Bayer (Pty) Ltd	**Date of revision of text: 02 August 2022**

PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

NEBIDO
1000 mg / 4 ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule/vial contains 1000 mg testosterone undecanoate in a 4 ml solution for injection (250 mg testosterone undecanoate/ml).
Sugar free
For the full excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear colourless to yellowish-brown oily solution

4. CLINICAL PARTICUARS

4.1 Therapeutic indications

Testosterone replacement in primary and secondary male hypogonadism.

4.2 Posology and method of administration

Posology

NEBIDO (1 ampoule/vial corresponding to 1000 mg testosterone undecanoate) is injected every 10 to 14 weeks. Injections with this frequency are capable of maintaining sufficient testosterone levels and do not lead to accumulation.

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

Individualisation of treatment
It is advisable to occasionally measure testosterone serum levels at the end of an injection interval. Serum levels below normal range would indicate the need for a shorter injection interval. In the case of high serum levels, an extension of the injection interval may be considered. The injection interval should remain within the recommended range of 10 to 14 weeks.

Special populations

Paediatric population
NEBIDO is not indicated for use in children and adolescents, and it has not been clinically evaluated in males under 18 years of age (see section 4.4).

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

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

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

Method of administration

For intramuscular (IM) use.
The injections must be administered very slowly (over 2 minutes). NEBIDO is strictly for intramuscular injection. Special care must be given to avoid intravasal injection. See section 6.6 to avoid injury when opening. The contents of an ampoule / vial are to be injected intramuscularly immediately after opening.

4.3 Contraindications

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

The use of NEBIDO in women is contraindicated.

4.4 Special warnings and precautions for use

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

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

Haemoglobin and haematocrit should be checked periodically in patients on long-term NEBIDO therapy to detect cases of polycythaemia (see section 4.8).

As a general rule, the risk of bleeding from using intramuscular injections in patients with acquired or inherited bleeding disorders always has to be taken into account. Testosterone and derivatives have been reported to increase the activity of coumarin derived oral anticoagulants (see also section 4.5).

Testosterone as contained in NEBIDO should be used with caution in patients with thrombophilia, or risk

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

Cases of benign and malignant liver tumours have been reported in users of androgen hormonal substances, such as NEBIDO. 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.

Caution should be exercised in patients predisposed to oedema, e.g., in case of severe cardiac, hepatic, or renal insufficiency or ischaemic heart disease, as treatment with NEBIDO may result in increased retention of sodium and water. In case of severe complications characterised by oedema with or without congestive heart failure, treatment must be stopped immediately (see section 4.8).

Testosterone may cause a rise in blood pressure and NEBIDO should be used with caution in men with hypertension.
Clinical trials with NEBIDO in children or adolescents under the age of 18 have not been conducted so far.

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

Pre-existing sleep apnoea may be potentiated.

Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication(s) and in combination with other anabolic androgenic steroids.

Testosterone abuse may result in dependence and withdrawal symptoms upon significant dose reduction or abrupt discontinuation of use.
Abuse of testosterone along with other anabolic androgenic steroids can lead to serious adverse reactions including cardiovascular (with fatal outcomes in some cases), hepatic and/or psychiatric events

NEBIDO must be injected strictly intramuscularly. Pulmonary microembolism of oily solutions can lead to signs and symptoms such as cough, dyspnoea, malaise, hyperhidrosis, chest pain, dizziness, paraesthesia, or syncope. These reactions may occur during or immediately after the injection and are reversible. Treatment is usually supportive, e.g. by administration of supplemental oxygen.
Suspected anaphylactic reactions after NEBIDO injection have been reported.

4.5 Interaction with other medicines and other forms of interaction

Medicines that affect testosterone

Barbiturates and other enzyme inducers
Interactions can occur with medicines that induce microsomal enzymes, which can result in increased clearance of NEBIDO.

