Shared Care Guideline
for
Testosterone Replacement Therapy (TRT)

This shared care guideline (SCG) has been written to enable the continuation of care by primary care clinicians of patients initiated on Testosterone Replacement Therapy by the Endocrinology team at BHNFT, where this is appropriate and in the patients' best interests. Primary care will only be requested to take over prescribing of Testosterone Replacement Therapy within its licensed indication unless specifically detailed otherwise below.

Introduction

Indication/Licensing information

- Licensed for Hypogonadism due to testosterone deficiency in adult men.
- The diagnosis of hypogonadism and its underlying disease should only be made by an experienced clinician usually an endocrinologist.

Background for Use

Hypogonadism is a clinical syndrome that comprises symptoms with or without signs and biochemical evidence of testosterone deficiency. Any condition which leads to failure of the normal physiological production of testosterone from the testes due to disruption of the hypothalamic-pituitary testicular axis, and one or more levels may cause the syndrome.

Symptoms associated with low testosterone include decreased sexual desire with or without impotence, fatigue, loss of muscle mass, mood depression and regression of secondary sexual characteristics.

Pharmacology

Testosterone and dihydrotestosterone (DHT), endogenous androgens, are responsible for the normal growth and development of the male sex organs and for the maintenance of secondary sex characteristics. These effects include the growth and maturation of the prostate, seminal vesicles, penis and scrotum; the development of male hair distribution on the face, chest, axillae and pubis; laryngeal enlargement, vocal chord thickening, alterations in body musculature and fat distribution.

Insufficient secretion of testosterone due to testicular failure, pituitary pathology or gonadotropin or luteinising hormone-releasing hormone deficiency results in male hypogonadism and low serum testosterone concentration.

Restoring testosterone levels to within the normal range can result in improvements over time in muscle mass, mood, sexual desire, libido and sexual function including sexual performance and number of spontaneous erections.

During exogenous administration of testosterone to normal males, endogenous testosterone release may be decreased through feedback inhibition of pituitary luteinising hormone (LH). With large doses of exogenous androgens, spermatogenesis may also be suppressed through inhibition of pituitary follicle stimulating hormone (FSH).

Androgen administration causes retention of sodium, nitrogen, potassium, phosphorus and decreased urinary excretion of calcium. Androgens have been reported to increase protein anabolism and decrease protein catabolism. The nitrogen balance is improved only with sufficient intake of calories and protein. Androgens have been reported to stimulate production of red blood cells by enhancing the production of erythropoietin.

Form

- Gel for transdermal application
- Intramuscular injection

Testosterone gels

Brand	Dose	Cost[1]
First line		
Testavan® 20mg/g Pack size: 85.5g ➢ One pump actuation delivers 1.15g of gel equivalent to 23mg of testosterone (pack delivers 56 metered doses)	The recommended starting dose is 23 mg testosterone (One pump actuation) applied once daily. The daily dose should not exceed three pump actuations or 69mg testosterone per day.	£25.22 per 56 days at the recommended starting dose (23mg testosterone daily)
Other preparations: For patients who are unable to tolerate Testavan.		
Testogel® – (50mg) Pack size: 30 sachets ➢ One sachet of 5g gel equivalent to 50mg of testosterone	The recommended dose is 5g of gel (i.e. 50 mg of testosterone) applied once daily at about the same time, preferably in the morning. The daily dose should not exceed 10g of gel per day.	£31.11 per 30 days at the recommended dose (50mg of testosterone daily)
Testogel® 16.2mg/g Pack size: 88g ➢ One pump actuation delivers 1.25g gel equivalent to 20.25mg of testosterone (pack delivers a minimum of 60 metered doses)	The recommended dose is 40.5mg testosterone (Two pump actuations) applied once daily at about the same time, preferably in the morning. The daily dose should **not** exceed four pump actuations or 81 mg testosterone per day.	£31.11 per 30 days at the recommended dose (40.5mg of testosterone daily)
Tostran® 20mg/g Pack size: 60g ➢ One pump actuation delivers 0.5g of gel equivalent to 10mg of testosterone (pack delivers 120 metered doses)	The recommended dose is 60mg testosterone (Six pump actuations) at approximately the same time each morning. The daily dose should not exceed eight pump actuations or 80mg testosterone per day.	£28.63 per 20 days at the recommended dose (60mg testosterone daily)

1 Prices obtained from March 2023 Drug Tariff

Clinicians should prescribe Testosterone preparations by brand to avoid interchanging the products.

