SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nebido 1000 mg/4ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for injection contains 250 mg of testosterone undecanoate corresponding to 157.9 mg of testosterone.
Each ampoule/vial with 4 ml of solution for injection contains 1000 mg of testosterone undecanoate corresponding to 631.5 mg of testosterone.

Excipient with known effect:
2000 mg benzyl benzoate per ampoule/vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injectionClear, colourless to pale yellowish-brown oily solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Testosterone replacement therapy in male hypogonadism, where testosterone deficiency is confirmed by clinical features and biochemical tests (see section 4.4)

4.2 Posology and method of administration

One ampoule/vial of Nebido (equivalent to 1000 mg testosterone undecanoate) is injected every 10 to 14 weeks. Injections at this frequency are able to maintain adequate testosterone levels without leading to accumulation.

Start of treatment
Serum testosterone levels should be measured before and at the beginning of treatment. Depending on serum testosterone levels and clinical symptoms, the interval between the first two injections may be reduced to a minimum of 6 weeks compared to the 10-14 weeks recommended for maintenance treatment. With this loading dose, steady-state serum testosterone levels are achieved more rapidly.

Maintenance and personalization 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 interval may be considered.

Special populations

Pediatric population
Nebido is not indicated for use in children and adolescents and its use has not been clinically evaluated in men under 18 years of age (see section 4.4).

Geriatric patients
Limited data do not suggest the 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 Nebido is contraindicated in men with a history or presence of liver tumours (see section 4.3).

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

Method of administration
For intramuscular use

Injections should be performed very slowly (over a period of 2 minutes). Nebido is strictly for intramuscular administration. Special care should be taken to inject Nebido deeply into the gluteal muscle, following the usual precautions for intramuscular administration. Special care should be taken to avoid intravascular injection (see section 4.4 under "Administration"). The contents of an ampoule/vial are injected intramuscularly immediately after opening. (For the ampoule see section 6.6 for instructions on safe opening of the ampoule).

4.3 Contraindications

The use of Nebido is contraindicated in men with:

- androgen-dependent carcinoma of the prostate or male mammary gland (breast)
- history or presence of liver tumors
- hypersensitivity to the active substance or to any of the excipients of the product (listed in section 6.1)

The use of Nebido in women is contraindicated.

4.4 Special warnings and precautions for use

Nebido is not recommended for use in children and adolescents.

Nebido should only be used in proven hypogonadism (hyper- or hypogonadotropic) and after all other possible causes of the symptoms have been excluded before starting treatment. Testosterone deficiency must be demonstrated by

clinical features (regression of secondary sex characteristics, change in body morphology, weakness, decreased libido, erectile dysfunction, etc.) and confirmed by two different blood testosterone measurements.

Elderly population
There is limited experience with the safety and efficacy of Nebido 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 account that serum testosterone levels normally decrease with increasing age.

Medical examination and laboratory tests

Medical examinations
Before starting testosterone therapy, all patients should undergo a thorough examination to exclude the risk of pre-existing prostate cancer. In patients receiving testosterone therapy, careful and regular prostate and breast monitoring should be performed according to recommended methods (digital rectal examination and serum PSA assessment), at least once a year and twice a year for elderly patients and patients at risk (with clinical or family risk factors). Local guidelines for the safety monitoring of testosterone replacement therapy should be taken into account.

Laboratory tests
Testosterone levels should be monitored at baseline and periodically during treatment. Clinicians should adjust dosage on an individual basis to ensure that eugonadal testosterone levels are maintained.
In patients receiving long-term androgen therapy the following laboratory parameters should be monitored regularly: haemoglobin and haematocrit, liver function tests and lipid profile (see section 4.8).
Due to the variability of laboratory values, all testosterone measurements should be performed in the same laboratory.

Tumors

Androgens can accelerate the progression of subclinical prostate cancer and benign prostatic hyperplasia.

Nebido should be used with caution in cancer patients at risk of hypercalcemia (and concomitant hypercalciuria) due to bone metastasis. Regular monitoring of serum calcium concentrations is recommended in these patients.

