NHS South Yorkshire Integrated Care Board Doncaster Place

NHS Nottingham and Nottinghamshire Bassetlaw Place-Based Partnership

Document title	Author	Version	Approval	Review Date
New initiation of Testosterone replacement therapy in men with hypogonadism and testosterone deficiency.	Dr RE Hubbard with input from Dr Z Madlom, Dr D Savage, Endocrinology at DBTH and reference to Barnsley Shared care and Sheffield guidance document as well as BSSM guidelines and Clinical practice guidelines from the Endocrine society	1.0 (May 2023)	Doncaster & Bassetlaw APC/ Doncaster Place MOG May 2023	May 2025

Shared Care Guideline for the **NEW** initiation of Topical (Testogel®, Tostran®) and injectable Testosterone (Nebido®) for adult male patients with hypogonadism.

This guideline **does not** include Sustanon® 250mg; Prescribing should be retained in secondary care.

Specialist responsibilities

- Assess the patient and provide diagnosis; ensure that this diagnosis is within scope of this shared care protocol (section 2) and communicated to primary care.
- Use a shared decision making approach; discuss the benefits and risks of the treatment with the patient and/or their carer and provide the appropriate counselling (see section 11) to enable the patient to reach an informed decision. Obtain and document patient consent. Provide an appropriate patient information leaflet.
- Assess for contraindications and cautions (see section 4) and interactions (see section 7).
- Conduct required baseline investigations and initial monitoring (see section 8).
- Initiate and optimise treatment as outlined in section 5.
- Once treatment is optimised, complete the shared care documentation, and send to patient's GP practice detailing the diagnosis, current and ongoing dose, any relevant test results and when the next monitoring is required. Include contact information (section 13).
- Prescribe sufficient medication to enable transfer to primary care, including where there are unforeseen delays to transfer of care.
- Conduct the scheduled reviews and monitoring in section 8 and communicate the results to primary care. After each review, advise primary care whether treatment should be continued, confirm the ongoing dose, and whether the ongoing monitoring outlined in section 9 remains appropriate.
- Provide advice to primary care on the management of adverse effects if required.

Primary care responsibilities

- Respond to the request from the specialist for shared care in writing. It is asked that this be undertaken within 14 days of the request being made, where possible.
- If accepted, prescribe ongoing treatment as detailed in the specialists request and as per section 5, taking into account, any potential drug interactions in section 7.
- Adjust the dose of Testosterone prescribed as advised by the specialist.
- It should be noted that Testosterone is a class 4 medication so should only be given for a maximum dose of 30 days' supply.
- Conduct the required monitoring as outlined in section 9. Communicate any abnormal results to the specialist.

- Manage adverse effects as detailed in section 10 and discuss with specialist team when required.
- Stop Testosterone and make an urgent referral to urology if PSA ≥3 and no other causes e.g. UTI, recent instrumentation. Contact the specialist if Hct >0.52 to obtain dose reduction advice.
- Stop treatment as advised by the specialist.

Patient and/or carer responsibilities

- Use Testosterone as prescribed and avoid abrupt withdrawal unless advised by the primary care prescriber or specialist.
- Attend regularly for monitoring and review appointments with primary care and specialist, and keep contact details up to date with both prescribers. Be aware that medicines may be stopped if they do not attend.
- Report adverse effects to their primary care prescriber. Seek immediate medical attention if they develop any symptoms as detailed in section 11.
- Report the use of any over the counter medications to their primary care prescriber and be aware they should discuss the use of Testosterone with their pharmacist before purchasing any OTC medicines.

1. Background

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This guideline has been developed to support Doncaster and Bassetlaw prescribers to be involved in shared care prescribing for testosterone for the licensed indication of male hypogonadism and/or testosterone insufficiency confirmed by clinical and biochemical features.

Endocrinology society guidelines advise against routine screening for hypogonadism, and routine prescribing for men over the age of 65 with low testosterone levels without symptoms. Those with symptoms can be offered testosterone therapy after discussion of the risk and benefits.

Often patients will present with a cluster of 2-3 symptoms which may include: -

- **Low libido**
- **Erectile dysfunction including loss of morning erections**
- Non-specific symptoms e.g. fatigue, reduced strength, loss of motivation, irritability, depression, hot flushes, sleep disturbances

Risk factors include:

- Patient with history of damage to testes – trauma, orchitis, chemotherapy or radiotherapy, un-descended testis
- Obesity, Type II diabetes
- Pituitary problems, hypothalamic disorders, Sarcoidosis
- Drugs e.g. opiates, anti-epileptic medications, steroids

It is important to establish if the cause is primary (i.e. testicular failure to produce Testosterone) or secondary (an issue with the pituitary-hypothalamic axis.) Late onset hypogonadism is also recognised, and this is associated with chronic conditions such as metabolic syndrome, obesity, COPD, type II diabetes, osteoporosis and HIV.