Testosterone injections

Nebido® 1000mg/4ml solution for injection vials (testosterone undecanoate 250mg/ml)
The recommended dosing regimen is 1g testosterone undecanoate (Nebido®) injected intramusculary every 10-14 weeks. When starting on testosterone undecanoate (Nebido®) for the first time, the first injection interval should be shortened to 6 weeks.

The patient should be on a stable dose of testosterone once they are discharged to primary care.

*Nebido® frequency and dose changes are dependent on the trough level. A testosterone level at any other time when a patient is on Nebido® is of **no clinical value**.*

Sustanon ® 250mg/ml solution for injection ampoules (testosterone decanoate 100 mg per 1 ml)
1ml injected every 3 weeks, adjusted according to response.

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

Responsibilities of the specialist clinician initiating treatment

Summary

- To assess the suitability of the patient for TRT (including confirming the patient has no contra-indications to treatment and considering the relevance of any cautions, including interactions).
- Discuss the pros and cons of treatment with the patient. Ensure the patient is aware of:
  - Brand and formulation of Testosterone Replacement Therapy
  - Dosage
  - Monitoring requirements
  - Side effects
  - To discuss the patient's responsibilities (see responsibilities of patients or carers section) in relation to the shared care agreement.
- To initiate TRT therapy, arrange prescriptions and evaluate over 6-12 months.
- To perform baseline tests and routine monitoring until the patient is stable (see details of baseline and routine tests which should be carried out by the specialist (see monitoring section below).
- Following stabilisation, write to the patient's GP requesting whether he or she is willing to participate in shared care. Provide the GP with a summary of information relating to the individual patient to support the GP in undertaking shared care. Enclose a completed Shared Care Agreement form (appendix A) with the letter when requesting GP to take over prescribing. Specialist should indicate specific diagnosis clearly and make sure the diagnosis is covered by the share care guidelines before requesting GP to take over prescribing.
- To liaise with the GP regarding changes in disease management, drug dose and missed clinic appointments.
- To review the patient's condition and TRT at least once a year (Annual endocrine clinic appointment).
- To monitor the patient for adverse events and report to the GP and where appropriate Commission on Human Medicines/MHRA (Yellow Card scheme).
- To provide the GP with contact details in case of queries.
- To provide patient / carer with contact details for support and help if required; both in and out of hours.

Specialists should be clear in their communication (letters) to GPs if they want GPs to take over prescribing or if the letter is just a treatment progress information / feedback.

Responsibilities of the primary care clinician

Acceptance of Responsibility by the Primary Care Clinician
It is optional for the primary care clinician to participate in taking on responsibility for shared care for the patient. Primary care clinicians will take on shared care only if they are willing and able.

Summary

- To reply to the request for shared care as soon as possible.
- To prescribe TRT by brand and formulation, and adjust the dose as recommended by the specialist.
- To ensure there are no interactions with any other medications initiated in primary care.
- To continue monitoring as agreed with secondary care in the monitoring section below.
- To inform the specialist if the patient discontinues treatment for any reason.
- To seek the advice of the specialist if any concerns with the patient's therapy. For example:
  - Patient or general practitioner is **not** comfortable to continue with the existing regime due to either change in condition or drug side effects.
  - Advice in respect of concordance.
- Discontinue Testosterone as directed by the specialist if required or immediately if an urgent need to stop treatment arises.
- To conduct an annual medication review or more frequently if required.
- To identify adverse events if the patient presents with any signs and liaise with the hospital specialist where necessary. To report adverse events to the specialist and where appropriate the Commission on Human Medicines/MHRA (Yellow Card scheme).

GPs should not routinely issue prescriptions until they are asked to take over prescribing by the specialist

Responsibilities of Patients or Carers

Summary

- To be fully involved in, and in agreement with, the decision to move to shared care.
- To attend hospital and primary care clinic appointments for reviews and routine monitoring. Failure to attend will potentially result in the medication being stopped.
- Present rapidly to the primary care prescriber or specialist should their clinical condition significantly worsen.
- Report any suspected adverse effects to their specialist or primary care prescriber whilst on TRT.
- To read the product information given to them.
- To apply TRT as prescribed or attend appointment of TRT injection including any monitoring.
- Inform the specialist, primary care prescriber or community pharmacist dispensing their prescriptions of any other medication being taken – including over-the-counter medication.

Clinical Particulars

The details of side-effects, cautions, contraindications and interactions are not a complete list and the current BNF (https://www.medicinescomplete.com/#/) and the SPC (https://www.medicines.org.uk/emc/) remain authoritative.

