Product Monograph

Nebido® (testosterone undecanoate)

NEBIDO®
Testosterone Undecanoate

Restore the man.

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Bayer

Index

Executive Summary

What is Nebido® ?

Nebido® is a testosterone preparation for intramuscular injection. One ampoule contains 1,000 mg testosterone undecanoate in 4 mL oily vehicle (castor oil). The shelf life of Nebido® is 5 years.

Nebido® produces testosterone concentrations in the physiological range and needs to be administered only about four times a year.

What is the Preparation of Nebido® Available on the Market?

Nebido® is available in packages containing one vial. This product requires no particular precautions for storage. However, it should not be stored in the refrigerator. The contents of one vial should be administered slowly by intramuscular injection.

What are the Indications for Nebido®?

Nebido® is indicated for testosterone replacement therapy for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests.

How Does Nebido® Act?

On testosterone concentrations in the blood
Pharmacokinetic studies have demonstrated that testosterone levels are restored to the physiological range within 3 days after the first administration of Nebido®. With an interval between injections of about 12 weeks, testosterone concentrations remain constantly within the physiological range. The first dosing interval may be reduced to six weeks, which enables steady state testosterone levels to be achieved more rapidly.

On clinical symptoms
Nebido® improves the symptoms associated with testosterone deficiency.
Nebido® exerts a positive effect on sexual function and mood, increases muscle mass and muscle strength and decreases body fat.

Which Side Effects May Occur with Nebido®?

The most frequent side effects observed with Nebido® are reactions at the injection site. These reactions are generally mild and transient. All other side effects observed in isolated cases are typical of testosterone (such as diarrhoea, joint pain, sweating, headache, acne, chest pain and gynaecomastia).

Pulmonary oil microembolism has been observed after injection during routine clinical practice and in rare cases lead to signs and symptoms such as cough, dyspnea, malaise, hyperhidrosis, chest pain, dizziness, paraesthesia, or syncope. These reactions may occur during or immediately after the injection and are reversible. 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 microembolism. Treatment is usually supportive, e.g. by administration of supplemental oxygen.

What is the Treatment Regimen to be Used?

Attention should be paid to the following recommendations for dosage:

- First and second administration of Nebido® 6 weeks apart.
- Subsequently, depending on the needs of the individual patient, an interval of about 12 weeks is recommended.
- The first interval between injections may also be shortened to six weeks for patients who have switched from other testosterone preparations to Nebido®, under observation of clinical symptoms.
- Ideally one ampoule of Nebido® is injected deeply into the gluteal muscle slowly over a period of approximately 2 minutes.
- Measurement of serum trough testosterone levels and clinical symptoms should be considered for individualization of therapy with Nebido®.
- Serum trough testosterone levels should be in the lower third of the normal range.
- Since steady state serum testosterone levels can be assumed to be achieved after the first six months of treatment, it appears advisable to control serum testosterone before the fourth injection (usual spacing between administrations provided).

When is the Use of Nebido® Contraindicated?

Nebido® may not be used in patients with carcinoma of the prostate, mammary gland carcinoma, previous or existing liver tumours, and hypersensitivity to the constituents of Nebido®.

Does Treatment with Nebido® Necessitate Particular Monitoring of the Prostate?

As with any testosterone treatment, before starting and during treatment with Nebido® regular monitoring of the prostate in accordance with recommended methods is necessary (digital rectal examination of the prostate, PSA measurement and transrectal ultrasound).

What are the Special Advantages of Nebido®?

- Rapidly achieved and maintained serum testosterone levels in the normal range
- Avoidance of unphysiological peaks and troughs in serum testosterone levels
- Only about 4 injections per year are required
- Proven clinical efficacy, good safety and tolerability profile, and convenience of use lead to high acceptance and patient compliance

About Nebido

Nebido® is the first long-acting testosterone injection for the treatment of male hypogonadism.

Nebido® contains 1,000 mg of testosterone undecanoate in a 4 mL oily solution in an innovative formulation which offers a superior kinetic profile.

After administration of Nebido®, testosterone levels remain within the physiological range for about 12 weeks. Therefore, only 4 injections per year are required in long-term testosterone therapy.

Nebido® avoids unphysiological peaks and troughs in serum testosterone.

It has been established in clinical studies that testosterone levels are already back to the normal range 3 days after the first administration of Nebido®.

Nebido® has been proven very effective in the treatment of male hypogonadism:

- Libido and sexual function improved
- Mood was positively influenced
- Muscle strength increased
- Body composition altered (decrease in fat mass, increase in lean body mass).

Nebido® has been shown to be well tolerated.

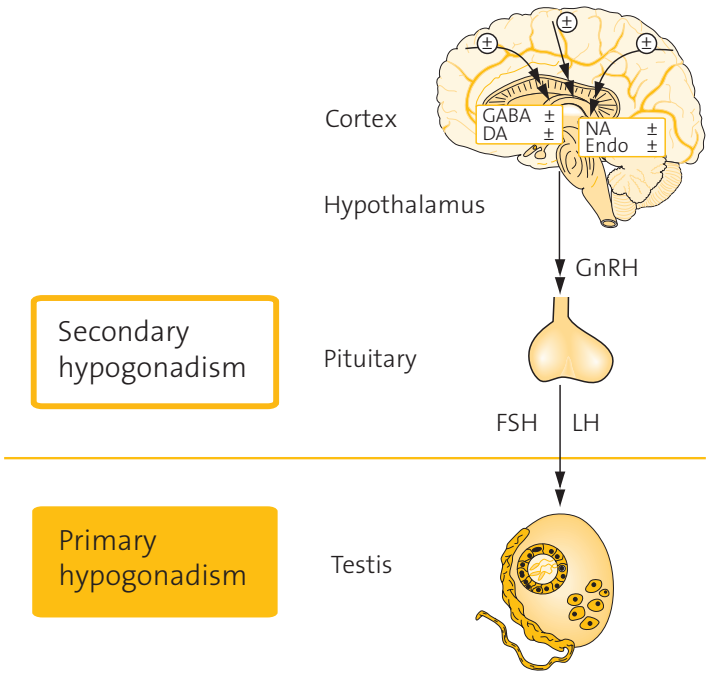
Use of Nebido® is discreet and guarantees outstanding patient compliance.

1 Introduction

Testosterone is the most important endogenous sex hormone in the male, produced in the testes. By itself and via its main metabolites, dihydrotestosterone (DHT) and oestradiol, testosterone exerts an influence on many physical and mental functions in men. The hormones act directly on the most diverse target organs, such as the sex organs, bones, muscles, blood-forming tissue, the brain, skin, and hair.[1, 2] How varied the effects of this can be is seen in the range of disorders which can appear as a result of testosterone deficiency. Clinical testosterone deficiency, or male hypogonadism, can be present at any age.

According to the definition, hypogonadism is the inadequate secretion of testosterone by the testes linked with corresponding symptoms (Figure 1). It has different causes: hypogonadism may be congenital or acquired or have causes related to the hypothalamus, pituitary, or testes.[1, 2]

Figure 1: Distinguishing between primary (testicular) and secondary (hypothalamic or pituitary) hypogonadism.[1]



For the diagnosis of hypogonadism, the age of the patient and his symptoms must be taken into consideration:

In children and adolescents, androgen deficiency is usually of genetic origin or has congenital causes. It is diagnosed when puberty is retarded or does not occur at all.[1]

Hypogonadism in the young adult appearing after puberty is usually acquired (testicular trauma, mumps, of teratogenic origin or caused by pituitary, hypothalamic, or general diseases). As the symptoms appear insidiously, this form of hypogonadism is not diagnosed until late in its development: sometimes it is not recognized until investigations are being undertaken because of infertility.[1, 2]

In men over 40 years, testosterone deficiency is in most cases a consequence of impairment of testicular function and/or hypothalamic-pituitary control. The process and the consequences of hormone deficiency in men occur gradually. Clinically, the symptoms encompass heterogeneous and less specific signs, and for this reason are often not immediately recognized as symptoms of testosterone deficiency.[1, 3]

Late-onset hypogonadism (LOH) is defined as a clinical and biochemical syndrome associated with advancing age and characterised by typical symptoms and a deficiency in serum testosterone levels. It may adversely affect quality of life and the function of multiple organ systems.[4]

The symptoms of hypogonadism are numerous and include:[4, 5]

- *Loss of sexual desire (libido), reduced sexual activity, and diminished erectile quality and frequency*
- *Fatigue, depressed mood, irritability, and decreased sense of well-being*
- *Diminished cognitive function*
- *Decreased lean body mass with reduction in muscle mass, strength*
- *Decreased vigour and energy*
- *Increased visceral fat and fat mass*
- *Metabolic syndrome, insulin resistance, and type 2 diabetes mellitus*
- *Sleep disturbances*
- *Reduced virility*
- *Male-factor infertility*
- *Delayed puberty*
- *Increased sweating, dry skin, and anaemia*
- *Decreased bone mineral density resulting in osteoporosis*

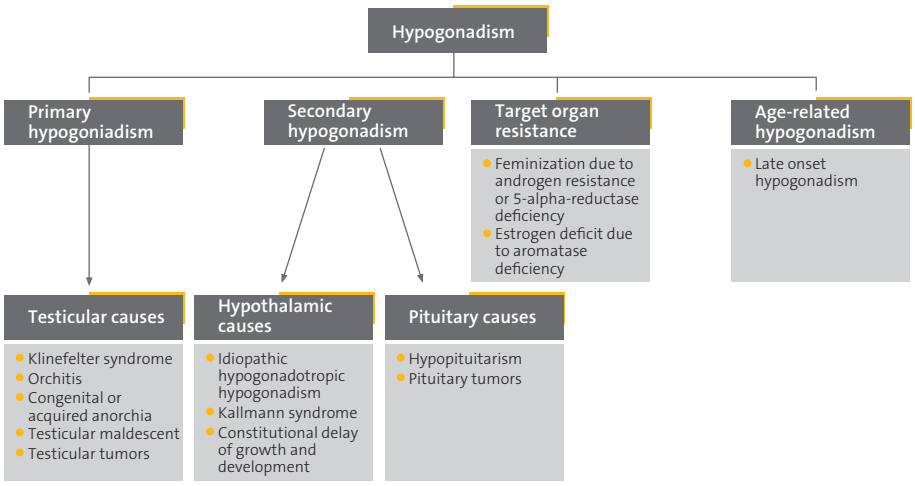
The aim of testosterone therapy in men with hypogonadism is to improve or reverse the associated symptoms by restoring levels of serum testosterone and its metabolites (oestradiol and DHT) to the eugonadal range. The most sensible method is replacement using testosterone or a testosterone ester. The choice of pharmaceutical form is important because the therapy should guarantee hormone levels within the physiological range: extreme fluctuations are to be avoided and high patient compliance is required.

This monograph outlines the aetiology of hypogonadism, the physiology and pathophysiology of testosterone, the definition and rationale for testosterone therapy, and the diagnosis of male hypogonadism. The pharmaceutical and pharmacological data and the clinical profile of Nebido® (the first long-acting injection for the treatment of male hypogonadism) are described in detail.

2 Aetiology

Male hypogonadism is characterised by a deficiency of endogenous testosterone production resulting in abnormally low levels of circulating testosterone. Hypogonadism can be caused by a number of disorders, the most frequently observed being idiopathic hypogonadotrophic hypogonadism, hypopituitarism, Klinefelter's syndrome, and late-onset hypogonadism (Figure 2).

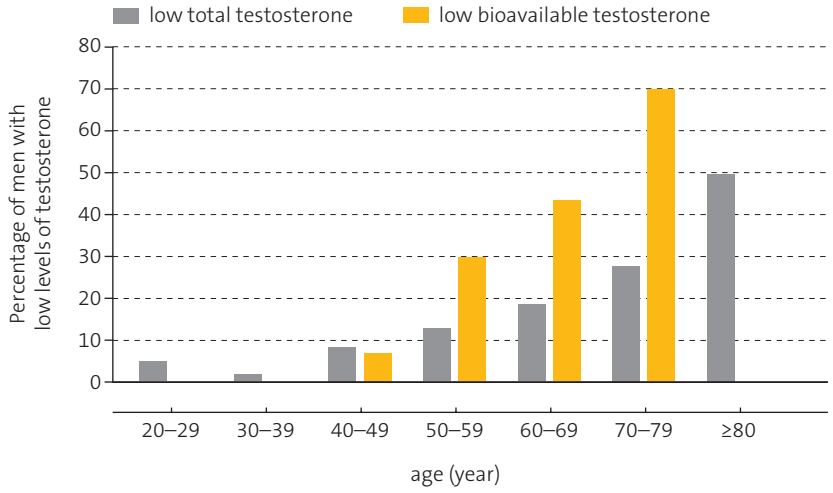
Figure 2: Classification of hypogonadism.



Idiopathic hypogonadotrophic hypogonadism is a constitutional disorder of gonadotrophin-releasing hormone (GnRH) secretion. Hypopituitarism may occur as a result of various diseases of the pituitary gland, e.g. adenoma or ischemia, as a consequence of radiotherapy, drug abuse, medications like cytostatics, cardiac drugs, diuretics, and antihypertensives, or after surgery. Klinefelter's syndrome is a congenital aberration of the number of chromosomes. The condition is caused by the presence of one or more extra X-chromosomes. The signs of Klinefelter's syndrome are almost unnoticeable in childhood. Occasionally, however, boys with the condition are referred for hypoplasia of the external genitalia or extra-long legs.

Many systemic diseases (e.g. diabetes mellitus, generalized infections, metabolic syndrome) correlate with low testosterone levels.[1] Therefore, hypogonadism as an early sign can contribute to an early diagnosis of the underlying condition. Another cause of male hypogonadism is the naturally occurring, age-related decrease of testosterone serum levels, which may lead to a state of androgen deficiency (Figure 3).

Figure 3: Prevalence of low levels of total and bioavailable testosterone as an index of male hypogonadism according to decade of life.[6]



Dark bars represent the percentage of the population with total testosterone levels below 11.3 nmol/L (325 ng/dL), and light bars represent the percentage of the population with bioavailable testosterone levels under 202 pmol/L (70 ng/dL).

3 Physiology and Pathophysiology

Testosterone is the most important steroid produced by the testis. In an adult man, the Leydig cells produce 5–7 mg of testosterone each day. Because testosterone is lipophilic, it passes easily through membranes and leaves the Leydig cells by diffusion. In the blood, 98% of testosterone is bound to transport proteins, and only 2% is free and hence biologically active.

Approximately 60% of the circulating testosterone is bound with high affinity to the β-globulin sex hormone binding globulin (SHBG), and 38% is loosely bound and transported by albumin. SHBG shows a higher affinity for testosterone than oestradiol. Thus, increased production of SHBG by the liver causes a shift in the ratio of testosterone to oestradiol by reducing the amount of free testosterone.[1]

Several lines of evidence suggest that not only free testosterone but also albumin-bound testosterone is available to the target tissues in case of an increased testosterone need. Therefore, the non-SHBG-bound testosterone is called "bioavailable testosterone". Free testosterone mediates androgenic effects, which are exerted at target organs via stimulation of the androgen receptor, a member of the superfamily of nuclear receptors.[7] The actions of testosterone are also mediated through conversion to active metabolites, such as DHT, derived from testosterone through reduction of the Δ4-bond. Aromatization of testosterone results in the formation of oestradiol, a chemical process of considerable importance for the balance between the two hormones.

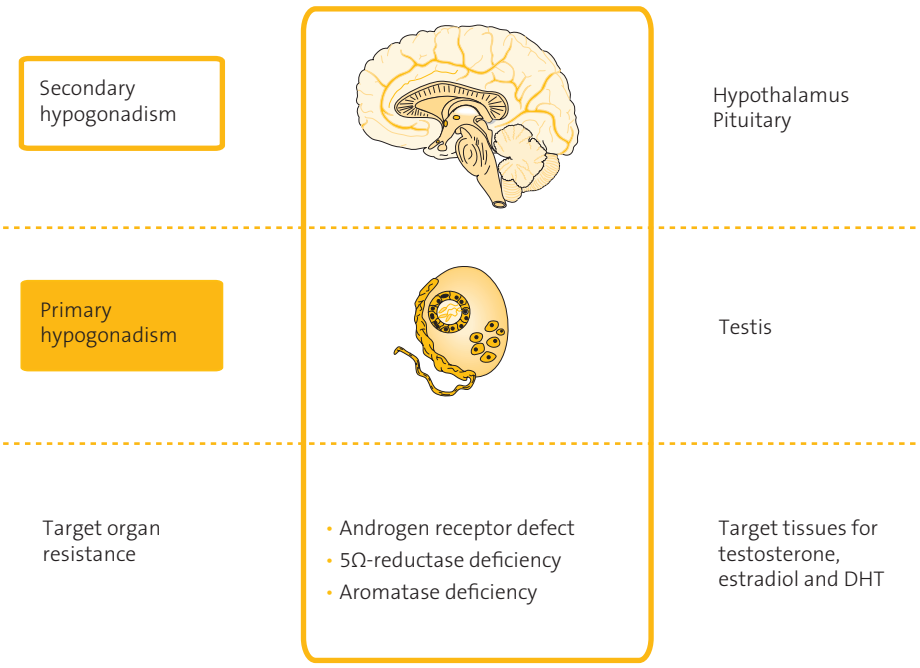
Hypogonadism represents a state of impaired testosterone secretion that may have its origin at the different levels of the hypothalamic-pituitary-gonadal axis (Figure 4):

Testicular failure with compensatory upregulation of the gonadotropins (primary or hypergonadotrophic hypogonadism)

Malfunction at the hypothalamus-pituitary level (secondary or hypogonadotrophic hypogonadism)

Enzyme defects in testosterone biosynthesis and luteinizing hormone (LH) receptor defects may also be causative factors for hypogonadism.

Figure 4: Classification of hypogonadism.