Blood Test	Primary hypogonadism	Secondary Hypogonadism
Testosterone	Low	Low
LH and FSH	High	Low/inappropriately normal
Prolactin	Normal	Normal/Raised

Initial diagnosis: To confirm testosterone deficiency in men; Two fasting blood testosterone levels at least 4 weeks apart before 10AM (as testosterone levels show diurnal variation)

Criteria for diagnosis as per BSSM guidelines: -

- Testosterone level of<8nmol/l is consistent with a diagnosis of hypogonadism
- 8-12nmol/l could be hypogonadal and can be considered for a trial of Testosterone Replacement Therapy. Hypogonadism is more likely to be present with a testosterone <10.4
- If >12nmol/l, not hypogonadal and does not require Testosterone replacement

2. Indications

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Hypogonadism due to androgen deficiency in men

3. Locally agreed off-label use

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This shared care does not refer to the off-label use of Testosterone in women – Please refer to the Sheffield shared care guideline which can be found here. https://www.intranet.sheffieldccg.nhs.uk/Downloads/Medicines%20Management/Shared%20Care%20protocols/SCP_testosterone_HRT_women.pdf?UNLID=554530876202211320164 6

This guideline does not refer to prescribing of Testosterone in trans man patients-Please refer to the guideline developed by Porter Brook clinic. https://www.shsc.nhs.uk/sites/default/files/2022-07/Trans%20man%20prescribing%20guidelines.pdf

Complex patients prescribed Sustanon 250 should remain under secondary care

4. Contraindications and cautions

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This information does not replace the Summary of Product Characteristics (SPC), and should be read in conjunction with it. Please see BNF & SPC for comprehensive information.

Contraindications:

- Prostate Cancer- PSA ≥ 3ng/ml unless prostate cancer excluded by urologist
- Male breast cancer
- History of liver tumours
- Hypercalcaemia
- Haematocrit >0.54

Cautions:

- Male Infertility
- Severe lower urinary tract symptoms due to benign prostatic enlargement
- Severe untreated sleep apnoea
- Severe, uncontrolled heart failure
- Uncontrolled hypertension
- MI or Stroke within the past 6 months
- Thrombophilia

5. Initiation and ongoing dose regime

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- Transfer of monitoring and prescribing to primary care is normally after the patient's dose has been optimised and with satisfactory investigation results. Due to the significant initial monitoring requirements, transfer to Primary Care would not be expected before 12 months of treatment.
- The duration of treatment & frequency of review will be determined by the specialist, based on clinical response and tolerability.
- All dose or formulation adjustments will be the responsibility of the initiating specialist unless directions have been discussed and agreed with the primary care clinician.
- Termination of treatment will be the responsibility of the specialist.

Initial stabilisation:

It is expected that a person will be under the care of the specialist for at least 12 months whilst the initial 3 monthly monitoring period is occurring.

The loading period must be prescribed by the initiating specialist.

Maintenance dose (following initial stabilisation):

The initial maintenance dose must be prescribed by the initiating specialist.

Conditions requiring dose adjustment:

Significant weight loss during treatment may require dose adjustment.

6. Pharmaceutical aspects -Testogel® 1st Line Treatment

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Route of administration:	**Topical**
Formulation:	**Pump 20.25mg/metered dose. 16.2mg/g.**
Administration details:	**2 pumps applied to clean dry healthy skin by the patient himself, on both upper arms and shoulders once daily, ideally in the morning as a thin layer and left to dry for 3-5 minutes. Wash hands after application and cover sites with clothing after gel has dried to avoid transfer.**
Other important information:	Therapy should be discontinued if the blood testosterone levels consistently exceed the normal range at the lowest daily dose of 20.25 mg or if blood testosterone levels in the normal range cannot be achieved with the highest dose of 81 mg. To obtain a full first dose, it is necessary to prime the canister pump. To do so, with the canister in the upright position, slowly and fully depress the actuator three times. Safely discard the gel from the first three actuations. It is only necessary to prime the pump before the first dose.