BNF therapeutic class	Section 6: Male sex hormone/Androgens
Cautions and Contraindications	**Cautions** Caution is advised in patients suffering from cardiac impairment, diabetes mellitus, elderly, 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. Testosterone may cause a rise in blood pressure and should be used with caution in men with hypertension. Caution is also advised in patients with epilepsy and migraine as these conditions may be aggravated. In pre-pubertal boys (fusion of epiphyses is hastened and may result in short stature)—statural growth and sexual development should be monitored. Testosterone should be used with caution in patients with thrombophilia or risk factors for venous thromboembolism (VTE). Testosterone 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. The treatment of hypogonadal men with testosterone may potentiate sleep apnoea in some patients, especially those with risk factors such as obesity or chronic lung disease. If the patient develops a severe application site reaction, treatment should be reviewed and discontinued if necessary. **Contraindication** Known or suspected prostate cancer or breast cancer in males; PSA >4ng/ml unless prostate cancer excluded by urologist; Male Infertility; Haematocrit >0.5; history of liver tumours; hypercalcaemia; Severe lower urinary tract symptoms due to benign prostatic enlargement; Severe untreated sleep apnoea; Severe, uncontrolled heart failure; Hypersensitivity to testosterone or any of the listed excipients.
Pregnancy and breast feeding	Testosterone Replacement Therapy is not indicated for pregnant or breastfeeding women. Pregnant women should avoid all contact with skin treated with Testosterone. In the event of contact with treated skin, the area should be washed with soap and water as soon as possible.
Adverse Drug Reactions	Common side effects include: Hot flush, hypertension, polycythaemia (stop treatment or reduce dose if severe polycythaemia occurs), prostate abnormalities, skin reactions, increased weight. High dose or long-term administration of testosterone occasionally increases the occurrences of water retention and oedema; hypersensitivity reactions may occur. Various kinds of application/injection site reactions can include: pain, discomfort, rash, erythema, pruritus, dermatitis, dryness, and skin irritation. Treatment should be reviewed and discontinued if necessary. Pulmonary microembolism of oily solutions (injection) 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 microembolism. Treatment is usually supportive, e.g. by administration of supplemental oxygen Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme: www.mhra.gov.uk/yellowcard.

Monitoring

Responsibilities of the specialist clinician initiating treatment

Baseline Tests (before starting testosterone replacement therapy)

- Bloods: fasting testosterone (before 11:00am), FSH, LH, PSA, LFTs, FBC, Lipid profile.
- Blood pressure
- BMI
- Bone mineral density (if required)

Routine monitoring (undertaken in secondary care)

- Serum Testosterone level (Gel): 2 to 4 hours after gel administration to determine the peak serum level.

  or

  Serum Testosterone level (Intramuscular): Prior to injection (but no more than 48 hours before) the next Nebido® injection is given to provide a trough testosterone level.
- PSA
- FBC (Haemoglobin, Haematocrit)
- Digital Rectal Examination (DRE) if indicated
- Other tests where indicated: LFTs, Lipid profile where applicable.

Hospital follow up at 3, 6 and 12 months after initiation and yearly thereafter.

Responsibilities of the primary care clinician

After stabilisation (usually by 12 months) patients are reviewed in clinic and care is transferred to GP along with an annual review in the Endocrine outpatients' clinic.

Routine monitoring (annual review – 6 months after endocrine appointment)

- Review patient symptoms and signs, specifically symptoms of prostatism, libido, early morning erections, sexual function, well being and history suggestive if polycythaemia.
- Bloods: FBC, PSA (if indicated during interim review should be carried out by the specialist. Blood tests can be requested and reviewed on ICE).

Testosterone monitoring summary

Parameter	Standard care	Special considerations
Testosterone serum level* (**Gel**)	2 weeks after starting or after a dose adjustment (appox. 2-3 weeks).	Peak Testosterone level between 15-25 nmol/L is an ideal target but also depends on the symptomatic response and can be adjusted on this basis. ➢ If levels <12 nmol/L, check patient compliance. ➢ If levels >30 nmol/L re-check Testosterone level as there may be day to day differences in absorption of testosterone from the skin. ➢ If levels >40nmol/l the testosterone should be re-checked along with an estradiol level to exclude skin contamination of gel over the venepuncture site. This is manifest if the testosterone level remains high but the estradiol is low. If the estradiol is significantly elevated with a high testosterone then this is confirmatory the patient is receiving excess testosterone

