SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nebido 1000 mg/4ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml solution for injection contains 250 mg testosterone undecanoate corresponding to 157.9 mg testosterone.

Each ampoule / vial with 4 ml solution for injection contains 1000 mg testosterone undecanoate corresponding to 631.5 mg 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 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 (see section 4.4).

4.2 Posology and method of administration

Posology

One ampoule / vial of Nebido (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.

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 individualisation 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

Paediatric population

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 4.4)

Geriatric patients

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

Patients with hepatic impairment

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

Patients with renal impairment

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

Method of administration
For intramuscular use.

The injections must be administered very slowly (over two minutes). 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 taken to avoid intravasal injection (see section 4.4 under "Application"). The contents of an ampoule / vial are to be injected intramuscularly immediately after opening. (For the ampoule see section 6.6 for instructions on opening the ampoule safely).

4.3 Contraindications

The use of Nebido is contraindicated in men with:
- androgen-dependent carcinoma of the prostate or of the male mammary gland
- past or present liver tumours
- hypersensitivity to the active substance or to any of the excipients (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 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.

Elderly population

There is limited experience on the safety and efficacy of the use of Nebido in patients over 65 years of age. Currently, there is no consensus about age specific testosterone reference values. However, it should be taken into account that physiologically testosterone serum levels are lower with increasing age.

Medical examination and laboratory tests

Medical examinations
Prior to testosterone initiation, all patients must undergo a detailed examination in order to exclude a risk of pre-existing prostatic cancer. Careful and regular monitoring of the prostate gland and breast must be performed in accordance with recommended methods (digital rectal examination and estimation of serum PSA) in patients receiving testosterone therapy at least once yearly and twice yearly in elderly patients and at risk patients (those with clinical or familial factors). Local guidelines for safety monitoring under testosterone replacement therapy should be taken into consideration.

Laboratory tests
Testosterone level should be monitored at baseline and at regular intervals during treatment. Clinicians should adjust the dosage individually to ensure maintenance of eugonadal testosterone levels.
In patients receiving long-term androgen therapy, the following laboratory parameters should also be monitored regularly: haemoglobin and haematocrit, liver function tests and lipid profile (see section 4.8).

Due to variability in laboratory values, all measures of testosterone should be carried out in the same laboratory.

Tumours

Androgens may accelerate the progression of sub-clinical prostatic cancer and benign prostatic hyperplasia.

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

Cases of benign and malignant liver tumours have been 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.

Cardiac, hepatic or renal insufficiency

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

Hepatic or renal insufficiency

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

Cardiac insufficiency

Caution should be exercised in patients predisposed to oedema, e.g. in case of severe cardiac, hepatic, or renal insufficiency or ischemic heart disease, as treatment with androgens may result in increased 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 4.8).

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

Clotting disorders

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

Testosterone and derivatives have been reported to increase the activity of coumarin derived oral anticoagulants (see also section 4.5)

Testosterone should be used with caution in patients with thrombophilia, or risk factors for venous thromboembolism (VTE), as there have been post-marketing studies and reports of thrombotic events (e.g. deep-vein thrombosis, pulmonary embolism, ocular thrombosis) in these patients during testosterone therapy. In thrombophilic patients, VTE cases have been reported even under anticoagulation treatment, therefore continuing testosterone treatment after first thrombotic event should be carefully evaluated. In case of treatment continuation, further measures should be taken to minimise the individual VTE risk.

Other conditions

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

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

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.

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

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

Drug abuse and dependence

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

Application

As with all oily solutions, Nebido must be injected strictly intramuscularly and very slowly (over two minutes). Pulmonary micro embolism of oily solutions can 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 observed during and immediately after each injection in order to allow for early recognition of possible signs and symptoms of pulmonary oily micro embolism. Treatment is usually supportive, e.g. by administration of supplemental oxygen.

Suspected anaphylactic reactions after Nebido injection have been reported.

Information about excipients

This medicine contains 2000 mg Benzyl benzoate in each 4 ml ampoule/vial which is equivalent to 500 mg/ml.

