testosterone enanthate, is able to eliminate the symptoms of androgen deficit. The active form, testosterone, is formed by cleavage of the side chain.

- **Pharmacokinetic properties**

Testosterone enanthate
Absorption
After intramuscular administration, testosterone enanthate becomes completely systemically available. The compound is gradually released from the depot with a half life of about 4.5 days and is cleaved into testosterone and enanthic acid. With a dose of 250 mg testosterone enanthate, patients receive a total dose of 180 mg testosterone. Around the time where maximum serum levels are achieved, average daily doses after 1 and 2 weeks correspond to 12 and 4 mg testosterone, respectively. Within approximately 4 weeks of drug administration, testosterone is completely released from the depot.

Distribution
Maximum concentrations of testosterone of 20 ng/ml were measured 1.5 - 3 days after i.m. administration of 250 mg of testosterone enanthate to young men. Thereafter, testosterone level in the plasma decreased with a half-life of about 4.5 days, which corresponds to the release rate from depot. Testosterone concentrations of ≥ 2ng/ml were maintained for 20 days and those ≥1ng/ml for 26 days.
Testosterone is highly bound to serum proteins, in particular to albumin and SHBG.

Metabolism
Testosterone which is generated by ester cleavage from testosterone enanthate is metabolized and excreted the same way as endogenous testosterone. The absolute bioavailability of testosterone from the ester is almost complete, indicating a rapid and efficient cleavage of the ester. The enanthic acid is metabolized by ß-oxidation in the same way as other aliphatic carboxylic acids.

Elimination
The metabolic clearance of testosterone is calculated to be 16±7 ml/min/kg and refers to 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 % with the bile.
Steady-state conditions
Injection of 250 mg testosterone enanthate every 3 - 4 weeks will not result in any clinically relevant accumulation of testosterone in serum.

- **Preclinical safety data**
Since testosterone enanthate is completely split by esterases into the free testosterone, the evaluation is carried out under consideration of the results with both esters.

  - Acute toxicity
  As with steroid hormones in general, the acute toxicity of testosterone is very low.

  - Chronic toxicity
  Investigations into the systemic tolerance following repeated administration revealed no findings which would be prohibitive of the use of the active substances at the doses necessary for therapy.

  - Mutagenic and tumorigenic potential
  In vitro investigations into a mutagenic effect using the testosterone released from the esters gave no indications of a mutagenic potential. Furthermore, on the basis of negative results in mutagenicity studies with other steroid hormones no such potential is to be expected in the case of Testoviron Depot. Studies aimed at assessing a possible tumorigenic effect following repeated administration have not been performed with Testoviron Depot. Such studies were not considered necessary since in systemic tolerance studies following repeated administration to rats and dogs over a period of six months no indications of a tumorigenic effect occurred. In addition, many years of clinical experience with Testoviron Depot have not given any indications of a tumorigenic effect in humans. Generally, however, it has to be remembered that naturally occurring as well as synthetically produced sexual steroids can promote the growth of certain hormone-dependent tissues and tumors.

  - Reproductive toxicity
  Fertility studies into germ cell damage have not been carried out with Testoviron Depot. Such studies were not considered to be necessary since long-term systemic tolerance studies gave no indication of toxic damage to the testicles, but only a centrally related inhibition of the spermatogenesis and oogenesis. On the other hand the temporary inhibition of spermatogenesis following treatment with Testoviron Depot 250 in humans gaveno indications that sperm cells are damaged in any way which might lead to malformations or impairment of fertility in the offspring. Tostoviron Depot should not be administered during pregnancy due to the possibility of virilization of the female fetus. However,investigations into embryotoxic, in particular teratogenic, effects gave no indication that further impairment of organ development is to be expected.

  - Local tolerability
  Local tolerance studies following intramuscular administration showed that testosterone enanthate did not increase the irritative effect already caused by the solvent alone. The solvent of Testoviron Depot has been used for many years in numerous formulations for human use. In this time no local irritative effects have been observed which could object to its further use.
  Investigations using the oily solvent contained in Testoviron Depot gave no indications of a sensitizing effect. Additional investigations into the sensitizing effect of testosterone propionate and testosterone enanthate have not been carried out. Many years of clinical experience have shown only sporadic cases in which allergenic reactions have been suspected. No clear sensitizing effect has been proven.
  On the whole, the available toxicological findings do not present any objections to the prescriptive use of Testoviron Depot in humans for the given indications and at the dosages prescribed.

