NORFOLK AND WAVENEY STP THERAPEUTICS ADVISORY GROUP (TAG)

SHARED CARE AGREEMENT

Shared care guidelines for use of Testosterone Therapy for boys in Infancy and Adolescence

Monitoring level - AMBER 2 - Prescribe the drug and perform a more intense level of monitoring, e.g. quarterly

Generic and Proprietary/Brand Name	
IM Testosterone esters - Sustanon 250® Testosterone proprionate, Testosterone Enantate **Oral** Testosterone undecanoate Restandol® Testocaps® **Topical** Testogel®, Tostran®	
Indications for shared care	
This shared care agreement is to support primary care with the management of boys with absent/delayed puberty requiring exogenous testosterone therapy under the care and supervision of paediatric endocrinologists. This includes boys with hypogonadotropic hypogonadism (HH) of various etiologies, androgen deficiency secondary to testicular failure (hyper gonadotrophic hypogonadism) of various etiology, and constitutional delay of growth and puberty (CDGP). The aim of testosterone replacement therapy is to mimic the normal pattern of puberty and mimic requirements at different stages of pubertal development. This guideline aims to provide the clinician with testosterone dosing regimens for pubertal induction, progression and post-pubertal maintenance. This agreement also includes the treatment of male infants with micropenis (due to hypogonadism), testosterone can be given during the 'mini-puberty' of infancy. The aims of treatment are to improve penile length, and to allow urination while standing up.	
Specialist Prescribing and Monitoring Responsibilities – summary. Full details in main body of document	**GP / Community Team - Primary Care Prescribing and Monitoring Responsibilities – summary. Full details in main body of document**
• Discuss the benefits/side effects of treatment with the patient and parents/carers. • Initiate treatment. Hospital specialist to prescribe the first injection. • Continue to prescribe until GP has taken over prescribing. • Monitor patients as described overleaf, or advise GP on what to monitor. Ensure copies of results are available to GP. • Communicate promptly with the GP when treatment is changed or needs to be changed by the GP, any results of the monitoring undertaken, and any assessment of adverse events. • Have a mechanism in place to receive rapid referral of a patient from the GP in the event of adverse effects or deteriorating clinical condition. • Review the patient's condition and monitor response to treatment regularly, at least every 6 months. • Ensure that clear backup arrangements exist for GPs to obtain advice and support. **Report adverse events to the MHRA, on a Yellow card www.mhra.gov.uk/yellowcard, to the GP and appropriate Medicines Optimisation team**	• If declining the request for shared care please indicate the reason for declining. • Prescribe and administer testosterone injection or prescribe testosterone tablets at the dose/frequency recommended. • Adjust the dose as advised by the specialist. • Report to and seek advice from the specialist on any aspect of patient care that is of concern and may affect treatment. • Refer back to the specialist if the patient's condition deteriorates, or if there are other concerns. • Stop treatment on the advice of the specialist or immediately if an urgent need to stop treatment arises. **Report adverse events to the MHRA on a Yellow Card (www.mhra.gov.uk/yellowcard), the specialist, and the appropriate Medicines Optimisation team.**

Contact for the TAG: jennifer.carroll@nhs.net

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Patient Information
• The Patient/Parent/Carer should report to the specialist or GP if they do not have a clear understanding of the treatment. • Share any concerns they have in relation to the treatment with the specialist or GP. • Inform specialist or GP of any other medication being taken, including over-the-counter, homeopathic, herbal or illicit substances. • Report any adverse effects or warning symptoms to the specialist or GP. **The patient may also choose to report any adverse drug reaction direct to the MHRA on a Yellow Card , available at pharmacies, GP surgeries or from the Yellow Card hotline (Freephone 0808 100 3352 during business hours). The form can also be downloaded from www.mhra.gov.uk/yellowcard**
Specialist Contact Details
• Dr Vipan Datta (01603 286349) • Dr E Webb and Dr R Alanoor (01603 286357) • Dr E Sotiridou (01603 286349) • Endocrinology Nurse Specialist karen.blair@nnuh.nhs.uk

GENERAL PRINCIPLES FOR SHARED CARE PRESCRIBING

- Shared Care is only appropriate if it provides the optimum solution for the patient.
- GPs are **invited** to participate. If GPs are not confident to undertake these roles, they are 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 if they are unwilling to do so.**
- Prescribing responsibility will only be transferred when it is agreed by the consultant and the patient's GP and when the patient's condition is stable or predictable.
- Safe prescribing must be accompanied by effective monitoring.
- **The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.**

Background to Treatment

Androgens are used as replacement therapy in androgen deficiency, in delayed puberty, and in those who are hypogonadal due to either pituitary or testicular disease. The aim of testosterone replacement therapy is to mimic the normal pattern of puberty and mimic requirements at different stages of pubertal development.

