Bath and North East Somerset, Swindon and Wiltshire Together

NHS BSW Prescribing guidance for Testosterone For Hypogonadism in Males

Amber Recommendation Guideline for Primary Care

This protocol provides prescribing and monitoring guidance for testosterone therapy for management of hypogonadism in adult cis male patients and does not cover any use of testosterone for treatment of children or of trans male patients. It should be read in conjunction with the Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc and the BNF.

Background for use:

Low testosterone (hypogonadism) is associated with a number of symptoms and signs. Symptoms include low libido and, if severe, erectile dysfunction in particular loss of nocturnal spontaneous erections, loss of energy, fatigue, depression, decrease in cognitive abilities and irritability. Low testosterone can also have negative effects on bone mass, which results in a significant risk of osteoporosis in hypogonadal men. Progressive reductions in muscle mass and anaemia may also be a consequence of low testosterone in men.

The causes for low testosterone may be either primary, i.e. gonadal failure, or secondary to hypothalamic or pituitary disease. Most of the non-gonadal causes are due to obesity and ageing.

Currently, there is no consensus about particular ages and their specific testosterone reference values. However, testosterone serum levels are lower with increasing age[1] and there is limited experience on the safety and efficacy of testosterone use in patients over 65 years of age.[1] **It is not recommended to routinely prescribe testosterone therapy to all men once they reach age 65 years of age or older with low total testosterone concentrations**.

Testosterone levels can also see a transient drop caused by general health, acute illness, malabsorption or malnutrition.

- **It is essential to establish a cause before starting treatment**
- Fertility intentions should always be discussed before starting Testosterone replacement. Testosterone replacement suppresses spermatogenesis.
- **Testosterone is <u>not</u> indicated for treatment of male infertility, fatigue, erectile dysfunction or male hypoactive sexual desire disorder with no hypogonadism.**

Who should be assessed for hypogonadism:

- Men with hypothalamic or pituitary conditions e.g. sellar mass
- Osteoporosis or low trauma fracture
- Erectile dysfunction (if other symptoms are suggestive of low testosterone)
- Type 2 diabetes with BMI > 30 kg/m2 or waist circumference > 94 cm in presence of symptoms of hypogonadism
- Men with infertility
- HIV associated with weight loss
- Chronic glucocorticoid therapy
- Chronic opioid therapy associated with symptoms of hypogonadism
- End-stage renal disease and maintenance haemodialysis
- Unexplained anaemia
- Androgen-anabolic steroid withdrawal
- Consideration should be given to routinely asking men if they have any symptoms of hypogonadism especially those at high risk. These include men with diabetes,

osteoporosis (fragility fractures), chronic opiate therapy, cardiovascular disease, erectile dysfunction and depression.

Diagnosis[2]:

It is advised that blood collection for total testosterone measurement be taken at 08:00-10am (fasting level). (Testosterone has a circadian rhythm - levels highest at 0600 - 0800h falling to a low at 1800 - 2000h.)
In the diagnosis of hypogonadism, two morning testosterone levels at least one week apart should be taken and SHBG and albumin is also tested at the same time to get free calculated testosterone. There is no clear cut-off below which a diagnosis is made. The testosterone level has to be taken into context with the symptoms and underlying disease.

- <8 nmol/L is consistent with a diagnosis of hypogonadism. For anyone with a total testosterone <8 or free calculated testosterone <0.178 nmol/l, they should have free testosterone level also measured.
- A total testosterone level of 8 – 12 nmol/L (or free testosterone 0.179-0.224nmol/l) could represent hypogonadism and patients may be considered for a trial of testosterone replacement therapy (TRT). Assessment should be done in secondary care and includes clinical history, calculation of free testosterone and investigation for evidence of structural pituitary or gonadal disease.
- A person with a total testosterone level>12 nmol/L (or free calculated testosterone >0.225 nmol/l) is not hypogonadal.

