Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986
This medicine is dispensed with a doctor's prescription only

Testoviron® Depot
Oily solution for injection

Each 1 ml ampoule contains:
testosterone enantate 250 mg
Inactive ingredients and allergens: See section 6 'Additional information'.

Read the entire leaflet carefully before you start using this medicine. This leaflet contains concise information about this medicine. If you have any further questions, consult your doctor or pharmacist.
This medicine has been prescribed to treat you. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar to yours.
The medicine is not intended for children below the age of 12 years.

1) What is this medicine intended for?

- Testoviron Depot is intended to be used in adult men for testosterone replacement, to treat various health problems caused by testosterone deficiency (male hypogonadism). Testosterone deficiency should be confirmed by two separate blood testosterone measurements in addition to presented clinical symptoms such as:
  - Impotence
  - Infertility
  - Reduced sex drive
  - Tiredness
  - Depressive mood
  - Bone loss caused by low hormone levels

  Testoviron Depot may be used only when testosterone deficiency has been confirmed clinically and by laboratory tests and when other possible underlying causes of the symptoms have been ruled out (see section 2 'Special warnings about using this medicine').

- For treating delayed puberty in adolescent boys.
  Only a doctor specializing in pediatric endocrinology is permitted to use Testoviron Depot for puberty induction. The dosing schedule is determined by the underlying clinical picture.

Therapeutic group: Testoviron Depot is a replacement for the male sex hormone testosterone and belongs to the group of medicines called androgens.

2) Before using this medicine

Do not use this medicine if:

- you are sensitive (allergic) to the active ingredient testosterone enantate or to any of the other ingredients of this medicine. For the list of inactive ingredients, see section 6 'Additional information',
- you have a prostate tumor or a breast tumor whose growth is stimulated by male sex hormones (androgens),
- you have or have had liver tumors,
- you have high blood calcium levels in the presence of cancerous (malignant) tumors,
- in newborn infants,
- in young children,
- in women.

Special warnings about using this medicine:
Before treatment with Testoviron Depot, tell your doctor if you have or have ever had:
- epilepsy
- heart, kidney or liver disease
- migraine
- temporary pauses in your breathing while you are asleep (sleep apnea), as these may get worse.
- cancer, as calcium levels in your blood may have to be regularly checked.
- high blood pressure or if you are being treated for high blood pressure, as testosterone can lead to a rise in blood pressure.
- blood clotting problems:
  - bleeding disorders (i.e. hemophilia)
  - thrombophilia (a blood clotting disorder that increases the risk of blood clots forming in the blood vessels).
  - factors that increase the risk for blood clots in a vein: previous blood clots in a vein, smoking, obesity, cancer, immobility, if one of your immediate family members has had a blood clot in the leg, lung or other organ at a young age (e.g., below the age of 50); or as you get older.

  How to recognise a blood clot: painful swelling of one leg or a sudden change in color of the skin, e.g., turning pale, red or blue, sudden shortness of breath, sudden unexplained cough which may bring up blood; or sudden chest pain, headache, severe lightheadedness/dizziness, severe abdominal pain, sudden vision loss. Seek urgent medical attention if you experience one of these symptoms.

- Male hormones may increase the growth of prostate cancer and prostate enlargement (benign prostatic hyperplasia). Before administering Testoviron Depot, your doctor should check you for the presence of prostate cancer. If you are elderly, there may be an increased risk of developing prostate enlargement when androgens such as Testoviron Depot are used. There is no clear evidence that androgens actually cause prostate cancer, but androgens can increase the growth of existing prostate cancer.
- Testoviron Depot can be used for the treatment of reduced testicular function only in cases of confirmed (hyper or hypogonadotropic) dysfunction and after prior exclusion of other underlying causes of the symptoms. Testosterone deficiency must be clearly shown to be present by clinical signs, such as regression of secondary sex characteristics, changes in body composition, rapid onset of fatigue, reduced sex drive and erection problems (impotence), it must be confirmed by two independent measurements of blood testosterone levels.
- Testoviron Depot should be injected into muscle only. Based on experience, the brief reactions that occur in rare cases during or immediately after injection of oily solutions (persistent cough, coughing fits, shortness of breath) can be avoided by injecting the solution very slowly.

