GMMMG Formulary Managed Entry Subgroup
TESTOSTERONE PREPARATIONS FOR HYPOGONADISM IN ADULT MEN- INFORMATION FOR PRIMARY CARE

RAG List Status
Testosterone products when used within licensed indications in men are classified GREEN (following specialist advice) by the Greater Manchester Medicines Management Group.

Licensed Indications
Male hypogonadism in adults when testosterone deficiency has been confirmed by clinical features and biochemical tests. Serum testosterone should be measured between 7 and 11am, with a reliable method, on at least 2 occasions, preferably 4 weeks apart. Ideally fasting levels should be obtained when able.

What is it for?
Testosterone treatment aims to restore testosterone levels to the physiological range in men with consistently low levels of serum testosterone and associated symptoms of androgen deficiency. The aim of testosterone treatment is to restore physiological androgen dependent functions and to improve quality of life, e.g. sense of well-being, sexual function, muscle strength and bone mineral density**.**

European Association of Urology Guidance
In adult-onset hypogonadism testosterone treatment may improve symptoms.

- Weight reduction, lifestyle modification and good treatment of comorbidities can increase testosterone and reduce associated risks for diabetes and cardiovascular diseases.
- Testosterone treatment can improve body composition, bone mineralisation, signs of the metabolic syndrome, male sexual problems, diabetes regulations, memory and depressive symptoms.
- A reduction in BMI and waist size, improved glycaemic control and lipid profile are observed in hypogonadal men receiving testosterone treatment

When should GPs be asked to prescribe?
GP will only be asked to prescribe when clinical features and biochemical tests have confirmed testosterone deficiency.

Preparations available
The choice and of product and route of administration is guided by patient preference, ease of use, and cost. Short-acting preparations are preferred to long-acting depot administration in the initial treatment phase, so that any adverse events that may develop can be observed early and treatment can be discontinued if needed.

FORMULATION	ADMINISTRATION	ADVANTAGES	DISADVANTAGES	ADVICE ON CHECKING LEVELS
Testosterone undecanoate capsules; *Restandol Testocaps®*	Oral capsules; 2-6 capsules every 6 hours	Convenience of oral administration Absorbed through the lymphatic system, with consequent reduction of liver involvement.	Variable levels of testosterone above and below the mid-range. Need for several doses per day with intake of fatty food.	There is considerable variability in testosterone in the same individual on different days, and among individuals (fat content of meals affects bioavailability)

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Testosterone propionate, phenylpropionate, isocaproate, and decanoate injection; *Sustanon®*	Intramuscular injection every 3 weeks	Short-acting preparation that allows drug withdrawal in case of onset of side-effects.	Possible injection site pain/reaction Contains peanut oil and should be avoided in peanut/ soya bean allergy.	Serum total testosterone levels should be checked 1 week after an injection of testosterone to assess whether levels are therapeutic Levels should be checked in accordance with the guidance on pages 3 & 4.
Testosterone enantate injection	Intramuscular injection every 2-3 weeks Can be reduced to every 3-6 weeks for maintenance.	Short-acting preparation that allows drug withdrawal in case of onset of side-effects.	Fluctuation of testosterone levels. Possible injection site pain/reaction	Serum total testosterone levels should be checked 1 week after an injection of testosterone to assess whether levels are therapeutic Levels should be checked in accordance with the guidance on pages 3 & 4.
Testosterone undecanoate injection; *Nebido®*	Intramuscular injection every 10-14 weeks Dose adjusted to maintain trough testosterone >12nmol/L	Steady state levels Reduced frequency of administration improves compliance	Long-acting preparation that cannot allow drug withdrawal in case of onset of side-effects. Possible injection site pain/reaction	Testosterone levels should be measured just prior to an injection (i.e., trough level) to ensure concentration is in the low-normal range.
Testosterone transdermal gels; *Testogel®, Testavan®, Tostran®, Testim®*	Topical gel, applied daily May require dose titration Patients with high BMI may require higher doses since obesity seems to affect the pharmacokinetics of transdermal testosterone preparations	Fast onset Provides uniform and normal serum levels for 24 hours Provides flexibility of dosing, ease of application, good skin tolerability; less erythrocytosis than injectable testosterone	Risk of interpersonal transfer: Patients applying transdermal gels should not wear a shirt for at least 10 minutes after application, and should ensure adequate drying before putting on a shirt. Sexual activity, showering, and swimming should be avoided for 4 hours after gel application to avoid transfer. Gel should be applied on the shoulder, upper arm, or abdomen for better absorption.	Testosterone level should be checked 2 to 4 hours after testosterone gel application, when peak absorption level is attained. Testosterone levels can be checked to see if they have reached therapeutic levels as early as 1 to 2 weeks after initiation of transdermal products.

