1. NAME OF THE MEDICINAL PRODUCT

Testoviron® Depot

250 mg/mL Oily solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL solution for injection contains 250 mg testosterone enantate, equivalent to 180 mg testosterone in oily solution.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oily solution for injection
Clear, yellowish oily solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Testosterone replacement therapy for male hypogonadism, when testosterone deficiency has been confirmed by clinical features and biochemical tests (see section 4.4 “Special warnings and precautions for use”).
- Puberty induction in boys with delayed puberty (*pubertas tarda*).

4.2 Posology and method of administration

Serum testosterone levels must be measured before the start and during initiation of therapy. Serum levels below the normal range would indicate that the injection interval must be shortened. If serum levels are excessive, prolongation of the injection interval can be considered.

To achieve low dose levels, corresponding aliquots (0.2 mL equivalent to 50 mg testosterone enantate, 0.4 mL equivalent to 100 mg testosterone enantate, etc.) must be removed from the 250 mg testosterone enantate ampoule using a 1 mL injection syringe with 0.01 mL graduations.
The injections must be administered very slowly (see sections 4.4 and 4.8). Care should be taken to inject Testoviron Depot deeply into the gluteal muscle, while observing the usual precautions for intramuscular injections. Special care must be given to avoid intravascular injections.

The intramuscular injection must be conducted immediately after opening the ampoule or pre-filled syringe.

Posology

Male hypogonadism
For long-term replacement in hypogonadism, 1 mL Testoviron Depot (equivalent to 250 mg testosterone enantate) is recommended every 2–3 weeks as a guide. Individual dosage can be modified depending on the clinical picture and serum testosterone levels measured.
In cases of rare, persistent and painful erection (priapism), the dose must be reduced or the therapy temporarily discontinued.

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

Puberty induction in boys with delayed puberty (pubertas tarda)
Puberty induction with testosterone enantate should be performed only by a physician experienced in paediatric endocrinology. (see section 4.4). The dosing schedule is predicated on the underlying pathological picture and should be guided by the relevant recommendations by professional associations.

Various dosage regimens have been used. Some with lower dosages initially with gradual increases as puberty progresses, with or without a decrease to maintenance levels. Other regimens use higher dosage to induce pubertal changes and lower dosage for maintenance after puberty. The chronological and skeletal ages must be taken into consideration, both in determining the initial dose and in adjusting the dose. Dosage is within the range of 50 to 200 mg every 2 to 4 weeks within 4 to 6 months.

Method of administration

Solution for injection for intramuscular use.

Special groups

Elderly patients
Limited data indicate that dose adjustment is not necessary in elderly patients (see section 4.4).

Patients with hepatic damage
No formal studies have been conducted in patients with impaired hepatic function. The use of Testoviron Depot is contraindicated in males with past or existing liver tumours (see section 4.3).

Patients with renal damage
No formal studies have been conducted in patients with impaired renal function.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Androgen-dependent carcinoma of the prostate or male mammary gland
- Past or existing liver tumours
- Hypercalcaemia in cases of malignant tumours
- Newborn infants
- Small children
- Women

4.4 Special warnings and precautions for use

Elderly patients treated with androgens may be at increased risk of developing prostatic hyperplasia. There is no clear evidence that androgens actually cause prostate cancer, but androgens can potentiate the growth of existing prostate cancer. Existing prostate carcinoma should therefore be excluded before use of testosterone preparations.

For the treatment of hypogonadism, Testoviron Depot may be used only if hypogonadism (hyper or hypogonadotropic) has been demonstrated and if other aetiology, responsible for the symptoms, has been excluded. Testosterone insufficiency must be clearly demonstrated in the clinical symptoms (regression of secondary sexual characteristics, change in body composition, asthenia, reduced libido, erectile dysfunction, etc.) and confirmed by two separate blood testosterone measurements.

There is limited experience on the safety and efficacy of the use of Testoviron Depot in patients over 65 years of age. Currently, there is no consensus about age-specific testosterone reference values. However, it should be taken into account that physiologically testosterone serum levels are lower with increasing age.