			dosage. The latter confirms that a dose reduction in testosterone is required. **Check with the patient:** The time of gel application and the blood sample is being taken 2 to 4 hours after gel administration. Inform patient not to apply the testosterone gel over venepuncture site as this will lead to high levels as a result of skin contamination.
	Testosterone serum level* (**Intramuscular**)	Baseline, at 6 weeks, at 10 weeks, 12 weeks thereafter pre-injection (pre-dose). This is measured **annually** once the patient is stabilised	Testosterone, normal range 8.4 – 28.7 nmol/L. ➢ If levels remain less than 8.4 nmol/L pre-injection dose, then injection interval may need to be shortened. ➢ If levels are greater than 28.7nmol/l pre-injection dose, then injection interval may need to be lengthened. ➢ Check FSH + LH in patients with primary hypogonadism.
	FBC* (Haemoglobin, Haematocrit)	Baseline, at 12 weeks and then annually	If greater than 18 g/dL discuss venesection with clinician responsible for care. Re-check FBC in 28 days.
	PSA*	Baseline, at 3 months, at 6 months and then annually	If PSA is greater than 4 ug/L exclude UTI and question patient regarding prostatic symptoms. Consider stopping treatment and referral to urology if PSA remains elevated. There is **no** evidence that TRT increases the risk of prostate carcinoma. It is well known that prostate carcinoma is more common with increasing age but is very rare before the age of 45 years. Men >45 years old on TRT in this age range should be assessed for the onset of co-incident prostate cancer as TRT would then need to be stopped. If clinically indicated (change in urinary symptoms, rising PSA) a DRE may be necessary at these time points. Referral to a urologist may be indicated. A small rise in PSA within the normal range may occur which is usual as the prostate returns to its normal size (having shrunk in some men as a result of testosterone deficiency). Usually increments of PSA in excess of 1.4ug/l over a 3 to 6 month period are unusual unless there is another cause such as a urinary tract infection or prostatitis. If there is a significant rise in PSA the level should first be repeated prior to referral

			to urology as PSA can rise for example as a result of cycling, sexual intercourse, urinary tract infection, urinary catheterisation, colonoscopy or sigmoidoscopy and benign prostatic enlargement.
	LFT (ALT) *	Baseline, at 12 weeks and then annually	If ALT is elevated to greater than 100 IU/L, repeat in 7 – 10 days. If continues to rise discuss with specialist clinician.
	Lipid profile	Baseline, at 3 months and then annually	Abnormal lipid profile (cholesterol greater than 5.5 nmol/L with HDL less than 1.0 nmol/L or triglycerides greater than 1.9 nmol/L) prior to or during Nebido® treatment should be investigated and treated in the context of overall health by the clinician responsible. Any significant worsening of the lipid profile on Nebido® should result in stopping treatment prior to further investigation.

**Monitoring undertaken at the annual review in secondary care. Any monitoring required at the interim review should also be carried out by the specialist. Blood tests can be requested and reviewed on ICE.*

Interactions

- When androgens are given simultaneously with anticoagulants, the anticoagulant effect can increase. Patients receiving oral anticoagulants require close monitoring of their INR especially when the androgen treatment is started, stopped or the dose of Testosterone is changed.
- The concurrent administration of testosterone with adrenocorticotropic hormone (ACTH) or corticosteroids may increase the likelihood of oedema; thus these drugs should be administered with caution, particularly in patients with cardiac, renal or hepatic disease.
- Improved insulin sensitivity may occur in patients treated with androgens who achieve normal testosterone plasma concentrations following replacement therapy. In diabetic patients, antidiabetics' medication might need reduction.
- Laboratory test interactions: Androgens may decrease concentrations of thyroxin-binding globulin, resulting in decreased total T4 serum concentrations and increased resin uptake of T3 and T4. Free thyroid hormone concentrations remain unchanged however, and there is no clinical evidence of thyroid dysfunction.
- Washing 2 hours after application doesn't have significant effect on blood testosterone levels.
- Interaction studies with body lotion and sunscreen products have not been performed.

Re-Referral guidelines

Patients who are being treated on the advice of the secondary care team, but are no longer being seen in that setting, may still need review should problems arise. The appropriate level of care and/or advice should be available from the secondary care team via Advice and Guidance in a timely manner without requiring a new referral.

Ordering information

Testosterone must be prescribed by brand name and formulation must be specified.

Communication and contact details

Specialist to primary care clinician
The specialist will inform the primary care clinician when they have initiated testosterone replacement therapy. When the patient is near completing the satisfactory initiation period, the specialist will write to the primary care clinician to request they take over prescribing and where possible give an indication as to the expected length of treatment. The specialist will also send a shared care request form to support the primary care clinician in undertaking shared care. (Appendix A)

Primary Care Clinician to specialist
If the primary care clinician has concerns over the prescribing of testosterone replacement therapy, they will contact the specialist as soon as possible.