GP Treatment Initiation & duration Info:

For commencement of prescribing, a letter from the specialist must be sent to the GP to explain the commencement of prescribing, initial dose and preparation to be prescribed by GP and date of next review by the specialist. The specialist will continue to review and monitor the patient and advise on dosage until the patient's dose is stable.
Failure to improve signs and symptoms (libido, sexual function and muscle function) within 6 months of starting treatment should prompt treatment discontinuation and investigation into other causes of symptoms by the specialist.
If patients fail to attend for review, recommend one further appointment is made but thereafter GP to stop prescribing until monitoring requirements have been met. This information about prescribing should be communicated to the GP.
The patient should remain under specialist care for at least 6 months to titrate the testosterone dosage and monitor for any PSA/Hb elevations if on a topical replacement product. Patents should be discharged from specialist care between 6 and 12 months, and primary care will take on the monitoring at 12 months then annually. For patients receiving testosterone injection, they will stay under specialist care for 18-24 months before being moved out to primary care.
In some cases, with obesity, treatment might not be needed long-term as patients may lose a considerable amount of weight and then be re-assessed for Testosterone requirements.
Benefits from testosterone would appear in majority of pts after 6 months of treatment.

GP responsibilities:

- Initial screening for hypogonadism in appropriate patients. If initial test showed low reference range testosterone - arrange a blood test 8-10am fasting for testosterone, SHBG, albumin, LH, FSH, Prolactin, PSA, FBC and refer to endocrinology if total testosterone <12 nmol/l (free testosterone <0,225) for further assessment and management

- Prior to referral for consideration of testosterone replacement, all patients must undergo a detailed examination in order to exclude a risk of pre-existing prostatic cancer: PSA, ask about urinary symptoms and DRE as indicated: if suspicion of possible ca prostate must be referred to urology for review before referral to endocrine for consideration of testosterone.
- LH, FSH and prolactin to establish whether primary or secondary
- Baseline FBC, PSA, LFTs
- Refer to secondary care for diagnosis and for further investigations to establish cause
- Accept handover of prescribing responsibility or raise concerns and accept handover for monitoring of patients who have been established on TT with proven benefits (6-24 months after initiation)
- Trough testosterone annually if on Nebido®; random testosterone (ideally 2 hours after gel application) annually if on testosterone gel. Dose change in testosterone is unlikely to be necessary once the patient is discharged on stable dose of testosterone (see below)
- FBC annually. Seek endocrine advice if hematocrit or hemoglobin raised
- Annual PSA
- Annual cardiovascular risk assessment – caution in use of testosterone in hypertension as may increase blood pressure (although this is a minimal effect once the patient is established on treatment).

Consultant responsibilities:

- Make diagnosis of hypogonadism and establish cause
- Discuss and manage fertility intentions/issues
- Baseline DEXA scan if appropriate
- Prior to testosterone initiation, all patients must undergo a detailed examination in order to exclude a risk of pre-existing prostate cancer: PSA, ask about urinary symptoms. In patients with abnormal (high/low SHBG) consider requesting SHBG/albumin/testosterone to get free testosterone for sufficient dose titration/monitoring.
- Advise GP as to type of testosterone replacement
- Review patient until stabilised on preferred Testosterone replacement product
- Bloods FBC, PSA until stabilised on preferred product usually this is at 3 months.
- Some patients, e.g. Klinefelter's, pituitary disorders, may remain under secondary care
- Some patients once stabilised on testosterone will be discharged to primary care but can be referred back in if any problems arise.

Treatment:

The form of testosterone replacement is patient choice. Gels are used when initiating testosterone therapy as they are easily reversible and dose can be adjusted in the event of adverse reactions. Patients may choose to switch to injections for long term therapy. If injections are preferred, then the first line is Nebido. Short acting intramuscular preparations of Testosterone esters are also available

Testosterone gels

Prescribed dose may be 20-60 mg /day titrated to target testosterone concentration. Testosterone concentration should be taken 2-4 hours after applying gel. Aim for serum testosterone concentration in the middle of the normal range (Free testosterone 0.3-0.4 nmol/l).

