This brochure was approved according to the guidelines of the Ministry of Health on May 2023

Safety information brochure for the medical staff regarding the use of Tenovamed Inovamed

which contains emtricitabine and tenofovir disoproxil fumarate, for the indication of pre-exposure prophylaxis (PrEP) against HIV-1 infection

Inovamed
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הוועד למלחמה באיידס
ISRAEL AIDS TASK FORCE

החברה הישראלית לרפואת איידס

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

The purpose of this program is to train physicians in prescribing Pre-exposure Prophylaxis (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.

Tenovamed Inovamed contains the active ingredients emtricitabine and tenofovir disoproxil fumarate, 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:

- **The medicinal product is to be used for the PrEP indication in order to reduce the risk of HIV-1 infection only in patients who were tested for HIV-1 and found to be negative prior to commencing PrEP. During continued administration of Tenovamed Inovamed, testing for HIV should be performed at least every 3 months to ensure that the user remains HIV-1-negative.**
- **Tenovamed Inovamed is to be used only as part of a comprehensive prevention program, since the medicine is not always effective in preventing of HIV-1 infection.**
- **The prevention program for PrEP should include regular follow-up of patients taking this medicinal product, in order to promote the importance of adherence to the recommended Tenovamed Inovamed dosage regimen, and to encourage safer sexual conduct.**

  The follow-up should be conducted by the prescribing physician in the lines of regular patient visits.
- **The follow-up should include testing for HIV-1 infection, sexually transmitted diseases (including syphilis, chlamydia, gonorrhea), hepatitis B (HBV) and hepatitis C (HCV) infections, kidney function and urinary protein tests, as well as questioning about side effects.**
- **Tenovamed Inovamed alone does not constitute a complete regimen for the treatment of HIV-1 infection, and HIV-1 treatment resistance mutations have emerged in patients with HIV-1 infection that is below the detection threshold (undetected), who administered the drug without an additional anti-retroviral medicinal product. Do not initiate or continue taking Tenovamed Inovamed if signs and/or symptoms of acute HIV-1 infection occur. Initiation of Tenovamed Inovamed for the PrEP indication needs to be postponed by at least one month, until HIV-1-negative status is confirmed.**

  Treatment should be initiated only after HIV-1-negative status is confirmed.
- **Strict adherence to the recommended dosage regimen is essential. Patients using Tenovamed Inovamed for the PrEP indication should be instructed on the importance of taking Tenovamed Inovamed at the recommended dosage, which is one tablet once a day, every day.**
- **Tenovamed Inovamed is not recommended for individuals with kidney function of CrCl < 60 mL/min.**
- **For patients with CrCl < 80 mL/min on testing of kidney function, the medicinal product should be prescribed only if the benefit outweighs the risk. In this case, kidney function should be regularly monitored.**

Tenovamed Inovamed for PrEP is indicated for individuals who meet both criteria A and B, as follows:

(criteria to help identify 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 who have 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.
- Use of sex for financial profit.
- Drug or alcohol use before and/or during sex without using 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 non-judgmental discussion regarding sex practices and sexual orientation

In order to improve communication and enable appropriate follow-up of patients who might benefit from PrEP, it is important to conduct an open, non-judgmental discussion about sexual practices, including between partners of the same sex.

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

- Tenovamed Inovamed, in the indication of PrEP, is contraindicated in patients with a positive or unknown HIV-1 status.
- Tenovamed Inovamed should be prescribed only to individuals who have been tested and found to be negative.
- Tenovamed Inovamed alone does not constitute a complete regimen for HIV-1 treatment.

Resistant mutations of HIV-1 were discovered in undiagnosed individuals who have taken only the drug, without additional anti-retroviral treatment. It is therefore necessary to follow the administration and monitoring guidelines detailed in this brochure and in the emtricitabine/tenofovir disoproxil physician's leaflet.