6. Pharmaceutical aspects - Tostran®

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Route of administration:	**Topical**
Formulation:	**2% Gel via metered dose pump (10mg/pump)**
Administration details:	**Starting dose is 6 pumps daily (60mg) applied at the same time each day to clean healthy skin to abdomen or both thighs, rubbed in gently with one finger until dry. The application site should be**

	covered with clothing. Hands should be washed with soap and water after application.
Other important information:	Consider alternating sites to reduce risk of a site reaction

6. Pharmaceutical aspects – Testosterone decanoate (Nebido®)
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Route of administration:	**Deep IM**
Formulation:	**1000mg/4ml**
Administration details:	Slow intramuscular injection into the gluteal muscle by a qualified health care professional with the patient laid down over 1-2 minutes to reduce the risk of lipid embolism. Given every 10-14 weeks.
Other important information:	**May be given every 8-14 weeks depending on Testosterone levels, usually at 10 weeks. Specialist to advise on dose frequency.**

7. Significant medicine interactions
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The following list is not exhaustive. Please see BNF or SPC for comprehensive information and recommended management.

- Warfarin – May need increased INR monitoring
- Co-administration with corticosteroids can increase the risk of oedema
- Anti-diabetic medication doses may require adjustment

8. Baseline investigations, initial monitoring and ongoing monitoring to be undertaken by specialist

Monitoring at baseline and during initiation is the responsibility of the specialist; only once the patient is optimised on the chosen medication with no anticipated further changes expected in immediate future will prescribing and monitoring be transferred to primary care.

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Baseline investigations by GP before referral:

- Assessment of symptoms consistent with testosterone deficiency
- PR examination, BMI, BP, assessment of cardiovascular risk factors
- FBC, UE, LFT, SHBG, bone profile, fasting lipids, LH, FSH, Prolactin, PSA
    - FSH and LH help distinguish between primary and secondary causes of hypogonadism.
    - SHBG is helpful as testosterone alone is not always reliable
- Two testosterone results <12 at least 1 week apart done ideally at 9AM but definitely before 10AM

Baseline investigations by specialist:

- FBC, UE, LFT, bone profile, fasting lipids, LH, FSH, Prolactin, Testosterone, PSA if not done in primary care
- Consideration of baseline DEXA scanning (if history of osteoporosis)

Initial monitoring by specialist:

- 2 weeks -FBC and Testosterone levels 2-4 hours post application of gel
- 3 months-FBC, LFT, lipid profile, PSA, Testosterone levels
- 6 months-FBC, PSA, Testosterone levels
- 12 months-FBC, LFT, PSA, lipid profile, Testosterone levels

Also: Testosterone levels 2-3 weeks after any dose changes are the responsibility of the specialist.

Note: For gel preparations blood levels should be taken 2-4 hours post dose. For injectable preparations up to 48 hours pre-next injection (trough levels)

Gels are often used initially as they enable a rapid dose stabilisation and allow assessment of treatment efficacy. It usually takes 2-3 weeks for a steady state testosterone level to be reached in the blood.

Ongoing monitoring:

- Yearly: FBC, LFT, PSA, BMI, testosterone levels and Blood pressure.
- PR examination is no longer routinely recommended in the BSSM guidelines unless there are new urinary symptoms or PSA rises by >1.4 in 12 months.
- There is no convincing evidence that testosterone replacement therapy causes prostate cancer but it can aggravate the symptoms of advanced or metastatic prostate cancer
- Testosterone levels – 2-4 hours post application for gel. Maximum 48 hours BEFORE next injection for IM injection.
- Consider DEXA every 2 years if history of osteoporosis

When a patient is reviewed, advise primary care AND the patient whether treatment should be continued, confirm the ongoing dose, and whether the ongoing monitoring outlined in section 9 remains appropriate. Testosterone replacement should be considered long term if the patient finds it beneficial, well tolerated and annual monitoring is up to date.

9. Ongoing monitoring requirements to be undertaken by primary care

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See section 10 for further guidance on management of adverse effects/responding to monitoring results.

Monitoring	Frequency
Medication review to ensure compliance with treatment and side effects.	**Yearly**
Assessment of any new urinary symptoms +/- PR examination if symptoms indicate, BMI and BP addressing cardiovascular risk factors	**Yearly**
FBC, UE, PSA, LFT, testosterone levels	**After 12 months, yearly**

10. Adverse effects and other management

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Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme. Visit www.mhra.gov.uk/yellowcard

For information on incidence of ADRs see relevant summaries of product characteristics

Common side effects include local application site reactions, acne, facial hair growth, weight gain, facial flushing, headache, hypertension, increase in PSA, increase in RBC, Hb and haematocrit. Androgens may accelerate the progression of sub-clinical prostatic cancer and benign prostatic hyperplasia. Gynaecomastia has also been reported. Sleep apnoea may be worsened; symptoms of excessive daytime sleepiness and witnessed apnoea should be inquired.

