NEBIDO® 1000mg/4ml
Solution for Injection

1. NAME OF THE MEDICINAL PRODUCT

Nebido 1000 mg/4ml, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule / vial contains 1000 mg testosterone undecanoate (corresponding to 631.5mg testosterone) in a 4-ml solution for injection (250mg testosterone undecanoate/ml).

For a full list of excipient(s), see section, "List of excipients".

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colorless to yellowish-brown oily solution.

4. CLINICAL PARTICULARS

4.1 Indication(s)

Testosterone replacement therapy for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests (see section 4.4, "Special warnings and precautions for use").

4.2 Dosage and method of administration

Method of administration

Solution for injection

Dosage regimen

Nebido (1 ampoule / vial corresponding to 1000 mg testosterone undecanoate) is injected every 10 to 14 weeks. Injections with this frequency are capable of maintaining sufficient testosterone levels and do not lead to accumulation.

The injections must be administered very slowly. Nebido is strictly for intramuscular injection. Care should be taken to inject Nebido deeply into the gluteal muscle following the usual precautions for intramuscular administration. Special care must be given to avoid intravasal injection. The contents of an ampoule or vial are to be injected intramuscularly immediately after opening. See section "Instructions for use/ handling" to avoid injury when opening.

- *Start of treatment*

Serum testosterone levels should be measured before start and during initiation of treatment. Depending on serum testosterone levels and clinical symptoms, the first injection interval may be reduced to a minimum of 6 weeks as compared to the recommended range of 10 to 14 weeks for maintenance. With this loading dose, sufficient steady state testosterone levels may be achieved

more rapidly.

- *Maintenance and individualization of treatment*

The injection interval should be within the recommended range of 10 to 14 weeks. 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 level may be considered.

Additional information on special populations

Paediatric patients

Nebido is not indicated for use in children and adolescents and it has not been clinically evaluated in males under 18 years of age (see section , "Special warnings and precautions for use").

Geriatric patients

Limited data do not suggest the need for a dosage adjustment in elderly patients (see section "Special warnings and precautions for use").

Patients with hepatic impairment

No formal studies have been performed in patients with hepatic impairment. The use of Nebido is contraindicated in men with past or present liver tumours (see section "Contraindications").

Patients with renal impairment

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

4.3 Contraindications

- Androgen-dependent carcinoma of the prostate or of the male mammary gland
- Hypercalcemia accompanying malignant tumours
- Past or present liver tumours
- Hypersensitivity to the active substance or to any of the excipients.

The use of Nebido in women is contraindicated.

4.4 Special warnings and precautions for use

Nebido 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.

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.

Haemoglobin and haematocrit should be checked periodically in patients on long-term androgen therapy to detect cases of polycythemia (see section, "Undesirable Effects").

As a general rule, the risk of bleeding from using intramuscular injections in patients with acquired or inherited bleeding disorders always has to be taken into account. Testosterone and derivatives have been reported to increase the activity of coumarin derived oral anticoagulants (see also section 'Interaction with other medicinal products and other forms of interaction').

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.

There is limited experience on the safety and efficacy of the use of Nebido in elderly 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.

Testosterone may cause a rise in blood pressure and Nebido should be used with caution in men with hypertension.

Medical examination

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 according 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).

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 be checked periodically: haemoglobin, haematocrit and liver function tests and lipid tests.

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.

Nebido should be used with caution in cancer patients at risk of hypercalcaemia (and associated hypercalcuria) due to bone metastases. Regular monitoring of serum calcium concentrations is recommended in these patients.

Cases of benign and malignant liver tumours have been reported 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 Nebido, a liver tumour should be included in the differential-diagnostic considerations.

Other conditions

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

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 cautions in these patients

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 retention of sodium and water. In case of severe complications characterized by oedema with or without congestive heart failure, treatment must be stopped immediately (see section 'Undesirable effects')
Nebido should be used with caution in patients with epilepsy and migraine, as the conditions may be aggravated.