Tests and follow up
A thorough medical examination is required before starting treatment with Testoviron Depot. Prostate cancer must be ruled out at this stage. During treatment, careful and regular medical examinations of the prostate and breast must be performed in accordance with currently established examination methods (at least once a year, or twice a year in elderly patients and patients at risk).
In addition to regular checks of blood testosterone levels, the following laboratory parameters should be regularly monitored during treatment with Testoviron Depot: hemoglobin (red blood pigment) and hematocrit (total volume of red blood cells), as well as liver enzymes, lipid panel. Testosterone measurements should always be performed in the same laboratory.

<u>Venous thromboembolism</u>
Events of venous thrombosis and embolism, including deep vein thrombosis and pulmonary embolism, have been reported in patients using testosterone containing preparations, such as Testoviron Depot.
Contact the doctor immediately if you experience the following symptoms:
- Pain, edema, warmth and redness in the lower extremities. The doctor will perform an evaluation for deep vein thrombosis.

- Acute shortness of breath. The doctor will perform an evaluation for pulmonary embolism.

Tumors
Androgens such as testosterone can accelerate the progression of pre-existing prostate cancer or non-cancerous prostate enlargement (benign prostatic hyperplasia).

Cancer patients with bone metastases may have high calcium levels in the blood and urine. Caution should therefore be exercised during treatment with Testoviron Depot (see in section 2 'Do not use this medicine if'). For this reason, it is recommended that calcium levels be regularly monitored in these patients during treatment with Testoviron Depot.

Cases of both benign (non-cancerous) and malignant (cancerous) liver tumors have been observed after the use of testosterone preparations. In isolated cases, these tumors may cause internal bleeding, which may be life-threatening. Tell your doctor if you experience unusual pain in the upper abdomen that does not stop within a short period of time.

Other illnesses
If you are suffering from severe heart, liver or kidney disease, treatment with Testoviron Depot may cause serious complications manifested by fluid retention in your body, sometimes accompanied by heart failure. In such cases, treatment must be stopped immediately.

The following blood tests will be carried out by your doctor before and during treatment: testosterone blood level, complete blood count.

Tell your doctor if you have high blood pressure or if you are treated for high blood pressure, as testosterone may cause a rise in blood pressure.

Caution should be exercised in patients predisposed to fluid accumulation in the tissues (edema), as treatment with androgens such as testosterone may increase sodium retention (see section 4 'Side effects').

The restrictions on the use of intramuscular injections that apply to patients with acquired or congenital blood clotting disorder, must be observed at all times. Caution should be exercised in patients with hypercoagulability, since hypercoagulability has been reported in this patient group during testosterone treatment in studies and post-marketing reports.
Testoviron Depot should be used with caution in patients with epilepsy or migraine, as these disorders may worsen.

Testosterone and its derivatives can increase insulin sensitivity, thereby reducing the dosages of insulin or other antidiabetic medicines needed for treatment. If you are being treated with insulin or other antidiabetic medicines, your doctor will closely monitor your blood sugar level, especially at the start and end of treatment with Testoviron Depot.

Pre-existing sleep apnea (brief cessations in breathing during sleep) may get worse.

Certain signs, such as irritability, nervousness, weight gain, persistent or excessively frequent erections, may indicate that the effect of Testoviron Depot is too strong. In this case, please talk to your doctor.

Do not continue to use Testoviron Depot if symptoms indicating too strong an effect persist or return during treatment at the recommended dosage.

Testoviron Depot is not suitable for the treatment of male sterility.

Effect of Testoviron Depot on thyroid laboratory tests

Androgens can affect the results of certain laboratory tests (thyroid test). If you are scheduled for such a test, tell the attending doctor that you are receiving testosterone treatment. However, the concentrations of the hormones investigated in these tests and responsible for the hormone effect remain unchanged. This means that symptoms such as those associated with an underactive thyroid are unlikely.

