The format of this leaflet was determined by the Ministry of Health and its content was checked and approved by it in May 2011.

1. NAME OF MEDICINAL PRODUCT

Testoviron Depot

Oily solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL solution for injection contains 250 mg testosterone enanthate in oily solution.

For a 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, method and duration 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 intravasal 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
- Androgen-dependent carcinoma of the prostate or male mammary gland
- Past or existing liver tumours
- Nephrotic syndrome
- Infants and small children
- Women

4.4 Special warnings and precautions for use

Testoviron Depot 250 should be used with caution in cancer patients at risk of hypercalcaemia (and associated hypercalciuria), in association with bone metastases. Regular monitoring of serum calcium concentrations is recommended in these patients.

Rare instances of benign and malignant liver tumours have been reported in patients receiving testosterone replacement therapy.

In patients suffering from severe cardiac, hepatic or renal insufficiency or ischemic heart disease, treatment with testosterone may cause severe complications characterised by oedema, with or without congestive cardiac insufficiency. In such cases, treatment must be stopped immediately.

Studies to demonstrate the efficacy and safety of Testoviron Depot 250 in patients with impaired renal or hepatic function have not been conducted. Testosterone replacement therapy should thus be used with caution in these patients.

The limitations associated with intramuscular injections in patients with acquired or inherited blood clotting irregularities must be observed at all times.

Testoviron Depot 250 should be used with caution in patients with epilepsy and migraine, as it may aggravate these disorders.

Diabetes patients treated with androgen who achieve normal testosterone plasma levels after testosterone substitution may experience lowered blood glucose, thereby reducing the need for insulin.

Certain clinical signs such as irritability, nervousness, weight gain, prolonged or frequent erections may indicate excessive androgen exposure and may require dosage adjustment. Testoviron Depot 250 should be discontinued if the symptoms of excessive androgen exposure persist or reappear during treatment with the recommended dosage regimen.

Pre-existing sleep apnoea may be exacerbated.

Testoviron Depot 250 is not suited for the treatment of male sterility.

In male hypogonadism

Testoviron Depot 250 should be used only if hypogonadism (hyper/hypogonadotrophic) has been demonstrated and if other aetiology, responsible for the symptoms, has been excluded before treatment is started. 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 serum testosterone level measurements.

For elderly patients (over 65 years of age), it should be taken into account that with increasing age, testosterone serum levels decrease in a physiological manner.

Medical examination

Prior to initiating testosterone treatment, all patients must undergo a detailed medical examination in order to exclude any risk of pre-existing prostatic cancer. Careful and regular monitoring of the prostate gland and breast must be performed in accordance with recommended methods (digital rectal examination and estimation of serum PSA) in patients receiving testosterone therapy, i.e. at least once yearly, or twice yearly in elderly patients and in patients at risk (patients with clinical or familial factors).

Since testosterone has a stimulating effect on blood formation and leads to increased haematocrit and haemoglobin values, in addition to laboratory testosterone concentration measurements, the following laboratory parameters should be checked periodically in patients on long-term androgen therapy: haemoglobin, haematocrit, and liver function tests.

Liver function tests should also be conducted on a regular basis.

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.

For delayed puberty in children and adolescents

Through peripheral conversion to oestrogen, testosterone may accelerate bone maturation, thereby reducing adult height. For longer-term or higher dosed therapy, radiological bone age measurements should be conducted in regular intervals.

The use of Testoviron Depot 250 can lead to positive results in drug tests.

Androgens such as those contained in Testoviron Depot 250 are not suitable for enhancing muscular development in healthy individuals or for increasing physical ability.

It is impossible to predict the health consequence of using Testoviron Depot 250 as a doping substance, 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 effects of oral anti-coagulants. Patients receiving oral anti-coagulants thus require close monitoring, especially at the beginning or end of androgen therapy. More frequent monitoring of prothrombin times and INR determinations is advised.

Other interactions

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.

Effects on laboratory test results

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

Phenobarbital increases the break-down of steroid hormones in the liver (possible impairment of efficacy).

4.6 Pregnancy and breast-feeding

Testoviron Depot 250 is not indicated for women; its use is prohibited in pregnant or breastfeeding women.

4.7 Effects on ability to drive and operate machinery

Testoviron Depot 250 does not affect the ability to drive or to operate machines.

4.8 Undesirable effects

The most common undesirable effect is pain at the injection site.

Adverse events associated with testosterone-containing medications have been reported in the literature:

System organ class	Adverse event
Blood and lymphatic system disorders	Polycythaemia (erythrocytosis) in rare cases
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
Musculoskeletal system	Muscle spasms
Nervous system and psychiatric disorders	Nervousness, aggression, depression
Respiratory, thoracic and mediastinal functional	Sleep apnoea

System organ class	Adverse event
disturbances	
Hepatobiliary disorders	Jaundice and abnormal liver function test in very rare cases

System organ class	Adverse event
Skin and subcutaneous tissue disorders	Various skin reactions (incl. acne, seborrhoea and hair loss [alopecia])
Reproductive system and breast disorders	Changes in libido, increased frequency of erections; in a high-dosed treatment with testosterone compounds an often reversible interruption or reduction of the spermatogenesis in the testes is to be expected and consequently also a reduction of the testes size; in rare cases testosterone replacement therapy for hypogonadism may cause persistent painful erections (priapism), prostatic abnormalities, prostatic carcinoma*, as well as urinary obstruction. Breast pain, gynaecomastia
General disorders and administration site complaints	High dose therapy or long-term therapy with testosterone may occasionally cause increased occurrences of water retention and oedema. Hypersensitivity reactions may occur. Pain and haematoma at the injection site

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

4.9 Overdose

In case of overdose, no other 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 enanthate is a derivative of the naturally occurring androgen, testosterone. The active form of testosterone is formed through complete cleavage by esterases.

