

Testosterone for men with secondary androgen deficiency, guidance for primary care prescribing

Testosterone is designated Amber Recommended in Pan Mersey area.

Diagnosis and referral by GP:

The GP to review males for symptomatic testosterone deficiency if presenting with 3 persistent sexual symptoms (see list below) **AND** must have at least 2 consecutive fasting (7-11am) reduced serum total testosterone concentrations (< 10nmol/L) 4 weeks apart in the absence of any acute illness.^{1,2}

If a patient clearly has multiple symptoms but total testosterone is 10-12nmol/L consider possible referral. Reported reference ranges for total testosterone levels can vary between different laboratories.

NB. Many of these symptoms are experienced even with normal testosterone levels but may be due to other causes.¹

Sexual Symptoms

- Erectile dysfunction (ED)
- Loss of early morning erections
- Low sexual desire, decreased libido
- Decreased spontaneous erections
- Gynaecomastia
- Incomplete/delayed sexual development
- Loss of axillary pubic hair

Other Physical/Psychological signs can include:

- Osteoporosis
- Osteoporotic fractures
- Type 2 diabetes
- Decreased muscle bulk/strength
- Hot flushes/sweats
- Mood changes such as irritability or increased sadness
- Decreased ability to concentrate on tasks, low energy or fatigue
- Metabolic syndrome
- Obesity – weight loss/lifestyle modification advice should be provided
- Side effects of other long-term medication e.g. oral glucocorticoids, opioids, antipsychotics, anticonvulsants

SUPPORTING INFORMATION

GP may need to manage obstructive sleep apnoea, poorly controlled heart failure, severe lower urinary tract infections, prostate issues or polycythaemia before consideration of investigations for testosterone replacement.

Patients will require other blood tests (see below) to confirm diagnosis before the patient can then be referred to the specialist for a decision on whether to initiate treatment.

Currently, there is no consensus about particular ages and their specific testosterone reference values. However, testosterone serum levels are lower with increasing age³ and there is limited experience on the safety and efficacy of testosterone use in patients over 65 years of age.³ **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.**⁴

Testosterone levels can also see a transient drop caused by general health, acute illness, malabsorption or malnutrition.^{1,2,5} Consider use of anabolic steroids and recreational drugs, eating disorders and excessive exercise.

Blood tests:^{1,2}

After two low total testosterone levels (< 10 nmol/L), GP to review patient and consider the extra tests **before** referral to secondary care to aid diagnosis.^{1,2,5}

- Luteinizing hormone (LH), to distinguish between primary (testicular) and secondary (pituitary-hypothalamic) hypogonadism
- Follicle stimulating hormone (FSH)
- Prolactin level (if prolactin level is raised with low LH and FSH consider possibility of pituitary tumour)
- Ferritin levels (to exclude haemochromatosis in hypogonadotropic hypogonadism)

Contra-indications to testosterone therapy:³

- Carcinoma of the breast or known or suspected carcinoma of the prostate, to avoid the possibility of accelerating tumour growth
- Those who wish to retain their fertility, due to suppression of sperm production
- Haematocrit if >54% - stop therapy until it decreases to a safe level and re-evaluate the patient for hypoxia and sleep apnoea, then reinstate therapy at a reduced dose.
- Severe chronic heart failure (NYHA class IV), hepatic or renal insufficiency or ischaemic heart disease may cause severe complications characterised by oedema with or without congestive cardiac failure. In such case, treatment must be stopped immediately.^{1,5}

Transfer of information to GP for initiation and length of treatment:

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 (see "Secondary Care" section below).

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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.

GP Monitoring:

- Annual review of benefits to treatment
- Any medication adverse effects noted
- Annual cardiovascular risk assessment – caution in use of testosterone in hypertension as may increase blood pressure.³
- Monitor for any possible risk of misuse or diversion

To start 12 months after initiation of treatment

Prostate specific antigen (PSA)	Annual review - If PSA is elevated, consider stopping treatment and refer to urology
Total Testosterone levels (maintain 10-31.8nmol/L)	Annual review, target mid normal levels
FBC (Haematocrit – remain <54%)	Annual review
Lipid profile	Annual review

Secondary Care

Specialist will complete before recommending treatment:

Physical examination, digital rectal examination (DRE), BMI check, prostate specific antigen (PSA) level and haematocrit.

Assess cardiovascular risk factors and optimise secondary prevention where needed.

The specialist will continue to review the patient after prescribing has been commenced by the GP and monitor as below and will also advise the GP on any dose alterations until the dose has been stabilised according to satisfactory testosterone levels.