- Testogel: sachet 40.5mg/2.5g: Titrated based on pre-dose morning testosterone levels.
- Testogel pump: 16.2 mg/g: 20.25mg per actuation: useful for accurate administration of other doses. Titrated based on pre-dose morning testosterone levels.
- Tostran 2% pump: 10 mg per pump actuation: useful for accurate administration of other

doses

- Testavan pump: 23 mg per actuation: Novel hands free applicator to reduce secondary transmission (most cost effective product – Nov 23)

Tostran gel pump 20mg/g (2%)		**Testavan gel pump 20mg/g (2%)**		**Testogel 40.5mg/sachet**		**Testogel pump 16.2mg/g (1%)**	
20mg	=2 pumps	23mg	=1 pump	20.25mg	=1/2 sachet	20.25mg	=1 pump
30mg	=3 pumps						
40mg	=4 pumps	46mg	=2 pumps	40.5mg	=1 sachet	40.5mg	=2 pumps
50mg	=5 pumps						
60mg	=6 pumps			60.75mg	=1+1/2 sachets	60.75mg	=3 pumps
70mg	=7 pumps	69mg	=3 pumps				
80mg	=8 pumps			81mg	=2 sachets	81mg	=4 pumps

Long-acting Testosterone undecanoate Nebido® administered intra-muscularly lasting up to 3 months. The initial injection should be followed by a second at 6 weeks, and subsequent injections every 10 - 14 weeks until the patient is on a stable dose. Dosage interval is based on trough
testosterone concentration taken in the week before next injection due. Aim trough testosterone in lower end of normal range (Free calculated testosterone around 0.220nmol/l)

Sustanon 250 mg/ml IM every 3 weeks. Potentially unpleasant peak and trough symptoms with higher risk of high haematocrit. Monitor with trough testosterone levels in few days before injection due and aim for lower end normal range. Not recommended for new patients but can be continued in existing patients if needed.

Testosterone Enantate 250mg/ml 150-200mg IM every 2 weeks or 50-100mg IM or S/C once a week. When administered S/C can be potentially be self-injected. For maintenance treatment: 250mg Testosterone Enantate intramuscularly every three to six weeks, according to individual requirement. Monitoring with trough Testosterone concentrations aiming for lower end of normal range. Potentially unpleasant peak and trough symptoms. Mainly reserved for patients who want to self-inject.

Contraindications:

- In cases of known or suspected prostatic cancer or breast carcinoma
- In cases of known hypersensitivity to the active substance or any of the excipients
- Past or present liver tumours (Nebido®)
- Hypercalcaemia & nephrosis (Testosterone enantate)
  For comprehensive information see relevant SPCs
- Testosterone replacement is not indicated for use in children and has not been evaluated clinically in males under 18 years of age

Do not use if/caution:

- Desire for fertility in the near term
- Polycythemia (hematocrit > 54%)
- Prostate-specific antigen > 4 ng per mL (4 mcg per L) or presence of nodules/induration on digital rectal examination (referral to a urologist is required before considering

testosterone therapy)

Precautions:

Prior to testosterone initiation, all patients must undergo a detailed examination in order to exclude a risk of pre-existing prostatic cancer: PSA, ask about urinary symptoms, DRE if high risk. (see specialist responsibilities). Androgens may accelerate the progression of sub-clinical prostatic cancer and benign prostatic hyperplasia.
Due to variability in laboratory values, all measures of testosterone should be carried out in the same laboratory.
In patients suffering from severe cardiac, 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 cases, treatment must be stopped immediately. In addition, diuretic therapy may be required.
Testosterone gels should be used with caution in cancer patients at risk of hypercalcaemia (and associated hypercalciuria), due to bone metastases. Regular monitoring of the serum levels of calcium in these patients is recommended.
Testosterone gels should also be used with caution in ischaemic heart disease, hypertension, thrombophilia, epilepsy and migraine

Drug interactions:

(See SPC for full list http://www.medicines.org.uk/emc/.)

Oral coumarins-based anticoagulant	Increased monitoring of international normalised ratio (INR) recommended particularly when androgens started or stopped.
Corticosteroids/adrenocorticotropic hormone (ACTH)	Increased risk of developing oedema. Co-administer with caution.