Contraindications

- Prostate cancer (locally advanced or metastatic) or unevaluated prostate nodule/induration; patients with elevated PSA levels should be reviewed by urology before initiation of testosterone replacement therapy
- Male breast cancer
- An active desire to have children
- Haematocrit >54%
- Severe chronic heart failure [New York Heart Association (NYHA) class IV]
- History of liver tumours
- Hypercalcaemia
- MI or stroke within the last 6 months
- Thrombophilia

Cautions

- Untreated sleep apnoea
- Chronic heart failure or ischaemic heart disease
- Hepatic or renal insufficiency
- Hypertension
- Epilepsy
- Migraine
- Diabetes mellitus
- Severe lower urinary tract symptoms

What are the main side-effects?

Local skin irritation is the main side effect of transdermal testosterone preparations.
Intramuscular dosing may cause intermittent supra-physiological testosterone levels with resulting fluctuations in mood and sexual behaviour, polycythaemia, gynaecomastia, and over-stimulation of the prostate.
Polycythaemia may occur- this is more common in older men treated with injectable testosterone, along with increased in haematocrit, haemoglobin, gynaecomastia, oedema, acne and other skin reactions.

Monitoring guidance for GPs

Regular follow-up is needed in patients receiving testosterone treatment, as potentially androgen-dependent symptoms and conditions may occur. The side-effects of testosterone treatment are limited, but their incidence and clinical relevance is as yet unclear. The primary aim of testosterone treatment is to alleviate the clinical symptoms of testosterone deficiency. Careful monitoring of changes in the clinical manifestations of testosterone deficiency should therefore be an essential part of every follow-up visit

- Assess the response to testosterone treatment at three, six and twelve months after the onset of treatment, and thereafter annually.
- Monitor testosterone, haematocrit at three, six and twelve months and thereafter annually. Decrease the testosterone dosage or switch testosterone preparation from intramuscular to topical or venesection, if haematocrit is above 0.54%. If haematocrit remains elevated, stop testosterone and reintroduce at a lower dose once haematocrit has normalised

- Assess prostate health by digital rectal examination and prostate-specific antigen (PSA) before the start of testosterone replacement therapy (TRT). Follow-up by PSA tests at three, six and twelve months and thereafter annually
- Assess men with cardiovascular diseases for cardiovascular symptoms before testosterone treatment is initiated and continue close clinical assessment during treatment.
- Failure to show signs of benefit for libido, sexual function, muscle function and improved body fat within 6 months of starting testosterone treatment should prompt treatment discontinuation and further investigation for other causes of the symptoms and referral back to the specialist.

REFERENCES

Please note that this information is a summary to guide prescribers – for further information on individual products please consult individual SPCs at www.medicines.org.uk

BMJ Best Practice: Hypogonadism in men. Last updated May 1st 2018. Available via:- https://bestpractice.bmj.com/topics/en-gb/1093/management-approach

European Association of Urology: Male Hypogonadism Clinical Guideline. Last updated 2018. Available via:- https://uroweb.org/guideline/male-hypogonadism/#6

Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline. March 2018. Available via:- https://www.endocrine.org/guidelines-and-clinical-practice/clinical-practice-guidelines/testosterone-therapy

The British Society for Sexual Medicine: Guidelines on adult testosterone deficiency with statements for UK practice. October 2017. Available via:- http://www.bssm.org.uk/wp-content/uploads/2017/12/guidelines-on-adult-testosterone-deficiency-with-statements-for-uk-practice.pdf