SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Testosterone enantate EVER Pharma 250 mg/ ml Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml ampoule contains 250 mg testosterone enantate corresponding to 180 mg testosterone.

Excipient(s) with known effect
342 mg benzyl benzoate per ampoule.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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.

4.2 Posology and method of administration

Posology

One 1 ml ampoule of [Nationally approved name] (corresponding to 250 mg testosterone enantate) is injected every two to three weeks. For maintenance treatment: 250 mg [Nationally approved name] intramuscularly every three to six weeks, according to individual requirement.

Start of treatment

Serum testosterone levels should be measured before and during initiation of treatment.

Maintenance and individualisation of treatment

Careful monitoring of serum testosterone levels is required during maintenance of treatment. It is advisable to measure testosterone serum levels regularly. Measurements should be performed at the end of an injection interval and clinical symptoms considered. These serum levels should be within the lower third of the normal range. 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.

Special populations

Paediatric population

[Nationally approved name] is not indicated for use in children and adolescents (see section 4.4).

Safety and efficacy have not been adequately determined in children and adolescents.

Elderly patients

Limited data do not suggest the need for a dosage adjustment in elderly patients (see section 4.4).

Patients with hepatic impairment

No formal studies have been performed in patients with hepatic impairment. The use of [Nationally approved name] is contraindicated in men with past or present liver tumours (see section 4.3).

Patients with renal impairment

No formal studies have been performed in patients with renal impairment.

Method of administration
For intramuscular injection.

The injection must be administered very slowly (over two minutes) (see sections 4.4 and 4.8).[Nationally approved name] is strictly for intramuscular injection. Care should be taken to inject [Nationally approved name] deeply into the gluteal muscle following the usual precautions for intramuscular administration. Special care must be taken to avoid intravasal injection (see section 4.4 under "Application"). The contents of an ampoule are to be injected intramuscularly immediately after opening. See section 6.6 for instructions on opening the ampoule safely.

4.3 Contraindications

The use of [Nationally approved name] is contraindicated in men with:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Androgen-dependent carcinoma of the prostate or of the male mammary gland
- Hypercalcaemia
- Past or present liver tumours
- Adenoma of the prostate.

The use of [Nationally approved name] in women is contraindicated.

4.4 Special warnings and precautions for use

[Nationally approved name] should be used only if hypogonadism (hyper- and hypogonadotrophic) has been demonstrated and if other aetiology, responsible for the symptoms, has been excluded before treatment is started. Testosterone insufficiency should be clearly demonstrated by clinical features (regression of secondary sexual characteristics, change in body composition, asthenia, reduced libido, erectile dysfunction etc.) and confirmed by two separate blood testosterone measurements.

In children, in addition to virilization, testosterone can accelerate growth and bone maturation, and cause premature fusing of the conjugation cartilages, leading to a reduction in final height. Consequently, [Nationally approved name] is not recommended for use in children and adolescents.

Elderly population

There is limited experience on the safety and efficacy of the use of [Nationally approved name] 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.

Medical examination and laboratory tests

Medical examinations
Prior to testosterone initiation, all patients must undergo a detailed examination in order to exclude a 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 at least once yearly and twice yearly in elderly patients and at risk patients (those with clinical or familial factors). Local guidelines for safety monitoring under testosterone replacement therapy should be taken into consideration.

Laboratory tests
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 measures of testosterone should be carried out in the same laboratory.

Tumours

Androgens may accelerate the progression of sub-clinical prostatic cancer and benign prostatic hyperplasia, especially in case of the use of high doses. To date, there is no evidence that they increase the risk of prostate cancer or benign prostatic hyperplasia. Likewise, there is no evidence that they can convert subclinical prostate cancer into clinically detectable prostate cancer, although this cannot be completely ruled out at this time. Therefore, it is imperative to rule out prostate cancer before starting treatment with testosterone preparations.

[Nationally approved name] should be used with caution in cancer patients at risk of hypercalcaemia (and associated hypercalciuria), due to bone metastases. Regular monitoring of serum calcium concentrations is recommended in these patients.