Clinical trials with Nebido in children or adolescents under the age of 18 have so far not been conducted.

In children testosterone, besides masculinization, can cause accelerated growth, bone maturation and premature epiphyseal closure, thereby reducing final height. The appearance of common acne has to be expected.

Improved insulin sensitivity may occur in patients treated with androgens who achieve normal testosterone plasma concentrations following replacement therapy.

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

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.

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.

Testosterone abuse may result in dependence and withdrawal symptoms upon significant dose reduction or abrupt discontinuation of use.

Abuse of testosterone along with other anabolic androgenic steroids can lead to serious adverse reactions including: cardiovascular (with fatal outcomes in some cases), hepatic and/or psychiatric events.

Nebido should be permanently withdrawn if symptoms of excessive androgen exposure persist or reappear during treatment with the recommended dosage regimen.

Suspected anaphylactic reactions after Nebido injection have been reported.

Application

As with all oily solutions, Nebido must be injected strictly intramuscularly and very slowly. Pulmonary microembolism of oily solutions can in rare cases lead to signs and symptoms such as cough, dyspnea, malaise, hyperhidrosis, chest pain, 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 supplemental oxygen.

Androgens may enhance insulin sensitivity. Therefore, the dosage of the hypoglycaemic agents may need to be lowered.

4.5 Interaction with other medicaments and other forms of interaction

Drugs that affect testosterone

- **Barbiturates and other enzyme inducers**

Interactions can occur with drugs that induce microsomal enzymes which can result in increased clearance of testosterone.

Effects of androgens on other drugs

- **Oxyphenbutazone**

Increased oxyphenbutazone serum levels have been reported.

- **Oral anticoagulants**

Testosterone and its derivatives have been reported to increase the activity of coumarin derivedoral anticoagulants, possibly requiring dose adjustment. Independent of this finding, the risk of bleeding from using intramuscular injections in patients with acquired or inherited bleeding disorders always has to be taken into account as a general rule. Patients receiving oral anti-coagulants require close monitoring, especially at the beginning or end of androgen therapy. Increase monitoring of the prothrombin time, and INR determinations, are recommended.

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 thyroxine-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 Pregnancy and lactation

Nebido is not indicated for use in women and must not be used in pregnant or breastfeeding women.

Fertility
Testosterone replacement therapy may reversibly reduce spermatogenesis (see section "Undesirable effects" and section "Preclinical safety data").

4.7 Effects on ability to drive and use machines

Nebido has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Regarding undesirable effects associated with the use of androgens, please also refer to section 4.4,"Special warnings and precautions for use".

The most frequently reported undesirable effects during treatment with Nebido are acne and injection site pain.

Table 1 below reports adverse drug reactions (ADRs) by MedDRA system organ classes (MedDRA SOCs)* reported with Nebido. The frequencies are based on clinical trial data. The ADRs were recorded in 6 clinical studies (N=422) and considered at least possibly causally related to Nebido.

Tabulated list of adverse reactions

Table 1: Categorised relative frequency of men with ADRs, by MedDRA SOC – based on pooled data of six clinical trials, N=422 (100.0%) **

System Organ Class	**Common (≥ 1/100 and < 1/10)**	**Uncommon (≥ 1/1000 and <1/100)**
Blood and lymphatic system disorders	Polycythaemia	Haematocrit increased Red blood cell count increased Haemoglobin increased
Immune system disorders		Hypersensitivity
Metabolism and nutrition	Weight increased	Increased appetite