PHARMACEUTICAL PARTICULARS

- **List of excipients**
Benzyl benzoate
Castor oil for injection

- **Incompatibilities**
None

- **Special precautions for storage**
Store below 30°C.
Protect from light.

- **Nature and contents of container**
Amber glass type I, ampoule of 1 ml.

- **Instructions for use / handling**
To be used according to the physician's advice.
Store all drugs properly and keep them out of reach of children.

- **Manufactured by**
Medipharm (Pvt.) Ltd.,
108-Kotlakhpat Industrial Estate, Lahore.
Licencee of
Bayer Pharma AG, Germany

ہدایات برائے خوراک:
ڈاکٹر کے مشورے کے مطابق استعمال کریں۔
30°C سے کم درجہ حرارت میں رکھیں۔
روشنی سے محفوظ رکھیں۔
بچوں کی پہنچ سے دور رکھیں۔

Bayer

Testoviron Depot

250 mg/ ml solution for injection

QUALITATIVE AND QUANTITATIVE COMPOSITION
1 ml Testoviron Depot 250 mg contains 250 mg testosterone enanthate (the equivalent of about 180 mg testosterone) in oily solution.
For a full list of excipients see list of excipients.

PHARMACEUTICAL FORM
Solution for injection.
Clear, yellowish oily solution.

CLINICAL PARTICULARS

- **Indications**
  Male hypogonadism
- **Dosage and method of administration**
  - **Method of administration**
    Solution for intramuscular injection.
    The injection must be administered extremely slowly (see Special warnings and precautions for use and Undesirable effects). The oily solution is injected immediately after its drawing up into the syringe.
  - **Dosage regimen**
    For the development and stimulation of still underdeveloped androgen-dependent target organs and for the initial treatment of deficiency symptoms: 250 mg i.m. every 2 - 3 weeks. To maintain an adequate androgenic effect, 250 mg i.m. every 3 - 4 weeks. Shorter injection intervals may be necessary depending on the individual requirement for hormone, but longer intervals of up to 6 weeks are also sufficient in many cases. Serum testosterone levels should be measured before start of treatment and occasionally during the treatment at the end of an injection interval. Serum levels below normal range would indicate the need for a shorter injection interval. In case of high serum levels an extension of the injection interval may be considered.
  - **Additional information on special populations**
    - **Children and adolescents**
      Testoviron is not indicated for use in children and adolescents (see Special warnings and precautions for use).
    - **Geriatric patients**
      Limited data do not suggest the need for a dosage adjustment in elderly patients (see Special warnings and precautions for use).
    - **Patients with hepatic impairment**
      No formal studies have been performed in patients with hepatic impairment. The use of Testoviron is contraindicated in men with past or present liver tumors (see Contraindications).
    - **Patients with renal impairment**
      No formal studies have been performed in patients with renal impairment.
- **Contraindications**
  Androgen-dependent carcinoma of the prostate or of the male mammary gland.
  Hypercalcemia accompanying malignant tumors.
  Past or present liver tumors.
  Hypersensitivity to the active substance or to any of the excipients.
- **Special warnings and precautions for use**
  Older patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia. Although there are no clear indications that androgens actually generate prostatic carcinoma, these can enhance the growth of any existing prostatic carcinoma. Therefore carcinoma of the prostate has to be excluded before starting therapy with testosterone preparations. As a precaution, regular examinations of the prostate are recommended in men. Hemoglobin and hematocrit should be checked periodically in patients on long-term androgen therapy to detect cases of polycythemia (see Undesirable effects).
  Cases of benign and malignant liver tumors, which may lead to life-threatening intra-abdominal hemorrhage, have been observed after the use of Testoviron Depot. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal hemorrhage occur, a liver tumor should be included in the differential-diagnostic considerations.
  Caution should be exercised in patients predisposed to edema, as treatment with Androgens may result in increased sodium retention (see Undesirable effects).
  In children testosterone, besides masculinization, can cause accelerated growth and bone maturation and premature epiphyseal closure, thereby reducing final height.
  Testoviron should not be used in women since, depending on the individual sensitivity to androgenic impulses, women may develop signs of virilization, e.g. acne, hirsutism, voice changes (particular care is necessary in women whose occupations involve singing or speaking!).
  Preexisting sleep apnea may be potentiated.
  Androgens are not suitable for enhancing muscular development in healthy individuals or for increasing physical ability.
  As with all oily solutions, Testoviron Depot must be injected strictly intramuscularly and very slowly. Pulmonary microembolism of oily solutions can lead to signs and symptoms such as cough, dyspnea and chest pain. There may be other signs and symptoms including vasovagal reactions such as malaise, hyperhydrosis, dizziness, paraesthesia, or syncope. These reactions may occur during or immediately after the injection and are reversible. Treatment is usually supportive, e.g. by administration of oxygen.
- **Interaction with other medicinal products and other forms of interaction**
  Phenobarbital increases the break-down of steroid hormones in the liver (possible impairment of efficacy).
  The clotting status should be monitored particularly closely when Testoviron Depot is administered together with coumarin derivatives.
- **Pregnancy and lactation**
  Testoviron is intended for use by men only. Testoviron is not indicated in pregnant or breast feeding women (see Preclinical safety data).
  Testosterone replacement therapy may reversibly reduce spermatogenesis (see Undesirable effects and Preclinical safety data).

