SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Testosterone Enanthate/Norma 250 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml solution for injection contains 250 mg of testosterone enanthate, equivalent to 180 mg of testosterone in oily solution.

Each ampoule 1 mL solution for injection contains 250 mg testosterone enanthate, equivalent to 180 mg testosterone.

Excipients with known effect:
Each ampoule contains 342.0 mg benzyl benzoate and 439.6 mg castor oil.

For the full list of excipients, 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
For the development and stimulation of androgen-dependent target organs and for the initial treatment of deficiency symptoms: 250 mg intramuscularly every 2-3 weeks.
For maintaining an adequate androgenic effect: 250 mg intramuscularly every 3-4 weeks.
Depending on the individual needs, shorter intervals between injections may be required, while in many cases longer intervals of up to 6 weeks between injections may also suffice.

Serum testosterone levels should be measured before starting treatment and periodically at the end of an injection interval. Serum levels below normal ranges indicate a need for shorter injection intervals, while in the case of high serum levels the injection interval should be extended.

Additional information on special patient populations

Paediatric population
The use of **Testosterone Enanthate/Norma** is not indicated in children and adolescents (see section 4.4).

Elderly patients
Limited data do not indicate a need for dose adjustment in elderly patients (see section 4.4).

Patients with hepatic impairment

No formal studies have been conducted in patients with hepatic impairment. The use of **Testosterone Enanthate/Norma** is contraindicated in patients with past or existing liver tumours (see section 4.3).

Patients with renal impairment
No formal studies have been conducted in patients with renal impairment.

Method of administration
Intramuscular injection.
The oily solution must be injected extremely slowly (see sections 4.4 and 4.8) immediately after being drawn into the syringe.

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.
- Hypercalcaemia secondary to malignant tumours.
- Past or existing liver tumours.
- Renal diseases, hypertension, severe liver dysfunction.

4.4 Special warnings and precautions for use

Coagulation disorders
As general rule, limitations on the use of intramuscular injections in patients with acquired or inherited bleeding disorders must always be observed. Testosterone and its derivatives have beenreported to increase the effect 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 postmarketing studies and reports revealed thrombotic events (e.g. deep vein thrombosis, pulmonary embolism, ocular thrombosis) in these patients during testosterone treatment. In thrombophilic patients, VTE cases have also been reported during anticoagulation treatment, therefore continuation of testosterone treatment after the first thrombotic event should be carefully considered. If treatment is continued, additional measures should be taken to minimise the individual risk of VTE.

Other conditions
There is limited experience regarding the safety and efficacy of testosterone enanthate in patients over 65 years of age. There is currently no consensus on age-specific reference values for testosterone. However, it should be taken into consideration that serum testosterone levels normally decrease with age.

Benign and malignant liver tumours have been reported following the use of testosterone enanthate, which can cause life-threatening intra-abdominal hemorrhage. If severe upper abdominal discomfort, liver enlargement or signs of intra-abdominal hemorrhage should occur, the possibility of liver tumour should be considered in the differential diagnosis.

Elderly patients treated with androgens may be at increased risk for developing prostatic hyperplasia. Although there is no clear evidence that androgens cause prostate cancer, they may promote the growth of an existing tumour. Therefore, prostate cancer must be ruled out before initiation of testosterone-based treatment.
As a preventive measure, periodic digital rectal examinations of the prostate are recommended.

Testosterone level should be monitored at baseline and at regular intervals during treatment. Physicians should adjust the dosage on an individual patient-by-patient basis to ensure normal testosterone levels maintenance.

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).

In patients with severe cardiac, hepatic or renal insufficiency or ischaemic heart disease, testosterone treatment may cause serious complications characterised by oedema with or without congestive heart failure. In such case, treatment should be discontinued immediately. Caution is required in patients predisposed to oedema, as androgen treatment may increase sodium retention (see section 4.8).

Testosterone may lead to an increase in blood pressure and **Testosterone Enanthate/Norma** should be used with caution in patients with hypertension.

If symptoms of excessive sexual stimulation should appear, treatment must be discontinued. In elderly, it should be ensured that the treatment does not result in excessive undesirable nervous, mental, or physical stimulation.

In children, testosterone, apart from masculinisation, can accelerate growth and bone maturation, causing premature closure of the epiphyses, resulting in reducing the final height.

Testosterone Enanthate/Norma should not be used in women as, depending on individual sensitivity to androgenic stimuli, jaundice and signs of virilisation, such as acne, hirsutism and voice changes, may occur.

Pre-existing sleep apnoea may be exacerbated.

Androgens are not indicated for boosting muscle growth in healthy individuals or for enhancing physical performance.

As all oily solutions, **Testosterone Enanthate/Norma** should be injected strictly intramuscularly and very slowly. Pulmonary microembolism caused by 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, hyperhidrosis, dizziness, paraesthesia, or syncope. These reactions may occur during or shortly after the injection and they are reversible. Treatment consists of supportive measures, e.g. oxygen administration.

