Testosterone Replacement in adult men (Testogel®/Tostran®/Nebido®/Sustanon®)

Amber with shared care

Shared Care Guidelines: For the treatment of Testosterone Deficiency

AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of medicine name and indication shared between the specialist and general practitioner (GP). GPs are **invited** to participate. If the GP is not confident to undertake these roles, then he or she is under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care is usually explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it. Patients with the condition are under regular specialist follow-up, which provides an opportunity to discuss drug therapy.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

RESPONSIBILITIES and ROLES

	Specialist responsibilities
1	Diagnosis of hypogonadism and its cause (primary/secondary) & assessing the patient's suitability for treatment.
2	Review patients symptoms and signs; prostatism symptoms plus history, libido, early morning erections, sexual function, well-being, history suggestive of polycythaemia.
3	Perform baseline blood tests before initiating treatment: 9am testosterone, FSH, LH, PSA, LFTs, FBC, prolactin, ferritin, SHBG. Blood pressure and BMI are also measured. Bone mineral density scanning should be considered if appropriate i.e. if osteoporosis or fracture.
4	Initiate treatment if using a topical option and provide at least 28 days' supply or until patient is stable. If the patient needs injectable testosterone, the GP will be asked to administer the first dose and then continue.
5	Discuss the benefits and side effects of treatment with the patient.
6	Ask the GP whether he or she is willing to participate in shared care, and agree with the GP as to who will discuss the shared care arrangement with the patient.
7	Supply GP with summary within 14 days of a hospital out-patient review or in-patient stay.
8	Review the patient's condition at 12 months (6 months if elderly), when testosterone levels, FBC, LFTs and PSA will be assessed. Monitor response to treatment regularly where indicated.
9	Give advice to the GP on when to stop treatment.
10	Report adverse events to the MHRA
11	Ensure that clear backup arrangements exist for GPs to obtain advice and support.

	General Practitioner responsibilities
1	Reply to the request for shared care as soon as practicable.
2	Prescribe medicine at the dose recommended and monitor as recommended (usually FBC, LFTs & PSA annually and digital rectal examination if required).
3	Review patients symptoms and signs; prostatism symptoms plus history, libido, early morning erections, sexual function, well-being, history suggestive of polycythaemia.
4	Refer promptly to specialist when any loss of clinical efficacy is suspected (e.g. worsening of disease-related symptoms, new symptoms suggestive of disease recurrence or progression) or intolerance to therapy occurs.
5	Report to and seek advice from the specialist on any aspect of patient care that is of concern to the GP and may affect treatment.
6	Conduct an annual face to face medication review or more frequent if required (e.g. in elderly patient).
7	Stop treatment on the advice of the specialist.
8	Report adverse events to the specialist and MHRA.

	Patient's role
1	Report to the specialist or GP if he or she does not have a clear understanding of the treatment.
2	Share any concerns in relation to treatment with medicine.
3	Report any adverse effects to the specialist or GP whilst taking the medicine.
4	Attend GP/specialist appointments for regular monitoring.

BACK-UP ADVICE AND SUPPORT

Contact details	Telephone No.	Bleep:	Fax:	Email address:
Specialist via consultant connect	-	7059	-	-

SUPPORTING INFORMATION

Summary of condition and licensed indications.

- Testosterone replacement therapy is indicated for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests in adults.

Testosterone is not indicated for treatment of male sterility or impotence.

Background Information

Low testosterone (hypogonadism) is associated with a number of symptoms and signs. Symptoms include sexual dysfunction, 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 red blood cell mass may also be a symptom of low testosterone in men. In general, the clinical manifestations of hypogonadism depend on the age at onset, the severity and the duration of the deficiency. Patients can experience one or many of these symptoms and signs.

The causes for low testosterone may be either primary, i.e. gonadal failure, or secondary to hypothalamic or pituitary disease. Primary hypogonadism is seen in Klinefelter syndrome, which a common condition occurring in 1:700 male births, or following radiotherapy, chemotherapy, infection or surgery to the testicles. It may also occasionally be seen in normal ageing males – the 'male menopause'. Most of the non-gonadal causes are due to pituitary tumours.