In children, testosterone may accelerate bone maturation as a result of peripheral conversion to oestrogen, thereby reducing adult height. In longer-term or higher-dose administration, radiological bone age measurements should therefore be conducted at regular intervals.

Testoviron Depot must not be used in women, as women may develop signs of virilisation, e.g. acne, hirsutism, voice changes (particular care is required in women professionally reliant on singing or speaking), depending on individual sensitivity to androgenic impulses.

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

Venous Thromboembolism
There have been postmarketing reports of venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients using testosterone products, such as Testoviron Depot. Evaluate patients who report symptoms of pain, edema, warmth and erythema in the lower extremity for DVT and those who present with acute shortness of breath for PE. If a venous thromboembolic event is suspected, discontinue treatment with Testoviron Depot and initiate appropriate workup and management.

Medical examination
Before the start of therapy with testosterone, all patients must undergo a detailed medical examination in order to exclude the risk of pre-existing prostatic cancer. In patients receiving testosterone therapy, careful and regular check-ups of the prostate gland and breast must be performed in accordance with currently established methods (digital rectal examination and monitoring of serum PSA) at least once yearly, or twice yearly in elderly patients and in patients at risk (with certain clinical or familial factors).

Testosterone level should be monitored at baseline and at regular intervals during treatment. Clinicians should adjust the dosage individually to ensure maintenance of eugonadal testosterone levels. In patients receiving long-term androgen therapy the following laboratory parameters should also be monitored regularly: haemoglobin, and haematocrit, liver function tests and lipid profile (see section 4.8).
Due to variability in laboratory values, all measuring of testosterone levels should be carried out in the same laboratory.

Tumours
Androgens may accelerate the development of sub-clinical prostatic cancer and benign prostatic hyperplasia.

Testoviron Depot should be used with caution in cancer patients at risk of hypercalcaemia (and associated hypercalciuria), e.g due to bone metastasis; see also section 4.3. It is recommended that serum calcium levels be regularly monitored in these patients.
Cases of benign and malignant liver tumours that can lead to life-threatening intra-abdominal bleeding have been observed following use of testosterone depot preparations.

Blood clotting disorders
As a general rule, the limitations of using intramuscular injections in patients with acquired or inherited bleeding disorders must always be observed.

Testosterone and its derivatives have been reported to increase the effect of coumarin-derived anticoagulants (see section 4.5).

Testosterone should be used with caution in patients with thrombophilia or risk factors for venous thromboembolism (VTE), as there have been post-marketing studies and reports of thrombotic events (e.g. deep-vein thrombosis, pulmonary embolism, ocular thrombosis) in these patients during testosterone therapy. In thrombophilic patients, VTE cases have been reported even under anticoagulation treatment, therefore continuing testosterone treatment after first thrombotic event should be carefully evaluated. In case of treatment continuation, further measures should be taken to minimise the individual VTE risk.

Other diseases
In patients suffering from severe cardiac, hepatic or renal insufficiency or ischaemic heart disease, treatment with testosterone can cause severe complications, characterised by oedema, with or without congestive cardiac failure. In this case, treatment must be stopped immediately.

Caution should be exercised in patients predisposed to oedema, as treatment with androgens can exacerbate sodium retention (see section 4.8).

Studies on the efficacy and safety of this medicinal product have not been conducted in patients with impaired renal or hepatic function. Testosterone therapy must therefore be performed only with caution in these patients. Testosterone may cause a rise in blood pressure and Testoviron Depot should be used in caution in men with hypertension.

Testoviron Depot should be used only with caution in patients with epilepsy or migraine, as it may aggravate these disorders.

In diabetic patients treated with androgens who achieve normal plasma testosterone levels after testosterone therapy, there may be a reduction in blood glucose, and hence a decrease in the need for insulin.

Certain clinical symptoms, such as irritability, nervousness, weight gain, persistent or frequent erections may indicate excessive androgen exposure and require a dose adjustment (see also section 4.2).