System Organ Class	Common (≥ 1/100 and < 1/10)	Uncommon (≥ 1/1000 and <1/100)
disorders		Glycosylated haemoglobin increased Hypercholesterolaemia Blood triglycerides increased Blood cholesterol increased
Psychiatric disorders		Depression Emotional disorder Insomnia Restlessness Aggression Irritability
Nervous system disorders		Headache Migraine Tremor
Vascular disorders	Hot flush	Cardiovascular disorder Hypertension Blood pressure increased Dizziness
Respiratory, thoracic and mediastinal disorders		Bronchitis Sinusitis Cough Dyspnoea Snoring Dysphonia
Gastrointestinal disorders		Diarrhoea Nausea
Hepatobiliary disorders		Liver function test abnormal Aspartate aminotransferase increased
Skin and subcutaneous tissue disorders	Acne	Alopecia Erythema Rash Rash papular Pruritus Dry skin
Musculoskeletal and connective tissue disorders		Arthralgia Pain in extremity Muscle spasm Muscle strain Myalgia Musculoskeletal stiffness Blood creatine phosphokinase increased
Renal and urinary disorders		Urine flow decreased Urinary retention Urinary tract disorder Nocturia

System Organ Class	Common (≥ 1/100 and < 1/10)	Uncommon (≥ 1/1000 and <1/100)
		Dysuria
Reproductive system and breast disorders	Prostate specific antigen increased Prostate examination abnormal Benign prostate hyperplasia	Prostatic intraepithelial neoplasia Prostate induration Prostatitis Prostatic disorder Libido increased Libido decreased Testicular pain Breast induration Breast pain Gynaecomastia Estradiol increased Blood testosterone- free increased Blood testosterone increased
General disorders and administration site conditions	Various kinds of injection site reactions***	Fatigue Asthenia Hyperhidrosis Night sweats

* The most appropriate MedDRA term to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.

** N=302 hypogonadal men treated with i.m. injections of 4 ml and N=120 of 3ml of TU 250 mg/ml

*** Various kinds of injection site reaction: Injection site pain, Injection site discomfort, Injection site pruritus, Injection site erythema, Injection site haematoma, Injection site irritation, Injection site reaction

Description of selected adverse reactions

Pulmonary microembolism of oily solutions can in rare cases lead to signs and symptoms such as cough, dyspnoea, malaise, hyperhidrosis, chest pain, dizziness, paresthesia, or syncope. These reactions may occur during or immediately after the injections and are reversible. Cases suspected by the company or the reporter to represent oily pulmonary microembolism have been reported rarely in clinical trials (in ≥1/10 000 and <1/1000 injections) as well as from post-marketing experience (see section “Special warnings and precautions for use”).

Suspected anaphylactic reactions after Nebido injection have been reported.

In addition to the above mentioned adverse reactions, nervousness, hostility, sleep apnoea, various skin reactions including seborrhoea, increased hair growth, increased frequency of erections and in very rare cases jaundice have been reported under treatment with testosterone-containing preparations.

Therapy with high doses of testosterone preparations commonly reversibly interrupts or reduces spermatogenesis, thereby reducing the size of the testicles; testosterone replacement therapy of hypogonadism can in rare cases cause persistent, painful erections (priapism). High-dosed or long-term administration of testosterone occasionally increases the occurrences of water retention and oedema.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC code: G03B A03

Testosterone undecanoate is an ester of the naturally occurring androgen, testosterone. The active form, testosterone, is formed by cleavage of the side chain.

Testosterone is the most important androgen of the male, mainly synthesized in the testicles, and to a small extent in the adrenal cortex.

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).

Insufficient secretion of testosterone results in male hypogonadism characterized by low serum testosterone concentrations. Signs and symptoms associated with male hypogonadism include but are not limited to, erectile dysfunction and decreased sexual desire, fatigue, depressive moods as well as a lacking of secondary sexual characteristics, their incomplete development, or their regression, an increased risk of osteoporosis, an increase of visceral fat and a decrease of lean body mass and muscle strength. Exogenous androgens are given to improve the deficient endogenous testosterone levels and related signs and symptoms.

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, hematopoiesis, kidney, liver).

The effects of testosterone in some organs arise after peripheral conversion of testosterone to estradiol, which then binds to estrogen receptors in the target cell nucleus e.g. the pituitary, fat, brain, bone, and testicular Leydig cells.