Testosterone is the most important male androgen; it is mainly synthesised in the testicles and to a smaller 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 further functions, e.g. in the skin, muscles, skeleton, kidney, liver, bone marrow, and CNS.

Dependent on the target organ, testosterone's spectrum of action is mainly androgenic (e.g. prostate, seminal vesicles, epididymis) or protein-anabolic (muscle, bone, haematopoiesis, kidney, liver).

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

5.2 Pharmacokinetic properties

Absorption

Testoviron Depot 250 is a depot preparation containing testosterone enanthate. It is injected intramuscularly, thereby circumventing the first-pass effect. Following intramuscular injection of the oily solution, testosterone enanthate is gradually released from the depot and is nearly completely cleaved by serum esterases into testosterone and heptanoic acid.

Steady state conditions

Following a single intramuscular injection of 250 mg of testosterone enanthate to healthy male volunteers, a mean C_{max} value of 14-19 ng/mL was ascertained within 0.5-5 days post application. In isolated cases, levels exceeding the normal range were measured up to 10-12 days post application. On average, the maximum concentrations were a factor of 1.4-1.9 higher than the upper normal range. Significant interindividual scatter was ascertained over the course of the measured testosterone levels. Testosterone levels returned to pre-treatment levels after two weeks. An open, 2-compartment simulation revealed that repeated application of testosterone enanthate in intervals of 3 weeks did not lead to an accumulation of testosterone levels in serum, thereby confirming decades of actual therapeutic practice, i.e. TE applied in 3-week intervals.

Distribution

In the serum of men, approx. 98 % of circulating testosterone binds to sexual hormone binding globulin (SHBG) and albumin. Only the unbound portion of testosterone is considered to be biologically active. Following intravenous infusion of testosterone in older men, the elimination half-life of testosterone was approximately one hour, with an apparent distribution volume of approx. 1.0 l/kg.

Metabolism

Testosterone enanthate which is generated by ester cleavage is metabolised and excreted as testosterone 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

Following intramuscular application, the half-life of this depot formulation is approximately 4.5 days.

Testosterone undergoes extensive hepatic and extra-hepatic metabolism. After the administration of radio-labelled testosterone, about 90% of the radioactivity appears in the urine as glucuronic and sulphuric acid conjugates; 6% appears in the faeces after

undergoing enterohepatic circulation. Renally excreted products include androsterone and etiocholanolone.

5.3 Preclinical safety data

Based on the acute toxicity data, testosterone enanthate can be classified as being virtually non-toxic when administered in a single dose. Even when inadvertently administered in doses several times greater than the prescribed treatment, no acute risk of poisoning is to be expected.

Animal experimental studies of systemic tolerance after repeated administrations revealed no findings that would rule out the use of this active substance at the doses necessary for therapy.

In-vitro investigations into genotoxic effects using testosterone released from the active substance did not indicate any mutagenic potential.

On account of the available endocrine-pharmacological basic data, the absence of a genotoxic effect (see below), as well as the results of pharmacokinetics studies with respect to metabolism, no further extensive characterisation of the active substance was conducted as regards possible tumourigenic potential, inasmuch as the pertinent animal experimental studies have shown that no relevant results are to be expected in humans.

Moreover, many years of clinical experience with Testoviron Depot 250 have given no indication of any tumourigenic effect in humans. As regards effects on the prostate, however, in general it has to be remembered that androgens can promote malignant prostatic tumour growth (see section 4.3 Contraindications).

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 treated male animals.

As regards local tolerance, no wholly solvent-related increase in slight local irritation has been ascertained to date in animal experimental studies. The solvent has been used for years in numerous formulations in humans, without any clinical local irritation being observed which might bring its continued use into question

Experimental studies with the solvent contained in Testoviron Depot 250 showed no evidence of a sensitising effect. Clinically, only isolated suspected cases of allergic reactions have been ascertained in association with Testoviron Depot 250, but from which no clearly sensitising effect can be derived.

6. PHARMACEUTAL PARTICULARS

6.1 List of excipients

Benzyl benzoate, refined castor oil.

Incompatibilities

None

6.2 Shelf-life

5 Years

6.3 Special precautions for storage

The prefilled syringes or ampoules should be stored in their outer cartons to protect their contents from exposure to light.

6.4 Nature and content of container

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

6.5 Special precautions for disposal and other handling

Store below 30°C. Unused medicinal product or waste materials should be disposed of according to national requirements.

MANUFACTURER
Bayer Schering Pharma AG, Berlin, Germany

REGISTRATION HOLDER
Bayer Israel Ltd 36 Hacharash St., Hod Hasharon 45240