Testoviron Depot should be permanently discontinued if symptoms of excessive androgen exposure persist or recur during therapy on the recommended dosing schedule.

Pre-existing sleep apnoea may be exacerbated.

<u>Drug abuse and dependence</u>
Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication(s) and in combination with other anabolic androgenic steroids. Abuse of testosterone and other anabolic androgenic steroids can lead to serious adverse reactions including: cardiovascular (with fatal outcomes in some cases), hepatic and/or psychiatric events. Testosterone abuse may result in

dependence and withdrawal symptoms upon significant dose reduction or abrupt discontinuation of use. The abuse of testosterone and other anabolic androgenic steroids carries serious health risks and is to be discouraged.

Administration
Like all oily solutions, Testoviron Depot must be injected precisely and very slowly via the intramuscular route. A pulmonary microembolism with oily solutions can lead to symptoms such as cough, dyspnoea, malaise, hyperhidrosis, chest pain, dizziness, paraesthesia or syncope. These reactions can occur during or immediately after the injection and are reversible. Treatment is usually carried out with supportive measures, e.g. with additional oxygen administration.

Excipient information
This medicinal product contains 342.0 mg benzyl benzoate in each ampoule/pre-filled syringe.
The use of Testoviron Depot can lead to positive results 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 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products that influence the effect of testosterone

Barbiturates and other enzyme inducers
Interactions may occur with medicinal products that induce microsomal enzymes. This may also result in increased testosterone clearance.

The effect of androgens on other medicinal products

Oxyphenbutazone
There have been reports of increased serum oxyphenbutazone levels.

Oral anticoagulants
Testosterone and its derivatives have been reported to increase the effects of coumarin-derived oral anticoagulants. Close monitoring is therefore required in patients receiving oral anticoagulants , especially at the beginning or end of androgen therapy. Increased monitoring of the prothrombin time and more frequent INR determinations are recommended. Adjustment of the oral anticoagulant dose may be necessary. Independently of this observation, the limitations for intramuscular injection in patients with hereditary or acquired bleeding disorders must always be observed.

ACTH and corticosteroids
The concurrent administration of testosterone with ACTH or corticosteroids can promote oedema formation; therefore, these active substances should be administered cautiously, particularly in patients with cardiac or hepatic disease or in patients predisposed to oedema.

Antidiabetics
Androgens can increase insulin sensitivity and thereby reduce the doses of insulin or other antidiabetics needed for treatment (see section 4.4).

Effects on laboratory tests

Androgens may decrease levels of thyroxine-binding globulin, thereby resulting in decreased total T4 serum levels and increased resin uptake of T3 and T4 in the uptake test. However, free thyroid hormone levels remain unchanged. There is no clinical evidence of impaired thyroid function.

4.6 Fertility, pregnancy and lactation

Pregnancy and breast-feeding
Testoviron Depot is contraindicated in women; its use is prohibited in pregnant or breast-feeding women (see section 4.3).

Fertility
Testosterone replacement therapy can reversibly suppress spermatogenesis (see sections 4.8 and 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

For undesirable effects that may occur when using androgens, see also section 4.4.
The most commonly observed undesirable effects are injection site pain, injection-site redness, cough and/or dyspnoea during or immediately after the injection.

The frequency of adverse drug reactions reported with Testosterone-Depot preparations is summarised by System Organ Class (according to MedDRA) and frequency in the table below.

The table contains undesirable effects from spontaneous reports and from scientific literature.