  Effects on ability to drive or use machines
  Not applicable.
- **Undesirable effects**
  - **Summary of the safety profile**
    Regarding undesirable effects associated with the use of androgens, please also refer to Special warnings and precautions for use.
    The most commonly reported adverse reactions with Testoviron Depot are injection site pain, injection site erythema, and cough and/or dyspnoea during or immediately after the injection.
  - **Tabulated list of adverse reactions**
    The table below includes adverse drug reactions from spontaneous reporting and from the scientific literature for which a frequency cannot be estimated from the available data.

System Organ Class[1]	Frequency unknown
Neoplasms benign and malignant	Benign and malignant liver tumors
Blood and lymphatic system disorders	Polycythemia
Immune system disorders	Hypersensitivity
Hepatobiliary disorders	Liver function test abnormal, jaundice
Skin and subcutaneous tissue disorders	Acne, Alopecia, Rash, Urticaria, Pruritus
General disorders and administration site conditions	Various kinds of injection site reactions such as Injection site pain, Injection site erythema, Injection site induration, Injection site swelling, Injection site inflammation
Investigations	Prostatic specific antigen increased
Reproductive system and breast disorders	Libido increased Libido decreased Gynaecomastia

[1]The MedDRA preferred term is used to describe a certain reaction and its synonyms and related conditions. ADR term representation is based on MedDRA version 13.1.

  - **Description of selected adverse reactions**
    Injections of oily solutions such as Testoviron Depot have been associated with systemic reactions: cough, dyspnea, chest pain. There may be other signs and symptoms including vasovagal reactions such as malaise, hyperhydrosis, dizziness, paraesthesia, or syncope.
    High-dosed or long-term administration of testosterone, including Testoviron Depot, increases the tendency to water retention and edema.
    Spermatogenesis is inhibited by long-term and high-dosed treatment with Testoviron Depot.
    If, in individual cases, frequent or persistent erections occur, the dose should be reduced or the treatment discontinued in order to avoid injury to the penis.
- **Overdose**
  No special therapeutic measure apart from termination of therapy with the drug or dose reduction is necessary after overdosage. Acute toxicity data shows that testosterone enanthate, the ester contained in Testoviron Depot, are to be classified as non-toxic following single intake. Even following single administration of a multiple of the dose required for therapy, no toxicity risk is to be expected.

PHARMACOLOGICAL PROPERTIES

- **Pharmacodynamic properties**
  Testoviron Depot contains a derivative of the natural male sex hormone testosterone as its active ingredients. Accordingly,