Monitoring for primary care[2]:

Conditions requiring dose adjustment:

- Patient experiencing side effects
- Raised PSA or haematocrit
- Raised or low/out of range trough testosterone level for patients on IM testosterone (aim is for trough level to be in the lower third of normal range): dose interval will need adjusting as above
- Raised or low/out of range serum testosterone taken 2-6 hours after gel application: may need adjustment of gel dose.
- New co-existing diagnosis e.g. Prostate cancer. In this case testosterone would most likely be stopped pending discussion with Urology (refer to Specialist)

Obtain urological consultation if there is:
• Substantial worsening of LUTS
•Detection of a prostatic abnormality on DRE

Monitoring

- on topical replacement: – 2-4 hours after application blood test: testosterone, PSA, FBC + SHBG/albumin (by specialist request in pts with initial abnormal results)

- On injectable replacement: (e.g. Nebido, Sustanon) – blood test prior to injection for testosterone, PSA, FBC + SHBG/albumin (by specialist request in pts with initial

abnormal results)

Monitoring: guidance and actions regarding PSA and FBC monitoring (at 12 months and annually)

PSA:

If PSA becomes raised above the normal range (see table 1), please inform Specialist and consider referral to Urology

Obtain urological consultation if there is (specialist clinic to advise):

- An increase in serum PSA concentration >1.4 ng/ml within 12-months of initiating Testosterone treatment.
- A confirmed PSA >4 ng/mL at any time

Normal age-specific range for PSA (Table 1)

Age Range	**40 - 49**	**50 - 59**	**60 - 69**	**70 – 79**	**≥ 80**	
Threshold for Urology referral based on PSA alone	**> 2.5**	***NEW* > 3.5**	***NEW* > 4.5**	***NEW* > 6.5**	***NEW* Normal fitness Very fit**	***NEW* > 20.0 >10**
Halve the threshold if on 5α Reductase Inhibitors	**> 1.25 (on 5αRI)**	**> 1.5 (on 5αRI)**	**> 2.0 (on 5αRI)**	**>2.5 (on 5αRI)**	**> 5.0 (on 5αRI)**	

FBC - Haematocrit/ Hct monitoring on testosterone replacement:

- Monitoring should be performed: baseline, 3 months, 6 months (by the specialist) and minimum of annually thereafter (by the GP) until stopped treatment.
- If elevated:
  - Hct > 0.52 GP to repeat bloods in 1-2 weeks to assess if transient and then reassess monitoring.
  - Hct > 0.54 GP to use A+G or referral to Endocrine Team to review the dose and rule out other causes.
  - Hct> 0.59 refer to haematology for venesection

Specialist contact information:

SFT Consultants/Nurse Specialists Contact via Secretaries		
Consultants' secretaries	Via Cinapsis	
Advice & Guidance		
RUH Consultants/Nurse Specialists		
RUH consultants (immediate advice)	Cinapsis	
RUH consultants (1-2 day advice)	Email or Cinapsis	ruh-tr.endocrinediabetes@nhs.net
GWH Consultants/Nurse Specialists		
GWH consultants (1-5 day response)	Cinapsis	

References:

1.) Summary of product characteristics Tostran 20mg/g transdermal gel.

2.) Society for Endocrinology Guidelines for Testosterone Replacement Therapy in Male Hypogonadism. Jayasena et al. Clinical Endocrinology 2022;96:200-219 Society for Endocrinology guidelines for testosterone replacement therapy in male hypogonadism - PubMed

Patient resources:

PIL to be provided on testosterone replacement therapy and on individual medicines:

- RUH testosterone in men: Patient Information Leaflet
- Testosterone | You and Your Hormones from the Society for Endocrinology
- Male hypogonadism | You and Your Hormones from the Society for Endocrinology
- PI_Male-hypogonadism_EN-2020.pdf (uroweb.org)
- What is Testogel® 16.2 mg/g gel - Testogel
- T Track App - Testogel
- 1 (medicines.org.uk)
- UK_PIL_Testavan P1 (medicines.org.uk)
- 160122_Testavan_Patient_Leavepiece_v14_DS.indd (ferringcloud1.com)
- Low Testosterone | Hypogonadism | Testosterone Therapy (nebido.com)
- SUSTANON 100MG/ML SOLUTION FOR INJECTION (medicines.org.uk)

Please note MHRA Drug Safety update January 2023: Topical testosterone (Testogel): risk of harm to children following accidental exposure