4.5 Interaction with other medicinal products and other forms of interaction

Oral anti-coagulants

Testosterone and derivatives have been reported to increase the activity of coumarin derived oral anti-coagulants. Patients receiving oral anti-coagulants require close monitoring, especially at the beginning or end of androgen therapy. Increased 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 thyroxin-binding globulin resulting in decreased total T4 serum levels and increased resin uptake of T3 and T4. Free thyroid hormone levels remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

4.6 Fertility, pregnancy and lactation

Fertility

Testosterone replacement therapy may reversibly reduce spermatogenesis (see sections 4.8 and 5.3).

Pregnancy and breastfeeding

Nebido is not indicated for use in women and must not be used in pregnant or breast-feeding women (see section 4.3).

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.

The most frequently reported undesirable effects during treatment with Nebido are acne and injection site pain.
Pulmonary micro embolism of oily solutions can 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. Cases suspected by the company or the reporter to represent oily pulmonary micro embolism have been reported rarely in clinical trials (in ≥ 1/10,000 and < 1/1,000 injections) as well as from postmarketing experience (see section 4.4).

Suspected anaphylactic reactions after Nebido injection have been reported.

Androgens may accelerate the progression of sub-clinical prostatic cancer and benign prostatic hyperplasia.

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), uncommon (≥ 1/1000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000). 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%), i.e. N=302 hypogonadal men treated with i.m. injections of 4 ml and N=120 with 3 ml of TU 250 mg/ml

System Organ Class	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1,000)**
Blood and lymphatic system disorders	Polycythaemia Haematocrit increased* Red blood cell count increased* Haemoglobin increased*		
Immune system disorders		Hypersensitivity	

System Organ Class	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)
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 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 [1] Pruritus Dry skin	
Musculoskeletal and connective tissue disorders		Arthralgia Pain in extremity Muscle disorders [2] Musculoskeletal stiffness Blood creatine phosphokinase increased	

System Organ Class	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)
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 changes Testicular pain Breast induration Breast pain Gynaecomastia Oestradiol increased Testosterone increased	
General disorders and administration site conditions	Various kinds of injection site reactions [3]	Fatigue Asthenia Hyperhidrosis [4]	
Injury, poisoning and procedural complications			Pulmonary oil microembolism**

* Respective frequency has been observed in relation to the use in testosterone containing products.

** Frequency is based on the number of injections.

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.

[1] Rash including Rash papular

[2] Muscle disorders: Muscle spasm, Muscle strain and Myalgia

[3] 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

[4] Hyperhidrosis: Hyperhidrosis and Night sweats

Description of selected adverse reactions

Pulmonary micro embolism 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 injections and are reversible. Cases suspected by the company or the reporter to represent oily pulmonary micro embolism have been reported rarely in clinical trials (in ≥ 1/10,000 and < 1/1,000 injections) as well as from postmarketing experience (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 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No special therapeutic measure apart from termination of therapy with the medicinal product or dose reduction is necessary after overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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). It also performs functions, e.g. in the skin, muscles, skeleton, kidney, liver, bone marrow, and CNS.

Dependent on the target organ, the spectrum of activities of testosterone is mainly androgenic (e.g. prostate, seminal vesicles, epididymis) or protein-anabolic (muscle, bone, haematopoiesis, kidney, liver).

The effects of testosterone in some organs arise after peripheral conversion of testosterone to oestradiol, 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 in serum levels of testosterone above basal values may be seen one day after administration.

Steady-state conditions

After the 1st intramuscular injection of 1000 mg testosterone undecanoate to hypogonadal men, mean Cmax values of 38 nmol/L (11 ng/mL) were obtained after 7 days. The second dose was administered 6 weeks after the 1st injection and maximum testosterone concentrations of about 50 nmol/L (15 ng/mL) were reached. A constant dosing interval of 10 weeks was maintained during the following 3 administrations and steady-state conditions were achieved between the 3rd and the 5th administration. Mean Cmax and Cmin values of testosterone at steady-state were about 37 (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.

Distribution

In serum of men, about 98% of the circulating testosterone is bound to sex hormone binding globulin (SHBG) and albumin. Only the free fraction of testosterone is considered as biologically active. Following intravenous infusion of testosterone to elderly men, the elimination half-life of testosterone was approximately one hour and an apparent volume of distribution of about 1.0 l/kg was determined.

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. The major active metabolites of testosterone are oestradiol and dihydrotestosterone.

Elimination

Testosterone undergoes extensive hepatic and extrahepatic metabolism. After the administration of radio-labelled 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 medicinal products include androsterone and etiocholanolone. Following intramuscular administration of this depot formulation the release rate is characterised by a half life of 90±40 days.