Effects of NEBIDO on other medicinal products

Oxyphenbutazone
Increased oxyphenbutazone serum levels have been reported.

Oral anticoagulants
Testosterone and its derivates, such as NEBIDO have been reported to increase the activity of coumarin derived oral anticoagulants, possibly requiring dose adjustment. Independent of this finding, the risk of bleeding from using intramuscular injections in patients with acquired or inherited bleeding disorders always has to be taken into account as a general rule.

Hypoglycaemics
NEBIDO may enhance the blood-sugar reducing effects of insulin. Therefore, the dosage of the hypoglycaemic agent may need to be lowered.

4.6 Fertility, pregnancy and lactation

Pregnancy and lactation
Not applicable.

Fertility
NEBIDO may reversibly reduce spermatogenesis (see section 4.8).

4.7 Effects on ability to drive and use machines

Dizziness has been reported as uncommon side effect (see section 4.8). Patients experiencing dizziness should avoid driving and use of machines.

4.8 Undesirable effects

Regarding side effects associated with the use of NEBIDO, please also refer to section 4.4.
The most frequent side effects under treatment with NEBIDO are acne and injection site pain.

Table 1 below reports adverse drug reactions (ADRs) [by MedDRA system organ classes*] reported with NEBIDO. The frequencies are based on clinical trial data and defined as Common (≥1/100 to <1/10) and Uncommon (≥1/1000 to <1/100). The ADRs were recorded in 6 clinical studies (N=422) and considered at least possibly causally related to NEBIDO.

System Organ Class	**Common**	**Uncommon**
Blood and lymphatic system disorders	Polycythaemia	Increased haematocrit Increased red blood cell count Increased haemoglobin
Immune system disorders		Hypersensitivity
Metabolism and nutrition disorders	Increased weight	Increased appetite Increased glycosylated haemoglobin Hypercholesterolaemia

System Organ Class	**Common**	**Uncommon**
		Increased blood triglycerides
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		Abnormal liver function test Increased aspartate aminotransferase
Skin and subcutaneous tissue disorders	Acne	Alopecia Erythema Rash Papular rash Pruritus Dry skin
Musculoskeletal and connective tissue disorders		Arthralgia Pain in extremity Muscle spasm Muscle strain Myalgia Musculoskeletal stiffness Increased blood creatinine phosphokinase
Renal and urinary disorders		Decreased urine flow Urinary retention Urinary tract disorder Nocturia Dysuria
Reproductive system and breast disorders	Increased Prostate specific antigen	Prostatic intraepithelial neoplasia Prostate induration

System Organ Class	**Common**	**Uncommon**
	Abnormal Prostate examination Benign prostate hyperplasia	Prostatitis Prostatic disorder Increased libido Decreased libido Testicular pain Breast induration Breast pain Gynaecomastia Increased estradiol Increased testosterone
General disorders and administration site conditions	Various kinds of injection site reactions***	Fatigue Asthenia Hyperhidrosis Night sweats

*The most appropriate [MedDRA] term to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed but should be taken into account as well.
**n=302 hypogonadal men treated with i.m. injections of 4 ml and N=120 of 3ml of TU 250 mg/ml
***Various kinds of injection site reaction: Injection site pain, Injection site discomfort, Injection site pruritus, Injection site erythema, Injection site haematoma, Injection site irritation, Injection site reaction
Pulmonary microembolism of oily solutions such as NEBIDO can lead to signs and symptoms such as cough, dyspnoea, malaise, hyperhidrosis, chest pain, dizziness, paraesthesia, or syncope. These reactions may occur during or immediately after the injections and are reversible. Cases suspected to represent oily pulmonary microembolism associated with NEBIDO injection have been reported in clinical trials (in ≥ 1/10 000 and < 1/1000) as well as from postmarketing experience (see section 4.4).