Testosterone blood levels are often found to be decreased in systemic diseases such as renal failure, liver cirrhosis, and diabetes.[8] Although a target organ resistance may imply the clinical features of hypogonadism, it is not primarily caused by hypogonadism, but instead, for example, by a loss of androgen receptor function. This androgen insensitivity syndrome manifests as genetic (XY) males who are phenotypical, though sterile, females.[9] Interestingly, these persons accept their sexual identity as women. This suggests that the androgen receptor is crucial not only for male morphologic development but also for the configuration of the male central nervous system.[10]

Relating to the main physiological roles of testosterone,[11] its deficiency manifests in several ways, many of which are non-specific, particularly in the adult male. This renders the diagnosis of testosterone deficiency as the cause even more difficult:

In children or adolescents, androgen deficits, which are mainly genetic or congenital, are diagnosed if puberty is missing or retarded

After puberty, hypogonadism of the young adult, which is most often acquired (trauma, malignancy, pituitary, hypothalamic, or general diseases), has unspecific symptoms and is often only diagnosed when infertility becomes obvious

In men over 50 years of age, an androgen deficit is in most cases a consequence of neuroregulatory defects at the hypothalamic and pituitary level, of the decreased size of the pituitary gland with aging, and the decrease in number of Leydig cells and/or their ability to produce testosterone. The declining secretion of testosterone with age can become clinically apparent depending on the endocrine capacity of the testes and the individual sensitivity for androgens. The resulting relative androgen deficiency is often aggravated by the increasing SHBG levels with age,[12] which lead to a further decrease of the free, biologically active fraction of testosterone. The clinical signs are heterogeneous and of little specificity and hence are not always recognized

Another topic of increasing interest is the functional interlink between the hypothalamic-pituitary-gonadal axis and the hypothalamic-pituitary-adrenal axis. Manipulation of one hormonal system is not without effect on the other. In humans, the underlying mechanisms and modalities are affected by stress. This dual systems approach holds promise in establishing further links between the neuroendocrinology of stress and the central bases of sex-dependent disorders, including psychiatric, cardiovascular, and metabolic disease.[13]

Nevertheless, a brief review of the biologic effects of androgens[14] indicates that the consequences of testosterone deficiency are severe, and in some cases dangerous and debilitating, and may be influenced beneficially by testosterone therapy (Table 1).

Table 1: Biological effects of androgens.	
Target tissue	**Biologic effect**
Reproductive tissues	Stimulation of prenatal differentiation and pubertal development of the testes, penis, epididymis, seminal vesicles, and prostate. In adults, maintenance of these tissues, central and peripheral modulation of erectile function,[15] initiation and maintenance of spermatogenesis.
Sexual function and behaviour	Key role in stimulating and maintaining sexual function in men. In hypogonadal men testosterone induces greater interest in sexual activity, while suppression of testosterone levels to the range of castrates in normal young men reduces sexual desire, sexual fantasies, and spontaneous erections. In non-human primates, aggression is directly correlated with serum testosterone levels, while in humans self-assessed aggression is less clearly correlated.
Muscle	Androgens increase nitrogen balance, lean body mass, and may increase body weight. Testosterone increases the size of the muscle cells with little effect on their number.
Skin and hair	Increase in sebum production, with acne as a possible consequence. Male hair pattern.
Liver	Increased synthesis of clotting factors, hepatic triglyceride lipase, sialic acid, α1-antitrypsin, and haptoglobin. Decreased production of SHBG, other hormone-binding proteins, transferrin, and fibrinogen.
Lipids	Androgens may decrease high-density lipoprotein (HDL)-cholesterol plasma concentrations in adolescent boys with delayed puberty and in hypogonadal men.
Bone	Hypogonadism is a risk factor for osteoporosis in men.[16] Androgens stimulate the proliferation of bone cells in vitro and improve bone mineral density in hypogonadal men.[17, 18]
Haematology and immunology	Stimulation of the erythropoietin production in the kidneys. Androgens exert suppressive effects on both humoral and cellular immune responses, and seem to represent natural anti-inflammatory hormones.[19, 20]

4 Definition, Rationale for Therapy

Androgens are important in every phase of male life. Testosterone is the most important human androgen. During the embryonal stage, testosterone determines the differentiation of the sexual organs, during puberty development toward the adult male phenotype is testosterone-dependent, and in the adult, testosterone maintains the male phenotype.

Diminished gonadal function is called hypogonadism. As a rule it manifests itself in decreased testosterone production. As a sex hormone with a multitude of influences on physiological processes, testosterone deficiency leads to several functional impairments, which are often the reason patients seek medical help, e.g. fatigue, weakness, loss of libido, erectile dysfunction (Table 2).

Men with erectile dysfunction and low serum testosterone may benefit from testosterone treatment alone. The combination of phosphodiesterase-5 inhibitors and testosterone may be indicated in those men who did not respond sufficiently to testosterone alone.[4, 21] The prevalence of male hypogonadism among men with erectile dysfunction is estimated to be around 20%.[22, 23]

Hypogonadism is highly prevalent among men with type 2 diabetes mellitus (T2DM), which is a frequent disorder in aging men. Recent guidelines suggest that diabetes in hypogonadal men should be evaluated and treated before or simultaneously with testosterone treatment.[4]

Testosterone replacement therapy has been shown to improve health outcomes in men with hypogonadism. Because Nebido® helps to prevent complications that are associated with high direct treatment costs, such as diabetes and fractures, Nebido® has been found to be cost-effective compared with no treatment.[24]

The usual way to find the correct diagnosis, which includes the consideration of clinical and biochemical (in this case, determination of serum hormone levels) findings, may prove difficult because symptoms may not be very specific and laboratory findings may not always provide a clear-cut picture, particularly when the decreased testosterone levels are close to the normal range. Specific tests to evaluate the individual's androgen sensitivity are not yet available so hypogonadism is often diagnosed with the physician's experience after careful exclusion of other diseases that may have caused the same symptoms. The observation of clear clinical benefits after initiating testosterone therapy is sometimes the only method to verify the indication ex iuvantibus.

4.1 Definition* of Hypogonadism

Table 2: Hypogonadism
Hypogonadism is a clinical condition characterised by low serum testosterone levels occurring in association with any of the signs and symptoms listed:
Sexual symptoms • Diminished libido • Erectile dysfunction • Difficulty achieving orgasm • Diminished intensity of the experience of orgasm • Diminished sexual penile sensation
Diminished energy, sense of vitality, or sense of well-being Increased fatigue Depressed mood Impaired cognition Diminished muscle mass and strength Diminished bone density Anaemia

*The definition is adapted from the 2002 position statement on diagnosis, treatment, and monitoring of hypogonadism by the Sexual Medicine Society of North America, a specialty society of the American Urological Association.

5 Diagnosis of Hypogonadism

The absence of universal clinical or biochemical markers renders the diagnosis of hypogonadism difficult, and clear clinical correlates are not always easily identified. Using the definition of hypogonadism as a state of testosterone deficiency, the most reliable biochemical parameter would be the determination of free or bioavailable testosterone levels. The respective techniques (equilibrium dialysis at 37 °C for free or ammonium sulphate precipitation for bioavailable testosterone) are time-consuming and not available in normal clinico-chemical laboratories. However, free testosterone can be determined from the values for total testosterone, SHBG, and total protein (or albumin).[1]

Recommendations of the International Society of the Study of the Aging Male (ISSAM), the International Society of Andrology (ISA) and the European Association of Urology (EAU) suggest that total testosterone and SHBG be determined between 7:00 am and 11:00 am due to the circadian rhythm of testosterone production by the testicles. The most widely accepted parameters to establish the diagnosis of male hypogonadism are the measurement of total testosterone and free testosterone, calculated from measured total testosterone and SHBG or measured by a reliable free testosterone equilibrium dialysis method. If testosterone levels are below or at the lower limit of the accepted normal young adult male values it is recommendable to perform a second determination of testosterone together with assessment of serum LH and prolactin to rule out other causes of low testosterone levels.[4] The clinical symptoms of hypogonadism may be less clearly identifiable in older individuals because of other age-related changes.

What appears controversial, however, is the biochemical definition of hypotestosteronemia. The normal range for testosterone in serum levels in men is described as being in the order of 12–35 nmol/L; for example, the mean total testosterone level (as determined with mass spectrometry) was 724 ng/dL (25.1 nmol/L) in non-obese healthy men aged 19–40 years.[25] There is slight variation around this range depending on assay type used by the laboratories. The range quoted by laboratories is for all adult men and does not take into consideration normal ranges for different age groups. There is no indication within the ranges given as to the median or mean levels for men of specific age groups. A number of biochemical definitions for hypotestosteronemia have been proposed, including a serum testosterone level below the lower range of normal for young male adults,[26] or serum testosterone levels between the 5th and 10th percentiles of the relevant assay range. Hypotestosteronemia levels quoted in the scientific literature vary between approximately 300 ng/dL (10.4 nmol/L) and 400 ng/dL (13.9 nmol/L);[27–30] which are consistent with levels for total testosterone and the onset of hypogonadal symptoms (decreased libido, energy and strength/endurance).[31, 32]

The recent recommendations on the investigation, treatment, and monitoring of late-onset hypogonadism in males suggest that total testosterone levels above 12 nmol/L (346 ng/dL) or free testosterone levels above 250 pmol/L (72 pg/mL) do not require therapy with testosterone. Total testosterone levels between 8 nmol/L and 12 nmol/L or free testosterone levels between 180 pmol/L and 250 pmol/L are regarded as borderline hypogonadal levels. A trial of testosterone treatment can be considered in those patients.[4]

6 Testosterone Therapy

Several preparations containing testosterone or testosterone esters are available for the treatment of male hypogonadism.[1, 5] The half-life of natural testosterone is very short, ranging from 10 to 20 minutes. Furthermore, orally administered testosterone does not produce clinically relevant elevation of testosterone levels. Therefore, chemically-modified testosterone and other routes of administration have to be used.

Administration routes of marketed products used in testosterone therapy include oral, sublingual, and buccal formulations, transdermal patches and gels, subdermal depots, and intramuscular (i.m.) injections.[5]

In hypogonadal patients, i.m. injections of testosterone enanthate (TE), administered every two to three weeks, still represent the standard form of testosterone therapy in most countries. In addition to the inconvenience of frequent visits to the doctor's office, patients complain of variations in mood, sexual function and physical capacity due to short-term fluctuations of serum testosterone levels resulting from the pharmacokinetic profile after i.m. injection of TE.[1]

The pharmacokinetics of injectable testosterone cypionate are comparable to those of TE, whereas testosterone propionate has a considerably shorter duration of action and must be injected two to three times per week.[1]

Among the testosterone esters, testosterone undecanoate (TU) is the only orally available ester on the market. An oral TU preparation has been available commercially since the late 1970s. A single dose of oral TU contains 40 mg TU in castor oil. Because of its short half-life of 1.6 h, up to three oral doses per day are necessary to maintain physiological testosterone levels. Following oral administration, TU is mainly absorbed from this preparation via the lymphatic system. This requires administration with a meal that contains a certain amount of fat. Absorption rates vary inter- and intra-individually, and the resulting testosterone serum levels are difficult to predict.[1]

Transdermal patches containing testosterone are available for application to the abdomen, back, thighs, upper arm, and the skin of the scrotum. Although physiological testosterone levels can be reached reliably, transdermal patches pose the risk of skin irritation and sensitization. The scrotal patches induce high DHT levels, the long-term consequences of which are still unknown. Furthermore, the necessity of scrotal shaving reduces patient compliance. While non-scrotal patches do not have this disadvantage, they too are cosmetically unattractive and inconvenient to use.[1]

A gel containing 1% testosterone for transdermal application became available in 2000. Daily administration of 5–10 g of gel on the upper arm, shoulder, or abdomen increases serum levels of testosterone to within the normal range. Patient acceptability of the gel is high.[1] However, there is a risk of transfer through skin contact with other people unless appropriate precautions are taken.[5, 33]

A buccal system for testosterone delivery has been developed with a tablet-like product that adheres to the gum surface of the mouth. Testosterone is absorbed into the blood stream through the gum and delivered directly into the superior vena cava, bypassing the gastrointestinal system and the liver. Twice-daily dosing is necessary to achieve mean average serum levels of testosterone within the normal range. Patients frequently report problems with the buccal delivery system not adhering to the gum.[34]

A 6-monthly subdermal testosterone implant (testosterone 800 mg) has been developed that offers the convenience of twice-yearly administration without significant fluctuation in serum testosterone levels. However, it is associated with a risk of infection and pellet extrusion, which occur in up to 10% of patients.[5, 33] A cross-over study in men with organic androgen deficiency (n=38) suggested that the subdermal testosterone implant and Nebido® have comparable efficacy; however, patients preferred Nebido®, mainly due to ease of administration.[35]

Nebido® has been developed in order to improve the tolerability of testosterone therapy and to provide a convenient option for life-long treatment. Nebido® is a depot formulation which allows the extension of the injection interval by a factor of almost 5, from the 2- to 3-week interval of the standard therapy with TE (i.e. 17 to 26 injections per year) to a 10- to 14-week interval with Nebido® (i.e. 4 injections per year). Furthermore, Nebido® generally maintains physiological testosterone levels, avoiding unphysiological peaks and troughs. Nebido® has also been shown to produce higher levels of total, free, and bioavailable testosterone compared with 4-weekly injections of testosterone cypionate and mixed testosterone esters in men with hypogonadism.[36] These product characteristics of Nebido® significantly improve both the convenience and tolerability of the therapy. In contrast to transdermal gels and short-acting injections which have shown poor patient compliance,[37, 38] Nebido® may improve medication compliance,[39, 40] which is of utmost importance to achieve maximal results in long-term therapy.

The pharmaceutical and pharmacological data on Nebido® are reviewed in detail in the following chapter (7. Pharmaceutical and Pharmacological Data).

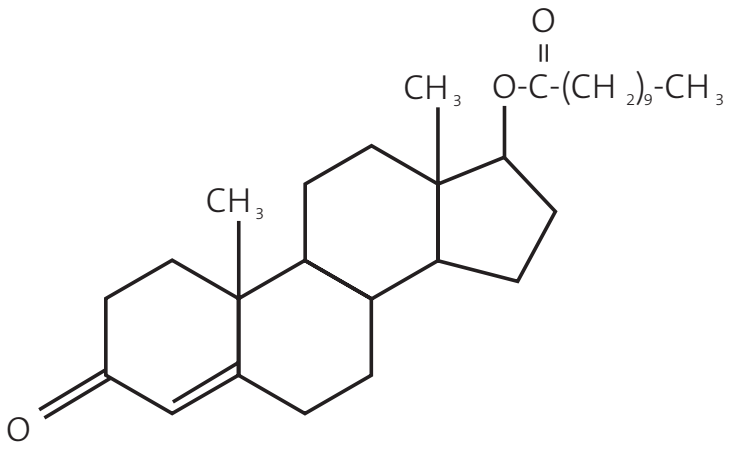
7 Pharmaceutical and Pharmacological Data

7.1 Physico-Chemical Properties

Chemistry of the Active Substance

The medically active component in Nebido® is TU (3-oxoandrost-4-en-17β-yl-undecanoate). TU is produced through esterification of natural testosterone in the 17β position. Testosterone is a steroid with 19 carbon atoms (chemical formula: $C_{19}H_{28}O_2$; Figure 5). Its chemical name is 17 beta-hydroxyandrost-4-en-3-one.

Figure 5: Chemical structure of testosterone undecanoate; TU.



Pharmaceutical Details

Nebido® is the first registered TU preparation for intramuscular injection in intervals of 10–14 weeks following an initial 6-week interval. One ampoule contains 1,000 mg of TU in 4 mL of oily vehicle and is available in a corresponding individual packaging. Nebido® contains the following additional constituents: refined castor oil and benzyl benzoate.[41]

Stability tests have shown that Nebido® is stable at a temperature of 30 °C for at least 24 months and at a temperature of 40 °C for at least 6 months so there are no particular precautions for storing the product. However, Nebido® should not be stored in the refrigerator. Its shelf life is 5 years.[41]

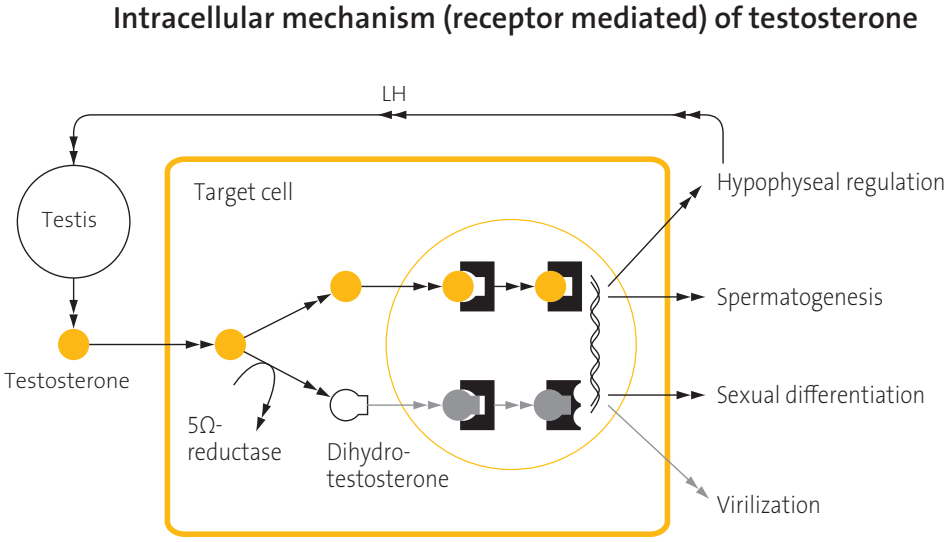
7.2 Pharmacodynamics

TU is an ester of natural testosterone. The active form, testosterone, is produced by hydrolyzation of the ester.

The main testosterone effects occur after the binding of testosterone to its specific receptor. The hormone receptor complex arrives in the cell nucleus where it modulates the transcription of certain genes after binding to the DNA (see Figure 6).[42]

The pharmacodynamic properties of TU are identical to the physiological action of testosterone described in chapter 3 of this monograph, Physiology and Pathophysiology.

Figure 6: The mechanism of action of testosterone.[43]



7.3 Pharmacokinetics

The major goal of testosterone therapy is the long-term elevation of serum testosterone levels to normal physiological levels in men with hypogonadism.

With Nebido®:

Stable serum testosterone concentrations within the physiological range are achieved in the first week after the first administration; the testosterone peaks exceeding the physiological range experienced with conventional i.m. injections such as testosterone enanthate or cypionate are largely avoided.

Serum testosterone levels are maintained within the physiological range when Nebido® is given at intervals of approximately 12 weeks following an initial interval of 6 weeks.

Serum concentrations of DHT and oestradiol follow the pattern of testosterone.

Gonadotrophin concentrations decrease with the increase in plasma testosterone concentration.