Cases of benign and malignant liver tumours have been observed in users of hormonal substances such as androgen compounds. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur in men using [Nationally approved name], a liver tumour should be included in the differential-diagnostic considerations and, if necessary, the preparation should be withdrawn (see section 4.3).

Cardiac, hepatic or renal insufficiency
In patients suffering from severe cardiac, hepatic or renal insufficiency or ischaemic heart disease, treatment with testosterone may cause severe complications characterised by oedema with or without congestive cardiac failure. In such case, treatment must be stopped immediately (see section 4.3).

Hepatic or renal insufficiency

There are no studies undertaken to demonstrate the efficacy and safety of this medicinal product in patients with renal or hepatic impairment. Therefore, testosterone replacement therapy should be used with caution in these patients.

Cardiac insufficiency

Caution should be exercised in patients predisposed to oedema, e.g., in case of severe cardiac, hepatic, or renal insufficiency or ischemic heart disease, as treatment with androgens may result in increased sodium and water retention. In case of severe complications characterized by oedema, with or without congestive heart failure, treatment must be stopped immediately (see section 4.8).
Testosterone may cause a rise in blood pressure and [Nationally approved name] should be used with caution in men with hypertension.

Clotting disorders

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

Testosterone and derivatives have been reported to increase the activity of coumarin derived oral anticoagulants (see also 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 conditions

[Nationally approved name] should be used with caution in patients with epilepsy, migraine, as the conditions may be aggravated.

Improved insulin sensitivity may occur in patients treated with androgens who achieve normal testosterone plasma concentrations following replacement therapy. Therefore, the dosage of hypoglycaemic agents may need to be lowered.

Certain clinical signs: irritability, nervousness, weight gain, prolonged or frequent erections may indicate excessive androgen exposure requiring dosage adjustment.

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.

Pre-existing sleep apnoea may be potentiated.

Athletes treated for testosterone replacement in primary and secondary male hypogonadism should be advised that the medicinal product contains an active substance which may produce a positive reaction in anti-doping tests.

Androgens are not suitable for enhancing muscular development in healthy individuals or for increasing physical ability.

[Nationally approved name] should be permanently withdrawn if symptoms of excessive androgen exposure persist or reappear during treatment with the recommended dosage regimen.

[Nationally approved name] should not be used in women since, depending on the individual sensitivity to androgenic impulses, women may develop signs of virilisation, e.g. acne, hirsutism, voice changes.

Drug abuse and dependence

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.

In children testosterone, besides masculinisation, can cause accelerated growth and bone maturation and premature epiphyseal closure, thereby reducing final height

Application

As with all oily solutions, [Nationally approved name] must be injected strictly intramuscularly and very slowly (over two minutes). Pulmonary microembolism of oily solutions can lead to signs and symptoms such as cough, dyspnoea 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. The patient should therefore be observed during and immediately after each injection in order to allow for early recognition of possible signs and symptoms of pulmonary oily micro embolism. Treatment is usually supportive, e.g., by administration of oxygen.

Suspected anaphylactic reactions after [Nationally approved name] injection have been reported.

Excipients
This medicine contains 342 mg benzyl benzoate in each 1 mL ampoule.

4.5 Interaction with other medicinal products and other forms of interaction

Medicines used to treat pain or inflammation
Medicines for treatment of inflammation or pain have influence on testosterone production.

Oral anticoagulants
The clotting status should be monitored particularly closely when [Nationally approved name] is administered together with coumarin derivatives, since this combination might result in an increased risk of bleeding by direct effect on coagulation and/or fibrinolytic systems. Increased monitoring of the prothrombin time, and INR determinations, are recommended. Adaptation of the dosage of the vitamin K antagonist during androgen treatment and when it is stopped.

Hypoglycaemics
The hypoglycaemic effect of antidiabetics may be enhanced, possibly requiring a reduction in dosage of the hypoglycaemic agent.

Other interactions
The concurrent administration of testosterone with ACTH or corticosteroids may enhance oedema formation; thus these active substances should be administered cautiously, particularly in patients with cardiac or hepatic disease or in patients predisposed to oedema.