System organ class	**Side effect**		
	Common (≥1/100 to <1/10)	Rare (≥1/10,000 to <1/1,000)	Unknown (frequency cannot be estimated based on the available data)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)			Benign and malignant liver tumours
Blood and lymphatic system disorders	Haematocrit increased, red blood cell count increased, haemoglobin increased		Polycythaemia (erythrocytosis)
Immune system disorders			Hypersensitivity reactions
Metabolism and nutrition disorders			Weight gain, changes in electrolyte values (retention of sodium, chloride, potassium, calcium and phosphate ions and water) under higher doses and/or

System organ class	**Side effect**		
	Common (≥1/100 to <1/10)	Rare (≥1/10,000 to <1/1,000)	Unknown (frequency cannot be estimated based on the available data)
			long-term therapy
Nervous system disorders			Nervousness, aggressiveness, depression, headache and fatigue
Respiratory, thoracic and mediastinal disorders			Sleep apnoea, upper airway infections
Gastrointestinal disorders			Constipation, diarrhoea, meteorism and abdominal pain
Hepatobiliary disorders			Jaundice and abnormal liver function tests
Skin and subcutaneous tissue disorders			Various skin reactions (including acne, redness, urticaria, pruritus and hair loss [alopecia])
Musculoskeletal and connective tissue disorders			Muscle cramps
Reproductive system and breast disorders			Changes in libido, increased erection frequency; high-dose use of testosterone preparations generally causes a reversible interruption or reduction in spermatogenesis and hence a decrease in testicular size; in rare cases, testosterone replacement therapy in hypogonadism can cause painful and persistent erection (priapism), prostate abnormalities, prostate cancer* as well as urinary outflow obstruction. Mastodynia, gynaecomastia
General disorders and administration site conditions			Various types of injection-site reactions (injection-site pain, injection-site induration, injection-site swelling, injection-site inflammation)
Investigations			Elevation of prostate-specific antigen

System organ class	Side effect		
	Common (≥1/100 to <1/10)	Rare (≥1/10,000 to <1/1,000)	Unknown (frequency cannot be estimated based on the available data)
Injury, poisoning and procedural complications		Pulmonary oil microembolism	

* Data are inconclusive as regards the risk of the emergence of prostate cancer in association with testosterone treatment.

Description of selected adverse reactions

Pulmonary oil microembolism
In rare cases, a pulmonary microembolism with oily solutions can lead to symptoms such as cough, dyspnoea, malaise, hyperhidrosis, chest pain, dizziness, paraesthesia or syncope. These reactions can occur during or immediate after the injection and are reversible. There have been rare suspected cases of oily pulmonary embolisms reported both in clinical studies (in ≥ 1/10,000 and <1/1,000 injections) and in post-marketing experience (see section 4.4).
Hostility/aggression has been reported to occur, as well as increased growth of body and facial hair, on treatment with testosterone-containing medicines.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

In case of overdose, no special therapeutic measures are required other than discontinuing the medicinal product or reducing the dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: androgens, 3-oxoandrosten (4) derivatives, ATC-code: G03B A03

Testosterone enantate is an ester of the naturally occurring androgen, testosterone. The active form of testosterone is formed through cleavage of the heptanoic acid side chain.

Testosterone is the most important male androgen, It is mainly formed in the testicles and to a minor extent in the adrenal cortex.

Testosterone is responsible for the expression of masculine characteristics during foetal, early childhood, and pubertal development; it subsequently acts to maintain the masculine phenotype and androgen-dependent functions (e.g. spermatogenesis, accessory sexual glands). It also performs other functions, e.g. in the skin, muscles, skeleton, kidney, liver, bone marrow and CNS.

Depending on the target organ, testosterone mainly shows an androgenic (e.g. prostate, seminal vesicles, epididymis) or protein-anabolic (muscle, bone, haematopoiesis, kidney, liver) spectrum of activity.

In some organs, testosterone acts after peripheral conversion to estradiol. This is then bound by the oestrogen receptors in the target cell nucleus, e.g. in pituitary, fat, brain, bone and testicular Leydig cells.

5.2 Pharmacokinetic properties

Absorption
After intramuscular administration, testosterone enantate becomes fully systemically available. The compound is gradually released from the depot with a half-life of about 4.5 days and cleaved into testosterone and heptanoic acid.
At a dose of 250 mg testosterone enantate, patients receive a total dose of 180 mg testosterone. The serum levels reached after 1 and 2 weeks are equivalent to those of a daily dose of 12 and 4 mg testosterone, respectively. About 4 weeks after administration of Testoviron Depot, testosterone is completely released from the depot.