Cases of benign and malignant liver tumors have been reported in users of hormonal substances such as androgens. If severe upper abdominal discomfort, liver enlargement, or evidence of intra-abdominal bleeding occurs in men using Nebido, liver tumour should be included in the differential-diagnostic considerations.

Cardiac, hepatic or renal insufficiency

In patients with severe cardiac, hepatic or renal insufficiency or ischemic heart disease, testosterone therapy may cause serious complications characterized by edema with or without congestive heart failure. In such a case, treatment should be discontinued immediately.

Hepatic or renal insufficiency

No studies have been conducted to demonstrate the efficacy and safety of the 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 with a predisposition to oedema, e.g. in case of severe cardiac, hepatic or renal insufficiency or ischaemic heart disease, as androgen therapy may lead to increased sodium and water retention. In case of serious complications characterised by oedema with or without congestive heart failure, treatment should be discontinued immediately (see section 4.8).

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

Clotting disorders

As a general rule, the restrictions applicable to the use of intramuscular injections in patients with acquired or hereditary bleeding disorders should always be observed.

Testosterone and its derivatives have been reported 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 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. Cases of VTE have been reported in thrombophilic patients even on anticoagulant therapy, therefore continuation of testosterone therapy after the first thrombotic event should be carefully evaluated. In case of continuation of therapy, additional measures should be taken to minimize the risk of VTE on an individual basis.

Other conditions

Nebido should be used with caution in patients with epilepsy and migraine, as these conditions may be aggravated.

In androgen-treated patients, in whom normal plasma testosterone concentrations are achieved after replacement therapy, insulin sensitivity may improve. Therefore, the dosage of hypoglycemic agents may need to be reduced.

Certain clinical signs: irritability, nervousness, weight gain, prolonged or frequent erections may indicate excessive exposure to androgens, in which case dose adjustment is required.

A pre-existing sleep apnoea may worsen.

Athletes receiving testosterone replacement therapy for primary and secondary male hypogonadism should be informed that the medicinal product contains an active substance that may give a positive result in an anti-doping test.

Androgens are not suitable for enhancing muscle growth in healthy individuals or for increasing physical fitness.

The use of Nebido should be permanently discontinued if symptoms of androgen excess persist or recur with the recommended dosage regimen.

Drug abuse and dependence

Testosterone has been abused, usually at doses higher than recommended for the approved indication and in combination with other anabolic androgenic steroids. Abuse of testosterone and other anabolic androgenic steroids can result in serious adverse reactions such as: cardiovascular (in some cases fatal), hepatic and/or psychiatric events. Testosterone abuse can lead to

symptoms of dependence and withdrawal, after a significant dose reduction or abrupt cessation of use. Abuse of testosterone and other anabolic androgenic steroids poses serious health risks and should be prevented.

Application

As with all oily solutions, Nebido should be injected strictly intramuscularly and very slowly (over a period of two minutes). Pulmonary microembolism from oily solutions may in rare cases lead to signs and symptoms such as cough, dyspnoea, malaise, hyperhidrosis, chest pain, dizziness, paraesthesia, or syncope. These reactions may occur during or immediately after the injection and are reversible. The patient should therefore be monitored during and immediately after each injection to allow for early recognition of possible signs and symptoms of pulmonary microembolism from oily solutions. Treatment is usually supportive, e.g. by administering supplemental oxygen.

Suspected anaphylactic reactions have been reported following Nebido injection.

Information about excipients:

This medicinal product contains 2000 mg of benzyl benzoate in each 4 ml ampoule/vial which is equal to 500 mg/ml.

4.5 Interactions with other medicinal products and other forms of interaction

Oral anticoagulants
Testosterone and its derivatives have been reported to increase the activity of coumarin oral anticoagulants. Patients receiving oral anticoagulants should be closely monitored, especially at the beginning or end of androgen therapy. Frequent monitoring of prothrombin time and determination of INR is recommended.