Contact names and details

Contact Details	Telephone number	Email
Professor Hugh Jones	01226 431896	hugh.jones@nhs.net
Dr Preethi Rao	01226 431896	preethirao@nhs.net
Medicines Information	01226 432857	gilliansmith2@nhs.net or medicinesinformation@nhs.net

References

- Shalender Bhasin, Juan P Brito, et al. 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
- British National Formulary, BNF accessed online www.medicinescomplete.com Accessed October 2022
- Drug Tariff (March 2023) - https://www.nhsbsa.nhs.uk/sites/default/files/2023-02/Drug%20Tariff%20March%202023.pdf. Accessed March 2023
- Nebido® 1000mg/4ml solution for injection vials – Summary of Product Characteristics (SmPC) https://www.medicines.org.uk/emc/product/3873/smpc#gref. Accessed March 2023.
- Sustanon ® 250mg/ml solution for injection ampoules – Summary of Product Characteristics (SmPC) https://www.medicines.org.uk/emc/product/5373/smpc#gref. Accessed March 2023.
- Testogel® 50mg sachets – Summary of Product Characteristics (SmPC) – https://www.medicines.org.uk/emc/product/6808/smpc**.** Accessed January 2023.
- Testogel® 16.2 mg/g gel – Summary of Product Characteristics (SmPC) – https://www.medicines.org.uk/emc/product/8919/smpc. Accessed October 2022.
- Testavan® 20 mg/g gel – Summary of Product Characteristics (SmPC) – https://www.medicines.org.uk/emc/product/13936/smpc. Accessed October 2022.
- Tostran® 20 mg/g gel – Summary of Product Characteristics (SmPC) – https://www.medicines.org.uk/emc/product/332. Accessed January 2023.
- https://www.england.nhs.uk/wp-content/uploads/2018/03/responsibility-prescribing-between-primary-secondary-care-v2.pdf

Development Process

This guidance has been produced by Imran Saleem Clinical Pharmacist SY ICB Barnsley Place following an AMBER classification status of Testosterone Replacement Therapy by the Barnsley Area Prescribing Committee. This guideline has been subject to consultation and endorsement by the endocrinologists and was ratified by the Area Prescribing Committee on 12th April 2023.

Appendix A – Shared Care request form (Amber) for Testosterone Replacement Therapy (TRT)

- Specialist to complete when requesting primary care clinician to enter a shared care arrangement.
- Primary care clinician to return signed copy of form. [Insert details of how to return the form e.g. to a safe haven e-mail address, postal address if the form should be returned by post]
- Both parties should retain a signed copy of the form in the patient's record.

From (**Specialist**): _____ **To** (**Primary care clinician**): _____

As per the agreed Barnsley shared care guideline for Testosterone Replacement Therapy (TRT), this patient is now suitable for prescribing to move to primary care.

The patient fulfils the criteria for shared care and I am therefore requesting your agreement to participate in shared care. I have carried out baseline tests and initial monitoring as detailed in the shared care guideline.

Patient details

Name: _____ NHS Number: _____

Address: _____ DOB: _____

Diagnosed condition: _____

Amber Drug details

Drug name: _____ Dose and frequency: _____

Date of initiation: _____ Length of treatment: _____

The patient has been provided with sufficient medication to last until: _____

The patient will be reviewed by the consultant on: _____

The patient should be reviewed by the primary care clinician by: _____

Monitoring

The following monitoring should be undertaken by the primary care clinician. Refer to the monitoring section of the shared care guideline.

Parameter	Date next test due	Frequency

Communication

Consultant
Telephone number: _____ Fax number:_____

Email address: _____

Specialist Nurse
Telephone number: _____ Fax number: _____

Email address: _____

Confirmation of acceptance of shared care

Specialist (Doctor/Nurse) name: _____

Specialist (Doctor/Nurse) signature: _____ Date: _____

I, [insert name of primary care clinician] can confirm I :

☐ accept the request to participate in shared care for the patient named above and will complete the monitoring as set out in the shared care guideline for this medicine/condition.

☐ reject the request to participate in shared care for the patient named above. The reason for this being ……

Signature of primary care clinician: _____Date:_____

To save resources you have been sent appendix A of the shared care document. The full document (Shared Care Guideline for Testosterone Replacement Therapy (TRT), *date approved April 2023)* can be accessed on the Barnsley BEST website at the following link:
http://best.barnsleyccg.nhs.uk/clinical-support/medicines/shared-care-guidelines/
Or via the Barnsley Area Formulary www.barnsleyformulary.nhs.uk