REGISTERED PACKAGE INSERT

SCHEDULING STATUS S5

PROPRIETARY NAME AND DOSAGE FORM

NEBIDO

Oily solution for injection

COMPOSITION

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

PHARMACOLOGICAL CLASSIFICATION

A. 21.7 Male sex hormones.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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

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 im 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 the 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

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

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 products include androsterone and etiocholanolone.

Steady-state conditions

Following repeated im 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.

INDICATIONS

Testosterone replacement in primary and secondary male hypogonadism.

CONTRA-INDICATIONS

Nebido must not be used in androgen-dependent carcinoma of the prostate or of the male mammary gland; hypercalcaemia accompanying malignant tumours; past or present liver tumours; hypersensitivity to the active substance or to any of the excipients.

The use of Nebido in women is contra-indicated.

WARNINGS

Older patients treated with Nebido may be at an increased risk for the development of prostatic hyperplasia. Although there are no clear indications that Nebido actually generates prostatic carcinoma, it can enhance the growth of any existing prostatic carcinoma. Therefore carcinoma of the prostate has to be excluded before starting therapy with Nebido.

As a precaution, regular examinations of the prostate are recommended in men.

Haemoglobin and haematocrit should be checked periodically in patients on long-term Nebido therapy to detect cases of polycythemia (see “Side-effects”).

Benign liver tumours and, rarely, malignant liver tumours have been reported in users of hormonal substances like, for example, testosterone compounds. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in men using Nebido.

Caution should be exercised in patients predisposed to oedema.

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

In children, besides masculinisation, Nebido can cause accelerated growth and bone maturation and premature epiphyseal closure, thereby reducing final height.

Pre-existing sleep apnoea may be potentiated.

Nebido is not suitable for enhancing muscular development in healthy individuals or for increasing physical ability.

Like all oily solutions, Nebido must be injected intramuscularly. Experience shows that the short-lasting reactions (urge to cough, coughing fits, respiratory distress) which occur in rare cases during or immediately after the injection of oily solutions can be avoided by injecting the solution extremely slowly.

INTERACTIONS

Nebido may enhance the blood-sugar reducing effects of insulin. The dosage of the hypoglycaemic agent may need to be lowered.

Interactions can occur with drugs that induce microsomal enzymes, which can result in increased clearance of Nebido (eg barbiturates).

Nebido may interfere with the metabolism of other drugs. Accordingly, plasma and tissue concentrations may be affected: eg increased oxyphenbutazone serum levels have been reported. Moreover, testosterone and derivates have been reported to increase the activity of oral anticoagulants, possibly requiring dose adjustment. Independently of this finding, as a general rule, the limitations of using intramuscular injections in patients with acquired or inherited blood clotting irregularities always have to be observed.

PREGNANCY AND LACTATION

Not applicable.

DOSAGE AND DIRECTIONS FOR USE

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.

Start of treatment

Serum testosterone levels should be measured before the 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.

Individualisation of treatment

It is advisable to occasionally measure testosterone serum levels at the end of an injection interval. Serum levels below normal range would indicate the need for a shorter injection interval. In the 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.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Side-effects

The following adverse events were reported in clinical trials, with a suspected relationship to Nebido:

Body system	Common* (≥ 1/100)
Digestive	Diarrhoea.
Musculoskeletal system	Leg pain, arthralgia.
Nervous system	Dizziness, increased sweating, headache.
Respiratory system	Respiratory disorder.
Skin and appendages	Acne, breast pain, gynaecomastia, pruritus, skin disorder.
Urogenital	Testicular pain, (prostate disorder**).
General disorders and administration site conditions	Injection site pain, subcutaneous haematoma at the injection site.

* Due to the small sample size of the studies, the frequency of each reported adverse event with a suggested causal relationship falls at least into the category common (≥ 1/100).

** One case with a small sized prostate with induration of the middle part.

In the literature the following adverse drug reactions from testosterone-containing preparations have been reported:

Body system	Side-effects
Blood and the lymphatic system disorders	Rare cases of polycythemia.
Metabolism and nutrition disorders	Weight gain.
Musculoskeletal system	Muscle cramps.
Nervous system	Nervousness, hostility, depression.
Respiratory system	Sleep apnoea.
Hepatobiliary disorders	In very rare cases jaundice and liver-function-test abnormalities.
Skin and appendages	Various skin reactions may occur including acne, seborrhoea, and balding.
Reproductive system and breast disorders	Libido changes, increased frequency of erections; 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).
General disorders and administration site conditions	High-dosed or long-term administration of testosterone occasionally increases the occurrences of water retention and oedema; injection site reactions and hypersensitivity reactions may occur.

Effects on ability to drive and use machines

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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

IDENTIFICATION

Clear yellowish oily solution.

PRESENTATION

5 ml amber glass ampoules containing 4 ml of oily solution.
6 ml brown glass vials closed with a gray bromobutyl stopper with ETFE foil-clad, and capped with a flanged closure with Al-shell and PP plastic button containing 4 ml of oily solution.

STORAGE INSTRUCTIONS

Store at or below 30°C. Protect from light. Store all medicines out of reach of children.

REGISTRATION NUMBER

A38/21.7/0641

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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