Licensed use and agreed local off-label use

Use in children is unlicensed but recommended in national guidelines for the induction of puberty and replacement therapy (in boys who are hypogonadal due to testicular or pituitary disease from the age of 12 yrs.) or the induction/augmentation of male puberty in puberty delay. The doses below are those recommended by the British Society of Paediatric Endocrinology national guidelines (2013 updated January 2019) for Sustanon® and oral testosterone undecanoate.

Criteria for Patient Selection

Before starting treatment endocrine assessment of the patient's LH, FSH, testosterone levels and where indicated testosterone response to HCG stimulation. Clinical assessment of Tanner puberty staging and testicular volumes before and during treatment. Assessment of growth and bone age Serum testosterone levels where indicated during treatment.

Form and strength of preparation

IM Testosterone esters - Sustanon 250® Testosterone proprionate, Testosterone Enantate
Oral Testosterone undecanoate (Restandol® Testocaps®)

Topical Testogel®, Tostran®

Side Effects and Management

Common or very common
Hot flush; hypertension; polycythaemia; prostate abnormalities; skin reactions; weight increased
Uncommon
Alopecia; asthenia; behaviour abnormal; depression; dizziness; dyspnoea; dysuria; gynaecomastia; headache; hyperhidrosis; insomnia; nausea; sexual dysfunction
Rare or very rare
Pulmonary oil microembolism
Frequency not known
Anxiety; epiphyses premature fusion; fluid retention; jaundice; oedema; oligozoospermia; paraesthesia; precocious puberty; prostate cancer; seborrhoea; sleep apnoea; urinary tract obstruction

Possible issues in childhood

- Premature epiphyseal closure and stunting of final height (if high doses taken)
- Mood swings, acne, behavioural disturbance
- Worsening of sleep apnoea
- Polycythaemia

- Gynaecomastia
- Weight gain
- Hypertension
- Cholestatic jaundice
- Electrolyte disturbance

Future possible issues in adulthood

- Suppression of spermatogenesis - discontinue when seeking fertility
- Acceleration of male pattern balding
- Worsening of benign prostatic hypertrophy, possible prostate cancer

Possible cardiovascular effects not substantiated on meta-analysis (Corona 2014)
Testosterone undecanoate | Drugs | BNF | NICE
Testosterone | Drugs | BNF | NICE
Sustanon 250, 250mg/ml solution for injection - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
Testosterone Enantate 250 mg/ ml Solution for Injection Ampoules - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Drug Interactions

- Testosterone has been reported to increase the activity of oral anti-coagulants such as warfarin and phenindione. It may also enhance the hypoglycaemic effect of anti-diabetic agents.
- Androgens may decrease levels of thyroxine-binding globulin resulting in decreased total serum levels, whilst free T3 and T4 thyroid hormone levels remain unchanged.

Testosterone | Drugs | BNF | NICE

Cautions and Contraindications

- Breast cancer in males
- History of liver tumours
- Hypercalcaemia
- Prostate cancer

Testosterone | Drugs | BNF | NICE

Initiation of therapy and ongoing dose regimen

Initiation of therapy will be arranged by the hospital consultant and given in secondary care.

Dosage and administration- hypogonadotrophic hypogonadism and testicular failure

Low doses are initiated and gradually increased to adult dosage over time, usually started between 12-13 years.

Intramuscular injection is the most commonly used method for puberty induction due to greater evidence base, experience and better known side effect profile.

Intramuscular testosterone regime

- **Preparations-**Testosterone esters (Sustanon 250®),testosterone proprionate, testosterone enantate are licensed in the UK. *(Testosterone undeconate (Nebido®) should **not** be used for puberty induction)*
- Dose 50-100mg monthly, increased by 50mg every 6 months until 200-250mg reached.
- 6 months after 250mg reached change to 250 mg 2-3 weekly.

Sustanon 250® contains arachis oil, and therefore should be used with caution in those with peanut allergy (and soya allergy, due to cross reactivity). The arachis oil does not contain peanut protein and therefore most individuals with peanut allergy will tolerate the preparation, unless their sensitivity is very high.

Oral (less commonly used due to variable absorption)
Testosterone undecanoate (Restandol® Testocaps™) starting at 40mg once daily increasing every 6 months to 40mg twice daily and then 40mg three times daily.
Transdermal testosterone gel regimes

- Preparation – 2% metered-dose testosterone gel (Tostran®). Each metered-dose application contains 0.5g of gel, which contains 10mg of testosterone.
- Dose – 10-20mg (1-2 metered applications), increasing by 10mg every 6 months until adult doses achieved
- Frequency – Once daily
- Adult dosing – 60-80mg once daily; Once 60mg once daily is reached, serum testosterone concentration can be measured 2 hours after application of Tostran®, with the dose increased to 80mg once daily if the testosterone level is suboptimal

This preparation is preferred as it allows more accurate dose delivery and easier titration compared to the sachet preparations.