Drug abuse and addiction
Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indications and in combination with other anabolic androgenic steroids. Abuse of testosterone and other anabolic androgenic steroids may lead to serious adverse events, including: cardiovascular events (in some cases fatal), hepatic and/or psychiatric events. Abuse of testosterone may lead to dependence and withdrawal symptoms in the event of significant dose reduction or abrupt discontinuation of use. Abuse of testosterone and other anabolic androgenic steroids carries serious health risks and should be discouraged.

Important information about excipients
Testosterone Enanthate/Norma contains castor oil which may cause severe allergic reactions.
Testosterone Enanthate/Norma contains 342.0 mg of benzyl benzoate in each 1 ml ampoule.

4.5 Interaction with other medicinal products and other forms of interaction

Medicines that interact with testosterone
Barbiturates and other enzyme inducers
Interactions may occur with medicines that induce microsomal enzymes which may lead to increased testosterone clearance.

Effects of androgens on other medicines
Oxyphenbutazone
Increased serum oxyphenbutazone levels have been reported.

Oral anticoagulants

Testosterone and its derivatives have been reported to increase the effects of coumarin-derived oral anticoagulants, possibly requiring dose adjustment. Regardless of this observation, the limitation of use of intramuscular testosterone injections in patients with acquired or hereditary bleeding disorders should always be considered as a general rule.
Patients on concomitant treatment with coumarin oral anticoagulants require close monitoring, especially at the beginning and end of androgen therapy. Frequent monitoring of prothrombin time and INR is recommended.

Hypoglycaemic agents
Androgens may increase insulin sensitivity. Therefore, the dosage of hypoglycaemic agents may need reduction.

4.6 Fertility, pregnancy and lactation

Pregnancy
Testosterone Enanthate/Norma is intended exclusively for use by men. The product is not indicated during pregnancy (see section 5.3).

Breast-feeding
Testosterone Enanthate/Norma is intended exclusively for use by men. The product is not indicated during breast-feeding (see section 5.3).

Fertility
Testosterone replacement therapy can reversibly reduce spermatogenesis (see section 4.8 and 5.3).

4.7 Effects on ability to drive and use machines

Testosterone Enanthate/Norma has no influence on the ability to drive and use machines.

4.8 Undesirable effects

For undesirable effects related to the use of androgens, please also refer to section 4.4.

The most commonly reported adverse reactions with testosterone enanthate are pain at the injection site, erythema at the injection site, cough and/or dyspnea during or immediately after the injection.

Tabulated list of adverse reactions
The following table lists adverse reactions from spontaneous reports and scientific literature for which frequency cannot be estimated from the available data.

System Organ Class (SOC)[§]	Common frequency	Not known frequency
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)		Benign and malignant liver tumours
Blood and lymphatic system disorders		Polycythaemia
Immune system disorders		Hypersensitivity
Metabolism and nutrition disorders		Increased appetite, hypercholesterolemia, increased blood triglycerides
Psychiatric disorders		Libido increased, libido decreased, depression, insomnia, restlessness, aggression, irritability,

		emotional disturbance
Nervous system disorders		Headache, dizziness, migraine, tremor
Vascular disorders		Hot flushes, hypertension
Respiratory, thoracic and mediastinal disorders		Cough, dyspnea, dysphonia, bronchitis, sinusitis, snore
Gastrointestinal disorders		Diarrhea, nausea
Hepatobiliary disorders		Jaundice
Renal and urinary disorders		Slow urinary flow, urinary retention, urinary tract disease, nocturia, dysuria
Skin and subcutaneous tissue disorders		Acne, alopecia, rash, urticaria, pruritus, erythema, hyperhidrosis, dry skin
Musculoskeletal and connective tissue disorders		Arthralgia, pain in the extremities, myalgia, muscle disorders[1], musculoskeletal stiffness
General disorders and administration site conditions		Various types of reactions at the injection site[2], fatigue, asthenia
Investigations	Weight gain, haematocrit increased, red blood cell count increased, haemoglobin increased	Prostate-specific antigen (PSA) increased, abnormal liver function tests, aspartate aminotransferase increased, glycosylated haemoglobin increased, blood pressure increased, blood testosterone increased, estradiol increased, blood creatine phosphokinase increased
Reproductive system and breast disorders		Gynecomastia, testicular pain, abnormal prostate examination, benign prostatic hyperplasia, prostate dysplasia, prostate hardening, prostatitis, prostate pathology, breast hardening, breast pain

[§]*The preferred MedDRA term is used to describe a specific adverse reaction, its synonyms and related conditions. The definition of adverse reactions is based on MedDRA version 26.1.*
[1]*Muscle disorders: muscle spasm, muscle strain*
[2] *Pain at injection site, erythema at injection site, injection site induration, swelling at injection site, inflammation at injection site, haematoma at injection site, reaction at injection site.*

Description of selected adverse reactions
Pulmonary microembolism of oily solutions may, in rare cases, cause signs and symptoms such as cough, dyspnea, malaise, hyperhidrosis, chest pain, dizziness, paraesthesia, or syncope. These reactions may occur during or immediately after injection and are reversible. Cases of suspected oily pulmonary microembolism, in the opinion of the company or the reporting physician, have been reported during post-marketing experience (see section 4.4).