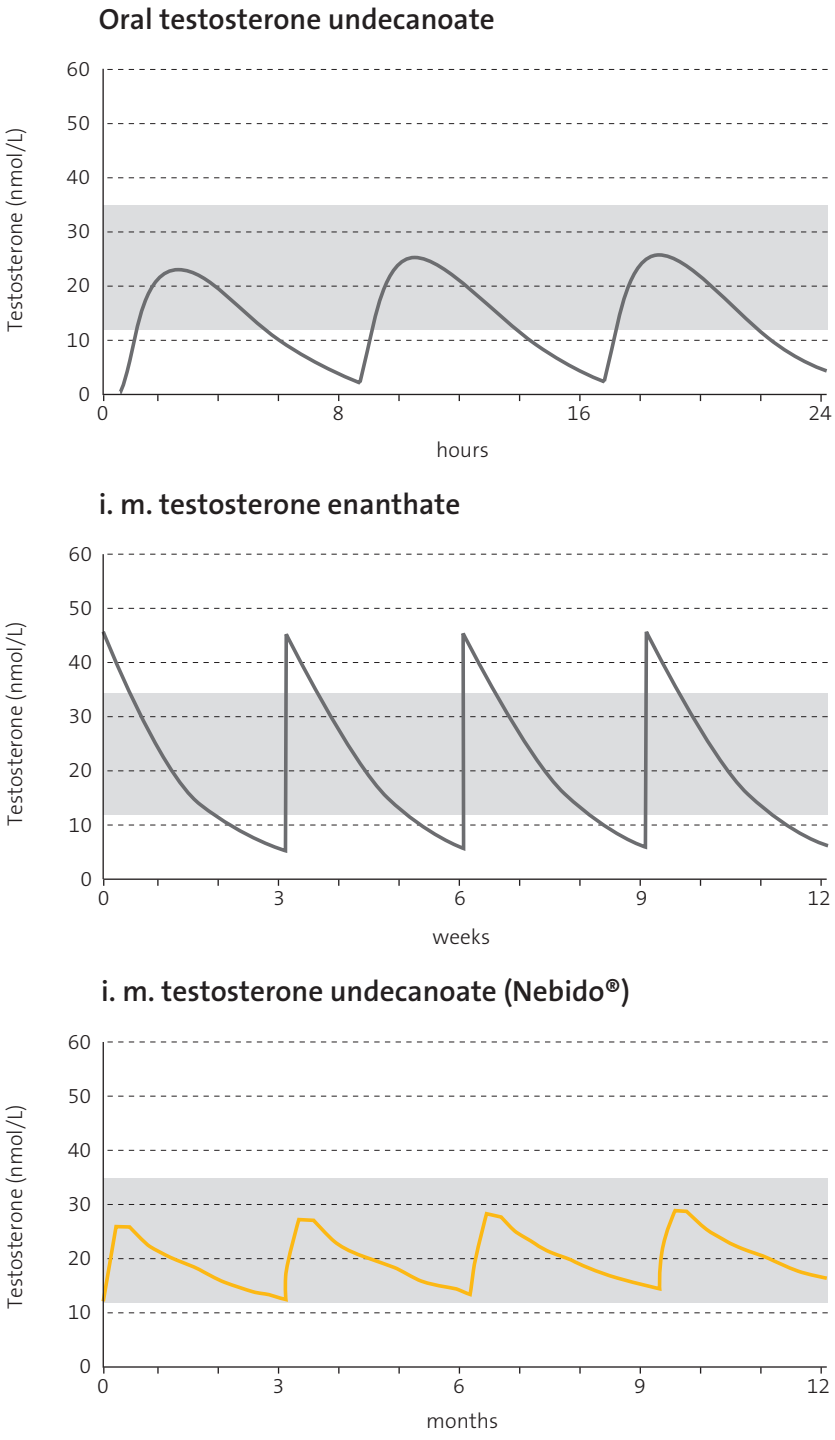
The administration of 40 mg of oral TU every 8 hours together with fat-rich food leads to short-term increases in serum testosterone rising to within the normal range. Afterwards, the levels decrease quickly (Figure 7).

The administration of 250 mg of injectable TE every 21 days i.m. leads initially to supraphysiological testosterone levels, then later to subnormal values. For about half of the period between injections the patient is over- or under-dosed (Figure 7).[44]

Administering TU 1,000 mg i.m. every 12 weeks leads to very stable concentrations over a long period, with the peaks and troughs not falling outside the normal range (Figure 7).[1]

These different durations of action are due to the half-lives, which are dependent on the testosterone ester, the galenic formulation, and the route of administration. Thus, the half-life of injectable TE i.m. is 4.5 days, and of oral TU is 1.6 hours.[1] Following i.m. administration of Nebido® the release rate is characterised by a half-life of approximately 90 days.[41]

Figure 7: Diagrammatic comparison of the kinetics of testosterone after 3 weeks of i.m. administration of testosterone enanthate, oral administration of testosterone undecanoate several times a day, and administration of Nebido® every 3 months.[1]



Attention should be given to the following recommendations for the administration of Nebido®:

First and second administration of Nebido® 6 weeks apart.

After that, keep to an interval between injections of about 12 weeks.

The first interval between injections must also be shortened for patients who have switched from other testosterone preparations to Nebido®.

Ideally one ampoule of Nebido® is injected deeply into the gluteal muscle very slowly over a period of approximately 2 minutes. The use of a 22G needle is recommended.

Measurement of serum trough testosterone levels and clinical symptoms should be considered for individualization of therapy with Nebido®.

Serum trough testosterone levels should be in the lower third of the normal range (i.e. 12–18 nmol/L).

Since steady state serum testosterone levels can be assumed to be achieved after the first six months of treatment, it appears advisable to control serum testosterone before the fourth injection for individualization of therapy (usual spacing between administrations provided).

7.3.1 Absorption

Following i.m. injection of Nebido®, TU is gradually released from the depot into the circulation and cleaved by serum esterases into testosterone and undecanoic acid.[30] An increase of serum levels of testosterone above basal values can already be measured one day after administration and maximum concentrations are reached within one to two weeks.[45]

7.3.2 Distribution, Metabolism and Elimination

Testosterone circulating in the blood is mainly (60%) bound to SHBG. Both the unbound (free) testosterone (2%) and the testosterone bound to albumin (38%) are biologically active.

Testosterone is metabolized primarily in the liver but also in other organs and tissues, such as the gastrointestinal mucosa, the skin, and adipose tissue. The metabolic reactions include oxidation of the 17-hydroxyl group, 5α-reduction of the double bond in ring A and 3-keto reduction. The enzymes involved are 5α- and 5β -reductases, 17β -hydroxysteroid dehydrogenase and 3α- and 3β -hydroxysteroid dehydrogenases. In addition, testosterone can be hydroxylated at different positions of the steroid skeleton. Several cytochrome P450 (CYP)-dependent enzymes are involved in these hydroxylation reactions, CYP3A4 being the most important one. The majority of metabolites are intrinsically inactive. The predominant metabolites are androstenedione, androsterone, and etiocholanolone.

The metabolism of testosterone can also produce active metabolites. Reduction by 5α-reductase produces DHT, a potent androgen, and aromatization by aromatase produces oestradiol, a potent estrogen. Conjugation of the metabolites with sulphuric or glucuronic acid generates highly polar and water-soluble metabolites which can be excreted via urine and faeces.

After the administration of radio-labeled 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-excreted products include androsterone and etiocholanolone.

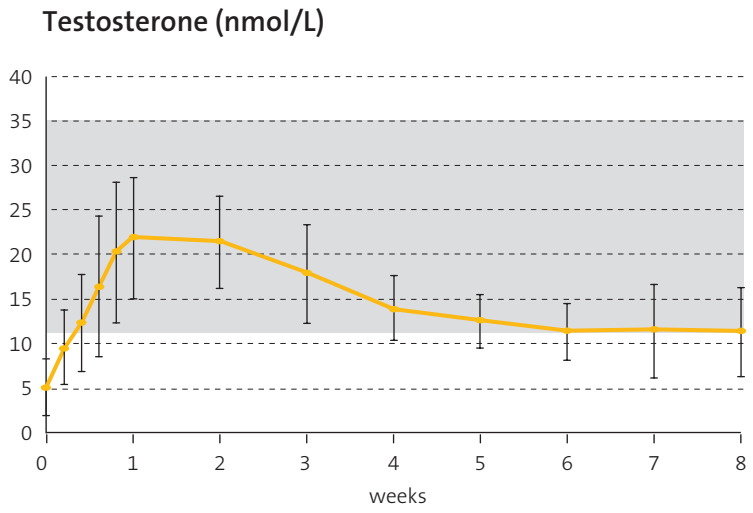
7.3.3 Pharmacokinetics of Testosterone, Oestradiol and DHT Following Injections of Nebido®

The pharmacokinetics of testosterone were investigated in hypogonadal men after single and multiple i.m. administration of Nebido® exploring different dosing regimens.

Single-Dose Administration

Following a single administration of Nebido® to 14 hypogonadal men, 2 days after the injection testosterone levels of 12.3 ± 1.7 nmol/L were reached and within 7 days, mean maximum testosterone concentrations were 22.0 ± 2.0 nmol/L and were reached within about 14 days post administration. Testosterone levels remained in the therapeutic range for 6–8 weeks (Figure 8).[45]

Figure 8: Mean serum testosterone levels (± standard deviation [SD]) in 14 hypogonadal men after a single i.m. administration of Nebido®.[45]



The oestradiol and DHT levels rose in parallel with the testosterone levels. Between day 7 and day 14 after the injection, DHT reached maximum values of 1.4 ± 0.3 nmol/L. The DHT level remained above the starting value for over 8 weeks (Figure 9). The serum oestradiol concentration rose significantly to a mean maximum value of 99.0 ± 9.0 pmol/L at day 14 after i.m. administration of Nebido® (Figure 10).[45]

Figure 9: Mean DHT serum concentrations (± SD) in 14 hypogonadal men after a single i.m. administration of Nebido®.[45]

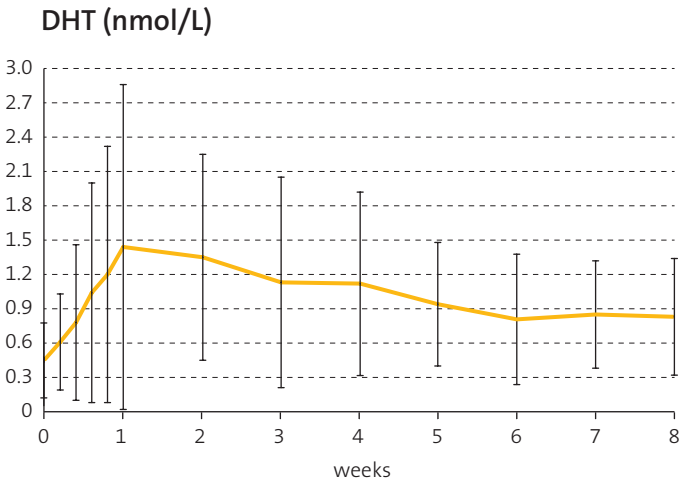
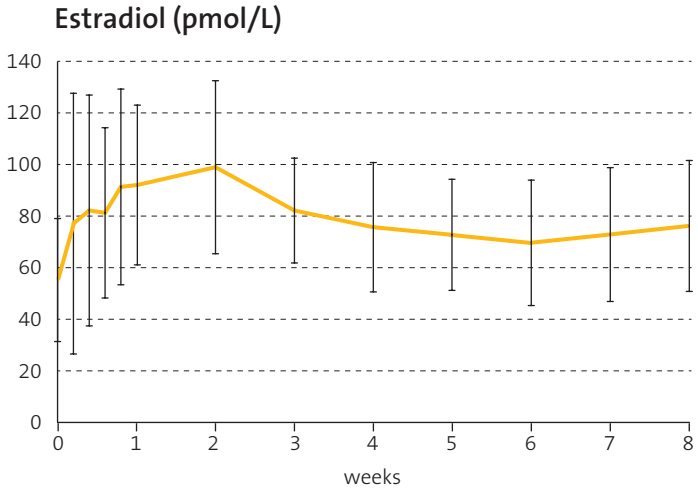


Figure 10: Mean oestradiol serum concentrations (± SD) in 14 hypogonadal men after a single i.m. administration of Nebido®.[45]



Multiple-Dose Administration

Kinetic investigations after repeated administration of Nebido® have been undertaken in several clinical studies.

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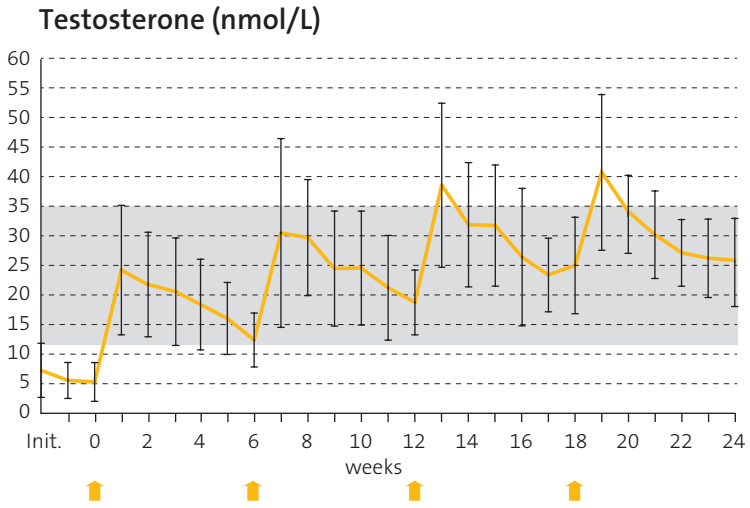
In an open-label study 14 hypogonadal men first received four injections of Nebido® at intervals of 6 weeks. After the third injection, mean maximum testosterone values above the normal range were observed (Figure 11).[46]

Figure 11: Mean serum testosterone concentrations (± SD) in 14 hypogonadal men after repeated i.m. administration of Nebido® at intervals of 6 weeks.[46]



Because of the observed accumulation of testosterone when Nebido® is administered at intervals of six weeks, 7 of the 14 patients subsequently received another 5 injections at intervals of 7–11 weeks, followed by 5 injections at intervals of 12 weeks. In only two patients did the treatment interval of up to 12 weeks lead to testosterone concentrations below the normal range right before the next injection; in all other patients, concentrations were within the normal range (Figure 12).[47]

This study demonstrated that testosterone levels do not accumulate with an injection interval of 12 weeks.[47]

Figure 12: Mean serum testosterone concentrations (± SD) in 14 / 7 hypogonadal men after repeated i.m. administration of Nebido® at intervals of 4 x 6 weeks, 5 x 7–11 weeks and 5 x 12 weeks.[47]

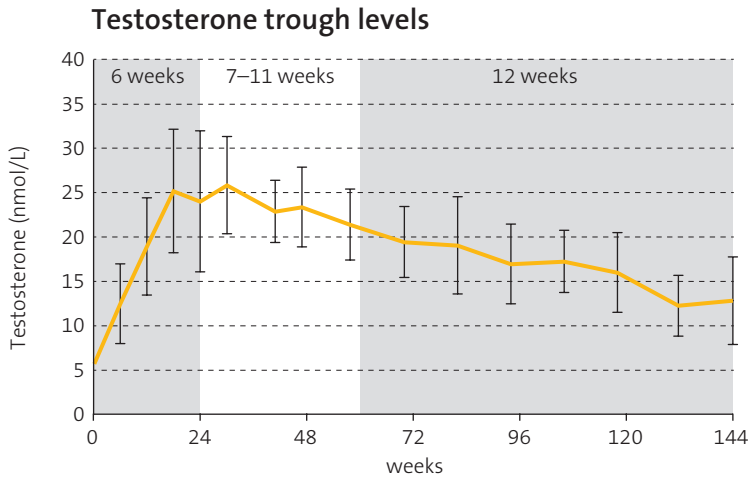
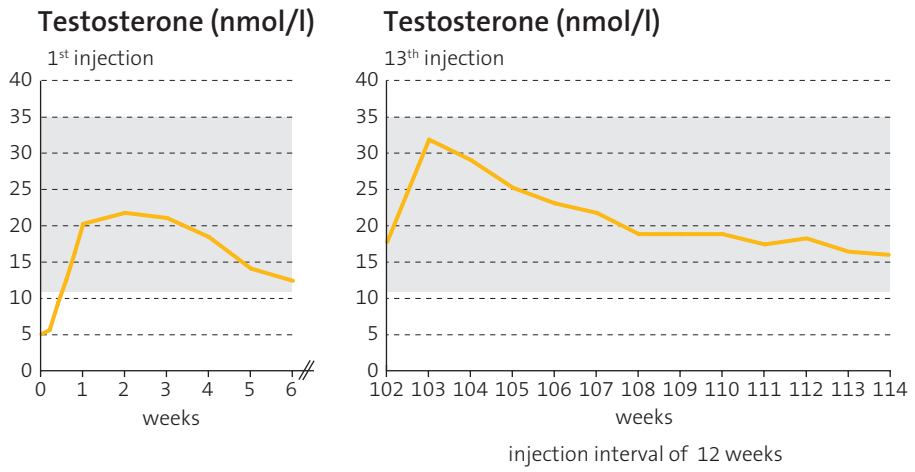


Figure 13 shows the serum testosterone concentrations after the first injection and after the 13th injection in long-term therapy with Nebido®.

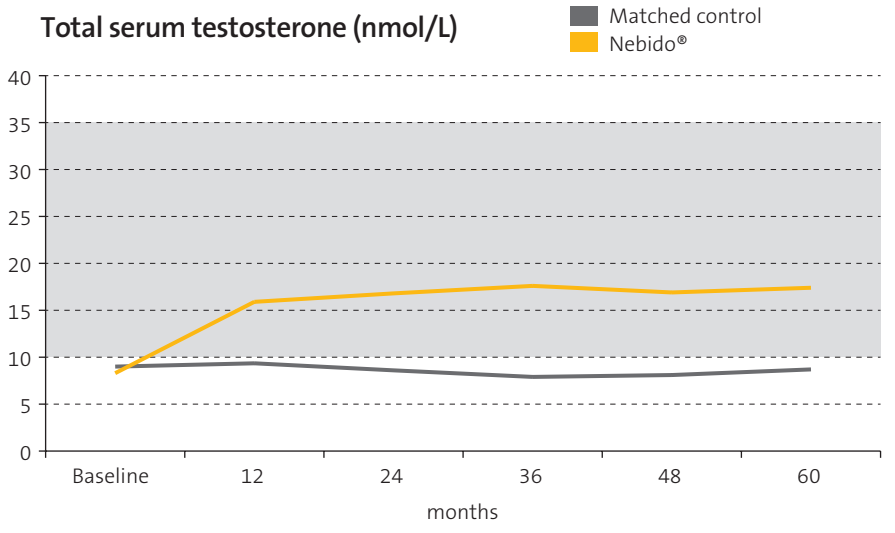
Two cumulative registry studies examined the use of Nebido® in (mainly elderly) men with subnormal plasma total testosterone levels. The first study enrolled 255 patients (mean age 58 years; mean plasma total testosterone 9.93 ± 1.38 nmol/L),[48] while the second enrolled 261 patients (mean age 59.5 years; mean plasma total testosterone 7.7 ± 2.1 nmol/L);[49] all patients received Nebido® (1,000 mg) administered at baseline and 6 weeks and thereafter every 12 weeks for up to 60 months. Both studies demonstrated significant increases in total testosterone; within the first 12 months trough levels were 18 and 16.2 nmol/L, respectively and then stabilised to ~18 nmol/L for the remainder of the observation periods.