Secondary Care Monitoring:^{1,2,4,5}

Specialist Endocrine Clinic	Frequency
Confirm improvement in patient signs and symptoms - Prostatism symptoms, libido, early morning erections, sexual function, history of polycythaemia.	At each visit
Digital rectal examination (DRE)	Start of treatment
Prostate specific antigen (PSA)	At initiation, 3-6months - If elevated, consider stopping treatment and refer to urology
Testosterone levels (maintain 10-31.8nmol/L)	Initiation, 3-6months
FBC (Haematocrit – remain <54%)	Initiation, 3-6months
LFTs	Check ALT – if it rises discuss with the clinician responsible for care

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Lipid profile	Baseline, 3-6 months - Check cholesterol prior to or during testosterone treatment.
Medication adverse effects	At each visit
bone mineral density (BMD)	Check lumbar spine or femoral neck (or both) after 1 to 2 years of testosterone therapy in hypogonadal men with osteoporosis or low-trauma fracture
Erythrocytosis develops with intramuscular (IM) therapy	Options: 1. Reduce dose 2. Reduce dose interval with lower dose per injection but similar overall total dose per month 3. Change to non-IM delivery mode. Erythrocytosis is much less common with transdermal formulations, and extremely rare with oral testosterone undecanoate. ¹

Treatments:³

The formulation choice should be based on the patient’s preference, consideration of pharmacokinetics, treatment burden, and cost. Another delivery mode should be considered if blood levels are not appropriate or if side effects such as polycythaemia occur.

Note – Testosterone products are schedule 4 Controlled Drugs.

	Formulation	Administration	Application	Peak/Trough levels
Testosterone gel	50mg/5g, 16.2mg/g, 20mg/g Dose equivalence: See individual Summary of Product Characteristics (SmPC)	Apply a thin layer once daily in the morning, to clean, dry, intact, skin of the shoulders and/or upper arms. For patients who wash in the morning, apply after washing, bathing or showering. It is not necessary to rub it into the skin. Allow drying for at least 3-5 minutes before dressing. Wash hands with soap and water after applications.	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 because testosterone gel leaves a residue on the skin that can be transferred to a woman or child who comes in close contact. Serum testosterone levels are maintained when the site is washed 6 hours after applying the gel.	Steady state plasma testosterone concentrations are reached approximately on the 2nd day of treatment. Peak serum testosterone concentrations can be measured 2-4 hours after application of gel within 7 – 14 days of starting (see individual product SmPC) . The dose may be reduced if the plasma testosterone concentrations are raised. If the concentrations are low, the dosage may be increased, not exceeding 10 g of gel per day.
Testosterone undecanoate (Nebido)	250mg/1ml (4ml amp or vial)	1g every 10-14 weeks by deep intramuscular injection. Initially may require a further dose after 6 weeks to achieve rapid steady state plasma testosterone levels.	For intramuscular use only. Administered very slowly (over two minutes). Care should be taken to inject Nebido	The frequency of injection may need to be adjusted (8-14 weeks) to maintain trough testosterone >10nmol/L . Measurements should be performed 1 week before the next injection is due

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		Then repeat every 10-14 weeks.	deeply into the gluteal muscle.	and clinical symptoms considered. Serum levels below normal range would indicate the need for a shorter injection interval. If serum levels are high, an extension of the injection interval may be considered.
Testosterone Injection (Sustanon)	Testosterone propionate 30mg, testosterone phenylpropionate 60mg, testosterone isocaproate 60mg, and testosterone decanoate 100mg/mL;	1mL every 3 weeks by deep intramuscular injection NB. Used to start treatment before administration of the 3-monthly injection.	No information available	No information available
Testosterone enantate	250mg/1ml	Initially 250mg every 2-3 weeks, maintenance 250mg every 3-6 weeks by slow intramuscular injection	The oily solution to be injected immediately after it is drawn up into the syringe	Take serum testosterone level midway between injections and adjust dose or frequency as necessary

NB. Testosterone undecanoate (Restandol) 40mg oral capsules - Not recommended as oral absorption is poor and blood levels are more likely to fluctuate leading to side effects.³

In the head-to-head comparison of individual testosterone treatments, there were no significant differences among products in their effect on depression or erectile function.⁷

Note: Men starting testosterone therapy can also be prescribed a [phosphodiesterase type 5 inhibitor](#) if no contra-indications.^{1,3}

For further information on each product see <https://www.medicines.org.uk/emc/>

References:

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