Laboratory test interactions: Androgens may decrease levels of thyroxin-binding globulin resulting in decreased total T4 serum levels and increased resin uptake of T3 and T4. Free thyroid hormone levels remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

4.6 Fertility, pregnancy and lactation

Pregnancy
[Nationally approved name] is intended for use by men only. [Nationally approved name] is not indicated in pregnant women (see section 5.3).

Lactation
[Nationally approved name] is intended for use by men only. [Nationally approved name] is not indicated in breast feeding women (see section 5.3).

Fertility
[Nationally approved name] replacement therapy may reversibly reduce spermatogenesis (see sections 4.8 and 5.3).

4.7 Effects on ability to drive and use machines

[Nationally approved name] has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most commonly reported adverse reactions during treatment with testosterone enantate are pain at the injection site, redness at the injection site, cough and/or dyspnoea during or immediately after injection.
Regarding undesirable effects associated with the use of androgens, please also refer to section 4.4.

Undesirable effects are listed by MedDRA System Organ Classes. Assessment of undesirable effects is based on the following frequency groupings:
Very common: ≥1/10
Common: ≥1/100 to <1/10
Uncommon: ≥1/1,000 to <1/100
Rare: ≥1/10,000 to <1/1,000
Very rare: <1/10,000
Not known: cannot be estimated from the available data

Tabulated list of adverse reactions

System Organ Class	**Undesirable effect**	**Frequency**
Neoplasms benign, malignant and unspecified (including cysts andpolyps)	Benign tumour of liver Malignant liver tumour	Not known
Blood and lymphatic system disorders	Polycythaemia	Not known
	Haematocrit increased Red blood cell count increased Haemoglobin increased	Common
Immune system disorders	Hypersensitivity	Not known
Metabolism and nutrition disorders	Weight increased	Common
	Hypercalcaemia Water retention	Not known
Psychiatric disorders	Depression Anxiety	Not known
Nervous system disorders	Headache Paraesthesia	Not known
Cardiac disorders	Disorder circulatory system	Not known
Gastrointestinal disorders	Abdominal disorder Intra-abdominal haemorrhage Nausea	Not known
Hepatobiliary disorders	Liver function test abnormal Jaundice Liver enlargement	Not known
Skin and subcutaneoustissue disorders	Acne Alopecia Rash	Not known

	Urticaria Pruritus Male pattern baldness	
Musculoskeletal and connective tissue disorders	Premature epiphyseal closure* Bone formation increased	Not known
General disorders and administration siteconditions	Injection site reaction** Asthenia Oedema	Not known
Investigations	Prostatic specific antigen increased	Not known
Reproductive system andbreast disorders	Libido increased Libido decreased Gynaecomastia Prostatic disorder Erection increased Spermatogenesis abnormal Precocious puberty*	Not known

*In pre-pubertal males
**Injection site pain, Injection site erythema, Injection site induration, Injection site swelling, Injection site inflammation

Description of selected adverse reactions

Injections of oily solutions such as [Nationally approved name] have been associated with systemic reactions: cough, dyspnoea, chest pain. There may be other signs and symptoms including vasovagal reactions such as malaise, hyperhidrosis, dizziness, paraesthesia, or syncope.

High-dosed or long-term administration of testosterone increases the tendency to water retention and oedema.

Spermatogenesis is inhibited by long-term and high-dosed treatment with Testosterone Enantate.

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.

The use of [Nationally approved name] could be associated with a common risk of increased hematocrit, red blood cell count and hemoglobin level. This frequency has been linked to the use of drugs containing testosterone.

Hostile and aggressive reactions as well as an increase in body hair have been reported under treatment with preparations containing testosterone.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.*

4.9 Overdose

No special therapeutic measure apart from termination of therapy with the drug or dose reduction is necessary after overdosage.

Acute toxicity data show that [Nationally approved name] can be classified as non-toxic following a single intake. Even in the case of an inadvertent administration of a multiple of the dose required for therapy, no acute toxicity risk is expected.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Androgens, 3-oxoandrosten (4) derivatives
ATC Code: G03BA03

[Nationally approved name] is an ester of the natural male sex hormone testosterone and exhibits all the pharmacological effects of the natural hormone. It differs in that it has a depot effect, due to the fact that [Nationally approved name] is only slowly degraded to testosterone in the body.