Figure 13: Mean serum testosterone concentrations (± SD) after the first and 13th injection of Nebido®.[47]



In a similar 60-month prospective study, treatment with Nebido® (n=20) was compared with no treatment (n=20) in men aged from 45 to 65 years with total serum testosterone levels below 11 nmol/L.[50] At baseline, there was no significant difference between total serum testosterone levels in control patients (9.0 ± 1.7 nmol/L) and Nebido® recipients (8.3 ± 2.4 nmol/L). However, over 12, 24, 36, 48 and 60 months, levels of total serum testosterone in the Nebido® group increased and were significantly higher than the control group (Figure 14).

Figure 14: Mean trough total serum testosterone among hypogonadal men who received Nebido® or no treatment (matched controls) for up to 60 months.[50]



Even after repeated administration, the courses of DHT and oestradiol levels followed that of total testosterone. The gonadotrophins (LH and follicle-stimulating hormone [FSH]) are effectively suppressed.[47] As a result, spermiogenesis decreases and reduction in testicular volume may occur. SHBG decreases slightly at the beginning of treatment with Nebido®, but following this SHBG levels remain constantly within the normal range.[46] Results from a study in 122 patients with hypogonadism confirmed the effect of multiple-dose administration of Nebido® on DHT levels; DHT levels were maintained within the normal physiological range, with no clinically abnormally high or low values.[51]

The following conclusions for the dosage regimen can be deduced from the results of the kinetic investigations on testosterone concentrations:

Three days after administration of Nebido® the testosterone plasma levels are restored to the eugonadal range.

A loading interval (second injection after 6 weeks) is required.

The first interval between injections must also be shortened to six weeks for patients who have switched from other testosterone preparations to Nebido®, under observation of clinical symptoms.

Even 12 weeks after administration of Nebido®, testosterone levels are usually still in the eugonadal range. Thus the recommended dosage interval is (Figure 15):

- *Interval between first two injections: 6 weeks*
- *Subsequent extension of the interval between injections to about 12 weeks[39]*

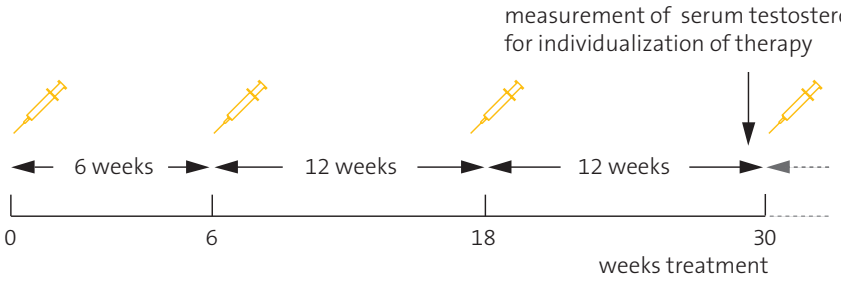
Measurement of serum trough testosterone levels and clinical symptoms should be considered for individualization of therapy with Nebido®.

Serum trough testosterone levels should be in the lower third of the normal range.

Since steady state serum testosterone levels can be assumed to be achieved after the first six months of treatment, it appears advisable to control serum testosterone before the fourth injection (usual spacing between administrations provided).

Injection Interval:

Figure 15: Recommended treatment regimen.



Additional Dosing Considerations

Although the majority of patients achieve testosterone levels within the eugonadal range within 18 weeks using the standard dosing schedule for Nebido®, adjustment of dosing frequency may need to be considered for some patients.

Patient characteristics that may affect dosing interval include:[52–54]

- Type and aetiology of hypogonadism
- Age
- Size (body weight, body mass index [BMI], body surface area)
- Baseline testosterone level
- Polymorphisms in genes affecting testosterone metabolism and androgen sensitivity

A retrospective study of 51 patients found that those with primary hypogonadism had significantly higher total testosterone and SHBG levels after 18 weeks of treatment with Nebido® than those with secondary hypogonadism.[52] In this study, age was positively correlated with total testosterone and bioavailable testosterone levels at 18 weeks, whereas body weight, BMI and body surface area were negatively correlated ($p \leq 0.05$ for all). Age ($p=0.05$) and baseline testosterone levels ($p<0.0001$) were independent predictors of the increase in total testosterone at 18 weeks.

Polymorphisms in glucuronosyltransferase genes and androgen receptor genes could theoretically affect testosterone concentrations during treatment with Nebido®. A study examining the impact of the UGT2B17 polymorphism in 207 hypogonadal men treated with Nebido® showed only modest influence on TU pharmacokinetics and minor differences in serum testosterone and LH levels. Men who were homozygous for the deletion polymorphism had reduced testosterone excretion rates and hence higher serum testosterone levels; however, marked inter- and intra-individual variability in testosterone levels was observed.[54] A study in 66 hypogonadal men who received ≥5 doses of Nebido® at 10–14-week intervals showed that those with longer CAG repeats in the androgen receptor gene, and hence lower testosterone levels, had reduced androgen effects.[53] A study in patients with postsurgical hypogonadotropic hypogonadism also found that CAG repeat length affected response to testosterone replacement therapy, with patients having shorter CAG repeats having greater increases in testosterone, oestradiol, and IGF-1 levels from baseline.[55] Similarly, in a retrospective study of 73 men with late onset hypogonadism, longer length of androgen receptor CAG repeat tract appeared to lower the extent of improvements in sexual function following testosterone-replacement therapy.[56]

7.4 Toxicology

The toxicity profile of Nebido® has been established mainly from the results of the preclinical studies that have been carried out with other testosterone esters or free testosterone.

No effects which might indicate an unexpected risk to humans were observed during repeated-dose toxicity studies after repeated administration of the enanthate ester of testosterone. TU was not mutagenic in the standard battery of in vitro and in vivo mutagenicity tests. Studies in rodents indicate a promoting effect of testosterone or its esters on the development of hormone-dependent tumours. No clear correlation between these data and the existence of an actual risk for humans could be established. However, it is known that sex hormones in general can enhance the development of hormone-dependent tissues and tumours.

8 Clinical Profile

The efficacy and safety of Nebido® have been evaluated in a number of clinical studies in patients with hypogonadism.[40, 45, 57–59, 55, 60] These include studies in patients with T2DM, metabolic syndrome, and/or obesity, and hypogonadism of different aetiologies.

A meta-analysis of 33 articles, including 11 randomized, placebo-controlled trials, found that injectable TU significantly increased lean mass, reduced fat mass and glycated haemoglobin (HbA_{1c}) and improved erectile function in both placebo-controlled and uncontrolled trials in men with hypogonadism.[57] Nebido® also had beneficial effects on other parameters, including waist circumference, body weight, BMI, serum lipid profile, bone mineral density (BMD), depression, and International Prostate Symptom Score (IPSS), in uncontrolled trials. The studies included in the meta-analysis enrolled a total of 3,359 patients who received injectable TU and 478 placebo-treated patients.

In IPASS, the largest worldwide prospective, observational study to date, Nebido® was found to be effective and well tolerated in patients with hypogonadism.[40] A total of 1,493 men were enrolled in 23 countries, and data from 1,438 patients who received a total of 6,333 injections (up to 5 injections per patient) were analysed. Clinical benefit was seen in both treatment-naïve patients and those with prior androgen treatment experience. Marked improvements in mental and psychosexual health, waist circumference, blood pressure (BP), and lipid profiles occurred during treatment with Nebido®. The proportions of patients with low/very low sexual desire/libido and moderate-to-severe erectile dysfunction decreased from baseline after 4 doses (from 64% to 10% and from 67% to 19%, respectively). Most patients reported being satisfied or very satisfied with their treatment (89%). Nebido® was well tolerated, with only 6% of patients experiencing adverse drug reactions, most of which were mild to moderate in intensity. The most common adverse reactions were increased haematocrit, increased prostate-specific antigen (PSA), and injection site pain (<1% each). The drop-out rate was 17.5%, which was remarkably low considering that 155 centres were involved in this open-label study design.

In a randomized controlled, Phase III study, Nebido® was compared over 30 weeks with TE 250 mg every three weeks (i.e. the standard form of treatment in many countries at the time of the study). The subsequent part of the study was an open study of >80 weeks. In this second part of the study all the patients received Nebido® injections at intervals of 12 weeks; 40 hypogonadal patients aged 18 to 64 years (mean age 38.7 ± 12.9 years) were included.

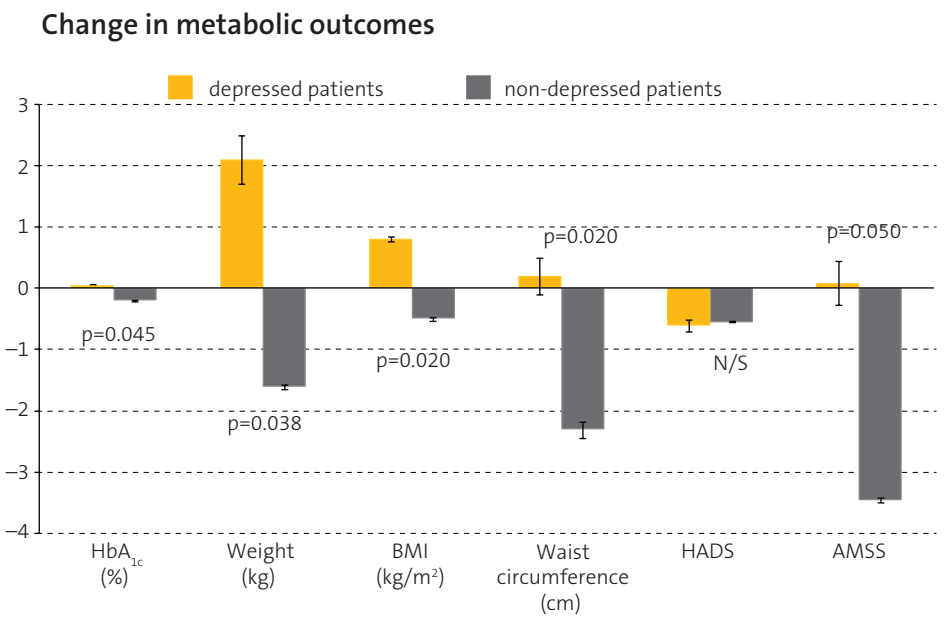
The study evaluated multiple efficacy parameters (body composition, muscle strength, sexual function and mood, BMD)[61–63] and safety and tolerability endpoints (erythropoiesis, local tolerance, prostate volume plus PSA concentrations, and laboratory test results).[45, 61–64] Nebido® significantly improved sexual function over 30 weeks and compared with TE, it had a better tolerability and safety profile.[61] After 144 weeks, grip strength was significantly improved over baseline in patients who received Nebido®.[62] Results at the 3-year follow up showed that Nebido® significantly increased HDL compared with baseline, while leptin levels, BMD, BP, liver function tests, haemoglobin and haematocrit levels remained stable. While there was an increase in prostate volume (2.3 mL, $p<0.05$) after 12 months, volumes remained stable over the subsequent 3 years; this was paralleled by an increase in PSA (0.08 mg/dL, $p<0.05$) without any further changes after 12 months.[63]

Studies in Patients with T2DM, Metabolic Syndrome, and/or Obesity

The prevalence of hypogonadism is high among men with diabetes and metabolic syndrome. Several clinical studies have shown that testosterone replacement therapy with Nebido® is effective in increasing serum testosterone levels and improving other endpoints including BMD, anthropometry, body composition, metabolic parameters, and sexual function in this patient population.[65–69] Furthermore, testosterone replacement may reduce the occurrence of, or improve, diabetic complications in men with hypogonadism and T2DM.[65, 70]

The effect of Nebido® on metabolic changes in an exclusive population of men with T2DM was reported in the randomized, double-blind, placebo-controlled BLAST study.[71–73] For the first 30 weeks, patients were treated with either Nebido® or placebo, followed by open-label treatment for 52 weeks. The trial enrolled 199 men with T2DM and total testosterone ≤12 nmol/L or free testosterone ≤250 pmol/L at baseline. Improvements in metabolic parameters were observed in patients treated with Nebido®, although those with depression had reduced clinical benefit (Figure 16).[72] Treatment with Nebido® produced a statistically significant reduction in HbA_{1c} at 6 and 18 weeks and after a further 52 weeks of open-label medication. The greatest improvement in glycaemic control was seen in patients with baseline HbA_{1c} >7.5%. There was a significant reduction in waist circumference, body weight, and BMI in men without depression; these improvements were related to achieving adequate serum levels of testosterone.

Figure 16: Effect of Nebido® treatment in patients with type 2 diabetes with and without depression.[72]



Analysis of the results according to baseline total testosterone level showed that those with severe hypogonadism (total testosterone ≤8 nmol/L or free testosterone ≤180 pmol/L) had a significant improvement in sexual function but not metabolic parameters (Figures 17 & 18). In contrast, patients with mild hypogonadism (total testosterone 8.1–12 nmol/L or free testosterone 181–250 pmol/L) had significant improvements in body weight, BMI, and waist circumference but not sexual function (Figures 17 & 18).[73]

The efficacy of Nebido® in patients with T2DM was also evaluated in a prospective, non-randomized study.[74] Of 212 men screened, 87 of whom had testosterone levels <300 ng/dL, 120 underwent follow-up. Nebido® was administered to 56 of the patients with hypogonadism, while 31 opted against treatment, and an additional 23 patients with eugonadal testosterone levels were observed for 3 months. Significant reductions in body weight and BMI were seen in hypogonadal men treated with Nebido®, but not in the untreated hypogonadal cohort. In addition, there was a significant positive correlation between the mean change in total testosterone and International Index of Erectile Function 5-item (IIEF-5) score in hypogonadal men. Increased serum testosterone correlated with reduced BMI, cholesterol, and triglyceride levels, and glycaemic control was also improved in patients treated with Nebido®.

Figure 17: Effect of Nebido® treatment in patients with mild or severe hypogonadism.[73]

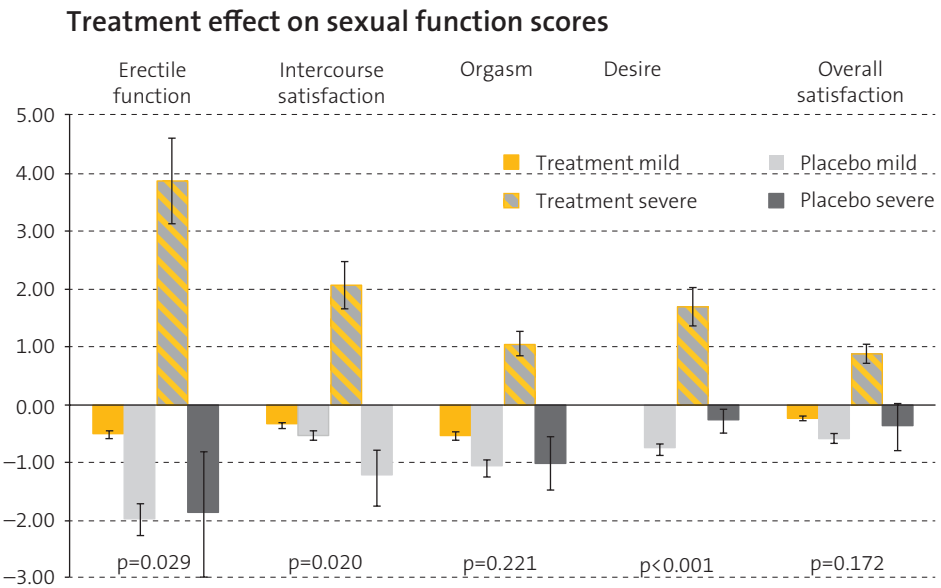
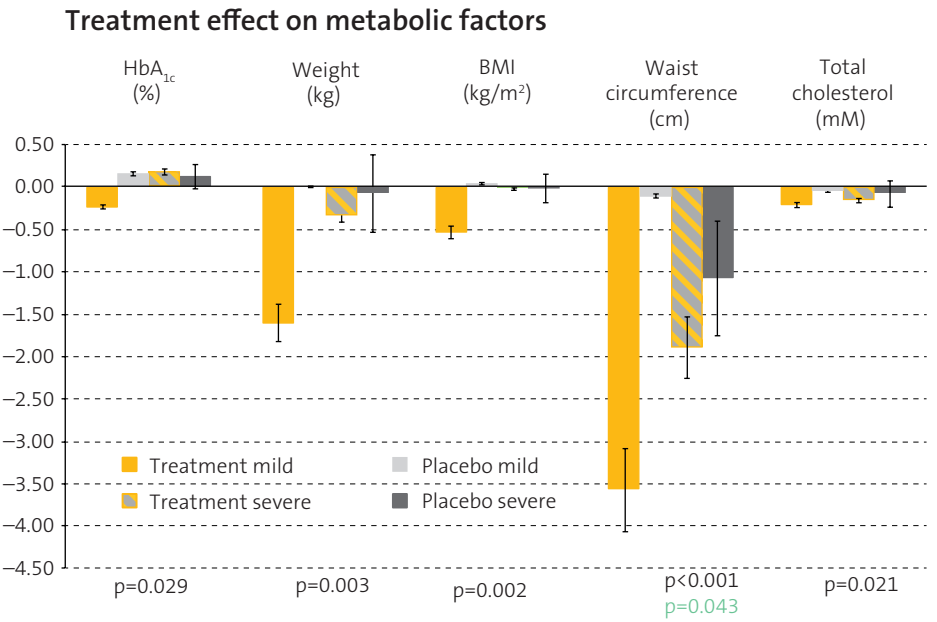


Figure 18: Effect of Nebido® treatment in patients with mild or severe hypogonadism.[73]



Nebido® was compared with oral TU in a randomized, double-blind, double-dummy study in 52 hypogonadal men with metabolic syndrome. Results showed that only Nebido® significantly increased testosterone levels and improved metabolic parameters (Homeostasis Model Assessment index of Insulin Resistance [HOMA-IR], fasting glucose, fasting insulin, waist circumference and fat mass) at 6 months.[75] Continued improvements in testosterone levels and metabolic parameters were seen after 12 months of Nebido® treatment. Patients in the oral TU group were switched to Nebido® at 6 months and significant increases in free and total testosterone were observed in this group at 12 months. Aging Male Symptoms (AMS) scores and IIEF-5 scores were significantly improved in Nebido® recipients. Nebido® was well tolerated in this study, with no major adverse events reported.

