Nebido® 1000 mg/4 ml
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 631.5 mg testosterone) in a 4-ml solution for injection (250 mg testosterone undecanoate/ ml).

For the full list of excipient(s) see section 'List of excipients'.

3. PHARMACEUTICAL FORM

Solution for injection

Clear, colorless to yellowish oily-brown 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 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. Special care must be given to avoid intravasal injection. See section 'Instructions for use/ handling' to avoid injury when opening.

▶ **Start of treatment**

Serum testosterone levels should be measured before start of treatment. The first injection interval may be reduced to a minimum of 6 weeks. With this loading dose, steady-state levels will be reached quickly.

▶ **Individualization of treatment**

It is advisable to measure testosterone serum levels occasionally 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. The injection interval should remain within the recommended range of 10 to 14 weeks.

Additional information on special populationsi

Pediatric 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 tumors (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 tumors

Past or present liver tumors

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

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 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, as there have been post-marketing studies and reports of thrombotic events in these patients during testosterone therapy.

Cases of benign and malignant liver tumors have been reported in users of hormonal substances, such as androgen compounds. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal hemorrhage occur in men using Nebido, a liver tumor should be included in the differential-diagnostic considerations.

Caution should be exercised in patients predisposed to edema, 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 edema with or without congestive heart failure, treatment must be stopped immediately (see section 'Undesirable effects').

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

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.

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, 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,dyspnoea, malaise, hyperhydrosis, 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.

Suspected anaphylactic reactions after Nebido injection have been reported.

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

Drug Abuse and Dependence

Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication and in combination with other anabolic androgenic steroids (AAS). Abuse of testosterone and other AAS are seen in adults and adolescents, including athletes and body builders. Testosterone and AAS abuse can lead to serious adverse outcomes particularly cardiovascular and psychiatric adverse events (See Section Adverse Effects/

Undesirable Effects).

If testosterone abuse is suspected, check serum testosterone concentrations to ensure they are within therapeutic range. However, testosterone levels may be in the normal or subnormal range in men abusing synthetic testosterone derivatives. Counsel patients concerning the serious adverse reactions associated with abuse of testosterone and AAS. Conversely, consider the possibility of testosterone and AAS abuse in suspected patients who present with serious cardiovascular or psychiatric adverse events.

Continued abuse of testosterone and other AAS may result in dependence and withdrawal symptoms. Individuals taking supratherapeutic doses of testosterone may experience withdrawal symptoms lasting for weeks or months which include depressed mood, major depression, fatigue, craving, restlessness, irritability, anorexia, insomnia, decreased libido and hypogonadotropic hypogonadism.

Drug dependence in individuals using approved doses of testosterone for approved indications has not been documented.

4.5 Interaction with other medicinal products 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 derived oral 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Not applicable.

Lactation

Not applicable.

Fertility

Testosterone replacement therapy may reversibly reduce spermatogenesis (see sections 'Undesirable effects' and 'Preclinical safety data').

4.7 Effects on ability to drive or use machines

No observed effects.

4.8 Undesirable effects

Summary of the safety profile

Regarding undesirable effects associated with the use of androgens,please also refer to section 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 and defined as Common (⩾1/100 to <1/10) and Uncommon (⩾1/1000 to <1/100). 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:Categorized 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	Uncommon
Blood and lymphatic system disorders	Polycythaemia	Hematocrit increased Red blood cell count increased Hemoglobin increased
Immune system disorders		Hypersensitivity
Metabolism and nutrition disorders	Weight increased	Increased appetite 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		Diarrhea 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 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 Oestradiol 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 3 ml 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, hyperhydrosis, 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 < 1/1,000 injections) as well as from postmarketing 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 apnea, 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 edema.

Abuse-Related Adverse Reactions

Serious adverse reactions have been reported in individuals who abuse testosterone and anabolic androgenic steroids (AAS) and include cardiac arrest, myocardial infarction, hypertrophic cardiomyopathy, congestive heart failure, cerebrovascular accident, hepatotoxicity, and serious psychiatric manifestations, including major depression, mania, paranoia, psychosis, delusions, hallucinations, hostility and aggression.

