

Testosterone

replacement therapy for male hypogonadism

Traffic light classification- Amber 2
Information sheet for Primary Care Prescribers

Relevant Licensed Indications

Testosterone replacement therapy (TRT) for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests.

Therapeutic Summary

Hypogonadism in men is a clinical syndrome that results from failure of the testis to produce physiological levels of testosterone (androgen deficiency) and a normal number of spermatozoa due to disruption of one or more levels of the hypothalamic-pituitary-testicular (HPT) axis.

Primary testicular failure may occur as a result of congenital (e.g. Klinefelter's Syndrome) or acquired causes. (e.g. testicular trauma, chemotherapy or radiation) and results in low testosterone levels, impairment of spermatogenesis, and elevated gonadotropin levels.

Secondary testicular failure is due to failure of the hypothalamus and/or pituitary as a result of congenital (e.g. Kallmann syndrome) or pituitary causes (e.g hyperprolactinaemia, pituitary adenoma) and results in low testosterone levels, impairment of spermatogenesis, and either low gonadotrophin levels or levels which are inappropriately in the normal range. Drug treatment with high dose opioid therapies can also be associated with secondary testicular failure.

Combined primary and secondary testicular failure results in low testosterone levels, impairment of spermatogenesis, and variable gonadotropin levels, depending on whether primary or secondary testicular failure predominates. Combined primary and secondary hypogonadism occurs with haemochromatosis, sickle cell disease, thalassemia, glucocorticoid treatment, alcoholism, and DAX-1 mutations, and in older men.

Testosterone treatment aims to restore testosterone levels to the physiological range in men with consistently low levels of serum testosterone and associated symptoms of androgen deficiency. The aim is to improve quality of life, sense of well-being, sexual function, muscle strength, exercise capability and bone mineral density.

Medicines Initiation

TRT will be initiated in Secondary Care by a Consultant Endocrinologist or Urologist.

Dosage and route of administration

Oral testosterone is ineffective and is not recommended. Treatment options are therefore:

Transdermal treatment

Tostran[®] 2% (testosterone) gel

Starting dose is 3g gel equivalent to 60mg testosterone (**6 depressions of canister dispenser**, 60 mg of testosterone) applied once daily at approximately the same time each morning. The dose can be applied to the abdomen (entire dose over an area of at least 10 by 30 cm), or to both inner thighs (one half of the dose over an area of at least 10 by 15 cm for each inner thigh). Daily rotation between the abdomen and inner thighs is recommended to minimise application site reactions.

Morning application is recommended to replicate natural circadian changes in blood testosterone levels,

The gel should be applied to clean, dry, intact skin. It should be rubbed in gently with one finger until dry, then the application site should be covered, preferably with loose clothing. Hands should then be washed with soap and water.

Intramuscular treatment

Testosterone undecanoate (Nebido[®]) injection

1000 mg/4 ml injected by deep IM injection into the gluteal muscle slowly over two minutes every 10 to 14 weeks.

A standard loading regimen is summarised below

0 weeks	1000mg Nebido
6 weeks	1000mg Nebido
18 week	1000mg Nebido

Injections are then continued every 10-14 weeks depending on the trough testosterone blood levels which ideally should be in the lower 1/3 of the local reference range prior to administration of the next Nebido injection.

Sustanon[®] (testosterone esters)

Sustanon[®] 250 injection (contains 30 mg Testosterone propionate, 60 mg Testosterone phenylpropionate, 60 mg Testosterone isocaproate, 100 mg Testosterone decanoate) 1ml by deep IM injection every 4 weeks initially.

The injection interval may be reduced to 3 weekly (occasionally 2 weekly) if trough testosterone levels are below the lower 1/3 of the local reference range (8-14 nmol/l in Nottingham).

With training some patients are able to self-administer Sustanon injections which may be a practical advantage in selected cases.

Nebido[®] injections are the preferred IM treatment due to their decreased frequency of administration and more stable plasma testosterone levels

Duration of treatment

Testosterone replacement therapy may be continued long term as long as patient is obtaining symptomatic benefit and no contraindications emerge with ongoing therapy.

Relevant Contraindications

- Androgen-dependent carcinoma of the prostate or breast
- Past or present liver tumours
- Unevaluated prostate nodule or induration
- PSA > 4 ng/ml (>3 ng/ml in individuals at high risk for prostate cancer, such as African Americans or men with first-degree relatives who have prostate cancer)
- Haematocrit > 0.54
- Untreated severe obstructive sleep apnoea
- Severe lower urinary tract symptoms associated with benign prostatic hypertrophy as indicated by American Urological Association (AUA)/ International Prostate Symptom Score (IPSS)>19
- Uncontrolled or poorly controlled Congestive Heart Failure
- Men desiring fertility (testosterone replacement therapy may suppress spermatogenesis)
- Hypersensitivity to the active substance or to any of the excipients. Sustanon 250 contains arachis oil and should not be given to patients known to be allergic to peanut or soya.