Diagnosis (also see testosterone investigation algorithm page 6).

There are several factors which are responsible for the difficulties in making a diagnosis of hypogonadism, which is why patients need referral to an endocrinologist to confirm the diagnosis and recommend treatment:

1. The symptoms of hypogonadism are non-specific and can be manifestations of other clinical conditions. Symptoms include fatigue, reduced physical endurance, lack of vigour, lack of motivation, mood disturbance, irritability and grumpiness, depression as well as the common symptoms of loss or reduction in libido, loss or reduction of morning erections and erectile dysfunction. It is important that there are a cluster of at least two or three symptoms.
2. The biochemical tests available can be difficult to interpret. It is mandatory that blood collection for total testosterone measurement be taken before 1100h in the morning. (Testosterone has a circadian rhythm - levels highest at 0600-0800h falling to a low at 1800-2000h).
3. Guidelines state that two morning testosterone levels at least one week apart should be taken only in the presence of symptoms. 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. Guidelines suggest that a fasting level of total testosterone at least on two occasions all first thing in the morning (09:00) with the presence of symptoms:-
    - <7.5nmol/l is consistent with a diagnosis of hypogonadism
    - 7.5-12nmol/l could be hypogonadal but free testosterone is more accurate so this will be reported by the laboratory. If free testosterone is low, a trial of testosterone replacement therapy (TRT) may be considered. Hypogonadism is more likely to be present with a testosterone <10.4nmol/l.
    - >12nmol/l subject is not hypogonadal.

Measurement of sex hormone binding globulin (SHBG) should be performed and this can be helpful in calculating the free or bioavailable testosterone in borderline cases.

4. Investigation to establish the underlying clinical condition causing the hypogonadism e.g. pituitary or parasellar tumour, empty sella syndrome, Klinefelters syndrome, haemochromatosis etc. The decision as to whether or not an MRI of the pituitary gland depends on clinical presentation, gonadotrophin levels and the presence of any other pituitary hormone deficiency or excess after basal and/or dynamic endocrine assessment.

It is therefore recommended that the diagnosis of hypogonadism and its underlying disease should only be made by an experienced clinician usually an endocrinologist.

Who should be assessed for Hypogonadism?

- Those men presenting with symptoms compatible with hypogonadism as described above.
- Men with hypothalamic-pituitary conditions e.g. sellar mass
- Osteoporosis or low trauma fracture
- Erectile Dysfunction
- Type 2 diabetes 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

Treatment aims

The clinical goals of any form of hormone replacement therapy are to correct the hormone level to the normal physiological range.

Initiation of testosterone replacement may restore secondary sexual characteristics, improve sexual function, well-being, muscle mass and bone mineral density. Patients must be counselled that testosterone therapy does not improve fertility.

The endocrinologist will investigate and treat the underlying cause where possible e.g. medical control of hyperprolactinaemia may restore testosterone levels and fertility as well as restoring normal vision; opioid withdrawal or weight loss may also lead to restoration of normal testosterone levels.

Treatment Schedule (including dosage and administration)

Testosterone is available as various topical preparations (e.g. Testogel®, Tostran®) and also injectable forms such as Nebido®.

Formulary Options	Form	Strength	Dosage	Quantity/pack	Price	Application
Testogel	Sachet OR pump- *new format (N.B. sachets have supply issues)*	50mg/5ml sachet or 16.2mg/g pump	Usually 50mg daily (dose range 25mg dose to 100mg)	30	£31.11	Apply to arms
Tostran	gel	2% (10mg metered application)	60mg (3g) daily MAX 80mg	60g multidose dispenser	£28.67	Apply to abdo/inner thighs
Nebido	Injection	250mg/ml	1g every 10-14 weeks	4ml ampoule	£87.11	IM
Sustanon	Injection	250mg/ml	250mg every 3 weeks	1ml ampoule	£2.45	IM

Testosterone Undecanoate depot i.m. injection - Nebido® (testosterone 250mg/ml):

Nebido® is a long-acting formulation of testosterone undecanoate which is administered intra-muscularly and lasts up to 3 months. The initial injection should be followed by a second at 6 weeks, and subsequent injections every 10-14 weeks depending on the trough level of testosterone just before each injection. It is given as slow deep intra-muscular injection over 1 to 2 minutes. The frequency of injection may need to be adjusted (8-14 weeks) depending on trough testosterone level.

