transmitted diseases. Therefore, other means of HIV-1 prevention, parallel to use of Emfovir S.K. 200/245 mg a safe sexual conduct (or encouraging safe sexual conduct),

should be used.

- Users should be counselled about safe sexual conduct that includes:
  - » Regular use of condoms
  - » HIV-1 status follow-up for the individuals and their partners
  - » Frequent tests for sexually transmitted diseases, especially syphilis, gonorrhea, and chlamydia
  - » Not sharing needles, syringes or other medical equipment

The importance of strict adherence to Emfovir S.K. 200/245 mg recommended dosage regimen

- The recommended dosage of Emfovir S.K. 200/245 mg is one tablet a day, every day.
- The effectiveness of Emfovir S.K. 200/245 mg for a PrEP indication is strongly correlated with adherence, as demonstrated by measurable drug levels in blood. All uninfected individuals using Emfovir S.K. 200/245 mg for a PrEP indication, should be counselled by the prescribing physician at frequent intervals to strictly adhere to the recommended Emfovir S.K. 200/245 mg dosing schedule in order to reduce the risk of acquiring HIV-1 infection.

Safety information about Emfovir S.K. 200/245 mg

A complete overview of adverse reactions can be found in the local Prescribing Information.

Before initiation of use, possible side effects, signs and symptoms of side effects, and ways of prevention and treatment, should be explained to the individual.

1. Kidney related side effects:

Kidney failure, reduction in kidney function, rising of creatinine levels, hypophosphatemia and renal tubular injury (including Fanconi syndrome) were reported with the use of the active ingredient tenofovir disoproxil, which is found in Emfovir S.K. 200/245 mg.

- Creatinine clearance (CrCl) should be assessed in every individual before prescription of Emfovir S.K. 200/245 mg.
- In individuals without risk factors of kidney injury, it is recommended that renal function (creatinine clearance and phosphate levels) is monitored after two to four weeks and after 3 months of treatment. After three months treatment, kidney function may be assessed every three to six months.
- In users with risk factors of kidney injury, kidney function should be more tightly monitored.
- Cases of acute kidney failure were reported in HIV-1 positive patients with risk factors for renal dysfunction that were treated with Emtricitabine/Tenofovir in

combination with high or multiple doses of non-steroidal anti-inflammatory drugs (NSAIDs). If Emfovir S.K. 200/245 mg is co-administered with an NSAID, renal function should be monitored adequately.

- Administration of Emfovir S.K. 200/245 mg with or after use of nephrotoxic drugs should be avoided. In case the combination is unavoidable, kidney function should be monitored weekly.
- Emfovir S.K. 200/245 mg should not be prescribed to individuals with creatinine clearance of less than 60 ml/min.
- Emfovir S.K. 200/245 mg may be prescribed to individuals with creatinine clearance of less than 80 ml/min only in case the benefits outweigh the potential risks.
- In case of reduction in phosphate levels under 1.5 mg/dl (0.48 mmol/l) or of creatinine clearance under 60 ml/min, kidney function should be re-assessed within one week including blood glucose and potassium levels and urine glucose levels.
- Treatment discontinuation should be considered in case of reduction in kidney function under 60 ml/min, reduction in serum phosphate under 1.0 mg/dl (0.32 mmol/l) or in case of progressive and unexplained kidney function reduction.

2. Bone changes

Bone abnormalities such as osteomalacia, which can manifest as persistent or worsening bone pain and can infrequently contribute to fractures, may be associated with tenofovir disoproxil-induced proximal renal tubulopathy.
Reduction in bone density was observed in individuals taking Emtricitabine/ Tenofovir. In case bone abnormalities are suspected, proper consultation with a specialist is required.