In hypogonadal men androgens decrease the body fat mass, increase the body lean mass, muscle strength, and prevent bone loss. Androgens may improve sexual function and also may exert positive psychotropic effects by improving mood.

5.2 Pharmacokinetic properties

• Absorption

Nebido is an intramuscularly administered depot preparation of testosterone undecanoate and thus circumvents the first-pass effect. Following intramuscular injection of testosterone undecanoate as an oily solution, the compound is gradually released from the depot and is almost completely cleaved by serum esterases into testosterone and undecanoic acid. An increase in serum levels of

testosterone above basal values can already be measured one day after administration.

• Distribution

In two separate studies, mean maximum concentrations of testosterone of 24 and 45 nmol/l were measured about 14 and 7 days, respectively, after single i.m. administration of 1000 mg of testosterone undecanoate to hypogonadal men. Post-maximum testosterone levels declined with an estimated half-life of about 53 days.

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. Following intravenous infusion of testosterone to elderly men, an apparent volume of distribution of about 1.0 l/kg was determined.

• Metabolism / Biotransformation

Testosterone which is generated by ester cleavage from testosterone undecanoate is metabolized and excreted the same way as endogenous testosterone. The undecanoic acid is metabolized by ß-oxidation in the same way as other aliphatic carboxylic acids.

• Elimination / Excretion
Testosterone undergoes extensive hepatic and extrahepatic metabolism. After the administration of radiolabeled testosterone, about 90% of the radioactivity appears in the urine as glucuronic and sulphuric acid conjugates and 6% appears in the faeces after undergoing enterohepatic circulation. Urinary products include androsterone and etiocholanolone.

• Steady-state conditions

Following repeated i.m. injection of 1000 mg testosterone undecanoate to hypogonadal men using an interval of 10 weeks between two injections, steady-state conditions were achieved between the 3rd and the 5th administration. Mean C_{max} and C_{min} values of testosterone at steady-state were about 42 and 17 nmol/l, respectively. Post-maximum testosterone levels in the serum decreased with a half-life of about 90 days, which corresponds to the release rate from the depot.

5.3 Preclinical safety data

- **Acute and Chronic Toxicity**

Toxicological studies have not revealed other effects than those which can be explained based on the hormone profile of Nebido.

- **Mutagenic and tumourigenic potential**

The potential carcinogenicity of testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical uterine tumours, which metastasized in some cases. There is suggestive evidence that injection of testosterone in some strains of female mice increases their susceptibility to hepatoma. Testosterone is known to act as a tumour promoter and has been shown to increase carcinomas in the liver of rats. There are rare reports of hepatocellular carcinoma in patients receiving long term therapy with androgens in high doses. Chronic androgen deficiency is a protective factor for prostatic disease and hypogonadal men receiving androgen replacement therapy require surveillance for prostate

disease similar to that recommended for eugonadal men of comparable age. Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic cancer.

Testosterone undecanoate was not genotoxic, as assessed in vitro for reverse gene mutations and chromosomal aberrations. An in vivo assay of chromosomal damage (micronucleus test in mice) was also negative.

- **Reproductive toxicity**

Fertility studies in rodents and primates have shown that treatment with testosterone can impair fertility by suppressing spermatogenesis in a dose-dependent manner. However, no embryolethal or teratogenic effects were observed in the offspring of testosterone-treated male rats.

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

Refer to outer carton.

6.4 Special precautions for storage

Store below 30ºC.

6.5 Presentations

1 x 4ml

6.6 Instructions for use / handling

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

Ampoule

The ampoule is for single use only.

Notes on handling the OPC (One-Point-Cut) ampoule

There is a pre-scored mark beneath the colored 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 colored point.

Vial

The vial is for single use only. After removal of the plastic cap (A) do not remove the metal ring (B) or the crimp cap (C).

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