5.3 Preclinical safety data

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

Testosterone has been found to be non-mutagenic in vitro using the reverse mutation model (Ames test) or hamster ovary cells. A relationship between androgen treatment and certain cancers has been found in studies on laboratory animals. Experimental data in rats have shown increased incidences of prostate cancer after treatment with testosterone.

Sex hormones are known to facilitate the development of certain tumours induced by known carcinogenic agents. The clinical relevance of the latter observation is not known.

Fertility studies in rodents and primates have shown that treatment with testosterone can impair fertility by suppressing spermatogenesis in a dose dependent manner.

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

5 years

The medicinal product must be used immediately after first opening.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Ampoule

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

Vial

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

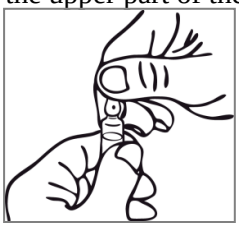
At cold storage temperatures the properties of this oil-based solution might temporarily change (e.g. higher viscosity, cloudiness). If stored at cold temperature, the product should be brought to room or body temperature before use.

The solution for intramuscular injection is to be visually inspected 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 discarded in accordance with local requirements.

Ampoule

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



Vial

The vial is for single use only. The content of a vial is to be injected intramuscularly immediately after drawing up into the syringe. After removal of the plastic cap (A) do not remove the metal ring (B) or the crimp cap (C).

7. MARKETING AUTHORISATION HOLDER

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07 July 2004
Date of latest renewal: 25 November 2008

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX - for ampoule

1. NAME OF THE MEDICINAL PRODUCT

Nebido 1000 mg/4 ml, solution for injection
Testosterone undecanoate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains
Testosterone undecanoate 250 mg

3. LIST OF EXCIPIENTS

Benzyl benzoate, castor oil refined

4. PHARMACEUTICAL FORM AND CONTENTS

1x4 ml ampoule with solution for injection

5. METHOD AND ROUTE(S) OF ADMINISTRATION

i.m. injection
For use as directed by medical practioner

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of thesight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For single use only
Discard any unused solution
For intramuscular injection only

8. EXPIRY DATE

EXP: {MM-YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:

SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

AMPOULE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Nebido 1000 mg/4 ml, solution for injection
Testosterone undecanoate

2. METHOD OF ADMINISTRATION

i.m. injection

3. EXPIRY DATE

EXP: {MM-YYYY}

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

4 ml ampoule

6. OTHER

For intramuscular injection only
For use as directed by a medical practitioner

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX - for vial

1. NAME OF THE MEDICINAL PRODUCT

Nebido 1000 mg/4 ml, solution for injection
Testosterone undecanoate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains
Testosterone undecanoate 250 mg

3. LIST OF EXCIPIENTS

Benzyl benzoate, castor oil refined

4. PHARMACEUTICAL FORM AND CONTENTS

1x4 ml vial with solution for injection

5. METHOD AND ROUTE(S) OF ADMINISTRATION

i.m. injection
For use as directed by medical practioner

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For single use only
Discard any unused solution
For intramuscular injection only

8. EXPIRY DATE

EXP: {MM-YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

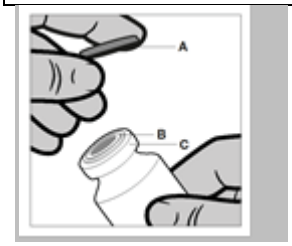
13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE



[To be completed nationally]

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Nebido 1000 mg/4 ml, solution for injection
Testosterone undecanoate

2. METHOD OF ADMINISTRATION

i.m. injection

3. EXPIRY DATE

EXP: {MM-YYYY}

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

4 ml vial

6. OTHER

For intramuscular injection only
For use as directed by a medical practitioner

PACKAGE LEAFLET

Package leaflet: Information for the user

Nebido 1000 mg/4 ml, solution for injection
Testosterone undecanoate

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Nebido is and what it is used for

Nebido contains testosterone, a male hormone, as the active ingredient.
Nebido is injected into a muscle in your body. There it can be stored and gradually released over a period of time. Nebido is used in adult men for testosterone replacement to treat various health problems caused by a lack of testosterone (male hypogonadism). These should be confirmed by two separate blood testosterone measurements and also include clinical symptoms such as:
- impotence
- infertility
- low sex drive
- tiredness
- depressive moods
- bone loss caused by low hormone levels

2. What you need to know before you are given Nebido

Do NOT use Nebido
- if you are allergic to testosterone undecanoate or any of the other ingredients of this medicine (listed in section 6)
- if you have androgen-dependent cancer or suspected cancer of the prostate or of the breast
- if you have or had a liver tumour

Nebido **is not** intended for use in women.