Precautions

- Symptomatic hypogonadal men who have been surgically treated for localised prostate cancer and who are currently without evidence of active disease (i.e. measurable PSA, abnormal rectal examination, evidence of bone/visceral metastasis) can be cautiously considered for a TRT. Treatment should be restricted to those patients with a low risk for recurrent prostate cancer (i.e. Gleason score < 8; pathological stage pT1-2; preoperative PSA < 10 ng/ml) and should not start before 1 year of follow-up.
- Care should be taken in patients with skeletal metastases due to the risk of hypercalcaemia/hypercalciuria developing from androgen therapy. Regular monitoring of the serum levels of calcium in these patients is recommended.
- Testosterone should be used with caution in patients with epilepsy and migraine as these conditions may be aggravated.
- Hypertension- testosterone may cause a rise in blood pressure
- Improved insulin sensitivity may occur in patients treated with androgens who achieve normal testosterone plasma concentrations following replacement therapy.
- Pre-existing cardiovascular disease, chronic cardiac failure, renal and hepatic impairment.
- Previous venous thromboembolism (especially associated with a thrombophilia)

Clinically relevant medicine interactions and their management

- Warfarin- testosterone may increase the anticoagulant effect- monitor INR especially when the treatment is started, stopped or the dose adjusted.
- ACTH or corticosteroids- increased likelihood of oedema; use with caution, particularly in patients with cardiac, renal or hepatic disease.
- Anti-diabetic medicines- androgens may improve glucose tolerance and decrease the need for insulin or other anti-diabetic medicines. Monitor patients at the beginning or end of treatment and at periodic intervals during.

Monitoring requirements

Baseline tests will be conducted in secondary care and should include haematocrit, Hb, assessment for cardiovascular risk factors, LFTs, lipid profile and PSA and enquiry about prostatic symptoms in men >40yrs. Ongoing monitoring should be conducted by secondary care until a patient is stable.

Timing of monitoring	Tests to be done						
	Testosterone level (3-5hrs post dose for gel , just prior to injection for IM (trough level)	PSA (+DRE if clinically indicated i.e. symptoms or rising PSA) in men >40 yrs	Hb & haematocrit	LFT	BMD	Lipid profile	Assess response to treatment
At 4-6 weeks (Gel only)	✓						✓
At 3- 6 months (Gel or Sustanon only)	✓	✓	✓	✓		✓	✓
At 4- months. (Nebido only- i.e. pre 3 rd dose)	✓	✓	✓	✓		✓	✓
At 12- months (all products)	✓	✓	✓	✓		✓	✓
Annually (all products)	✓	✓	✓	✓		✓	✓
Every 2-3 years (all products)					✓ if history of osteoporosis or low trauma fracture		

Adverse effects and criteria for review and discontinuation of the medicine

 See individual product [SPCs](#) for more detailed information on side effects

Side Effect	Action
Poor response to treatment	<p>Effects on libido may appear after 3 weeks of treatment, and plateau at 6 weeks. Changes in erectile function and ejaculation may require up to 6 months. Effects on quality of life, and depressive mood, may become detectable within 1 month, may take longer and sometimes up to 12 months.</p> <p>Discuss treatment discontinuation with specialist if poor response persists.</p>
Haematocrit >0.54	<p>Stop therapy until haematocrit decreases to a safe level (may take weeks or months depending on the preparation used; evaluate the patient for hypoxia and sleep apnoea; re-initiate therapy with a reduced dose and monitor trough testosterone levels closely.</p>
Testosterone level outside of therapeutic range (aim to raise serum testosterone level into the mid-normal range.)	<p>Increase/ decrease dose as appropriate. With gel preparation make sure there is no gel contamination of the venepuncture site.</p>
<p>An increase in serum PSA concentration >1.4 ng/ml within any 12-month period of testosterone treatment</p> <p>or</p> <p>A PSA velocity of >0.4 ng/ml per yr using the PSA level after 6 months of testosterone administration as the reference (only applicable if PSA data are available for a period exceeding 2 yr).</p>	<p>Refer to urologist</p>
Detection of a prostatic abnormality on digital rectal examination.	<p>Refer to urologist</p>
An AUA/ IPSS prostate symptom score of >19.	<p>Refer to urologist</p>
Exacerbation of cardiovascular symptoms (oedema etc)	<p>Stop treatment and discuss with specialist</p>
Application site reaction with gel formulation	<p>Usually mild to moderate in severity and improves with continued application. Seek advice from specialist regarding alternative formulation if persists</p>
Injection related reactions such as cough, dyspnoea, malaise, hyperhidrosis, chest pain, dizziness, paraesthesia, or syncope with injection formulation	<p>Ensure injection is administered slowly. Observe patient 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</p>

Acne and oily skin	Treat as needed
Gynaecomastia	Seek advice from specialist
Significant rise in LFTs or worsening lipid profile	Seek advice from specialist

Information given to patients

- Testosterone replacement therapy (TRT) may improve symptoms, but in hypogonadal men who have a chronic illness and are obese: weight reduction, lifestyle modification and good treatment of comorbidities is more important than just TRT.
- Athletes should be informed that testosterone treatment, may give positive results in a doping test.
- Testosterone gels leave a testosterone residue on the skin that can be transferred to a woman or child who might come in close contact. If a testosterone gel is used, advise patients to cover the application sites with a shirt and to wash the skin with soap and water before having skin-to-skin contact. Serum testosterone levels are maintained when the application site is washed 4–6 h after application of the testosterone gel.

Cost and availability

Tostran[®] 2% Gel 60g= £28.67

Testosterone undecanoate (Nebido[®]) injection 1g/4ml= £87.11

Sustanon[®] 250 1ml= £2.45

References

Dohle et al. European Association of Urology Guidelines on Male Hypogonadism, 2015

Bhasin S et al. Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline. Journal of Clinical Endocrinology & Metabolism, June 2010, Vol. 95(6):2536-2559.

Tostran 2% Gel Summary of Product Characteristics. Last updated 20/02/2017

Restandol Testocaps Summary of Product Characteristics. Last updated 15/12/2016

Nebido Summary of Product Characteristics. Last updated 18/01/2017

Sustanon 250 Summary of Product Characteristics. Last updated 03/01/2017

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In consultation with Consultant Endocrinologists and Mr Bazo, Associate Specialist in Urology at NUH