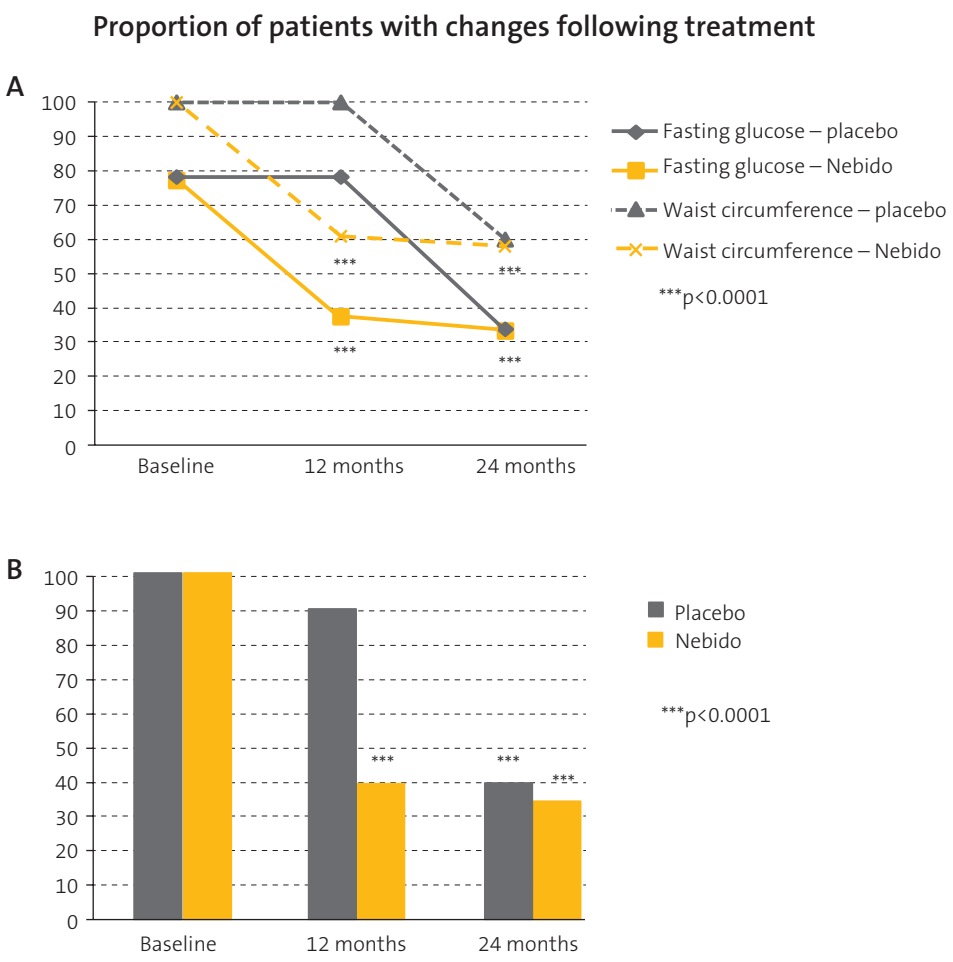
In a randomized, double-blind, placebo-controlled Phase III trial in 184 men with hypogonadism and metabolic syndrome, treatment with Nebido® for 30 weeks significantly improved body weight, BMI and waist circumference compared with placebo.[76] Levels of leptin, insulin, and some inflammatory markers decreased. However, there were no changes in serum glucose or lipid levels.

Treatment with Nebido® increased serum testosterone levels and improved LUTS and signs of non-alcoholic liver steatosis as well as metabolic parameters in a cohort of 117 elderly men with hypogonadism and metabolic syndrome.[77] Plasma testosterone levels were significantly increased from baseline at 1 year. Significant reductions in IPSS, prostate volume, PSA level and residual bladder volume were observed. Significant improvements in liver function were observed after 1 year, with reductions (from baseline) in alanine aminotransferase (ALT), aspartate aminotransferase (AST) as well as C-reactive protein (CRP) levels – a marker of inflammation.[78] The number of patients with metabolic syndrome according to National Cholesterol Education Program (NCEP) criteria decreased from n=74 at baseline to n=42 after 1 year. Similarly, improvements in metabolic parameters and liver enzyme levels and increased testosterone levels were observed in a cohort of 122 hypogonadal men treated with Nebido® at 1 year, with further improvement through 2 years.[79] Nebido® was well tolerated, with no significant increase in prostate volume or IPSS. Although haematocrit and haemoglobin levels significantly increased from baseline, they did not exceed the upper limit of reference values for most patients.[80]

Treatment with Nebido® for 2 years improved metabolic parameters and cardiovascular risk factors in a randomized, double-blind, double-dummy study in 50 patients with metabolic syndrome and LOH.[81] Patients in this study were randomized 4:1 to receive Nebido® 12-weekly or daily doses of placebo gel. Nebido® significantly reduced waist circumference and fasting glucose levels from baseline, and significantly reduced the proportion of patients with metabolic syndrome after 1 year ($p<0.0001$ for all; Figure 19). At 1 year, Nebido® recipients had significant improvements in insulin resistance (HOMA-IR, $p<0.001$), carotid intima media thickness ($p<0.0001$) and hsCRP levels ($p<0.001$) compared with those receiving placebo. As a result, the placebo-group patients were switched to Nebido® for the remainder of the study; at 2 years these patients also had a significant improvement in HOMA-IR ($p<0.001$) and significantly fewer were classified as having metabolic syndrome compared with baseline ($p<0.0001$). There was no significant change in BMI, and the reduced numbers of patients

with metabolic syndrome were therefore considered primarily due to reductions in waist circumference and visceral fat mass, increased fat-free mass, and improved HOMA-IR.

Figure 19: Changes in A) fasting glucose and waist circumference and B) proportion of patients with features of metabolic syndrome in patients metabolic sydrome and late-onset hypogonadism.[81]



(A) Changes in fasting glucose and waist circumference in the placebo and Nebido® arm, respectively. After 12 months placebo treatment, no modification of both parameters is observed. After 12 months, patients were shifted to Nebido® treatment, and at month 24, they showed a significant improvement in both fasting glucose and waist circumference compared with placebo ($p<0.0001$). After 12 months Nebido® treatment, a significant improvement in both fasting glucose and waist circumference compared with placebo is observed ($p<0.0001$), that is maintained after 24 months of treatment ($p<0.0001$). (B) Modification in the percentage of patients showing metabolic syndrome features (according to NCEP-ATPIII criteria) after placebo and Nebido®, respectively. After 12 months of placebo, no modification is found; after 12 months, patients shifted to Nebido® treatment and at month 24, 40% ($p<0.001$) match for NCEP-ATPIII criteria of metabolic syndrome. After 12 months of Nebido® treatment, 40% ($p<0.0001$) of patients match NCEP-ATPIII criteria. After 24 months, 35% ($p<0.0001$) of patients completely revert their metabolic syndrome as defined by NCEP-ATPIII criteria.

Normalization of serum testosterone levels in obese men with hypogonadism, including those with T2DM, produced significant improvements in metabolic parameters in a 5-year registry study.[82] The study included 181 patients, 72 of whom had T2DM. Significant and progressive reductions in body weight, waist circumference, and BMI were observed from baseline through 5 years (all $p<0.0001$ vs. baseline and vs. previous year) in the overall population and the subgroup with T2DM. Significant improvements were also seen in lipid profiles, serum glucose, HbA_{1c}, and BP (all $p<0.0001$) Similar results were seen in a subgroup of 156 obese men with hypogonadism and T2DM treated with Nebido® for up to 6 years in another registry study.[83].

A single-centre, open-label, cumulative registry study in 255 men with hypogonadism (approximately 95% with BMI >25 kg/m^2) also showed that treatment with Nebido® produced significant and progressive reductions in body weight, waist circumference, and BMI over 5 years (all $p<0.0001$).[48] Significant improvements were also seen in lipid profiles (total, low-density lipoprotein [LDL]- and HDL-cholesterol, triglycerides), BP, HbA_{1c}, blood glucose, CRP, and ALT and AST levels ($p<0.0001$ for all).[84] Total testosterone increased to approximately 18 nmol/L during the first 12 months of treatment, and was maintained at physiological levels for the remainder of the study.[48, 84]

8.1 Clinical Efficacy

Main Outcomes:

Nebido® is effective in the therapy of male hypogonadism.

Nebido® has a favourable effect on body composition by increasing muscle mass and decreasing fat mass in hypogonadal men.

Nebido® may reduce body weight, BMI and waist circumference upon long-term treatment in hypogonadal men.

Muscle strength improves under therapy with Nebido® in hypogonadal men.

Sexual function parameters in hypogonadal men are improved with Nebido® compared with baseline.

In hypogonadal men, Nebido® exerts a positive effect on mood, thus improving self-confidence and activity, and reduces fatigue and the feeling of exhaustion.

Nebido® may improve glycaemic control under long-term treatment in hypogonadal men.

8.1.1 Body Composition

Data from clinical studies have shown that treatment with Nebido® improves body composition.

Lean body mass correlates positively with testosterone concentration; total fat mass and percentage of body fat correlate negatively with the level of testosterone.

Studies in elderly men with hypogonadism have also shown that treatment with Nebido® significantly improves body composition.[81, 85–87] Thus, an open-label study in hypogonadal men aged 50–65 years (n=50) evaluated the effects of 12 months of treatment with Nebido® on body composition following initial treatment with testosterone gel for 12 months.[86, 87] Lean mass increased from baseline by 2.35% and 4.5%, after 12 and 24 months respectively. Fat mass also decreased by 4.2% and 9.1%, after these respective intervals. Patients gained proportionally more muscle mass in the limbs than the trunk. Significant increases in lumbar spine ($p<0.001$) and hip BMD ($p<0.037$) were observed at 12 and 24 months.

In 101 men with cirrhosis and low testosterone levels, measures of body composition were improved with 12 months of Nebido® treatment in a randomized, double-blind, placebo-controlled study.[88] Compared with placebo recipients, those treated with Nebido® had significantly increased appendicular lean mass (+1.69kg; p=0.021) and total lean mass (+4.74kg; p=0.008), as well as reduced fat mass (–4.34kg; $p<0.001$). Bone mass, BMD, and haemoglobin also increased with testosterone treatment.

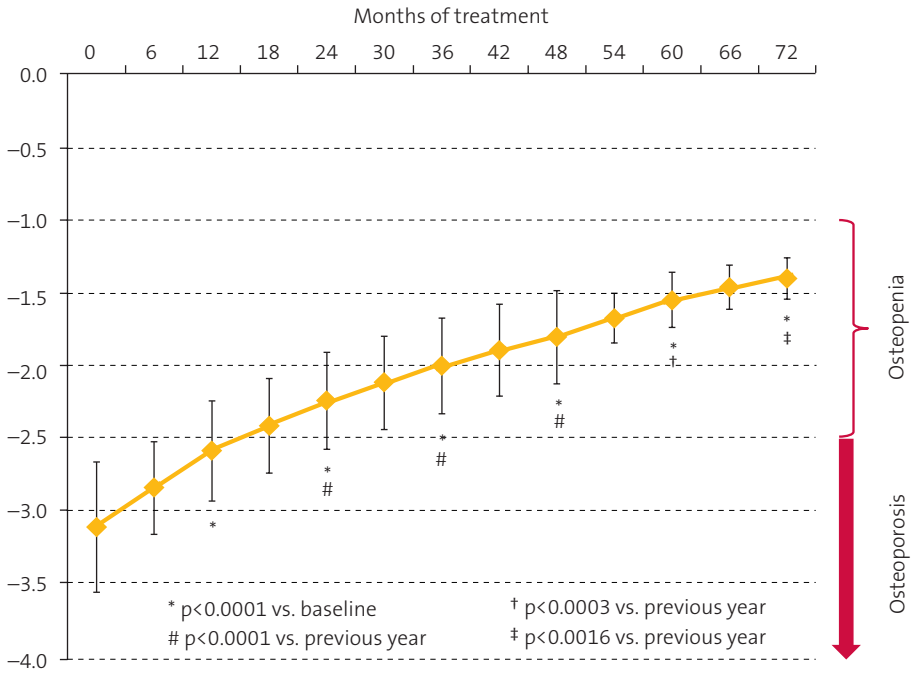
A randomized, double-blind, placebo controlled study of 100 obese, hypogonadal men who undertook dietary restriction for 10 weeks followed by weight maintenance for 46 weeks compared the effect of 56 weeks of Nebido® with matching placebo on parameters of body composition. Compared with placebo recipients, men who received Nebido® had greater reductions in fat mass (mean adjusted between-group difference: –2.9 kg; p=0.04) and visceral fat (–2678 mm^2; p=0.04). During the period of dietary restriction, both groups lost similar amounts of lean mass (Nebido® vs placebo: –3.9 vs –4.8 kg; p=0.36), but those receiving Nebido® regained lean mass during the maintenance period, such that the lean mass lost at study end was significantly less than that lost by placebo recipients (–0.6 vs –4.0 kg; p=0.002).[89]

Increasing testosterone levels to the eugonadal range can improve BMD in men with hypogonadism,[17,18] including those with Klinefelter's syndrome.[90]

A three-year prospective study in middle-aged men with late onset hypogonadism and metabolic syndrome illustrated that long-term treatment with Nebido® produced a significant increase in BMD (vertebral and femoral) that was related to increases in serum testosterone levels.[18]

Furthermore, a prospective registry study examined the effects of up to 6 years of treatment with Nebido® in men with osteoporosis and hypogonadism.[17] Testosterone levels increased significantly from baseline, and were maintained in a eugonadal range. Significant and progressive improvements in T-scores were observed over 6 years, with osteoporosis improving to osteopenia (Figure 20).

Figure 20: T-scores during testosterone administration.[17]



8.1.2 Anthropometric Measures – Weight Loss and Metabolic Parameters

Weight Loss

The effect of increasing serum testosterone to normal levels has been shown to have a sustained effect on weight loss.[48, 82, 91] A 5-year observational study in 181 hypogonadal men with obesity showed that Nebido® not only normalized testosterone levels but significantly reduced waist circumference (by 11 cm), body weight (by 21 kg) and BMI (by 6 units; all p<0.0001). Furthermore, these parameters were also significantly reduced in men with T2DM.[82] These results represented the obese subgroup of an open-label study in 255 hypogonadal men that reported progressive reductions in body weight (16 kg), waist circumference (9 cm) and BMI (4 units) over a 5-year observation period.[48] Another 5-year study found that Nebido® significantly improved body weight, waist circumference and BMI, as well as other cardiovascular-related endpoints (cholesterol, triglycerides, blood glucose and BP) among 261 men with late-onset hypogonadism and erectile dysfunction.[91] The results appeared to be independent of age.[92]

The effects of Nebido® on reducing body weight have also been shown to occur in conjunction with improvements in metabolic parameters. In a matched-control study to examine the effects of long-term testosterone treatment on metabolic outcomes, patients who received Nebido® not only had significantly ($p<0.0001$) reduced body weight (15 kg) and waist circumference (9 cm), but also significant ($p<0.0001$) improvements in insulin sensitivity (HOMA-I -2.8), total/HDL cholesterol ratio (–2.9) and BP (systolic –23 and diastolic –16 mmHg).[50] The improvements observed in this group of patients occurred without any effect on IPSS, maximum urinary flow rate, post-void residual volume, or prostate size.[93] A single-centre, prospective registry study of 115 men with hypogonadism followed up for a mean of 7.56 years (maximum 10 years) showed that treatment with Nebido® resulted in significant ($p<0.0001$) reductions from baseline in body weight (97.3kg to 84.7 kg), BMI (30.8 to 27.1 kg/m^2) and waist circumference (106.5 to 92.3 cm).[94] These men also had significant ($p<0.0001$) improvements from baseline in lipid profile, glycaemic parameters, BP and CRP.

In 58 men with hypogonadism and symptoms of testosterone deficiency, treatment with Nebido® for 54 weeks improved total cholesterol levels from baseline ($p=0.002$), body fat ($p=0.003$) and fat ratio ($p<0.001$), and significantly increased haemoglobin levels and haematocrit ($p<0.001$).[95] In these patients body weight, BMI, and muscle were increased from baseline ($p<0.001$). The prevalence of anaemia was decreased from baseline to the end of treatment (29.6% vs 10%; $p<0.001$).

A study conducted in 88 patients with symptomatic late-onset hypogonadism who received Nebido® demonstrated significant improvements in anthropometric and metabolic parameters. After 12 months of treatment, significant reductions in BMI ($p<0.0001$), waist circumference ($p<0.002$), HbA_{1c} ($p<0.0001$) and improvements in lipid profile were observed in all patients. Haemoglobin and haematocrit also showed significant increases ($p<0.0001$ in both cases).[96]

A long-term (median duration of follow-up: 7 years) prospective observational study conducted in 656 men with testosterone deficiency and symptoms of hypogonadism showed that treatment with Nebido® results in significant ($p<0.001$) reduction in mortality due to cardiovascular disease compared with no treatment. During the observational period two deaths occurred in the treatment group and none were due to cardiovascular disease, while 21 deaths occurred in the control group, 19 of which were due to cardiovascular disease (myocardial infarction: n=5, stroke: n=4, heart failure: n=7, thromboembolism: n=2, lung embolism: n=1). After 10 years the incidence of death was 0.1145 in the control group compared with 0.0092 in the treatment group and the reduction in mortality was estimated to be between 66% and 92%. In addition, after 8 years of treatment measures of blood glucose, systolic and diastolic BP, lipid profile, body weight and waist circumference improved significantly in the treatment group compared with the control group ($p<0.0001$ for all measurements).[97]

In a study of 411 obese men with hypogonadism identified from two prospective registry studies, 8 years of treatment with Nebido® resulted in improvements in weight, waist circumference and BMI, irrespective of obesity severity.[98] Improvements were also seen in glycaemic parameters, lipid profile, and quality of life parameters in the overall population. Long-term treatment with Nebido® was also shown to be safe and effective at reducing some parameters of obesity in a group of 428 men treated for 8 years in Thailand.[99] A review of the medical records for these men showed significant ($p<0.05$) improvements in waist circumference and body fat, as well as cholesterol, LDL, and IPSS score. While IIEF-15 scores, testosterone, PSA and BMD also increased significantly ($p<0.05$), there were no differences in BMI, high-density lipoprotein or triglyceride levels, or AMS scores.