The following adverse reactions have also been reported in men: transient ischemic attacks, convulsions, hypomania, irritability, dyslipidaemias, testicular atrophy, subfertility, and infertility. The following additional adverse reactions have been reported in women: hirsutism, virilisation, deepening of voice, clitoral enlargement, breast atrophy, male-pattern baldness, and menstrual irregularities.

The following adverse reactions have been reported in male and female adolescents: premature closure of bony epiphyses with termination of growth, and precocious puberty.

Because these reactions are reported voluntarily from a population of uncertain size and may include abuse of other agents, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

TBC

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Nebido® 1000 mg/ 4 ml

TBC

Material No.	9304XXXX	Previous Mat. No.	-	Laetus Code	-
CMO Mat. No.	-			Colors & Collating Marks	BLACK
Customer Mat. No.	-				
Class. No.	-				
Product Name	LF-NEBIDO 1000MG SOLU VIAL				
Font Size	9 pt				
Dimension	210x 594 mm	Grain Direction	-	Date/Version	05.07.2024 V1

4.9 Overdose

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

Chronic Overdose Caused by Abuse

Chronic overdose caused by abuse of testosterone and other anabolic androgenic steroids (AAS) can lead to serious adverse outcomes particularly cardiovascular and psychiatric adverse events (See Sections Warnings and Precautions and Adverse Effects/ Undesirable Effects).

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 fetal, 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.

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.

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 of 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 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 feces 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 Cmax and Cmin 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 toxicity

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

▶ Chronic toxicity

No effects which might indicate an unexpected risk to humans were observed during systemic toxicity studies in a rodent or non-rodent species after repeated administration of either the undecanoate or the enanthate ester of testosterone.

▶ Mutagenic and tumorigenic potential

In vitro and in vivo investigations into a mutagenic effect of testosterone undecanoate itself as well as studies on testosterone itself gave no indications of a mutagenic potential.

Studies in rodents indicate a promoting effect of testosterone or of its esters on the development of hormone-dependent tumors. Generally, it should be born in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumors.

▶ Reproduction toxicity

Fertility studies in rodents and primates have shown that treatment with testosterone can impair fertility by suppressing spermatogenesis in a dose-dependent manner. Furthermore, no embryolethal or teratogenic effects were observed in the offspring of testosterone treated male rats. Administration of Nebido may cause virilization of female fetuses in certain development stages. However, investigations into the embryotoxic, in particular teratogenic, effects gave no indication that further impairment of organ development is to be expected.

▶ Local tolerance and contact-sensitizing potential

The local tolerance study on pigs following intramuscular administration showed that Nebido does not increase the irritative effects already caused by the solvent.

6. PHARMACEUTICAL PARTICULARS

List of excipients

Benzyl benzoate

Castor oil, refined

Incompatibilities

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

Storage Condition

Store below 30˚ C

Instructions for use/handling

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

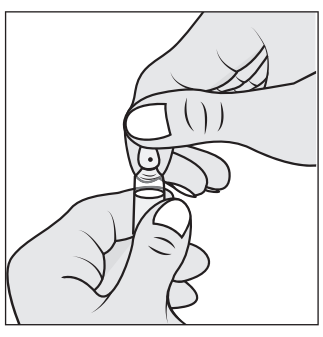
Ampoule

The ampoule is for single use only.

The contents of an ampoule are to be injected intramuscularly immediately after opening the ampoule.

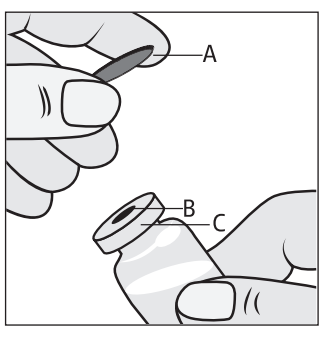
Notes on handling the OPC (One-Point-Cut) ampoule:

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).



Availablity
Ampoule : 4 ml per box
Vial: 4 ml per box
Not all pack sizes are available in the market
Manufacturer
Bayer AG, Germany
Berlin
Germany
Date of text revision: July 2024

Material No.	9304XXXX	Previous Mat. No.	-	Laetus Code	-
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