Other interactions
The concomitant administration of testosterone and ACTH or corticosteroids may increase the risk of oedema. Therefore, these active substances should be administered with caution, particularly in patients with cardiac or hepatic disease or in patients predisposed to oedema.

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

4.6 Fertility, pregnancy and lactation

Fertility
Testosterone replacement therapy may cause a reversible decrease in spermatogenesis (see sections 4.8 and 5.3)

Pregnancy and breastfeeding

The use of Nebido is contraindicated in women and should not be used during pregnancy and lactation (see section 4.3).

4.7 Effects on ability to drive and use machines

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

Undesirable effects

Summary of the safety profile

Regarding adverse reactions related to the use of androgens, please also refer to section 4.4.

The most common side effects reported during treatment with Nebido are acne and pain at the injection site.
Pulmonary micro embolism from oily solutions may rarely lead to signs and symptoms such as cough, dyspnoea, malaise, hyperhidrosis, chest pain, dizziness, paraesthesia or syncope. These reactions may occur during or immediately after the injections and are reversible. Cases of suspected pulmonary micro embolism from oily solutions have been reported rarely in clinical studies (≥ 1/10,000 and < 1/1,000 injections) and from post-marketing experience by the company or the reporting entity (see section 4.4).

Suspected anaphylactic reactions have been reported following Nebido injection.

Androgens can accelerate the progression of subclinical prostate cancer and benign prostatic hyperplasia.

Table 1 below lists the adverse drug reactions (ADRs) by MEdDRA System Organ Class (MEdDRA SOCs) reported with Nebido. Frequencies are based on clinical trial data and are defined as Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1000 to < 1/100) and Rare (≥ 1/10,000 to < 1/1,000). The adverse reactions were reported in 6 clinical trials (N=422) and are considered at least possibly causally related to Nebido.

Table of adverse reactions

Table 1: Categorized relative frequency of male adverse reactions by MedDRA SOC – based on pooled data from six clinical studies, N=422 (100.0%), i.e. N=302 men with hypogonadism treated with 4 ml intramuscular injections and N=120 with 3 ml of TU 250 mg/ml

Category Organ Class	**Common (≥1/100 to <1/10)**	**Uncommon (≥ 1/1,000 to < 1/1,000)**	**Rare (≥ 1/10,000 to < 1/1,000)**
Disorders of the hematopoietic and lymphatic system	PolycythemiaIncreased hematocrit* Increased red blood cell count * Increase in hemoglobin*		
Immune system disorders		Hypersensitivity	
Metabolic and nutritional disorders	Increased weight	Increased appetite Increased glycosylated hemoglobin Hypercholesterolemia Increased blood triglycerides Increased blood cholesterol	
Psychiatric disorders		Depression Emotional disorder Insomnia Restlessness Aggression Irritability	
Nervous system disorders		Headache Migraine Tremor	
Vascular disorders	Excitement	Cardiovascular disorders Hypertension Dizziness	
Respiratory, thoracic and mediastinal disorders		Bronchitis Sinusitis Cough Shortness of breath Snoring Dysphonia	
Gastrointestinal disorders		Diarrhea Nausea	
Hepatobiliary disorders		Abnormal liver function values Increased aspartate aminotransferase (AST)	

Skin and subcutaneous tissue disorders	Acne	Alopecia Erythema Rash [1] Itching Dry skin	
Musculoskeletal and connective tissue disorders		Arthralgia Pain in the extremities Muscle disorder [2] Musculoskeletal stiffness/rigidity Increased blood creatine phosphokinase	
Renal and urinary disorders		Decreased urine flow Urinary retention Urinary tract disorders Nocturia Dysuria	
Reproductive system and breast disorders	Increased prostate-specific antigen Pathological examination of the prostate Benign prostatic hyperplasia	Prostate dysplasia Prostate sclerosis Prostatitis Prostate disorders Libido disorder Testicular pain Breast induration Breast pain Gynecomastia Increased estradiol Increased testosterone levels	
General disorders and administration site conditions	Reactions of various kinds at the injection site [3]	Fatigue Weakness Hyperhidrosis[4]	
Injury, poisoning and procedural complications			Pulmonary oil microembolism **

* The relevant category has been observed in association with use in products containing testosterone.
** Frequency is based on the number of injections.