Analysis of the effect of testosterone interruption on weight loss and metabolic parameters has shown a regression of improvements during treatment cessation, suggesting that treatment with Nebido® should be lifelong in order for continued benefits to be seen.[100,101] In a group of 262 middle-aged and elderly men with hypogonadism enrolled in a registry, temporary interruption of Nebido® in 147 men for a mean of 16.9 months (resulting in a reduction of total testosterone to hypogonadal levels[101]) led to reversal of improvements in body weight, lipid profile, glycaemic parameters, BP and CRP that had been seen with previous Nebido® therapy, while those who continued therapy had continuous improvements in these parameters.[100] Upon resumption of Nebido® treatment, these parameters improved once more. In addition to worsening of anthropometric measures, AMS, IIEF and IPSS scores worsened when Nebido® was interrupted, as did residual voiding volume, bladder wall thickness and PSA levels.[101]

8.1.3 Muscle Strength

Muscle strength was determined by grip strength measurements using a hand dynamometer in a study by Minnemann et al. This method assesses the isometric strength of the arm muscles quantitatively and with high reproducibility. Strength of grip noticeably improved during treatment with Nebido® and TE. Strength increased further during continuation of the study with Nebido® alone for 114 weeks (Figure 21).[62, 63]

8.1.4 General Well-Being and Sexual Function

Testosterone replacement therapy with Nebido® has been shown to improve mood and sexual function in men with hypogonadism.[91, 102]

The Sexual Activity Questionnaire (SAQ) was used to assess mood and sexual function; when taking Nebido® and TE the numbers of morning erections as well as the total number of erections (Figure 22) and the number of ejaculations increased. In both groups satisfaction with sexual life improved. Sexual desire and sexual fantasies increased.[61, 64]

Nebido® led to an improvement in the ability to concentrate, in self-confidence, in activity and in more positive moods. In contrast, feelings of fatigue and exhaustion were reduced (Figure 23).[64]

Figure 21: Development of muscle strength during long-term treatment with Nebido® and testosterone enanthate.[62]

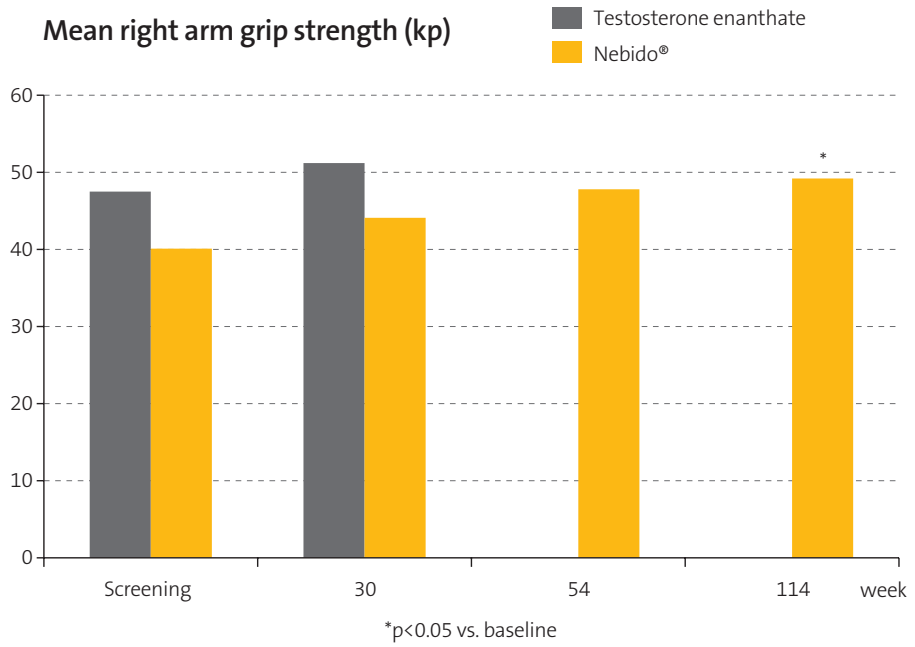


Figure 22: Weekly number of morning erections during 30 weeks of treatment with Nebido® and testosterone enanthate.[64]

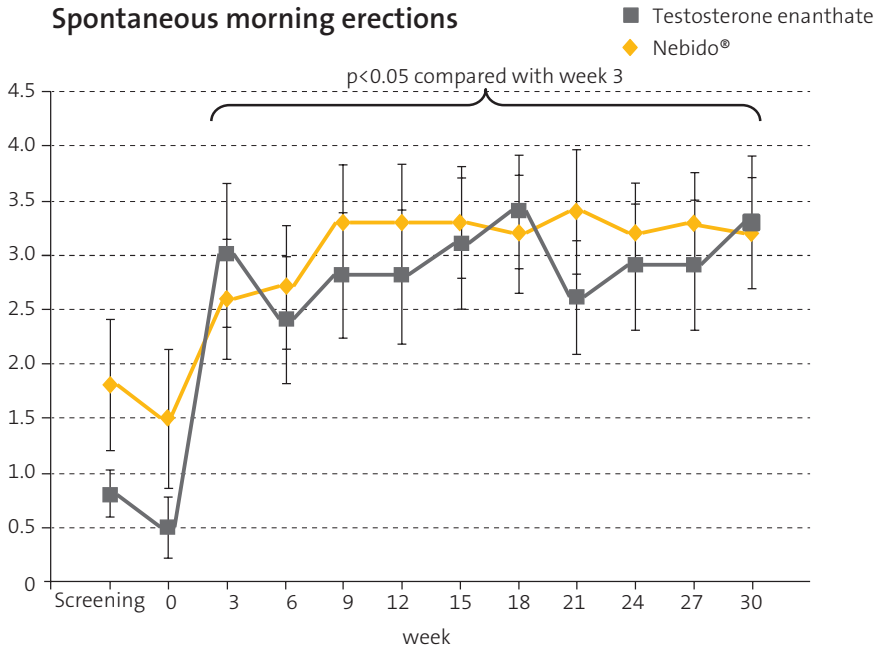
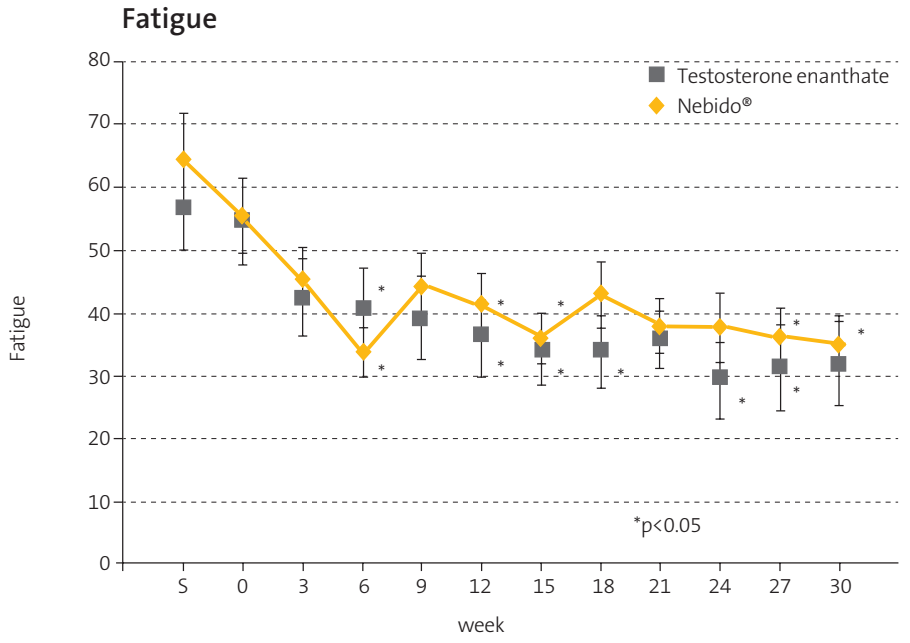


Figure 23: Decrease of fatigue during 30 weeks of treatment with Nebido® and testosterone enanthate.[64]



Long-term treatment with Nebido® or 3-weekly TE injections produced comparable improvements in sexual function in hypogonadal men at 30 weeks, and maintained these effects through 65 weeks.[61, 64] Both treatments produced rapid improvements in sexual function, with efficacy seen within 3 weeks. Although efficacy of the two treatments was similar, Nebido® had the advantage of requiring less frequent administration than TE.

Confirming results previously published from an open-label study in 133 Korean men,[58] in the BLAST study there was an improvement in all sexual function domains and overall satisfaction (all $p<0.05$) after 30 weeks of double-blind treatment with Nebido®, with benefit seen as early as 6 weeks and continued improvement through 18 months.[71] The AMS score significantly improved in non-depressed men ($p=0.02$) but depression at baseline was associated with reduced benefit with respect to sexual function and psychological scores (Figure 24). In men taking phosphodiesterase (PDE)-5 inhibitors, there was no change in erectile function during the double-blind phase, but a 9-point improvement in erectile function occurred during open-label treatment (Figure 25). After 30 weeks, 46% of patients felt that treatment had improved their health (vs. 17% for placebo), increasing to 70% after open-label treatment. Greater effects were seen in less obese and older patients.

Figure 24: Treatment effect in BLAST (baseline vs. 30 weeks) in men with and without depression.[71]

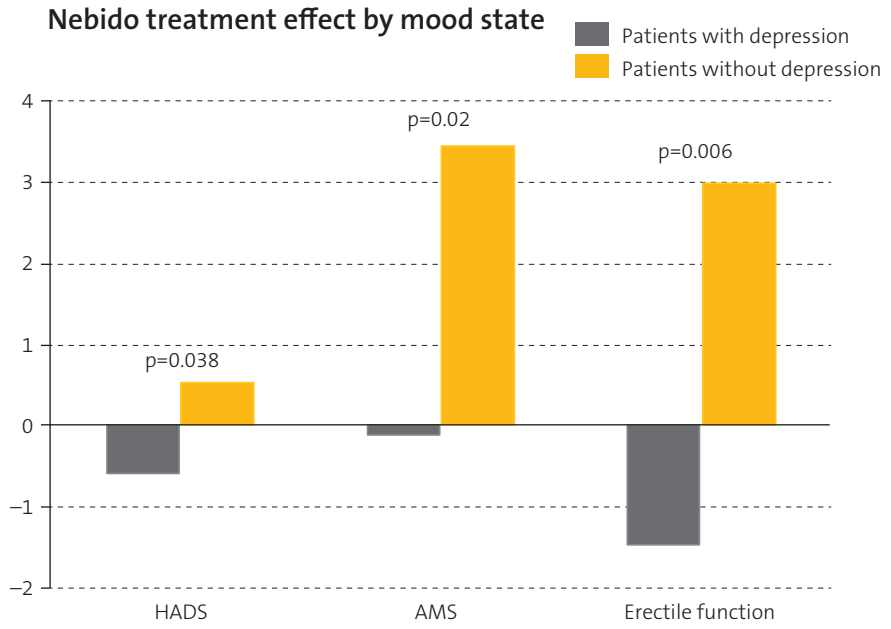
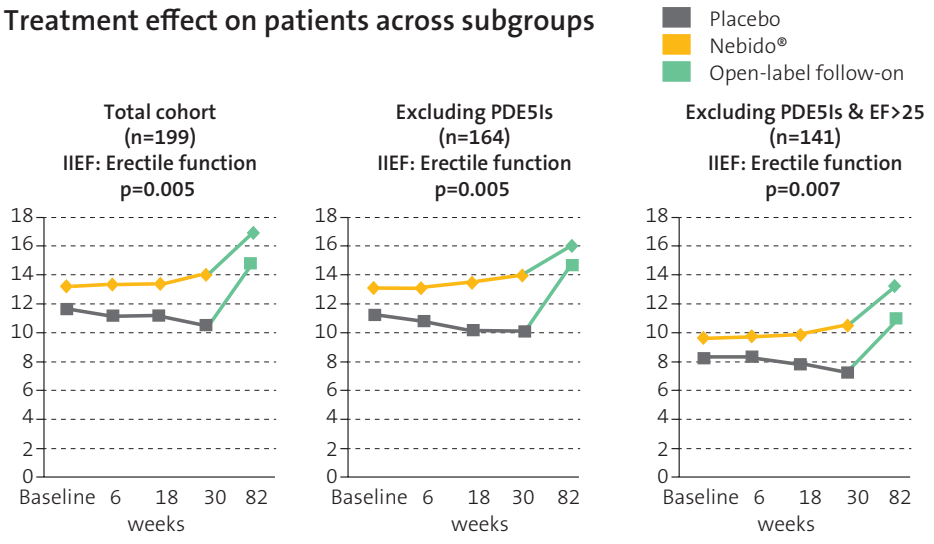


Figure 25: Treatment effect in BLAST, including the open-label phase [71]

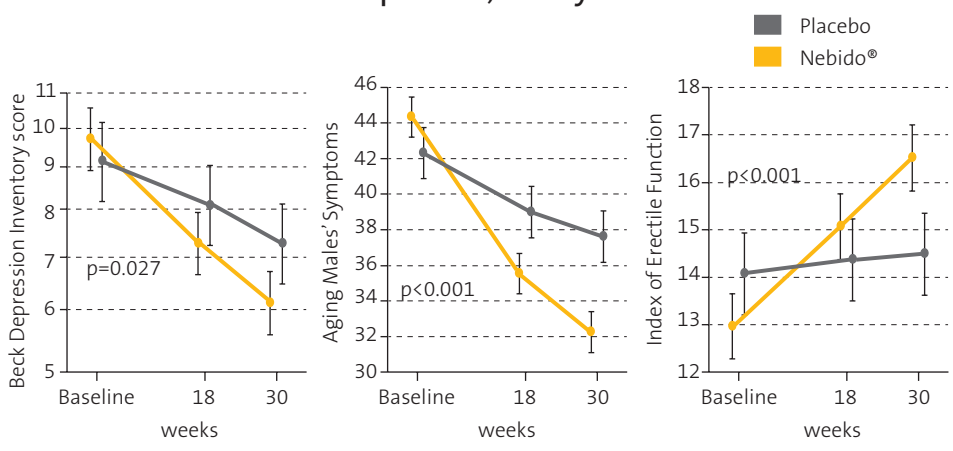


In a prospective study of 88 patients with erectile dysfunction due to late-onset hypogonadism, Nebido® was shown to improve the objective and subjective parameters of andrological health. At the end of the 12-month treatment period, significant increases were observed in both the frequency (mean increase 1.27 times) and duration (mean increase 5.12 min) of nocturnal penile tumescence ($p<0.0001$ for all measurements). In addition, blood flow through the cavernous arteries was altered, with a significant increase in peak systolic velocity and a significant decrease in end diastolic velocity detected after 12 months of treatment. Furthermore, significant improvements in IIEF scores were recorded at 6 and 12 months ($p<0.0001$).[103]

In a randomized, double-blind, placebo-controlled Phase III trial in 184 men with hypogonadism and metabolic syndrome, treatment with Nebido® produced significant improvements in depression, AMS, and IIEF-5 scores compared with placebo at 30 weeks (Figure 26).[104] The greatest effects on mood and sexual function were observed in men with the lowest baseline testosterone levels.

Additional results from the BLAST study, investigating treatment with Nebido® in men with T2DM and mild or severe hypogonadism, showed that men with severe hypogonadism (total testosterone ≤8.0 nmol/L or free testosterone ≤0.18 nmol/L) reported an improvement in erectile function from baseline and versus placebo after 30 weeks' treatment, according to IIEF-15 scores. Intercourse satisfaction and sexual desire scores also improved at 6, 18 and 30 weeks versus baseline and placebo in these men after Nebido® treatment.[105]

Figure 26: Changes over time in mean scores of the amended version of the Beck Depression Inventory (BDI-IA; on a logarithmic scale), Aging Males' Symptoms (AMS) scale, and International Index of Erectile Function (IIEF).[101]



P values by multilevel regression analysis (i.e. mixed models) for the time * group effect. Error bars represent 95% confidence intervals.

Another analysis of 857 men with T2DM who were initially screened as part of the BLAST study showed that low testosterone levels (total testosterone ≤12.0 nmol/L or free testosterone ≤0.25 nmol/L) was associated with increased mortality, and that men with normal testosterone levels or men with low testosterone levels who received testosterone replacement therapy had significantly ($p<0.05$) reduced mortality; this association was independent of PDE-5 inhibitor therapy.[106]

A prospective 30-week study examined the effect of four doses of Nebido® in combination with the PDE-5 inhibitor vardenafil in 30 patients with late-onset hypogonadism and erectile dysfunction. Treatment with Nebido® and where desired, vardenafil, was associated with significant increases in IIEF-5 at week 30 and 46 and significant reduction in AMS score at weeks 12, 30 and 46.[107]

Nebido® was effective in improving the symptoms of testosterone deficiency in a randomized placebo-controlled study conducted in 82 obese patients with low levels of testosterone (≤12nmol/L) and receiving a very low-energy diet for 10 weeks followed by weight maintenance for 46 weeks. Patients with more severe symptoms at baseline experienced greater improvements at the end of the study. After 56 weeks of treatment mean adjusted unit difference in AMS score was –0.34 ($p=0.04$). In patients with erectile dysfunction at baseline, Nebido® was associated with a significant improvement in the IIEF score compared with placebo ($p=0.025$).[108]

Nebido® produced greater improvements in metabolic parameters and AMS and IIEF scores than those achieved during 9 months of initial treatment with testosterone gel in elderly hypogonadal men with metabolic syndrome and sexual dysfunction.[109,110] Testosterone levels significantly increased from baseline after 9 months of testosterone gel treatment, but a further increase was observed after 3 months of treatment with Nebido® ($p<0.05$). This suggests a dose-response relationship between achieved testosterone levels and sexual function and metabolic parameters.