Warnings and precautions

Talk to your doctor before using Nebido if you have or have ever had:

- epilepsy
- heart, kidney or liver problems
- migraine
- temporary interruptions in your breathing during sleep (apnoea), as these may get worse
- cancer, as the level of calcium in your blood may need to be tested regularly
- high blood pressure or if you are treated for high blood pressure, as testosterone may cause a rise in blood pressure.
- blood clotting problems
    - bleeding disorders (i.e. haemophilia)
    - thrombophilia (an abnormality of blood coagulation that increases the risk of thrombosis - blood clots in blood vessels)
    - factors that increase your risk for blood clots in a vein: previous blood clots in a vein; smoking; obesity; cancer; immobility; if one of your immediate family has had a blood clot in the leg, lung or other organ at a young age (e.g. below the age of about 50); or as you get older.

    How to recognise a blood clot: painful swelling of one leg or sudden change in colour of the skin e.g. turning pale, red or blue, sudden breathlessness, sudden unexplained cough which may bring up blood; or sudden chest pain, severe light headedness or dizziness, severe pain in your stomach, sudden loss of vision. Seek urgent medical attention if you experience one of these symptoms.

If you are suffering from severe heart, liver or kidney disease, treatment with Nebido may cause severe complications in the form of water retention in your body sometimes accompanied by (congestive) heart failure.
The following blood checks should be carried out by your doctor before and during the treatment: testosterone blood level, full blood count.

If your liver is not working
No formal studies have been performed in patients with liver impairment. You will not be prescribed Nebido if you have ever had a liver tumour (see ***"****Do not use Nebido").*

Children and adolescents
Nebido **is not** for use in children and adolescents. There is no data available on the use of Nebido in males under 18 years of age.

Elderly patients (65 years or older)
There is no need for your doctor to adjust the dose if you are over 65 (see *"Medical examination/follow up"*).

Muscle building and drug tests
Nebido is **not** suitable for building muscles in healthy individuals or for increasing physical strength. Nebido might lead to positive results in drug tests.

Drug abuse and dependence
Always take this medicine exactly as your doctor or pharmacist has told you.
Abuse of testosterone, especially if you take too much of this medicine alone or with other anabolic androgenic steroids, can cause serious health problems to your heart and blood vessels (that can lead to death), mental health and/or the liver.
Individuals who have abused testosterone may become dependent and may experience withdrawal symptoms when the dosage changes significantly or is stopped immediately. You should not abuse this medicine alone or with other anabolic androgenic steroids because it carries serious health risks. (See "*Possible side effects*".)

Medical examination/Follow-up
Male hormones may increase the growth of prostate cancer and enlarged prostate glands (benign prostatic hypertrophy). Before your doctor injects Nebido, he/she will examine you to check that you do not have prostate cancer.
Your doctor will regularly examine your prostate and breast, especially if you are elderly. He/she will also take regular blood samples.
Following the use of hormonal substances such as androgen compounds, cases of benign (non-cancerous) and malignant (cancerous) liver tumours have been observed to occur.

Other medicines and Nebido
Tell your doctor or pharmacist if you are using or have recently used or might **use any other medicines**, including medicines obtained without a prescription. The doctor may need to adjust the dose if you are using any of the following:

- the hormone ACTH or corticosteroids (used to treat various conditions such as rheumatism, arthritis, allergic conditions and asthma): Nebido may increase the risk of water retention, especially if your heart and liver are not working properly
- blood-thinning tablets (coumarin derived oral anticoagulants) since this can increase the risk of bleeding. Your doctor will check the dose.
- medicines used to treat diabetes. It may be necessary to adjust the dose of your blood sugar reducing medicine. Like other androgens, testosterone may increase the effect of insulin.

Please be sure to inform your doctor if you suffer from a disturbance of blood clotting, because this is important for your doctor to know before deciding to inject Nebido.

