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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 in male hypogonadism, in cases where testosterone deficiency has been confirmed on the basis of clinical and laboratory evidence (see section 4.4 "Special warnings and precautions for use").
- ◆ Inducing puberty in boys with delayed puberty (*pubertas tarda*).

4.2 Posology and method of administration

Testoviron Depot 250 is injected intramuscularly. Experience shows that transitory reactions which occur in rare cases during or immediately after oily injections (urge to cough, coughing fits, respiratory distress) can be avoided by injecting the solution very slowly.

Testosterone serum levels should be measured before initiating treatment, as well as during therapy.

The injections must be administered very slowly. Care should be taken to inject Testoviron Depot 250 deeply into the gluteal muscle, while observing the usual precautions for intramuscular administration. Special care must be given to avoid intravascular injection.

The intramuscular injection must be conducted immediately after opening the ampoule.

- *Testosterone replacement therapy for male hypogonadism in adults*

Initial treatment

The contents of one ampoule or one prefilled syringe are applied intramuscularly in intervals of 2 to 3 weeks.

Maintenance treatment

To maintain an adequate androgenic effect in adults, injections should be given in the recommended intervals of 2 to 3 weeks. Shorter or longer intervals between injections may be needed, depending on individual hormone requirements.

- *Inducing puberty in boys with delayed puberty*

When used to induce puberty in boys, a dose of 50 to not more than 100 mg testosterone enanthate is administered over 4 to 6 months, followed by a 3-month pause in therapy. The treatment can be repeated if necessary (note: a 14-day regimen of 50 mg is recommended for the 100 mg/month dose)

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 only little experience with the use of Testoviron Depot in patients over 65 years of age. At present, there is no consensus about age-specific testosterone reference values. However, it should be taken into account that physiological serum testosterone levels decrease 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).

In addition to laboratory checks on testosterone concentrations, the following laboratory parameters should also be checked periodically in patients before and during long-term androgen therapy: haemoglobin, haematocrit and liver function tests (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.

Other diseases

In patients suffering from severe cardiac, hepatic or renal insufficiency or ischaemic heart disease, therapy with testosterone can cause serious complications, characterised by oedema, which may or may not be accompanied by congestive heart failure. In this case, therapy must be discontinued 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.

The restrictions on the use of intramuscular injections that apply to patients with acquired or congenital blood coagulation disorders must be observed.

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.

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.

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

Oral anticoagulants

Testosterone and its derivatives have been reported to increase the effect of oral anticoagulants. Patients receiving oral anticoagulants thus require close monitoring, especially at the beginning or end of androgen therapy. More frequent monitoring of prothrombin times and INR determinations is advised.

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.

Phenobarbital

Phenobarbital increases the breakdown of steroid hormones in the liver (impaired efficacy is possible).

Other interactions

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

Fertility

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

Pregnancy and breast-feeding

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

4.7 Effects on ability to drive and use machines

Testoviron Depot has no 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 following table contains undesirable effects from spontaneous reports and the scientific literature. The frequency of undesirable effects cannot be estimated from the available data.

System organ class	Undesirable effect
Neoplasms, benign and malignant	Benign and malignant liver tumours
Blood and lymphatic system disorders	Polycythaemia (erythrocytosis)
Immune system disorders	Hypersensitivity reactions
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])
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
Musculoskeletal system	Muscle cramps
Nervous system disorders and psychiatric disorders	Nervousness, aggressiveness, depression, headache and fatigue
Respiratory, thoracic and	Sleep apnoea, upper airway infections

System organ class	Undesirable effect
mediastinal disorders	
Gastrointestinal disorders	Constipation, diarrhoea, meteorism and abdominal pain
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
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 long-term therapy

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

Injections of oily solutions such as Testoviron Depot may be associated with the following systemic reactions: cough, dyspnoea and chest pain. Other symptoms may occur, including vasovagal reactions such as malaise, hyperhidrosis, dizziness, paraesthesia or syncope.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il>) or by email (adr@MOH.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.

Metabolism

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 β -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

Benzyl benzoate, castor oil.

6.2 Incompatibilities

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

6.3 Shelf-life

5 years

This medicinal product must be used immediately after opening.

6.4 Special precautions for storage

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

Store below 30°C.

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.

7. MANUFACTURER

Bayer Pharma AG, Berlin, Germany

8. REGISTRATION HOLDER

Bayer Israel Ltd 36 Hacharash St., Hod Hasharon 45240