Special populations
Elderly individuals (65 years and older)
There is limited experience with safety and efficacy of using Testoviron Depot in patients above the age of 65. However, it should be taken into account that physiological testosterone levels in the blood decrease with increasing age.
If you are over the age of 65, the doctor will generally not adjust (increase) your dose.

If your liver is no longer working properly
No formal studies have been conducted in patients with impaired liver function. Testosterone treatment should therefore proceed with caution if your liver is no longer working properly. If you have or have ever had a tumor in the liver, the doctor will not prescribe you Testoviron Depot (see section 2 'Do not use this medicine').

If your kidneys are no longer working properly
No formal studies have been conducted in patients with impaired kidney function. Testosterone treatment should therefore proceed with caution if your kidneys are no longer working properly.

Children and adolescents
The safety and efficacy of Testoviron Depot in children aged up to 12 years have not been established.

In adolescent boys, Testoviron Depot may be used only after careful consideration of the benefit/risk balance. Testosterone may accelerate bone maturation as a result of conversion to estrogen, a female sex hormone, thereby reducing adult height. Upon long term treatment or administration of a higher dose, radiological bone age measurements should be conducted at regular intervals.

Effects of misuse for doping purposes
The use of Testoviron Depot can lead to a positive result in doping tests.
Androgens such as those contained in Testoviron Depot are not suitable for enhancing muscular development in healthy individuals or for boosting physical performance.
It is impossible to predict the health consequences of using Testoviron Depot as a doping agent; serious health risks cannot be ruled out (see section 4 'Side effects').

Drug abuse and dependence
Always take this medicine exactly as the doctor or pharmacist has told you.
Abuse of testosterone, especially if you take too much of this medicine or in combination with other anabolic androgenic steroids, may cause serious health problems to your heart and blood vessels (that may lead to death), mental health and/or the liver.
Individuals who have abused testosterone may become dependent and may experience withdrawal symptoms when the dose changes significantly or is stopped immediately. Do not abuse this medicine or in combination with other anabolic androgenic steroids because it carries serious health risks (see section 'Side effects').

Drug interactions
If you are taking or have recently taken other medicines, including nonprescription medications and dietary supplements, tell your doctor or pharmacist. Also tell your doctor or pharmacist if you may take other medicines. It is particularly important to inform the doctor or pharmacist if you are taking:
The effect of the following active substances or groups of medicines may be influenced if administered in combination with Testoviron Depot:

- medicines to treat nervousness and sleep disorders (barbiturates and other enzyme inducers)
- medicines to treat pain or inflammation (oxyphenbutazone)
- Testosterone can increase the effect of medicines preventing blood clotting (oral anticoagulants). In patients receiving treatment with oral anticoagulants, close monitoring of the clotting status (more frequent prothrombin time and INR tests) is therefore required, especially at the start and end of treatment with Testoviron Depot.
- medicines to treat diabetes. It may be necessary to adjust the dose of medicines used to regulate blood sugar levels, because testosterone, like other insulins, may enhance the effect of insulin.
- ACTH (a certain pituitary hormone) or corticosteroids (adrenal cortex hormones). Co-administration of testosterone and ACTH or corticosteroids can increase the risk of edema formation (accumulation of fluid in the tissues). For this reason, these treatments should be administered with caution, especially in patients with heart or liver disease or in patients prone to edema.

Please make sure you tell your doctor if you have a bleeding disorder, because it is important for your doctor to know this before deciding to inject Testoviron Depot.

Other possible interactions
Androgens may affect the results of thyroid function tests (see also section 2 'Before using this medicine').

Pregnancy and breastfeeding
Testoviron Depot is not intended for use in women and must not be used in pregnant or breastfeeding women.
Use in women may cause virilization symptoms (acne, excessive hair growth, voice change).

Fertility
Testosterone treatment can temporarily suppress sperm production, thereby impairing fertility.

Driving and using machines
Testoviron Depot has no or negligible influence on the ability to drive and use machines.

Important information about some of this medicine's ingredients
Testoviron Depot contains 342.0 mg of benzyl benzoate in each 1 mL ampoule.

3) How to use this medicine?

Always use this medicine according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure about your dose or about how to take this medicine. Only your doctor will determine your dose and how you should take this medicine.