Up to 5 years' treatment with Nebido® has been shown to improve measures of health quality in 261 men with late-onset hypogonadism.[111] A mean 4.25 years of treatment resulted in significant ($p<0.05$) reductions in IPSS scores from baseline to 3 months, and further reductions were seen up to 63 months of follow-up. Similar improvements were seen in AMS and IIEF-5 scales in these men.

A randomized, double-blind, placebo-controlled study of 67 obese men with sleep apnoea who received testosterone replacement therapy for 12 weeks showed that those treated with testosterone had an increase in sexual desire versus placebo recipients.[112] Other sexual function outcomes were not different between groups, and testosterone therapy did not affect quality of life, measures of sleepiness, weight loss or neurocognitive function in these patients.

While Nebido® has been shown to improve sexual function in hypogonadal men,[102] it has also demonstrated activity in men who do not respond to PDE-5 inhibitor treatment. Among 29 hypogonadal men with metabolic syndrome and erectile dysfunction that did not respond to prior PDE-5 inhibitors, Nebido® improved erectile dysfunction and sexual desire.[113] Use of Nebido® in combination with a PDE-5 inhibitor also appears to be feasible.[21, 114] Although 58.2% of patients with erectile dysfunction responded to Nebido® alone in a prospective, observational, longitudinal study, 51 patients did not respond to this treatment. Of these, 34 agreed to treatment with vardenafil 20 mg on an as-needed basis. Thirty of these patients responded well to combination therapy, with significant improvements in IIEF Sexual Health Inventory for Men and partner scores.[21] A randomized study found that among 60 patients taking Nebido®, combination with once-daily tadalafil 5 mg was more effective than tadalafil on an as-needed basis in improving IIEF scores and Global Assessment Question assessments of erectile function.[114]

There is some evidence to suggest that Nebido® improves erectile function in men with venous leakage.[115–117] A study in hypogonadal patients with venous leakage and erectile dysfunction who did not respond to PDE-5 therapy showed that treatment with Nebido® improved IIEF-5 scores at 18 and 30 weeks in the majority of patients (20/29). Reductions in venous leakage were also observed. The improvements in erectile function may have been due to remodelling of erectile tissue.[117]

Nebido® has been shown to improve overall health-related quality of life (HRQoL) in men with hypogonadism. Assessment of HRQoL using the AMS scale in a placebo-controlled study in 120 men showed significant improvements in total score and psychological and somatovegetative domain scores, and a non-significant improvement in sexual domain scores in Nebido® versus placebo recipients at week 48.[118] The Short Form-12 (SF-12) showed a significant improvement in mental health but not physical health composite scores with Nebido® versus placebo after adjustment for baseline differences.[119]

In contrast, a study conducted over the period of 2 years in young and middle-aged patients with hypogonadism (mean age 30.5 years) showed no improvement in quality of life (measured by World Health Organization's Brief Quality of Life Questionnaire) or emotional state (Profile of Mood States scale). It did, however, demonstrate that treatment with Nebido® resulted in significant improvements in executive function and psychomotor speed (Trail Making Test B, p=0.025) and attention capacity and psychomotor speed (Wechsler Adult Intelligence Scale, p=0.046), as well as marginally significant improvements in attention and visual scanning abilities (Trail Making Test A, p=0.050).[120]

8.1.5 Lower Urinary Tract Symptoms (LUTS)

Treatment with Nebido® has been shown to improve LUTS in older hypogonadal men.[121–123]

Treatment with Nebido® significantly improved total IPSS score and storage and voiding symptom scores at 1 year in 17 patients with LUTS who were not receiving treatments for benign prostate hyperplasia.[122] In patients receiving Nebido® (in addition to medications for benign prostate hyperplasia) clinical benefit was observed with respect to AMS score and BMI, but there were no significant changes in IPSS or uroflowmetry parameters. No significant changes in PSA were observed in either cohort.

A 5-year single-centre, prospective, observational, longitudinal registry study (n=261) found that long-term treatment with Nebido® significantly improved LUTS as well as metabolic parameters.[123] A significant reduction in IPSS was observed after initiation of treatment ($p<0.05$), independent of weight loss or use of vardenafil. These results were independent of the baseline age of the patients.[92]

8.2 Safety

In Clinical Studies:

Nebido® proved to be very well tolerated.

The use of Nebido® did not lead to clinically significant modifications in the clinico-chemical parameters studied, except for a beneficial change in the lipid profile, and the slight increase in haemoglobin and haematocrit.

Patient compliance was considered to be very good.

Results from long-term clinical studies show that, in general, side effects were rare during treatment with Nebido®[46,62,124,125]. Side effects such as diarrhoea, joint pain, sweating, headache, acne, chest pain and gynaecomastia are known, although rare, general side effects of testosterone. In the studies with Nebido® particular attention was paid to local tolerability (at the injection site), to possible effects on the urogenital system, and to special test parameters.

Since these studies were reported, the tolerability of Nebido® has been established further in clinical studies, including those in special patient populations such as men with T2DM, metabolic syndrome, and/or obesity. Nebido® was generally well tolerated in these populations.

8.2.1 Local Tolerability

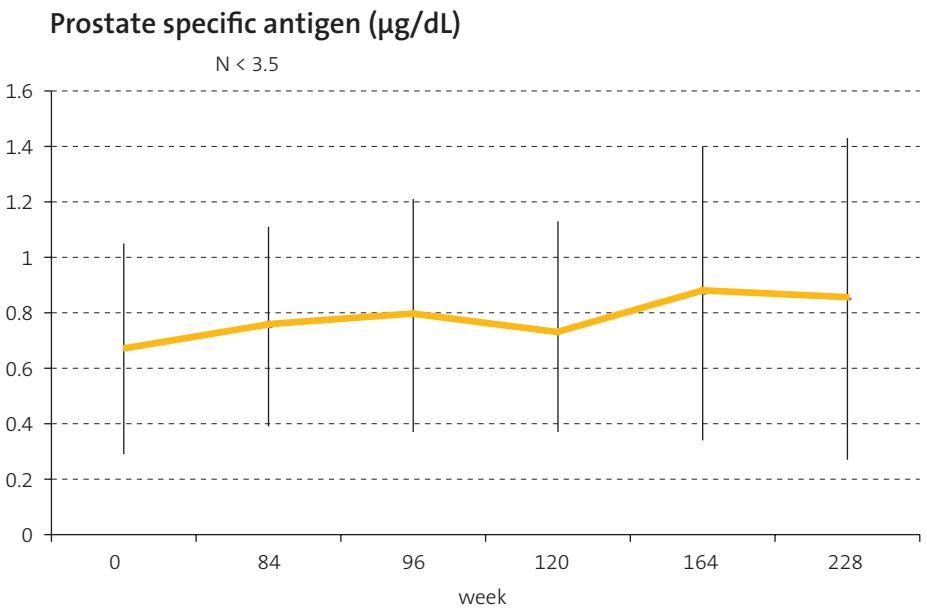
The most frequently reported side effect of treatment with Nebido® was pain at the injection site. A prospective study examining injection-site pain in men receiving Nebido® found gluteal injection to be well tolerated.[126] Although 80% of the 125 patients reported pain during injection, pain peaked immediately post-injection and was of only moderate severity. Pain persisted for only 1–2 days, with complete resolution by day 4, and few patients required analgesics. Patients who had experienced an earlier painful injection reported increased injection site pain, whereas older and obese patients reported less pain.

In summary, data on local tolerability following i.m. injection of Nebido® indicate that it is well tolerated.

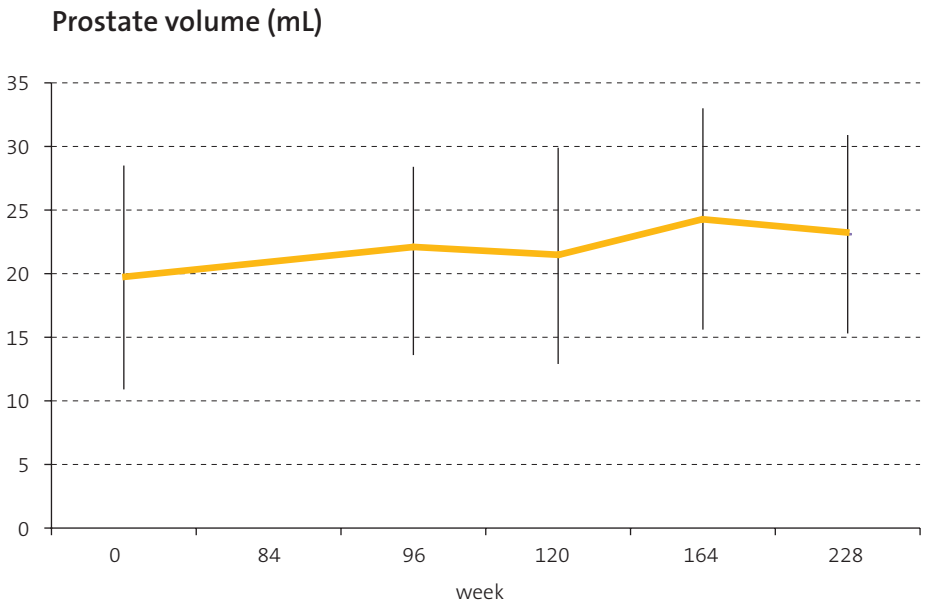
8.2.2 Prostate

Treatment with Nebido® is not associated with adverse events related to the prostate.[62] No clinically significant pathological findings of the prostate were observed during treatment with Nebido®. Prostate volume increased slightly but remained within normal limits (Figure 27).

Figure 27: Changes in prostate specific antigen levels and prostate volume during long-term treatment with Nebido®.[63]



Change from 0.67±0.38µg/dL to 0.75±0.35µg/dL (p<0.05)



Change from 19.7±8.8 mL to 22.0±8.4 mL (p<0.05)

Overall, the data were not suggestive of any relevant effect of Nebido® on the prostate or on serum PSA levels. The few abnormal findings of clinical significance were not attributable to the treatment with Nebido®. Subsequent studies have also suggested a lack of adverse effects on PSA levels, and data from long-term registry studies of patients receiving Nebido® (n=1,023) with follow-up durations of up to 17 years have not shown an increased risk of prostate cancer compared with long-term screening studies.[127] In 25 men with hypogonadism who received 1 year of Nebido® and underwent prostate biopsy before and after treatment, there was no difference in serum total and free PSA levels (p>0.1), IPSS scores (p=0.061) or prostate volume (p=0.150).[128] In a prospective study of 88 hypogonadal patients, treatment with Nebido® resulted in a significant increase in PSA after 12 months, however rectal examinations revealed no abnormal findings.[96] In a retrospective study of men treated with Nebido® for ≥2 years in clinical practice, significant increases in PSA (increase of >1.4 µg/L or PSA >4 µg/mL) occurred in 20 of 162 patients at any time point.[129] Elevations of PSA were transient for 11 of these patients and there were no cases of prostate cancer.

Although Nebido® is currently contraindicated in patients with prostate cancer, recent guidelines for the management of hypogonadism suggest that testosterone replacement therapy can be used with caution in selected patients who have undergone surgical treatment of prostate cancer at least 1 year earlier when there is no evidence of active disease.[5, 127] A study in patients receiving brachytherapy for prostate cancer (n=20) showed no significant increase in PSA level or progression or recurrence of prostate cancer during treatment with Nebido® for a median of 31 months.[130] It should be noted that this was a small study with a relatively short follow-up duration so results cannot be considered definitive.

8.2.3 Erythropoiesis

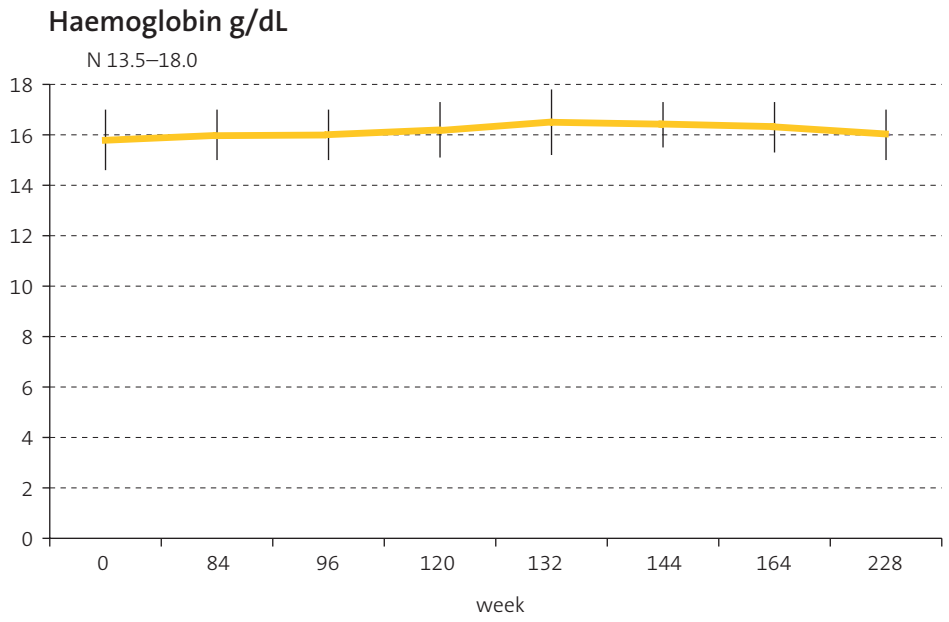
Treatment with Nebido® led to an increase in haematocrit and haemoglobin within the normal range in the first 30 weeks of treatment, but remained stable thereafter without any values above the upper limit of normal (Figure 28).[62, 63]

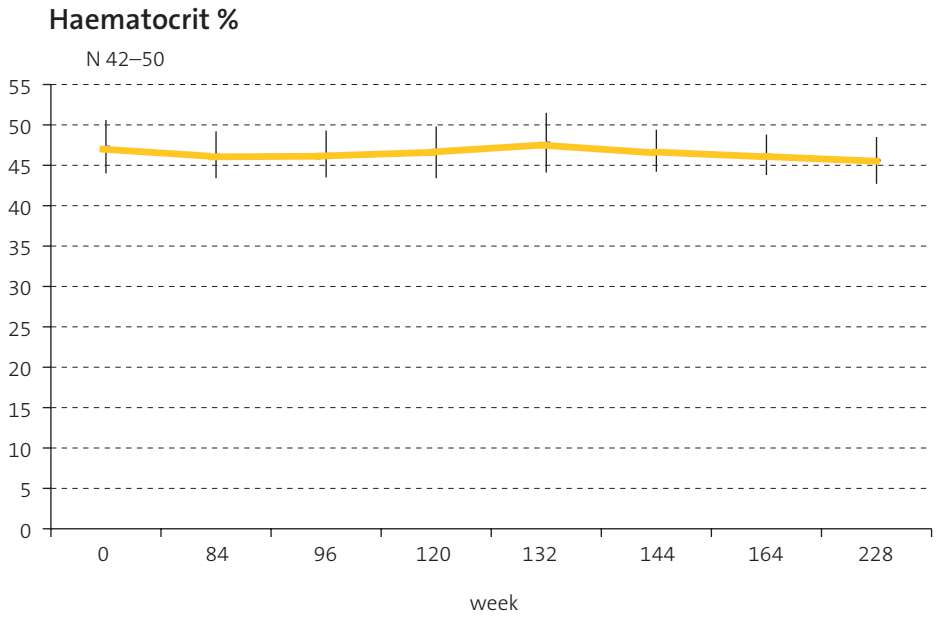
Similar effects on haemoglobin and haematocrit were seen in a retrospective study of 179 men with primary or secondary hypogonadism treated with Nebido® in the clinical practice setting, 162 of whom completed ≥2 years of treatment.[129] Significant increases from baseline were seen for both haemoglobin and haematocrit (p<0.001); however, both remained within the normal range. These increases were considerably smaller for patients previously treated with a different testosterone product than testosterone-naïve patients, but were comparable for these cohorts at 1 year.

In a prospective observational study of 347 patients who received a total of 3,022 injections over a 3.5 year period, mean haematocrit was 0.44 ± 0.04 (standard deviation). A total of 25 (7%) patients had levels >0.50, 14 (4%) >0.52 and 3 (1%) >0.54.[131]

The event rate for haematocrit elevations above the normal physiological range was only 0.02% in a meta-analysis of 33 studies, including 11 placebo-controlled trials, in which 3,359 patients were treated with injectable TU.[57]

Figure 28: Haematocrit and haemoglobin changes during long-term treatment with Nebido®.[63]





8.2.4 Lipid Profile and Hepatic Function

The observed changes in the lipid profile under treatment with Nebido® are considered beneficial. Serum concentrations of total cholesterol, LDL cholesterol and triglycerides were significantly reduced and HDL significantly increased in a registry study of 255 men who received Nebido® for up to 60 months (Figure 29).[84]

Nebido® was associated with a significant reduction in total cholesterol from baseline at 12 and 24 months ($p<0.01$ and $p<0.05$, respectively) in a clinical practice setting. This retrospective study involved 179 men, 162 of whom completed ≥2 years of treatment.[129] However, the change in total cholesterol from 12 to 24 months was not significant, nor were there any significant changes from baseline in triglycerides or LDL- or HDL-cholesterol levels. In a meta-analysis of 33 studies, including 11 placebo-controlled trials, serum lipid profile improved in patients treated with injectable TU.[57] However, no significant change was seen when only the placebo-controlled trials were analysed.