Result	Suggested response
As well as responding to absolute values in laboratory tests, a rapid change or a consistent trend in any value should prompt caution and extra vigilance *The table below has been reproduced from the Barnsley guidance with consent from the author.*	
Testosterone levels	Normal range 8.4 – 28.7 nmol/L. Aim for 15-25. 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.
FBC, haematocrit	If greater than 18 g/dL discuss venesection with clinician responsible for care. Check FBC in 28 days. Consider dose reduction or change to preparation.
LFT's	If ALT is elevated to greater than 100 IU/L, repeat in 7 – 10 days. If continues to rise discuss with clinician responsible for care.
PSA	If PSA is greater than 3 ug/L exclude UTI and question patient regarding prostatic symptoms. Consider stopping treatment and referral to urology if PSA remains elevated.
Cholesterol, HDL, Triglycerides	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
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.
Substantial worsening of LUTS or prostate abnormality on PR examination	Refer to urologist
Acne	Treat as required
Gynaecomastia	A+G to endocrinologist
Exacerbation of cardiovascular symptoms e.g. oedema	Stop treatment and A+G to endocrinologist

11. Advice to patients and carers

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The specialist will counsel the patient with regard to the benefits and risks of treatment and will provide the patient with any relevant information and advice, including patient information leaflets on individual medicines.

The patient should be advised to report any of the following signs or symptoms to their primary care prescriber without delay:

The patient should be advised:

- If they experience acute leg swelling, shortness of breath or acute limb weakness they should attend the local emergency department.
- If they develop symptoms of urinary urgency, frequency, dysuria, difficulty initiating stream or terminal dribbling an MSU should be arranged, and the patient reviewed by the GP.

12. Pregnancy, paternal exposure and breast feeding

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It is the responsibility of the specialist to provide advice on the need for contraception to male and female patients on initiation and at each review, but the ongoing responsibility for providing this advice rests with both the primary care prescriber and the specialist.

Testosterone can be topically transferred to others.

Paternal exposure: Testosterone prescribing is not suitable for those experiencing infertility.

13. Specialist contact information

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Name: Dr S Muniyappa, Dr R Teklebeehan, Dr A Oprescu

Role and specialty: Consultant Endocrinologist's

Email address: advice-dbth.diabsec@nhs.net

14. Additional information

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Where patient care is transferred from one specialist service or GP practice to another, a new shared care agreement must be completed. Ensure that the specialist is informed in writing of any changes to the patient's GP or their contact details.

15. References

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- https://www.sheffieldccgportal.co.uk/pathways/primary-care-management-pathway-low-testosterone-in-adult-men
- https://best.barnsleyccg.nhs.uk/clinical-support/medicines/shared-care-guidelines/Testosterone%20Shared%20Care%20Guidlines.pdf?UNLID=579747845202210162026 6
- https://www.guidelines.co.uk/mens-health/bssm-guideline-on-adult-testosterone-deficiency/453888.article
- http://www.bssm.org.uk/wp-content/uploads/2018/02/BSSM-Practical-Guide-High-Res-single-pp-view-final.pdf

16. Other relevant national guidance

- Shared Care for Medicines Guidance – A Standard Approach (RMOC). Available from https://www.sps.nhs.uk/articles/rmoc-shared-care-guidance/

- NHSE policy – Responsibility for prescribing between primary & secondary/tertiary care. Available from https://www.england.nhs.uk/publication/responsibility-for-prescribing-between-primary-and-secondary-tertiary-care/
- General Medical Council. Good practice in prescribing and managing medicines and devices. Shared care. Available from https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-practice-in-prescribing-and-managing-medicines-and-devices/shared-care
- NICE NG197: Shared decision making. Last updated June 2021. https://www.nice.org.uk/guidance/ng197/.

17. Local arrangements for referral

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Define the referral procedure from hospital to primary care prescriber & route of return should the patient's condition change.

Once patient has been stabilised at 12 months of monitoring, consideration for referral back to primary care should be considered.

The treatment plan should include the expected length of treatment and the dose frequency if using injectable testosterone therapy which will often be lifelong.

Queries should be submitted via Endocrinology advice and guidance.

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