Mechanism of action
The drug is a synthetic androgen and anabolic steroid and hence is an agonist of the androgen receptor (AR), the biological target of androgens like testosterone and dihydrotestosterone (DHT).

It has strong androgenic effects and moderate anabolic effects, which make it useful for producing masculinization and suitable for androgen replacement therapy.

Testosterone enanthate is a testosterone ester and a long-lasting prodrug of testosterone in the body. Because of this, it is considered to be a natural and bioidentical form of testosterone.

Pharmacodynamic effects
Dependent on the target organ, the spectrum of activities of testosterone is mainly androgenic (e.g. prostate, seminal vesicles, epididymis) or protein-anabolic (muscle, bone, haematopoiesis, kidney, liver).
Testosterone is responsible for the expression of masculine characteristics during foetal, early childhood, and pubertal development and thereafter for maintaining the masculine phenotype and androgen-dependent functions (e.g. spermatogenesis, accessory sexual glands). It also performs functions, e.g. in the skin, muscles, skeleton, kidney, liver, bone marrow, and CNS.

In hypogonadal subjects, testosterone produces arrest of bone growth, by fusion of the growth plates, generally preceded by a growth spurt, development of the external and internal genitalia, growth of hair growth, shedding of the voice, appearance of libido, general effect of protein anabolism, development of skeletal musculature, reduced urinary elimination of nitrogen, sodium, potassium, chlorine, phosphorus and water.

N.B.: Testosterone does not cause testicular development: it decreases pituitary secretion of gonadotropins.

5.2 Pharmacokinetic properties

Absorption
After receiving 200 mg intramuscular injection of testosterone enanthate, the peak serum levels (1233 ± 484 ng/ml) were achieved within 24 hours post-administration in hypogonadal subjects. The concentrations were above normal physiological levels for approximately 9 days.

Distribution
In serum of men, about 98% of the circulating testosterone is bound to sex hormone binding globulin (SHBG) and albumin. Only the free fraction of testosterone is considered as biologically active.

Biotransformation
Testosterone which is generated by ester cleavage from testosterone enantate is metabolized and excreted the same way as endogenous testosterone.

Elimination
Roughly 90% of an intramuscular dose of testosterone is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and its metabolites; about 6% is excreted in feces, mostly in an unconjugated form. After receiving 200 mg intramuscular injection of testosterone enanthate, the apparent half-life was 4.2 days in hypogonadal subjects.

5.3 Preclinical safety data

Studies in animals showed that the formulation has minimal potential for causing sensitisation or local irritation following intramuscular injection. Long-term systemic studies showed no evidence of testicular toxicity although a temporary inhibition of spermatogenesis may occur. No fertility studies with [Nationally approved name] have been carried out. [Nationally approved name] should not be administered during pregnancy due to the possibility of virilisation of the female foetus. However, investigations into embryotoxic, in particular teratogenic, effects gave no indication that further impairment of organ development may occur.

In vitro investigations of mutagenicity gave negative results.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl benzoate
Castor oil, refined

6.2 Incompatibilities

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

6.3 Shelf life

30 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

1 ml solution in an amber glass ampoule.
Pack sizes of 1, 3, 5, or 10 ampoules in a carton box.

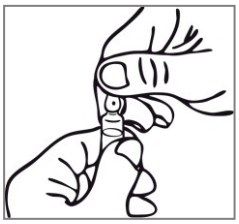
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The product should be inspected visually for particles prior to administration. Only clear solution free from particles should be used.

The medicinal product is for single use only and any unused solution or waste material should be discarded in accordance with local requirements.

Notes on handling the OPC (One-Point-Cut) ampoule:
There is a pre-scored mark beneath the coloured point on the ampoule eliminating the need to file the neck. Prior to opening, ensure that any solution in the upper part of the ampoule flows down to the lower part. Use both hands to open; while holding the lower part of the ampoule in one hand, use the other hand to break off the upper part of the ampoule in the direction away from the coloured point.



7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: [To be completed nationally]

10. DATE OF REVISION OF THE TEXT

17 July 2024