Sustanon 250mg/1ml is a solution in oil. Each ampoule contains 1 ml arachis oil containing the following active substances:

30 mg Testosterone propionate, 60 mg Testosterone phenylpropionate, 60 mg Testosterone isocaproate & 100 mg Testosterone decanoate. The total amount of testosterone per ml is 176 mg.

Usually, one deep intramuscular injection of 1ml per 3 weeks is adequate; the dose should be adjusted to the response of the individual patient.

Contra-indications and precautions for use

Testosterone is contra-indicated:

- in cases of known or suspected prostate cancer or breast carcinoma
- in cases of known hypersensitivity to testosterone or to any of the excipients

Testosterone supplementation in patients e.g. presenting with erectile dysfunction or non-specific symptoms but without confirmed abnormal biochemistry is inappropriate, ineffective and carries with it significant risks e.g. of stroke.
Testosterone should be used with caution in cancer patients at risk of hypercalcaemia (and associated hypercalciuria), due to bone metastases. Regular monitoring of blood calcium levels is recommended in these patients.
In patients suffering from severe cardiac, hepatic or renal insufficiency, or ischaemic disease, treatment with testosterone may cause severe complications characterized by oedema with or without congestive cardiac failure. In such case, treatment must be stopped immediately. In addition, diuretic therapy may be required.
Testosterone should be used with caution in patients with ischaemic heart disease.
Testosterone may cause a rise in blood pressure and so testosterone should be used with caution in men with hypertension.
There is limited experience on the safety and efficacy of the use of testosterone in patients over 65 years of age. It should be taken into account that physiologically testosterone blood levels decrease with age.
Testosterone should be used with caution in patients with epilepsy, sleep apnoea and migraine as these conditions may be aggravated.
Certain clinical signs: irritability, nervousness, weight gain, prolonged or frequent erections may indicate excessive androgen exposure requiring dosage adjustment.
If no precautions are taken, testosterone gel can be transferred to other persons by close skin to skin contact at any time after dosing, resulting in increased testosterone serum levels and possibly adverse effects. The physician should inform the patient carefully about the risk of testosterone transfer and about safety instructions. Testosterone should not be prescribed in patients with a major risk of non-compliance with safety instructions (*e.g.* severe alcoholism, drug abuse, severe psychiatric disorders). See individual products Summary of Product Characteristics (SPC) for further detail.

Side-effects
The most common adverse events associated with testosterone replacement therapy are: increased haematocrit; worsening prostatism; raised prostate-specific antigen (PSA) levels; sleep apnoea; acne; local skin reaction with topical gels; mild weight gain and fluid retention in patients with cardiac dysfunction.
Refer to the SPC for a full list of adverse effects. If the patient reports adverse effects or no improvement in symptoms, seek advice from the specialist.
None of the licensed testosterone replacement products have black triangle (▼) status. Serious suspected reactions (even if well recognised or causal link uncertain) should be reported to the MHRA.

