Testosterone

replacement therapy for adult male hypogonadism

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

Relevant Licensed Indications

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

Therapeutic Summary

Male Hypogonadism, also known as Testosterone Deficiency, is a disorder associated with decreased functional activity of the testes, with decreased production of androgens and/or impaired sperm production. It may adversely affect multiple organ functions and quality of life (QoL). The prevalence increases with age.

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

Prescribe by BRAND to avoid inadvertently interchanging products

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

A) Transdermal treatment

Testogel 16.2mg/g gel
Starting dose is 2 pump actuations of gel (40.5mg of testosterone) applied once daily at about the same time, preferably in the morning. The dosage may be increased stepwise by the doctor, by increments of one pump actuation of gel, up to a daily administration of 4 pump actuations (81mg testosterone) of gel.

One pump actuation delivers 1.25g of gel containing 20.25mg of testosterone.

Spread the gel gently as a thin layer onto clean, dry, healthy skin over upper arms and shoulders. It is not necessary to rub it on the skin. Allow to dry for at least 3-5 minutes before dressing. Cover the application site(s) with clothing after the gel has dried.

Wash hands with soap and water after application.

Tostran® 2% (testosterone) gel
Starting dose is 3g gel equivalent to 60mg testosterone (**6 depressions of canister dispenser**) 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 daily dose should not exceed 4 g of gel (80 mg testosterone).

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.

Testavan® 20mg/g (testosterone) gel

The recommended starting dose of Testavan is 23 mg testosterone (one pump actuation) applied once daily at about the same time, preferably in the morning to clean, dry, intact skin of the upper arm and shoulder using the applicator. Dosage may be increased to 69 mg (three pump actuations). Patients should be instructed to only make one pump actuation onto the applicator at a time. When more than one pump actuation is required to achieve daily dose, the procedure is repeated to the other upper arm and shoulder.

After use, the applicator should be cleaned with a tissue and the protective lid restored on top of the applicator. The used tissue paper should be safely thrown away and if the gel was touched with the hands during the application procedure, patients should be instructed to wash their hands with water and soap immediately after applying Testavan.

Patients should be advised to let the application site dry completely before getting dressed.

B) 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.

Depending on serum testosterone levels and clinical symptoms, the first injection interval may be reduced to 6 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)

In general, the dose should be adjusted to the response of the individual patient. The injection interval varies from 1ml every two weeks (if trough testosterone levels are below the lower 1/3 of the local reference range of 8-14 nmol/l in Nottingham) to 1ml every four weeks. 1ml by deep IM injection per 3 weeks is often adequate.

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 >48% (>50% for men living at high altitude)
- Untreated severe obstructive sleep apnoea
- Severe lower urinary tract symptoms associated with benign prostatic hypertrophy as indicated by International Prostate Symptom Score (IPSS)>19
- Uncontrolled or poorly controlled Congestive Heart Failure
- Myocardial infarction or stroke within the last 6 months, or thrombophilia
- 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 undetectable post-operative PSA) 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

- Coumarin anticoagulants (Warfarin/Acenocoumarol/Phenindione)- 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 (2-6 hrs 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 & haemat-ocrit	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 3rd dose)	✔	✔	✔	✔		✔	✔
At 12- months (**all products)**	✔	✔	✔	✔		✔	✔
Annually (**all products)**	✔	✔	✔	✔		✔	✔
Every 1-2 years (**all products)**					✔ if history of osteopor-osis		

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	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. Discuss treatment discontinuation with specialist if poor response persists.
Haematocrit >0.54	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.
Testosterone level outside of therapeutic range (aim to raise serum testosterone level into the mid-normal range.)	Increase/ decrease dose as appropriate. With gel preparation make sure there is no gel contamination of the venepuncture site.
An increase in serum PSA concentration >1.4 ng/ml within any 12-month period of testosterone treatment *or* A confirmed PSA of >0.4 ng/ml at any time	Refer to urologist
Detection of a prostatic abnormality on digital rectal examination.	Refer to urologist
Substantial worsening of LUTS	Refer to urologist
Exacerbation of cardiovascular symptoms (oedema etc.)	Stop treatment and discuss with specialist
Application site reaction with gel formulation	Usually mild to moderate in severity and improves with continued application. Seek advice from specialist regarding alternative formulation if persists
Injection related reactions such as cough, fluctuation in mood or libido, dyspnoea, malaise, hyperhidrosis, chest pain, dizziness, paraesthesia, or syncope with injection formulation	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
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.
- Care should be taken so that the testosterone product is not accidentally transferred onto the skin of someone else. Advise of methods to reduce the risks of accidental exposure, including washing their hands with soap and water after application, covering the application site with clean clothing (such as a t-shirt) once the gel has dried, and washing the application area with soap and water before physical contact with another person- See MHRA advice. Washing 2 hours after application does not have a significant effect on blood testosterone levels.
- When using pump formulations it is necessary to prime the canister pump prior to the first dose being administered; with the canister in the upright position, slowly and fully depress the actuator until gel appears then a further three times for Testogel®, six times for Tostran® and twice for Testavan®. Safely discard the gel from these actuations. It is only necessary to prime the pump before the first dose.

Cost and availability

Testogel® 16.2mg/g gel 88g= £31.11
Tostran® 2% Gel 60g= £28.63
Testavan® 20mg/g (testosterone) gel 85.5g =£25.22
Testosterone undecanoate (Nebido®) injection 1g/4ml= £87.11
Sustanon® 250 1ml= £2.45

References

1. EAU GUIDELINES ON SEXUAL AND REPRODUCTIVE HEALTH- hypogonadism 2023.
2. Tostran 2% Gel Summary of Product Characteristics. Last updated 07/02/2020
3. Nebido Summary of Product Characteristics. Last updated 08/03/2023
4. Sustanon 250 Summary of Product Characteristics. Last updated 21/12/2022
5. Shalender Bhasin, Juan P Brito, Glenn R Cunningham, Frances J Hayes, Howard N Hodis, Alvin M Matsumoto, Peter J Snyder, Ronald S Swerdloff, Frederick C Wu, Maria A Yialamas, Testosterone Therapy in Men with Hypogonadism: An Endocrine Society Clinical Practice Guideline, *The Journal of Clinical Endocrinology & Metabolism*, Volume 103, Issue 5, May 2018, Pages 1715–1744, https://doi.org/10.1210/jc.2018-00229
6. Testogel 16.2mg/g gel - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk). Last updated 26 October 2022
7. BNF online
8. Hackett G, Kirby M, Edwards D, et al. British Society for Sexual Medicine Guidelines on Adult Testosterone Deficiency, With Statements for UK Practice. J Sex Med 2017;14:1504e1523.
9. Al-Sharefi A et al. How to manage low testosterone level in men: a guide for primary care. British Journal of General Practice 2020; 70: 364–365
10. Testavan 20mg/g transdermal gel Summary of Product Characteristics. Last updated 28/07/2022

Version Control- **Testosterone Replacement Therapy for Adult Male Hypogonadism**			
Version	Author(s)	Date	Changes
2.1	Shary Walker	17/09/2020	- Inserted "Adult" on title - Sustanon dose regimen update - Links added for Sustanon inj. Guide, testosterone SCP & info guide
2.2	Shary Walker		- Testogel pump info added - Brand prescribing
3	Lynne Kennell	July 2023	- Document review. Link to MHRA advice about product transfer added, addition of MI, stroke, thrombophilia to contraindication, amendment to timing recommendations for testosterone level monitoring for those on gel formulation, addition of Testavan, update to priming instructions for Tostran in line with MHRA.