Nebido may also affect the results of some laboratory tests (e.g. thyroid gland). Tell your doctor or the laboratory staff that you are using Nebido.

Pregnancy and breast-feeding
Nebido is not for use in women and must not be used in pregnant or breast-feeding women.

Fertility
Treatment with high doses of testosterone preparations commonly may reversibly stop or reduce sperm production (see also under “Possible side effects”).

Driving and using machines
Nebido has no observed effect on your ability to drive or use machines.

Nebido contains benzyl benzoate
Nebido contains 2000 mg benzyl benzoate in each 4 ml ampoule/vial which is equivalent to 500 mg/ml.

3. How to use Nebido

Your doctor will inject Nebido (1 ampoule / vial) very slowly into a muscle. He/she will give you the injections every 10 to 14 weeks. This is enough to maintain sufficient testosterone levels without leading to a build-up of testosterone in the blood.

Nebido is strictly for intramuscular injection. Special care will be taken to avoid injection into a blood vessel (see **“***Administration*”).

Start of treatment
Your doctor will measure your blood testosterone levels before starting treatment and during the early stages of treatment. Your doctor may give you the second injection after only six weeks in order to quickly reach the necessary testosterone level. This will depend on your symptoms and testosterone levels.

Maintaining your Nebido levels during treatment
The injection interval should always be within the recommended range of 10 to 14 weeks.
Your doctor will measure your testosterone levels regularly at the end of an injection interval to make sure it is at the right level. If the level is too low, your doctor may decide to give you injections more often. If your testosterone levels are high, your doctor may decide to give you injections less often. Do not miss your injection appointments. Otherwise, your optimum level of testosterone will not be maintained.

If you think that the effect of Nebido is too strong or too weak, talk to your doctor.

If you use more Nebido than you should
Symptoms of having too much Nebido include:
- irritability
- nervousness
- weight gain
- long-lasting or frequent erections

Tell your doctor, if you have any of these. Your doctor will inject it less often or will stop treatment.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The **most common side effects** are acne and pain where the injection is given.

Common side effects (may affect up to 1 in 10 patients):
- abnormally high levels of red blood cells
- weight gain
- hot flushes
- acne
- enlarged prostate and associated problems
- various reactions where the injection was given (e.g. pain, bruising or irritation)

Uncommon side effects (may affect up to 1 in 100 patients):
- allergic reaction
- increased appetite, changes in blood test results (e.g. increased blood sugars or fats)
- depression, emotional disorder, insomnia, restlessness, aggression, or irritability
- headache, migraine, or tremor
- cardiovascular disorder, high blood pressure, or dizziness
- bronchitis, sinusitis, cough, shortness of breath, snoring, or voice problems
- diarrhoea, or nausea
- changes in liver test results
- hair loss, or various skin reactions (e.g. itching, reddening or dry skin)
- joint pain, pain in limbs, muscle problems (e.g. spasm, pain or stiffness), or an increased creatine phosphokinase in the blood
- urinary tract disorders (e.g. decreased flow of urine, urinary retention, urge to pass urine at night)
- prostatic disorders (e.g. prostatic intraepithelial neoplasia, or hardening or inflammation of the prostate), changes in sexual appetite, painful testicles, painful, hardened or enlarged breasts, or increased levels of male and female hormones
- tiredness, general feeling of weakness, excessive sweating, or night sweat

Rare side effects (may affect up to 1 in 1000 patients):
- The oily liquid Nebido may reach the lungs (pulmonary micro embolism of oily solutions) which can in rare cases lead to signs and symptoms such as cough, shortness of breath, feeling generally unwell,

excessive sweating, chest pain, dizziness, “pins and needles”, or fainting. These reactions may occur during or immediately after the injection and are reversible.

Suspected anaphylactic reactions after Nebido injection have been reported.

In addition to the side effects listed above the following have been reported following treatment with preparations containing testosterone: nervousness, hostility, brief interruptions in breathing during sleep, various skin reactions including dandruff and oily skin, increased hair growth, more frequent erections, and very rare cases of yellowing of the skin and eyes (jaundice).

Treatment with high doses of testosterone preparations commonly stops or reduces sperm production, although this returns to normal after treatment ceases. Testosterone replacement therapy of poorly functioning testicles (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 (swelling due to fluid retention).