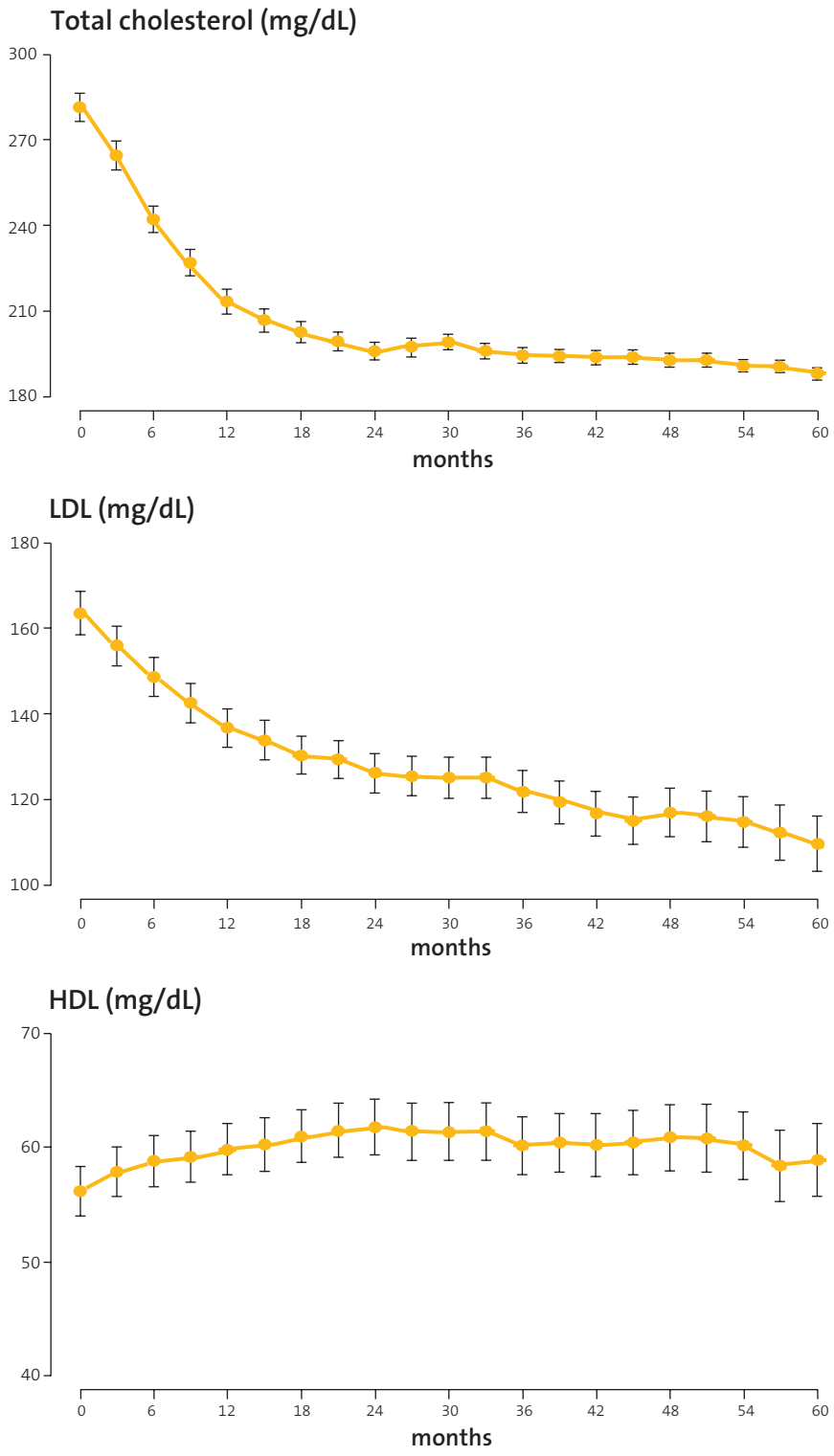
A study conducted in 88 men with late-onset hypogonadism reported corrections in the lipid profile after treatment with Nebido®. Significant reductions in total cholesterol ($p<0.0001$) and triglycerides ($p=0.016$) and increase in HDL-cholesterol ($p<0.0002$) were observed at 12 months. No significant changes in liver enzymes (serum AST and serum ALT) were detected.[96]

Treatment with Nebido® over 8 years was associated with significant reductions in lipid parameters in a long-term prospective observational study of 656 patients with testosterone deficiency and symptoms of hypogonadism. Compared with no treatment, Nebido® was associated with significant and progressive reductions in total cholesterol, LDL and triglycerides ($p<0.0001$ for all measurements). While the total cholesterol/HDL ratio decreased in both groups, statistical significance was reached only in patients treated with Nebido®. Moreover, significant reductions in the levels of liver AST and ALT were observed in patients that received treatment compared with controls, indicating a reduction in the liver fat content and inflammatory processes.[97]

In a matched-control study of 20 obese hypogonadal men with metabolic syndrome and 20 matched controls (for whom Nebido® was unaccepted or contraindicated), eligible patients received Nebido® every 12 weeks for 60 months. After 24 months, total cholesterol and LDL were significantly reduced ($p=0.0001$) and HDL was significantly increased ($p=0.0001$) compared with the matched controls;[93] at 60 months, significant reductions in triglycerides and the ratio of total:HDL cholesterol were observed.[50]

In a registry study of 255 men with subnormal plasma total testosterone levels who received Nebido® for up to 5 years, a number of significant improvements were observed in lipids and hepatic parameters. Levels of total serum cholesterol, LDL and triglycerides declined significantly ($p<0.0001$), while HDL levels increased.[82] Additionally, AST and ALT levels significantly decreased ($p<0.0001$), suggesting that liver function is improved with Nebido®.[84] In a 4-year study and an 18-week randomized, placebo-controlled trial, hepatic function remained stable during treatment although in the latter, a reduction in liver fat content was assessed by diagnostic imaging.[63, 132]

Figure 29: Changes in total cholesterol, LDL and HDL cholesterol levels during long-term treatment with Nebido®.[84]



8.2.5 Sleep Apnoea

It is possible that testosterone replacement therapy may potentiate sleep apnoea. Studies have shown mild worsening of sleep-disordered breathing in obese men with sleep apnoea treated with Nebido®.[133, 134] However, these effects were time-limited and, although statistically significant after 7 weeks of treatment, were not significantly different from placebo at 18 weeks.

8.2.6 Allergic Reactions

A case of anaphylaxis has been reported in a patient treated with Nebido®.[135] However, skin testing identified the benzyl benzoate component of the vehicle, rather than TU or castor oil, to be the trigger for the reaction. Nonetheless, physicians administering Nebido® should be aware of the potential for serious allergic reactions to its components.

8.3 Studies of Nebido® in Other Indications

Note: Nebido® has not been approved for use in the following indications.

8.3.1 Female-to-Male Transsexuals

Continuous androgen therapy is required to induce and maintain virilization in female-to-male transsexuals ("trans-men") before and after sex reassignment surgery, and to prevent adverse effects associated with sex hormone deficiency, such as osteoporosis, following ovariectomy.[136, 137] Nebido® has been evaluated in this setting in several small clinical studies of ≥1 year in duration. These studies used the same dosing protocol as for hypogonadal men.

Treatment with Nebido® produced durable increases in serum testosterone to eugonadal levels for men within 18 weeks.[136, 137] Increases in libido and deepening of the voice occurred,[138, 139] and patients experienced amenorrhea.[138, 140] and increased clitoral growth.[138, 141] Lean mass increased and fat mass decreased within 1 year,[140] and patients were satisfied with their virilization in these studies.[136, 137, 140] Testosterone therapy increases facial and body hair and produced androgenic alopecia in some patients.[138, 139, 142] Nebido® was well tolerated, with minimal or no adverse events observed in studies in trans-men.[136, 137] A possible effect of testosterone therapy is acne, although this appears to peak at 6 months and most patients have mild or no lesions with long-term use.[142]

8.3.2 Induction of Puberty

Treatment with Nebido® was effective in inducing puberty in two small studies in apubertal males aged ≥17 years.[143, 144] Serum testosterone levels increased, and development of secondary sexual characteristics was observed. Nebido® was well tolerated and the only adverse event reported was a rapid-onset male pattern baldness (occurring in one of seven patients in one study).

8.3.3 Patients with Cardiovascular Disease

Studies in older men with chronic heart failure (CHF), cardiovascular disease (CVD), or chronic, stable angina pectoris suggest that treatment with Nebido® may have beneficial effects.[145–149]

Men with hypogonadism and a previous history of CVD (n=77; mean age 61 years) receiving Nebido® for up to 8 years had significant ($p<0.05$) weight loss and decreases in waist circumference, as well as a significant improvement in lipid profile and reductions in blood pressure ($p<0.0001$). Glucose parameters and markers of inflammation were also improved from baseline ($p<0.0001$), and there were no adverse cardiovascular events reported; taken together, these results suggest that long-term Nebido® therapy can have benefits in improving cardiometabolic risk factors, and may also be effective as an add-on therapy to reduce cardiovascular events.[149]

In elderly men (median age 70 years) with CHF, Nebido® significantly improved exercise capacity, muscle strength, baroreflex sensitivity and glucose metabolism at 3 months, and increased BMI, in a study in 70 male patients (all $p<0.05$).[146] In another study, treatment with Nebido® for 24 weeks significantly reduced insulin, HOMA-IR, and aldosterone levels in men with hypogonadism, metabolic syndrome, and CHF (all $p<0.0007$).[147] However, Nebido® had no significant effect on BMI, waist circumference, serum lipids, or glucose levels. This study included 26 men who consented to testosterone treatment. A longer duration of treatment may be required to show benefit.

In 39 men with hypogonadism and CHF, 4 months of testosterone replacement plus exercise training increased muscle sympathetic nerve activity, and improved muscle wasting and functional capacity.[150]

Treatment with Nebido® demonstrated short-term protective effects in exercise-induced ischemia in a placebo-controlled study in 13 men with stable chronic angina.[148]
Compared with placebo, Nebido® increased time to ischemia (12±18 vs. 129±48 seconds; $p=0.02$) and haemoglobin levels (–0.03±0.5 vs. 0.4±0.6 g/dL; $p=0.04$), and reduced BMI (1.3±1.0 vs. –0.3 kg/m^2 ; $p=0.04$) and triglyceride levels (0.3±1.2 vs. –0.36±0.4 mmol/L, $p=0.05$).

8.3.4 Patients with Crohn's Disease

A pilot study (n=13) in men with hypogonadism who had Crohn's disease found that normalization of testosterone levels improved Crohn's disease activity index (CDAI) scores and CRP levels.[151] Patients with Crohn's disease were compared with 110 similar-aged men with sexual/urological problems who also had subnormal testosterone levels. All received Nebido® for 24 months. Men with Crohn's disease had higher CRP levels than controls at baseline (22.7 vs. 3.5 mg/dL, p=0.001). After testosterone levels normalized, CRP in Crohn's disease patients decreased to 6.9 mg/dL and CDAI decreased from 243 at baseline to 89. The white blood cell count decreased, while haemoglobin and haematocrit increased. The mechanism by which testosterone therapy improves Crohn's disease symptoms could be via immunosuppressive effects and consequent reduction of chronic inflammation in the intestinal wall.

The results of this pilot study were confirmed in the long-term follow-up of the same group. The number of hypogonadal patients with Crohn's disease had increased to 92 men, with 14 hypogonadal men with Crohn's disease who had opted against testosterone treatment serving as a control group. After a maximum observation time of 7 years, the CDAI had dropped from 239 at baseline to 72, while CRP decreased from 12.9 to 1.8 ($p<0.0001$ for both). There were no changes in the control group.[152]

8.3.5 Patients with Other Autoimmune Diseases

Studies have shown that approximately 10% of men with type 1 diabetes mellitus (T1DM) can be hypogonadal, typically those who are older or obese. In a group of nine men with T1DM, hypogonadism and erectile dysfunction, long-term (≥6 years) treatment with Nebido® improved erectile function as well as glycaemic and cardiovascular risk profiles, with serum glucose, HbA_{1c}, weight, waist circumference, and lipid profiles all improving over the observational period.[153] In contrast, a randomized controlled study conducted in 13 patients with T1DM and hypogonadism reported improvements in lipid profile (decrease in total cholesterol, $p<0.005$, and LDL-cholesterol, $p=0.004$), but no effect on insulin sensitivity, HbA_{1c}, basal glucose, anthropometric parameters or BP in patients treated with Nebido® over the course of 22 weeks compared with those who received placebo.[154]

A study of 15 hypogonadal men with psoriasis treated with Nebido® showed similar improvements in disease-related symptoms over time.[155] During the first 24 months of therapy, there were significant improvements in the scores for Psoriasis Area and Severity Index and Physician Global Assessment for Psoriasis, which were subsequently sustained. Treatment with Nebido® also reduced CRP levels, obesity, and lipid profiles in these men.

9 Conclusion

Nebido® represents an innovative formulation for testosterone therapy.

Nebido® is the first long-acting testosterone preparation for intramuscular injection.

Nebido® needs to be administered only about 4 times per year for restoration of testosterone levels to the eugonadal range.

Unphysiologically high peaks in testosterone levels are largely avoided after the administration of Nebido®.

Use of Nebido® is discreet and guarantees excellent patient compliance.

Nebido® is effective in the treatment of male hypogonadism:

- improvement in libido and sexual function
- improvement in haematological parameters
- improvement in body composition
- increased muscle strength
- a positive effect on mind and mood
- improved metabolic parameters

Nebido® proved to be very well tolerated. Reactions at the injection site and other side effects specific to testosterone occurred only in individual cases.

Changes of prostate size, of serum PSA levels and of haematological parameters were without clinical significance and remained within normal ranges.

As with any androgen therapy, the use of Nebido® is contraindicated in known cases of carcinoma of the mammary or prostate glands. The prostate and haematological parameters must be regularly monitored during the treatment.[4,42]

10 Glossary

ALT	Alanine aminotransferase
AMS	Aging Male Symptoms
AST	Aspartate aminotransferase
BMI	Body mass index
BMD	Bone mineral density
BP	Blood pressure
CDAI	Crohn's disease activity index
CHF	Chronic heart failure
CRP	C-reactive protein
CYP	Cytochrome P450
DHT	Dihydrotestosterone
EAU	European Association of Urology
FSH	Follicle-stimulating hormone
GnRH	Gonadotrophin-releasing hormone
HbA_{1c}	Glycated haemoglobin
HDL	High-density lipoprotein
HOMA-IR	Homeostasis Model Assessment index of Insulin Resistance
HRQoL	Health-related quality of life
i.m.	Intramuscular
IIEF-5	International Index of Erectile Function 5-item
ISA	International Society of Andrology
ISSAM	International Society of the Study of the Aging Male
IPSS	International Prostate Symptom Scores
LDL	Low-density lipoprotein
LH	Luteinizing hormone
LOH	Late-onset hypogonadism
LUTS	Lower urinary tract symptoms
NCEP	National Cholesterol Education Program
PDE	Phosphodiesterase
PSA	Prostate-specific antigen
SAQ	Sexual Activity Questionnaire
SD	Standard deviation
SF-12	Short Form-12
SHBG	Sex hormone binding globulin
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TE	Testosterone enanthate
TU	Testosterone undecanoate (3-oxoandrost-4-en-17β-yl-undecanoate)

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12 Nebido® – Summary of Product Characteristics

1. Name of the medicinal product

Nebido® 1000 mg/4 mL 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.

For a 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 of confirmed 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 evaluated clinically 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 special precautions for use

Nebido® is not recommended for use in children and adolescents.

Nebido® is not indicated for use in women.

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.

The following laboratory parameters should be checked periodically: testosterone, haemoglobin, haematocrit, and liver function tests.

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. Regular monitoring of serum calcium concentrations is recommended in these patients.

Benign and malignant liver tumours have been reported in patients receiving testosterone replacement therapy.

In patients suffering from severe cardiac, hepatic or renal insufficiency or ischaemic 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.

The limitations of using intramuscular injections in patients with acquired or inherited blood clotting irregularities always have to be observed.

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

Athletes should be advised that Nebido® 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.

As with all oily solutions, Nebido® must be injected strictly intramuscularly and very slowly (over two minutes). 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.

Medical examination

Prior to testosterone initiation, all patients must undergo a detailed examination in order to exclude a risk of pre-existing prostatic cancer. Careful and regular monitoring of the prostate gland and breast must be performed in 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.

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 (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.

Other conditions

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. 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.

Caution should be exercised in patients predisposed to oedema, as treatment with androgens may result in increased sodium retention (see section 4.8).

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

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.

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.

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 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 lactation

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

Regarding undesirable effects associated with the use of androgens, please also refer to section 4.4.

Most frequent undesirable effects: acne and injection site pain.

Suspected anaphylactic reactions after Nebido injection have been reported.

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

Other common adverse drug reactions (ADRs): polycythaemia, weight increased, hot flush, prostate specific antigen increased, prostate examination abnormal, benign prostate hyperplasia, injection site reactions (injection discomfort, pruritus, erythema, haematoma, irritation and reaction).

Uncommon ADRs: Haematocrit increased, red blood cell count increased, haemoglobin increased, hypersensitivity, increased appetite, glycosylated haemoglobin increased, hypercholesterolaemia, blood triglycerides increased, blood cholesterol increased, depression, emotional disorder, insomnia, restlessness, aggression, irritability, headache, migraine, tremor, cardiovascular disorder, hypertension, dizziness, bronchitis, sinusitis, cough, dyspnoea, snoring, dysphonia, diarrhoea, nausea, liver function test abnormal, aspartate aminotransferase increased, alopecia, erythema, rash, pruritus, dry skin, arthralgia, pain in extremity, muscle disorders, musculoskeletal stiffness, blood creatine phosphokinase increased, urine flow decreased, urinary retention, urinary tract disorder, nocturia, dysuria, prostatic intraepithelial neoplasia, prostate induration, prostatitis, prostatic disorder, libido changes, testicular pain, breast induration, breast pain, gynaecomastia , oestradiol increased, testosterone increased, fatigue, asthenia, hyperhidrosis. Pulmonary oil microembolism is listed as a rare ADR.

Other known ADRs of testosterone containing preparations: nervousness, hostility, sleep apnoea, various skin reactions including seborrhoea, increased hair growth, increased frequency of erections, rare cases of persistent, painful erections (priapism), in very rare cases jaundice.

Therapy with high doses of testosterone commonly reversibly interrupts or reduces spermatogenesis, thereby reducing the size of the testicles. 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.

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: G03B A03

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

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

Testosterone is responsible for the expression of masculine characteristics during foetal, early childhood, and pubertal development and thereafter for maintaining the masculine phenotype and androgen-dependent functions (e.g. spermatogenesis, accessory sexual glands). 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.

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)
Blood and lymphatic system disorders	Polycythemia	Haematocrit increased Red blood cell count increased Haemoglobin increased
Immune system disorders		Hypersensitivity
Metabolism and nutrition disorders	Weight increased	Increased appetite Glycosylated haemoglobin increased Hypercholesterolemia 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
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]

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

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 β-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 radiolabelled 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

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.

7. Marketing authorization holder

[To be completed nationally]

8. Marketing authorization number(s)

[To be completed nationally]

9. Date of first authorization/renewal of the authorization

Date of first authorisation: 07 July 2004

Date of latest renewal: 25 November 2008

10. Date of revision of the text

[To be completed nationally]

Notes:

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Bayer

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