Distribution
A peak testosterone concentration of 20 ng/mL was measured 1.5–3 days after IM administration of 250 mg testosterone enantate in young men. Thereafter, the plasma testosterone level declined with a half-life of about 4.5 days, corresponding to the release rate from the depot. Testosterone concentrations of ≥ 2 ng/mL were maintained for 20 days and testosterone concentrations ≥ 1 ng/mL for 26 days.
Testosterone is highly bound to serum proteins, especially to albumin and SHBG.

Biotransformation
Testosterone enantate which is generated by ester cleavage, is metabolised and excreted as testosterone in the same way as endogenous testosterone. Heptanoic acid is metabolised by ß-oxidation in the same way as other aliphatic carboxylic acids. The chief active metabolites of testosterone are estradiol and dihydrotestosterone.

Elimination
The metabolic clearance of testosterone is 16 ± 7 mL/min/kg and indicates hepatic and extra-hepatic metabolism of testosterone. The metabolites of testosterone are eliminated with a half-life of 7.8 days. About 90% is excreted renally and about 10% via the enterohepatic circulation.
Renally excreted products include androsterone and etiocholanolone.

Steady state conditions
Injection of 250 mg testosterone enantate every 3 - 4 weeks does not result in any relevant accumulation of the serum testosterone level.
In healthy male volunteers after single intramuscular injection of 250 mg testosterone enantate, mean C_{max} values of 14-19 ng/mL were reached within 0.5 -5 days post-administration. In isolated cases, levels exceeding the upper normal range were measured up to 10 - 12 days post-administration. On average, peak concentrations were higher than the upper normal range by a factor of 1.4 -1.9. At the same time, there was significant interindividual variation in the progression of testosterone levels. Testosterone levels returned to pre-treatment levels after two weeks. Simulation based on an open, 2- compartment model reveals that there is no accumulation of serum testosterone levels upon repeated administration of testosterone enantate at 3-week intervals, which confirms decades of standard therapeutic practice with testosterone enantate at 3 -week intervals.

5.3 Preclinical safety data

Toxicity studies revealed no effects other than those that can be explained on the basis of the hormonal profile of Testoviron Depot.

Mutagenic and tumorigenic potential
Testosterone was shown in vitro to be non-mutagenic in the reverse mutation test (Ames test) and in the hamster ovary cell assay. In animal studies, a relationship was found between androgen treatment and the development of certain cancer types. Experimental data in rats showed an increased incidence of prostate cancers after treatment with testosterone.
Sex hormones are known to promote the development of certain tumours induced by known carcinogens. The clinical relevance of this observation is not known. As regards effects on the prostate,

however, in general it has to be remembered that androgens can promote the growth of certain hormone-dependent tissues and tumours (see section 4.3).

Toxicity to reproduction
Fertility studies with rodents and primates showed that treatment with testosterone can dose-dependently impair fertility by suppressing spermatogenesis.
The possibility of effects on a woman's pregnancy due to treatment of her male partner cannot be deduced from the results of an animal fertility study using male animals treated with androgens.

6. PHARMACEUTAL PARTICULARS

6.1 List of excipients

castor oil, Benzyl benzoate,.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf-life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 30°C.
Keep the ampoules in the outer carton in order to protect from light.

6.5 Nature and contents of container

Pack with 1 ampoule containing 1 mL
Pack with 100 ampoules, each containing 1 mL

6.6 Special precautions for disposal and other handling

The solution intended for intramuscular injection should be visually inspected prior to use; only clear, particle-free solutions must be used.
This medicinal product is intended for single use only. Any unused remaining portions must be discarded.
No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Bayer AG, Berlin, Germany

8. REGISTRATION HOLDER

Bayer Israel Ltd 36 Hacharash St., Hod Hasharon 45240

Revided on March 2021 according to MoH guidelines