3. Hepatitis B (HBV) infection

The safety and efficacy of Emfovir S.K. 200/245 mg for PrEP in individuals with HBV or HCV infection has not been established. There is a risk of acute severe exacerbation of hepatitis in patients positive for Hepatitis B after discontinuing Emtricitabine/ Tenofovir. As a result,

- HBV infection status should be tested in all individuals before Emfovir S.K. 200/245 mg initiation.
- HBV negative individuals can be offered a vaccination before initiation of Emfovir S.K. 200/245 mg.
  HBV positive individuals should not stop taking Emfovir S.K. 200/245 mg without speaking to their doctor first. Discontinuation of Emfovir S.K. 200/245 mg therapy in patients infected with HBV may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue Emfovir S.K. 200/245 mg should be closely monitored with both clinical and laboratory follow-ups tests for at least several months after stopping Emfovir S.K. 200/245 mg. If appropriate, resumption of

hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since posttreatment exacerbation of hepatitis may lead to hepatic decompensation.

4. Lactic acidosis

Lactic acidosis is a rare but potentially life-threatening side effect.
Lactic acidosis occurs more often in women, particularly if they are overweight, and in people with liver disease. The following may be signs of lactic acidosis:

- deep rapid breathing
- drowsiness
- nausea, vomiting
- stomach pain

Individuals with predisposing factors such as decompensated liver disease or receiving concomitant medications known to induce lactic acidosis are at increased risk of experiencing severe lactic acidosis, during use of Emfovir S.K. 200/245 mg, including fatal outcomes.

5. Usage of Emfovir S.K. 200/245 mg in pregnancy

The information regarding safety of usage in pregnancy is limited but does not indicate fetal teratogenesis or toxicity. Thus, the potential risk should be assessed compared to the benefit in administration of Emfovir S.K. 200/245 mg with appropriate follow-up.

6. Usage of Emfovir S.K. 200/245 mg in lactation

The drug is secreted to breast milk, and its clinical effect on the baby is unclear. Therefore, lactation should be avoided while taking Emfovir S.K. 200/245 mg.

For additional information about Emfovir S.K. 200/245 mg and the HIV PrEP indication, please refer to the product label.

Side effect reporting:

Side effects can be reported to the Ministry of Health using the online form for side effect reporting that is found in the Ministry of Health homepage:
www.health.gov.il

or via the link:
https://sideeffects.health.gov.il

or through the registration holder K.S. Kim International (SK-Pharma) Ltd. via:
report@sk-pharma.com

SK-PHARMA

Table of examinations and dates for their implementation

Medical Service	Frequency
Doctor visit	Before treatment initiation and afterwards every three months.
• Receive information regarding all medications taken by the individual, in order to assess drug-drug interactions • Inquiry about side effects	Before treatment initiation. Additional assessment and inquiry at least every three months. Additional inquiry is recommended after the first month of treatment.
Recommended Kidney function assessment: Creatinine clearance (CrCl), phosphate levels and urine protein levels.	Creatinine – before treatment initiation. Creatinine and phosphate levels - should be assessed after two to four weeks and three months after treatment initiation. After three months of treatment and if creatinine and phosphate levels are stable, kidney functions can be assessed every three to six months.
HIV – ELISA/EIA/ tests from fourth-generation or "last generation" approved test* that is performed by a recognized MoH laboratory. * According to MoH guideline 8/13: Guidelines for diagnostic tests for HIV carriers, June 2013.	Before treatment initiation and afterwards at least every three months and if signs/symptoms of acute HIV-1 infection occur.
Test for sexually transmitted diseases (syphilis, gonorrhea, and chlamydia)	Before treatment initiation and afterwards periodically if there are no clinical symptoms.
Hepatitis B serology: 1. HBsAb 2. HBcAb (Hepatitis B core Antibody) - total, IgG and IgM 3. HBsAg (Hepatitis B surface Antigen)	Before treatment initiation. An individual that was not vaccinated (HBsAb NEGATIVE) – can be referred to receive vaccination. Test 2, 3: for an individual that was not vaccinated, periodically during treatment if no clinical signs are present.
Hepatitis C serology: Hepatitis C Ab	Before treatment initiation and periodically during treatment, if no clinical signs are present.

החברה הישראלית לרפואת איידס

הוועד למלחמה באיידס
ISRAEL AIDS TASK FORCE

מאושר בהתאם להנחיות משרד הבריאות
تمت الموافقة عليه طبقا لتعليمات وزارة الصحة
Approved according to the guidelines of the ministry of health

SK-EMFO-RMP_eng_bhpi_042024_V3