Suspected anaphylactic reactions after NEBIDO injection have been reported.
In addition to the above-mentioned adverse reactions, nervousness, hostility, sleep apnoea, various skin reactions including seborrhoea, increased hair growth, increased frequency of erections and in very rare cases jaundice have been reported under treatment with testosterone containing preparations.
Therapy with high doses of NEBIDO commonly reversibly interrupts or reduces spermatogenesis, thereby reducing the size of the testicles; testosterone replacement therapy of hypogonadism can in rare cases cause persistent, painful erections (priapism). High-dosed or long-term administration of NEBIDO occasionally increases the occurrences of water retention and oedema.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the " **6.04 Adverse Drug Reaction Reporting Form",** found online under SAHPRA's publications: http://www.sahpra.org.za/Publications/index/8

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

5.2 Pharmacokinetic properties

Absorption
NEBIDO is an intramuscularly administered depot preparation of testosterone undecanoate and thus circumvents the first-pass effect. Following intramuscular injection of testosterone undecanoate as an oily solution, the compound is gradually released from the depot and is almost completely cleaved by serum esterases into testosterone and undecanoic acid. An increase of serum levels of testosterone above basal values can already be measured one day after administration.

Distribution
In two separate studies, mean maximum concentrations of testosterone of 24 and 45 nmol/l were measured about 14 and 7 days, respectively, after single i.m. administration of 1000 mg of testosterone undecanoate to hypogonadal men. Post maximum testosterone levels declined with an estimated half-life of about 53 days.

In the serum of men, about 98% of the circulating testosterone is bound to SHBG and albumin. Only the free fraction of testosterone is considered as biologically active. Following intravenous infusion of testosterone to elderly men, an apparent volume of distribution of about 1,0 l/kg was determined.

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

Elimination
Testosterone undergoes extensive hepatic and extrahepatic metabolism. After the administration of radio-labelled testosterone, about 90% of the radioactivity appears in the urine as glucuronic and sulphuric acid conjugates and 6% appears in the faeces after undergoing enterohepatic circulation. Urinary products include androsterone and etiocholanolone.

Steady state conditions
Following repeated i.m. injection of 1000 mg testosterone undecanoate to hypogonadal men using an interval of 10 weeks between two injections, steady-state conditions were achieved between the 3rd and the 5th administration. Mean C_{max} and C_{min} values of testosterone at steady state were about 42 and 17 nmol/l, respectively. Post-maximum testosterone levels in the serum decreased with a half-life of about 90 days, which corresponds to the release rate from the depot.

5.3 Pre-clinical safety data

Not Applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Benzyl benzoate
Castor oil refined

6.2 Incompatibilities
Not Applicable

6.3 Shelf life
60 months
NEBIDO should be sued immediately after opening.

6.4 Special precautions for storage
Store at or below 30°C. Protect from light.

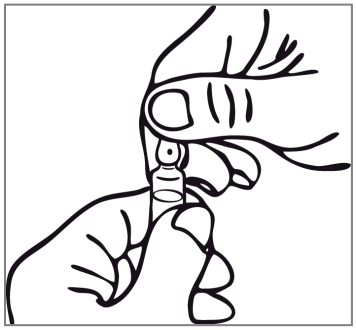
6.5 Nature and contents of container
Ampoule
5 ml brown glass (type 1) ampoules containing 4 ml of oily solution.
Pack size 1x 4 ml

Vial
6 ml brown glass (type I) vials closed with a gray bromobutyl stopper with ETFE foil-clad and capped with a flanged closure with Al-shell and PP plastic button containing 4 ml of oily solution.
Pack size 1 x 4 ml solution

6.6 Special precautions for disposal and other handling of the product.

NEBIDO should be visually inspected for particles prior to use. Only clear solutions free from particles should be used.

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



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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Bayer (Pty) Ltd
(Reg No: 1968/011192/07)
27 Wrench Road
Isando
1609

8. REGISTRATION NUMBER

A38/21.7/0641

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

8 April 2005

10. DATE OF REVISION OF TEXT

02 August 2022