Before initiation of Tenovamed Inovamed treatment for the PrEP indication

- Negative HIV-1 status must be confirmed using an antigen/antibody combination test.
- If symptoms of acute viral infection occur and there is a suspicion of HIV exposure in the last month, initiation of PrEP treatment should be postponed for at least one month, until negative HIV-1 status is re-confirmed.
- The exclusive setting in which Tenovamed Inovamed 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 use of Tenovamed Inovamed for the PrEP indication

- Negative HIV-1 status should be confirmed with repeated testing at frequent intervals, at least every 3 months.
- Also, tests should be performed for detection of sexually transmitted diseases, for hepatitis B and C, kidney function and proteinuria, as well as questioning about side effects. The frequency of the tests is presented in the table below.
- If symptoms of acute viral infection occur and there is a suspicion of HIV exposure, treatment with Tenovamed Inovamed should be stopped until negative HIV-1 status is confirmed.

Tenovamed Inovamed should be used as part of a comprehensive prevention program

- Tenovamed Inovamed alone does not constitute a complete regimen for HIV-1 treatment, and does not protect against infection with other sexually transmitted diseases. Therefore, in parallel to the use of Tenovamed Inovamed, additional measures for the prevention of HIV-1 infection should be employed, practicing safe sex (or encouraging safe sex practices).
- Users should be advised regarding safe sex practices, including:
  - Consistent use of condoms.
  - Follow-up of HIV-1 status of patients and their partners.
  - Frequent testing for sexually transmitted diseases, and especially syphilis, gonorrhea, and chlamydia.
  - Not sharing needles, syringes or other medical equipment.

The importance of strict adherence to the recommended dosage regimen of Tenovamed Inovamed

- The recommended dosage of Tenovamed Inovamed is one tablet a day, every day.
- The effectiveness of Tenovamed Inovamed for the PrEP indication in reducing the risk of HIV-1 infection is strongly correlated with adherence to the treatment regimen, as demonstrated by measurable blood levels of the medicine.

All uninfected individuals using Tenovamed Inovamed for a PrEP indication should be counseled by the prescribing physician at frequent intervals to strictly adhere to the recommended Tenovamed Inovamed dosing schedule in order to reduce the risk of acquiring HIV-1 infection.

Safety information about Tenovamed Inovamed

A complete review of adverse reactions of this medicine can be found in the local physician's leaflet for emtricitabine/tenofovir disoproxil.

Before initiation of use, possible side effects, signs and symptoms of side effects, and means for prevention and treatment should be explained to the treatment candidate.

1. Renal side effects:

Kidney failure, reduced kidney function, elevated creatinine levels, low phosphate levels and renal tubular injury (including Fanconi syndrome) have been reported with the use of the active ingredient tenofovir disoproxil fumarate, which is contained in Tenovamed Inovamed.

- Creatinine clearance (CrCl) must be tested in every candidate prior to giving a prescription for Tenovamed Inovamed.
- For patients with no risk factors for renal injury, it is recommended to monitor kidney function (creatinine clearance and phosphate levels) after 2-4 weeks and after 3 months of treatment. After 3 months, kidney function may be tested every 3-6 months.
- In patients with risk factors for renal injury, kidney function should be monitored more closely.
- Cases of acute renal failure have been reported in HIV-1-positive patients with risk factors for renal dysfunction who were treated with the active ingredient tenofovir disoproxil fumarate, which is contained in Tenovamed Inovamed, in combination with high or multiple doses of non-steroidal anti-inflammatory drugs (NSAIDs).

  If Tenovamed Inovamed is given in combination with an NSAID, kidney function should be monitored accordingly.
- Administration of the product with or after use of nephrotoxic drugs should be avoided. In case the combination cannot be avoided, kidney function should be monitored weekly.
- Tenovamed Inovamed should not be prescribed to individuals with creatinine clearance of less than 60 mL/min.
- Tenovamed Inovamed may be prescribed to individuals with creatinine clearance lower than 80 mL/min only if the benefit outweighs the potential risks.
- If phosphate levels decrease to less than 1.5 mg/dL (0.48 mmol/L) or if creatinine clearance decreases to less than 60 mL/min, kidney function should be retested within one week, including blood glucose and potassium levels and urine glucose levels.
- Consider discontinuation of treatment in cases of reduction of kidney function to less than 60 mL/min, reduction of serum phosphate level to less than 1.0 mg/dL (0.32 mmol/L) or in case of progressive and unexplained reduction in kidney function.