For testosterone products in general a common risk of increased red blood cell count, haematocrit (percentage of red blood cells in blood) and haemoglobin (the component of red blood cells that carries oxygen), were observed by periodic blood tests.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Nebido

Keep this medicine out of the sight and reach of children.

This medicinal product does not require any special storage conditions.

Do not use this medicine after the expiry date which is stated on the carton and the label after "EXP". The expiry date refers to the last day of that month.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Nebido contains

The active substance is testosterone undecanoate 250 mg/ml (corresponding to 157.9 mg testosterone). One ampoule / vial contains 1000 mg testosterone undecanoate (corresponding to 631.5 mg testosterone).

The other ingredients are benzyl benzoate and refined castor oil.

What Nebido looks like and contents of the pack

Nebido is a clear, yellowish oily liquid. The contents of the packs are:

1 brown glass ampoule / brown glass vial with 4 ml solution for injection

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

[to be completed nationally]

Manufacturer

Bayer AG
D – 13342 Berlin
Germany

This medicinal product is authorised in the Member States of the EEA under the following names:

- Cyprus, Czech Republic, Greece, Denmark, Estonia, Latvia, Luxembourg, Malta, Poland and Portugal: **Nebido**
- Austria: **Nebido 1000 mg/4 ml Injektionslösung**
- Belgium: **Nebido 1000 mg/4 ml, oplossing voor injectie**
- Croatia: **Nebido 1000 mg/4 ml otopina za injekciju**
- Finland: **Nebido 1000 mg/4 ml injektioneste, liuos**
- France: **Nebido 1000 mg/4 ml, solution injectable**
- Germany: **Nebido 1000 mg Injektionslösung**
- Hungary**: Nebido 250 mg/ml oldatos injekció**
- Iceland: **Nebido 1000 mg/4 ml stungulyf, lausn**
- Italy**: NEBID 1000 mg/4ml soluzione iniettabile**
- Lithuania**: Nebido 1000 mg/4 ml injekcinis tirpalas**
- Netherlands: **Nebido 1000 mg/4 ml**
- Norway**: Nebido 1000 mg/4 ml injeksjonsvæske, oppløsning**
- Slovak Republic: **Nebido 1000 mg/4 ml injekčný roztok**
- Slovenia**: Nebido 1000 mg/4 ml raztopina za injiciranje**
- Spain: **REANDRON 1000 MG/ 4 ML SOLUCIÓN INYECTABLE**
- Sweden: **Nebido, 1000 mg/4 ml injektionsvätska, lösning**
- UK and Ireland: **Nebido 1000mg/4ml, solution for injection**

This leaflet was last revised in {MM/YYYY}.

The following information is intended for healthcare professionals only:

At cold storage temperatures the properties of this oil-based solution might temporarily change (e.g. higher viscosity, cloudiness). If stored at cold temperature, the product should be brought to room or body temperature before use.

The solution for intramuscular injection is to be visually inspected prior to use and only clear solutions free from particles should be used.

The contents of an ampoule / vial are to be injected intramuscularly immediately after opening the ampoule / vial.
The medicinal product is for single use only and any unused solution should be discarded.

Administration

Special care must be given to avoid intravasal injection.

As with all oily solutions, Nebido must be injected strictly intramuscularly and very slowly. Pulmonary micro embolism of oily solutions can 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. Treatment is usually supportive, e.g. by administration of supplemental oxygen.

Suspected anaphylactic reactions after Nebido injection have been reported.

Warnings

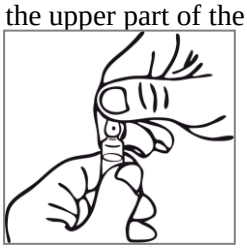
Careful and regular monitoring of the prostate gland and breast must be performed in accordance with recommended methods (digital rectal examination and estimation of serum PSA) in patients receiving testosterone therapy at least once yearly and twice yearly in elderly patients and at risk patients (those with clinical or familial factors).

Besides laboratory tests of the testosterone concentrations in patients on long-term androgen therapy the following laboratory parameters should be checked periodically: haemoglobin, haematocrit, and liver function tests and lipid profile.

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

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

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



Notes on handling the vial:

The vial is for single use only. The content of a vial is to be injected intramuscularly immediately after drawing up into the syringe. After removal of the plastic cap (A) do not remove the metal ring (B) or the crimp cap (C).