The administration of testosterone, including **Testosterone Enanthate/Norma**, in high doses or for prolonged treatments may induce anxiety states, hypercalcaemia, and increase the tendency to fluid retention and oedema.

Caution is, therefore, advised when administering testosterone therapy to patients with such tendencies, particularly those with renal or cardiovascular insufficiency, asthma, or epilepsy.
High doses of testosterone or its derivatives suppress the secretion of gonadotropins, resulting in atrophy of the interstitial tissue and seminiferous tubules of the testis.
Prolonged treatment with high doses of testosterone enanthate reversibly inhibits or reduces spermatogenesis.

If, in individual cases, frequent or persistent erections (priapism) occur, the dosage should be reduced or treatment discontinued to avoid penile lesions.

Hostility/aggressiveness and increased hair growth have been reported during treatment with testosterone-containing preparations.

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 ADR Reporting Website: https://medicinesauthority.gov.mt/adrportal

4.9 Overdose

In case of overdose, no special therapeutic measures are necessary, other than discontinuation of treatment or dose reduction.
Acute toxicity studies, however, indicate that testosterone enanthate, the ester contained in **Testosterone Enanthate/Norma**, can be classified as non-toxic following a single administration. Even in the case of administration of a single dose several times the therapeutic dose, no toxicity risk is expected.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Testosterone Enanthate/Norma contains testosterone enanthate as its active ingredient, a derivative of the natural male sex hormone testosterone and therefore can eliminate the symptoms of androgen deficiency. The active form, testosterone, is produced by cleavage of the side chain.

5.2 Pharmacokinetic properties

Absorption
Following intramuscular administration, the systemic availability of testosterone enanthate is complete. The compound is released from its depot gradually with a half-life of about 4.5 days and is degraded into testosterone and enanthic acid.
With a dose of 250 mg of testosterone enanthate, patients receive a total testosterone dose of 180 mg. Within about 4 weeks after administration, testosterone release from its depot is complete.

Distribution
A peak testosterone concentration of 20 ng/ml was measured 1.5-3 days after intramuscular administration of 250 mg testosterone enanthate in young men.

Thereafter, plasma testosterone levels decreased with a half-life of about 4.5 days, corresponding to the release rate from the depot. Testosterone concentrations ≥ 2 ng/ml maintained for 20 days, while testosterone concentrations ≥1 ng/ml maintained for 26 days.

Testosterone binding to serum proteins, particularly albumin and sex hormone-binding globulin, is high.

Biotransformation
Testosterone generated by hydrolysis of testosterone enanthate, is metabolised and excreted in the same way as the endogenous testosterone.
The absolute bioavailability of testosterone from the ester is almost complete, thus demonstrating a rapid and efficient hydrolysis of the ester.
Enanthic acid is metabolised by β-oxidation in the same way as other aliphatic carboxylic acids.

Elimination
Metabolic clearance of testosterone is 16±7 ml/min/kg and is related to hepatic and extra-hepatic metabolism. Testosterone metabolites are eliminated with a half-life of 7.8 days, about 90% via the kidneys and about 10% via the bile.

Steady-state conditions
Injection of 250 mg of testosterone enanthate every 3-4 weeks does not result in clinically significant accumulation of testosterone in serum.

5.3 Preclinical safety data

Acute toxicity
As is generally the case with steroid hormones, the acute toxicity of testosterone is very low.

Chronic toxicity
Investigations on systemic tolerability following repeated administration did not reveal any data that would recommend against using the active ingredient at therapeutically required doses.

Mutagenic and carcinogenic potential
In vitro mutagenicity studies with testosterone released from the ester did not provide any indication of mutagenic potential.
No studies have been conducted to evaluate a potential carcinogenic effect of testosterone enanthate after repeated administration. Such studies were not considered necessary, since systemic tolerability studies for repeated administration for 6 months in rats and dogs showed no evidence of a carcinogenic effect.

Reproductive toxicity
No preclinical fertility studies have been conducted regarding potential germ cell damage. Preclinical studies indicate entral inhibition of spermatogenesis and oogenesis.

Local tolerability
Local tolerability studies following intramuscular administration, have shown that testosterone enanthate does not increase the irritation caused by the solvent itself.
Studies conducted with the oily solvent contained in **Testosterone Enanthate/Norma**, did not reveal any sensitising effect. No further studies have been conducted on the sensitizing effect of testosterone enanthate. No obvious sensitizing effect has been demonstrated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl benzoate

Castor Oil

6.2 Incompatibilities

With aqueous solutions.

6.3 Shelf life

24 months for product stored according to the instructions.

6.4 Special precautions for storage

Do not store above 25°C. Protect from light.

6.5 Nature and contents of container

Cardboard box containing a brown glass ampoule and a package leaflet.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

The product should be visually inspected for particles prior to administration. Only clear solution without visible particles should be used.

7. MARKETING AUTHORISATION HOLDER

NORMA HELLAS S.A.
54 Menandrou Street, 10431 Athens.
Tel.: +30 210 52 22 282
Fax: +30 210 52 41 368
email: info@normahellas.gr

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