The most appropriate MEDRA term to describe a specific adverse reaction is listed. Synonyms or related conditions are not listed, but should also be considered.
1. Rash including papular rash.
2. Muscle disorder: Muscle spasm, muscle sprain and myalgia.
3. Various types of injection site reactions: Injection site pain, injection site discomfort, injection site pruritus, injection site erythema, injection site haematoma, injection site irritation, injection site reaction.
4. Hyperhidrosis: Excessive sweating and night sweats.

Description of selected adverse reactions
Pulmonary micro embolism from oily solutions may in rare cases lead to signs and symptoms such as cough, dyspnea, malaise, hyperhidrosis, chest pain, dizziness, paresthesia, or syncope. These reactions may occur during or immediately after

injections and are reversible. Cases of suspected pulmonary micro embolism from oily solutions have been reported rarely in clinical studies (in ≥ 1/10,000 and < 1/1,000 injections) as well as from post-marketing experience by the company or the reporting entity (see section 4.4).

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 when treated with testosterone-containing preparations.

Treatment with high-dose testosterone preparations usually reversibly stops or reduces spermatogenesis, thereby reducing testicular size. Testosterone replacement therapy for hypogonadism may in rare cases cause persistent, painful erections (priapism). High-dose or long-term administration of testosterone occasionally increases the occurrence of water retention and oedema.

Reporting suspected adverse reactions
The reporting of suspected adverse reactions after the marketing authorisation of the medicinal product is important. It allows the continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the the ADR Reporting Website:
www.medicinesauthority.gov.mt/adrportal.

4.8 Overdose

After overdose, no special therapeutic measure is necessary other than stopping treatment with the drug or reducing the dosage.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Androgens, 3-oxyandrostene derivatives (4) ATC code:
G03B A03

Testosterone undecanoate is an ester of the natural androgen testosterone. The active form, testosterone, is created by cleavage of the side chain.

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

Testosterone is responsible for the expression of male characteristics during embryonic, early childhood and adolescent development, and subsequently for the maintenance of the male phenotype and androgen-dependent functions (e.g. spermatogenesis, accessory gonads). It also performs various functions, e.g. in the skin, muscle, skeleton, kidney, liver, bone marrow and CNS. Depending on the target organ, the spectrum of testosterone activities is mainly androgenic (e.g. prostate, seminal vesicles, epididymis) or protein anabolic (muscle, bone, haematopoiesis, kidney, liver).

The effects of testosterone on certain organs occur after the peripheral conversion of testosterone to oestradiol, which then binds to oestrogen receptors in the nucleus of the target cell, e.g. pituitary cells, adipocytes, brain cells, bone cells and testicular Leydig cells.

5.2 Pharmacokinetic properties

Absorption

Nebido is a depot intramuscularly administered preparation of testosterone undecanoate, which thus bypasses the effects of first-pass metabolism. After intramuscular injection of testosterone undecanoate as an oily solution, the active substance is released from its storage site gradually, and is almost completely broken down by serum esterases into testosterone and undecanoic acid. An increase in serum testosterone levels above baseline values can already be measured one day after administration.

Steady-state conditions

After the first intramuscular injection of 1000 mg testosterone undecanoate in hypogonadal men, mean Cmax values of 38 nmol/L (11 ng/mL) were achieved after 7 days. The second dose was administered 6 weeks after the first injection and peak testosterone concentrations of approximately 50 nmol/L (15 ng/mL) were achieved. A constant interval of 10 weeks was maintained for the next 3 administrations and steady-state conditions were achieved between the third and fifth administrations. Mean testosterone Cmax and Cmin values at steady-state conditions were approximately 37 nmol/L (11 ng/mL) and 16 nmol/L (5 ng/mL), respectively. The median intra- and inter-individual variability (coefficient of variation %) of Cmin values was 22% (range: 9-28%) and 34% (range: 25-48%), respectively.