Monitoring

Endocrine Clinic – Annual Review	**General Practitioner – Annual Review** (To be arranged 6 months after endocrine appointment)
Patient symptoms and signs – prostatism symptoms + history, libido, early morning erections, sexual function, well-being, history suggestive of polycythaemia. Blood tests – FBC (Haemoglobin, Haematocrit), PSA, Trough Testosterone (for injection only). Peak testosterone levels are taken 2-4 hours after application of testosterone gel to determine the peak serum level. (Other tests where indicated), LFTs, lipid profile where applicable.	Patient symptoms and signs – prostatism symptoms + history, libido, early morning erections, sexual function, well-being, history suggestive of polycythaemia. Digital Rectal Examination (DRE) if indicated. **<u>If indicated during interim primary care review:</u>** Blood tests – FBC, PSA, LFTs* (A request for interim monitoring will come from the specialist following on from the patient's annual review in secondary care) **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.* <u>Aim to maintain:</u> o Haematocrit < 52 -54%. Higher levels may need temporary drug cessation, and then re-introduction of testosterone at a lower dose. o PSA <1.4 ug/L increase annually. Rapid or sustained rises require urological evaluation (Cause for concern would be a PSA increase 1ng/ml over baseline or a PSA velocity greater than 0.35 ng/ml per year)

Endocrine Clinic – Annual Review	**General Practitioner – Annual Review** (To be arranged 6 months after endocrine appointment)
	Topical testosterone: Check blood testosterone 2 weeks after commencement with blood taken 3-4 hours after gel application. Inform patient not to apply testosterone gel over venepuncture site as this will lead to high levels as a result of skin contamination. If testosterone is below 12nmol/l then check patient compliance prior to checking the level. The absorption of testosterone from the gel can be variable. Once patient compliance has been confirmed and the level is <12nmol/l then the dose needs to be increased. If the testosterone level is >30nmol/ then the dose should be reduced.

Careful and regular monitoring of the prostate gland and breast must be performed in accordance with recommended methods (digital rectal examination and estimation of serum prostate specific antigen (PSA) in patients receiving testosterone therapy).

If PSA becomes raised above the normal range, seek specialist advice.
Normal age-specific range for PSA used by the RUH is:

- age <50 = <2.5µg/l
- age 50-54 = <3.0µg/l
- age 55-59 = <3.5µg/l
- age 60-69 = <4 µg/l
- age ≥70 = <6.5µg/l

Currently, there is no consensus about age specific testosterone reference values. However, it should be taken into account that physiologically testosterone serum levels are lower with increasing age.

Drug Interactions

- Due to changes in anticoagulant activity (increased effect of the oral anticoagulant by modification of hepatic synthesis of coagulation factor and competitive inhibition of plasma protein binding) increased monitoring of the prothrombin time and international normalized ratio (INR) are recommended. Patients receiving oral anticoagulants require close monitoring especially when androgens are started or stopped.
- Concomitant administration of testosterone and ACTH or corticosteroids may increase the risk of developing oedema. As a result, these medicinal products should be administered cautiously, particularly in patients suffering from cardiac, renal or hepatic disease.
- Interactions with laboratory tests: androgens may decrease levels of thyroxin binding globulin, resulting in decreased T_4 serum concentrations and in increased resin uptake of T_3 and T_4. Free thyroid hormone levels, however, remain unchanged and there is no clinical evidence of thyroid insufficiency.
- Changes in insulin sensitivity, glucose tolerance, glycaemic control, blood glucose and glycosylated haemoglobin levels have been reported with androgens. In diabetic patients, antidiabetics' medication might need reduction.

Refer to the Summary of Product Characteristics for a full list of interactions and further detail.