The recommended dosage is usually:

For male hypogonadism
The recommended initial dose is 1 ml Testoviron Depot (equivalent to 250 mg testosterone enantate) every 2-3 weeks. The dosage can be adjusted by the doctor, according to the clinical picture and the serum testosterone levels measured.

In rare cases, persistent and painful erections of the penis may occur during treatment. In such cases, the dosage must be reduced or the treatment temporarily stopped.

For treatment of delayed puberty in adolescent boys
There are several recommended dosing regimens. Some of them start at low dosages, with a gradual increase upon puberty induction, with or without dosage reduction, until the maintenance dosage is reached. Other dosing regimens start at high dosage for puberty induction and then low maintenance dosages. The chronological age and the bone age will be taken into account when your doctor determines the dosing regimens, both the initial and the maintenance dosage. The recommended dosages will usually be in the range of 50-200 mg, every 2-4 weeks, for a period of 4-6 months.

Do not exceed the recommended dose.

Mode of administration: The injection will be performed only by the doctor or the medical staff into the buttock muscle. Testoviron Depot should be injected into the muscle very slowly to reduce the risk of physical reactions (see section 4 'Side effects'). The intramuscular injection should be performed immediately after opening the ampoule.

Your doctor will measure the testosterone level in your blood before the start of treatment, occasionally during treatment and at the end of treatment. If the testosterone level is too low, your doctor may decide to give you injections more frequently. If your testosterone level is too high, your doctor may decide to give you injections less often. Do not miss your injection appointments. Otherwise, your optimal testosterone levels cannot be maintained. If you feel that the effect of Testoviron Depot is too strong or too weak, contact your doctor.

Instructions for handling the preparation
The solution for injection must be visually inspected prior to use. Only clear, particle-free solutions may be used.
Testoviron Depot is intended for single use. Any unused residues must be discarded.
In the absence of information from studies, Testoviron Depot must not be mixed with other medicines**.**

If you have accidentally taken a higher dose than recommended, no special therapeutic measures are required other than discontinuing the medicine.
If a child has accidentally swallowed some medicine, immediately see a doctor or go to a hospital emergency room and bring the medicine package with you.

Adhere to the treatment as recommended by your doctor.
Do not miss your injection appointments. Otherwise, your optimal testosterone levels cannot be maintained.
Even if your health improves, do not stop taking this medicine without consulting your doctor.

Do not take medicines in the dark! Check the label and dose <u>every time</u> you take medicine. Wear glasses if you need them.
If you have any further questions about using this medicine, consult your doctor or pharmacist.

4) Side effects

Like with all medicines, using Testoviron Depot may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them.

The most common side effects observed during or immediately after the injection are: pain and itching (redness) at the injection site, cough and/or shortness of breath.

Additional side effects:

<u>Common side effects</u> <u>- may affect 1-10 in 100 users</u>
- <u>Blood and lymphatic system disorders:</u> increase in hematocrit (red blood cell volume), increase in red blood cell count and increase in hemoglobin.

<u>Rare side effects</u> <u>- may affect 1-10 in 10,000 users</u>
- <u>Complications related to injuries, poisoning and surgeries:</u> pulmonary microembolism caused by oily solutions.

<u>Side effects of unknown frequency</u> <u>- the frequency of these side effects cannot be estimated from the existing information</u>
- <u>Gastrointestinal disorders:</u> constipation, diarrhea, bloating, abdominal pain.