2. Bone changes

Bone abnormalities such as osteomalacia, which may manifest as persistent or worsening bone pain and can infrequently contribute to fractures, may be associated with proximal renal tubulopathy caused by tenofovir disoproxil.

Reduction in bone density has been observed in patients taking the medicinal product. If bone anomalies are suspected, appropriate specialist consultation is required.

3. Hepatitis B virus (HBV) infection

The safety and efficacy of Tenovamed Inovamed for PrEP in patients with HBV or HCV infection has not been established.

There is a risk of acute severe flare up of hepatitis in patients positive for Hepatitis B after discontinuing the medicinal product. Therefore:

- HBV infection status should be tested in all individuals before Tenovamed Inovamed initiation.
- HBV-negative individuals may be offered a vaccination prior to initiation of Tenovamed Inovamed treatment.
- HBV-positive individuals should not stop taking Tenovamed Inovamed without speaking to their physician first. Discontinuation of Tenovamed Inovamed therapy in patients infected with HBV may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue Tenovamed Inovamed should be closely monitored with both clinical and laboratory follow ups tests for at least several months after stopping Tenovamed Inovamed. If appropriate, resumption of hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment 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 patients with liver disease. Possible signs of lactic acidosis are:

- Deep and rapid breathing
- Drowsiness
- Nausea, vomiting
- Stomach pain

Patients with predisposing factors, such as decompensated liver disease, or who are taking concomitant medicines known to induce lactic acidosis, are at increased risk for the occurrence of severe lactic acidosis during the use of the medicinal product, including fatal outcomes.

5. Use of Tenovamed Inovamed during pregnancy

Information regarding safety of usage during pregnancy is limited but does not indicate fetal teratogenesis or toxicity. The potential risk should therefore be weighed against the benefit of taking Tenovamed Inovamed, including appropriate follow-up.

6. Use of Tenovamed Inovamed during lactation

The medication is secreted into breast milk, and its clinical effect on the baby is unclear. Lactation should therefore be avoided while taking Tenovamed Inovamed.

For further information about Tenovamed Inovamed and the HIV PrEP indication, please refer to the physician's leaflet for emtricitabine/tenofovir disoproxil.

Reporting side effects:

Side effects can be reported to the Ministry of Health by the online form for reporting side effects that is found on the Ministry of Health homepage:
www.health.gov.il
or by entering the link:
https://sideeffects.health.gov.il
or through the registration holder:
pv@inovamed.co.il

Table medical tests and frequency

Medical Service	Frequency
Physician visit	Prior to treatment initiation and every 3 months after this.
- Obtaining information about all medications that the treatment candidate is taking, in order to assess drug-drug interactions. - Questioning about side effects.	Prior to treatment initiation. Additional assessment and questioning at least once every 3 months. Additional questioning is recommended after the first month of treatment.
Recommendation for kidney function assessment: creatinine clearance (CrCl), phosphate levels and urine protein levels.	Creatinine – prior to treatment initiation. Creatinine and phosphate levels – should be assessed after 2-4 weeks and 3 months after treatment initiation. After 3 months of treatment, continued testing of kidney function may be performed every 3-6 months if creatinine and phosphate levels remain stable.
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.	Prior to treatment initiation and at least once every 3 months after this, and in the event that signs or symptoms of acute HIV-1 infection occur.
Tests for the presence of sexually transmitted diseases (syphilis, gonorrhea and chlamydia).	Prior to treatment initiation and periodically after this if there are no clinical symptoms.
Serological tests for hepatitis B: 1. HBsAb 2. HBcAb (Hepatitis B core Antibody) – total, IgG and IgM 3. HBsAg (Hepatitis B surface Antigen)	Prior to treatment initiation. A person who has not been vaccinated (HBsAb-negative) – may be referred to receive a vaccination. Tests 2 and 3: for a person who has not been vaccinated – periodically during treatment if there are no clinical signs.
Serological tests for hepatitis C: Hepatitis C Ab	Prior to treatment initiation and periodically during treatment, if there are no clinical signs.

Inovamed Ltd.
P.O.B. 62, Even Yehuda 40500
Telephone: 03-7150600

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