Allocation

In male serum, approximately 98% of circulating testosterone is bound to SHBG (Sex hormone binding globulin) and albumin. Only the free fraction of testosterone is considered biologically active. After intravenous injection of testosterone in elderly men, the elimination half-life of testosterone was approximately one hour and the apparent volume of distribution was determined to be approximately 1.0 l/kg.

Biotransformation

Testosterone produced by the cleavage of the testosterone undecanoate ester is metabolized and excreted in the same way as endogenous testosterone. Undecanoate

Testosterone is metabolized by β-oxidation in the same way as other aliphatic carboxylic acids. The main active metabolites of testosterone are estradiol and dihydrotestosterone.

Elimination

Testosterone undergoes extensive hepatic and extrahepatic metabolism. After administration of radiolabelled testosterone, approximately 90% of the radioactivity appears in the urine conjugated with glucuronic and sulfuric acids and 6% appears in the faces via enterohepatic circulation. Urinary products include androsterone and etiocholanolone. After intramuscular administration of this depot formulation, the release rate is characterized by a half-life of 90±40 days.

5.3 Preclinical safety data

Toxicological studies did not demonstrate any effects other than those associated with the hormonal properties of Nebido.

Testosterone has been found to be non-mutagenic in vitro, using the reverse mutation model (Ames test) or hamster ovary cells. Animal studies have shown an association between androgen therapy and certain types of cancer. Data from experiments in rats have shown an increased incidence of prostate cancer after testosterone treatment.

It is known that sex hormones facilitate the growth of certain tumours, which are caused by known carcinogens. The clinical significance of this observation is unknown.

Fertility studies in rodents and primates have demonstrated that testosterone treatment can negatively affect fertility by dose-dependently suppressing spermatogenesis.

6. PHARMACEUTICAL INFORMATION

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 Lifetime

5 years
The medicinal product should be used immediately after first opening.

6.4 Special precautions when storing the product

This medicinal product does not require any special storage conditions.

6.5 Nature and components of the container

Ampoule
5-ml brown glass (type I) ampoules, containing a fill volume of 4 ml
Pack size: 1 x 4 ml

Vials
6-ml brown glass (type I) vial with gray bromobutyl (foil-clad ETFE) injection stopper and bordered cap, containing a fill volume of 4 ml

Pack size: 1 x 4 ml

6.6 Special precautions for disposal and other handling

At cold temperatures the properties of this oily solution may temporarily change (e.g. higher density, turbidity). If stored at cold temperatures, the product should be allowed to reach room or body temperature before use.

The solution for injection for intramuscular administration should be inspected visually prior to use and only clear solutions free from particles should be used.
The medicinal product is for single use only and any unused solution should be disposed of in accordance with local requirements.

Ampoule
Notes on handling the OPC (One-Point-Cut) ampoule:
There is a pre-scored mark below the coloured dot on the ampoule which eliminates the need to file the 'neck' of the ampoule. Before opening, make sure that the solution from the top of the ampoule flows to the bottom. Use both hands to open it: while holding the lower part of the ampoule in one hand, use the other to break the top of the ampoule in a direction away from the coloured dot.

Vial
The vial is intended for single use only. The contents of the vial are injected intramuscularly immediately after filling the syringe. After removing the plastic cap (A) do not remove the metal ring (B) or the clamping sleeve (C).

7. PARALLEL IMPORT LICENSE NUMBER

JV Healthcare Ltd., 1st Floor, 'Navi'
Building, Pantar Road, Lija, LJA ,
Malta

8. PARALLEL IMPORT LICENSE NUMBER

PI 77026201A

9. DATE OF FIRST APPROVAL / RENEWAL OF THE LICENSE

23rd July 2025

10. DATE OF REVISION OF THE TEXT