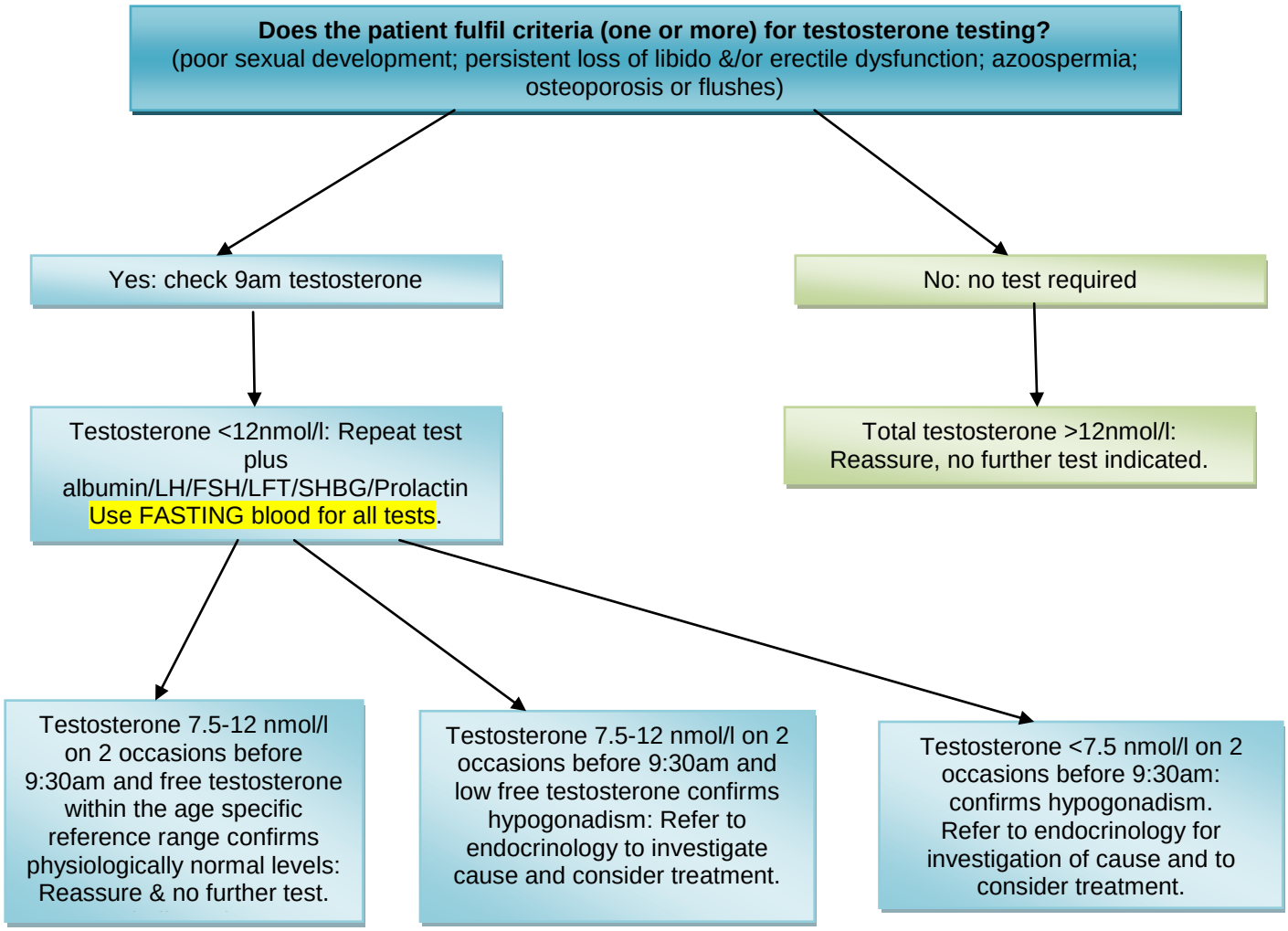
Cost

At current prices (March 2018), one year's treatment with topical testosterone products is approximately £360.

References

Summary of Product Characteristics Testogel: https://www.medicines.org.uk/emc/product/8919 accessed 11/3/18
Summary of Product Characteristics Tostran: https://www.medicines.org.uk/emc/product/332
Summary of product characteristics Nebido: https://www.medicines.org.uk/emc/product/3873 accessed 14/3/18
Summary of Product Characteristics Sustanon: https://www.medicines.org.uk/emc/product/5373/smpc accessed 14/3/18

Testosterone investigation algorithm



In males with persistently low (i.e. confirmed on 9am sample) total testosterone (7.5-12 nmol/L) the biochemistry laboratory will calculate free testosterone. The free testosterone result along with reference ranges will be reported in a comment with the rest of the hormone profile results.