- Benign and malignant neoplasms (including cysts and polyps): benign (non-cancerous) and malignant (cancerous) liver tumors.
- Blood and lymphatic system disorders: significant increase in red blood cells (polycythemia, erythrocytosis).
- Immune system disorders: hypersensitivity reactions.
- Hepatobiliary disorders: abnormal liver function test results, yellowing of the skin and eyes (jaundice).
- Kidney and urinary tract diseases: disorders of the urinary tract (e.g., weak urine flow, urinary retention, nocturia – urination during the night, dysuria – burning upon urination)
- Skin and subcutaneous tissue disorders: various skin reactions (including acne, redness, hives, itching and hair loss), dry skin.
- General disorders and injection area conditions: various injection site reactions, including pain, itching, skin hardening, swelling and inflammation. Laboratory tests: increase in prostate-specific antigen (PSA), increase in estradiol in the blood, increase in creatine phosphokinase in the blood. Increase in glycated hemoglobin level, increase in aspartate aminotransferase, increase in cholesterol in the blood, hypercholesterolemia.
- Musculoskeletal and connective tissue disorders: muscle disorders (e.g., muscle cramps, muscle tension, muscle stiffness, muscle pain).
- Psychiatric disorders: emotional disorders such as nervousness, aggressiveness, depression.
- Nervous system disorders: headache and fatigue, migraines or tremors.
- Respiratory, thoracic and mediastinal disorders: brief cessations in breathing during sleep (sleep apnea), upper airway infections, bronchitis, sinusitis, snoring.
- Reproductive system and breast disorders: altered sex drive (libido), increased erection frequency; high-dose use of testosterone generally causes a reversible interruption or reversible reduction in sperm production and hence a decrease in testicular size. In rare cases, use of Testoviron Depot to treat reduced testicular function (hypogonadism) can cause painful and persistent erections (priapism), prostate abnormalities, prostate disorders (e.g., benign prostate hyperplasia, prostate dysplasia, hardening or inflammation of the prostate, prostate cancer - data are inconclusive with respect to association between testosterone treatment and the risk of developing prostate cancer), painful testicles, urinary flow obstruction, chest pain, painful/hardened/enlarged breasts (gynecomastia)
- Metabolism and nutrition disorders: weight gain, electrolyte changes (retention of sodium, chloride, potassium, calcium and inorganic phosphates and water) at high doses and/or during long-term therapy, increased appetite, changes in blood test results (e.g., increase in blood glucose, blood fats).

The oily solution of Testoviron Depot can get into the lungs (pulmonary microembolism caused by oily solutions), which, in rare cases, cause signs and symptoms such as cough, shortness of breath, generally feeling unwell, intense sweating, chest pain, dizziness, sensation of “pins and needles” (pricking) or fainting. These reactions may occur during or immediately after the injection and are reversible. The treatment is usually supportive care (oxygen administration).

Hostility/aggression, as well as increased growth of body and facial hair, have been reported to occur upon treatment with testosterone-containing medicines.

If you experience side effects after the use of Testoviron Depot, please tell the attending doctor, who will decide on any corrective measures to be taken. Side effects for which you may need to consult a doctor immediately, or which require discontinuation of treatment, are listed in section 2 ‘Special warnings about using this medicine’.

If you experience any side effect, if any side effect gets worse, or when you experience a side effect not mentioned in this leaflet, consult your doctor.

Side effects can be reported to the Ministry of Health by following the link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects, or by using this link: https://sideeffects.health.gov.il

5) How to store the medicine?

- Avoid poisoning! To avoid poisoning, keep this, and all other medicines, in a closed place, out of the reach and sight of children and/or infants. Do not induce vomiting unless explicitly instructed to do so by a doctor.
- Do not use the medicine after the expiry date (exp. date) that appears on the package. The expiry date refers to the last day of that month.
- Store at a temperature below 30˚C. Keep the ampoule in the carton package to protect from light.
- Use the ampoule immediately after opening.
- The solution must be visually inspected prior to use, and should be used only if it is clear and free of particles.
- Testoviron Depot is intended for single use. Any injection residues must be discarded.

6) Additional information

- In addition to the active ingredient testosterone enantate, this medicine also contains:
  castor oil, benzyl benzoate
- What the medicine looks like and contents of the pack:
  Testoviron Depot is a clear yellowish oily solution.
  The preparation is marketed in packs of one ampoule containing 1 ml or 100 ampoules containing 1 ml each.
  Not all pack sizes may be marketed.
- **Registration holder's name and address:** Bayer Israel Ltd., 36 Hacharash St., Hod Hasharon 45240.
- **Manufacturer's name and address:** Bayer AG, Berlin, Germany.

Revised in November 2025.

Registration number of the medicine in the National Drug Registry of the Ministry of Health:
048 61 23357 00