- Preparation – 1% testosterone gel sachets (Testogel®), containing 50-100mg of testosterone in each 5-10g sachet
- Dose – 10-20mg (approximately one-third of a 50mg/5g sachet), increasing by one-third of a sachet yearly until 50mg daily achieved
- Frequency – Once daily (or alternate days initially)
- Adult dosing – 50-100mg once daily

Care must be taken to specify gel rather than cream when prescribing topical testosterone preparations for pubertal induction and maintenance in hypogondaism, as the testosterone content of each per application varies significantly.

Dosage and administration-Constitutional Delay in Growth and Puberty

Intramuscular regime

- **Preparations-**Testosterone esters (Sustanon 250®), testosterone enantate, testosterone proprionate are licensed in the UK. *(Testosterone undeconate (Nebido®) should **not** be used for puberty induction)*
- Dose 50-100mg monthly
- Duration 3-6 months

Oral

- Testosterone undecanoate (Restandol® Testocaps®)
- 40 mg once daily
- Duration 3-6 months

Micropenis in infancy
Intramuscular

- Preferred preparation - Testosterone propionate
- Dose – 25mg
- Frequency – Monthly
- Duration – 3 months

Testosterone propionate is preferred as it is not made up in any vehicles which may be toxic to infants. However, availability can be an issue, in which case testosterone enantate can be

cautiously used. Testosterone enantate contains benzyl benzoate and castor oil - the latter has been associated with severe anaphylactoid reactions4 and the safety profile of benzyl benzoate in infants is not known. **Sustanon 250® (containing a mixture of testosterone esters) is contraindicated in infancy as it contains benzyl alcohol5, which carries the risk of a severe and potentially fatal toxic reaction6**

Topical

- Preparation – Testosterone 1-5%* cream
- Dose – 1 application
- Frequency – Three times daily
- Duration – 3-6* weeks
- Care must be taken to specify cream rather than gel when prescribing topical testosterone preparations for micropenis in infancy, as the testosterone content of each per application varies significantly.

Duration of therapy / How the treatment will be reviewed and if appropriate, stopped

- For pubertal induction in CDGP - 3-6 months and review.
- For hypogonadism - can take 2-3 years for complete pubertal changes.
- For hypogonadotropic hypogonadism and testicular failure - lifelong ongoing care to be shared with adult services.
- For micro penis 3 months

Baseline assessment and ongoing monitoring – by Specialist

- Before starting treatment, endocrine assessment of the patient's LH, FSH, testosterone levels and where indicated testosterone response to HCG stimulation.
- Clinical assessment of Tanner puberty staging and testicular volumes before and during treatment. Assessment of growth and bone age.
- To review in clinic every 3-6 months depending on therapeutic indication.
- Clinical assessment of Tanner puberty staging and testicular volumes before and during treatment.
- Assessment of growth and bone age Serum testosterone levels where indicated during treatment.

GP / Community Team or other Primary Care monitoring responsibilities

No GP monitoring responsibilities unless previously agreed with the specialist to do so, for example monitoring of the patient's height and weight by the practice nurse or routine phlebotomy for serum testosterone.

Consultant / Specialist prescribing responsibilities

- Discuss the benefits/side effects of treatment with the patient and parents/carers.
- Initiate treatment. Hospital specialist to prescribe the first injection.
- Continue to prescribe until GP has taken over prescribing.
- Monitor patients as described overleaf or advise GP on what to monitor. Ensure copies of results are available to GP.
- Communicate promptly with the GP when treatment is changed or needs to be changed by the GP, any results of the monitoring undertaken, and any assessment of adverse events.
- Have a mechanism in place to receive rapid referral of a patient from the GP in the event of adverse effects or deteriorating clinical condition.
- Review the patient's condition and monitor response to treatment regularly, at least every 6 months.
- Ensure that clear backup arrangements exist for GPs to obtain advice and support.

Report adverse events to the MHRA, on a Yellow card www.mhra.gov.uk/yellowcard, to the GP and appropriate Medicines Optimisation team

GP prescribing responsibilities

- If declining the request for shared care please indicate the reason for declining.

- Prescribe and administer testosterone injection or prescribe testosterone tablets at the dose/frequency recommended.
- Adjust the dose as advised by the specialist.
- Report to and seek advice from the specialist on any aspect of patient care that is of concern and may affect treatment.
- Refer back to the specialist if the patient's condition deteriorates, or if there are other concerns.
- Stop treatment on the advice of the specialist or immediately if an urgent need to stop treatment arises.

Report adverse events to the MHRA on a Yellow Card (www.mhra.gov.uk/yellowcard), the specialist, and the appropriate Medicines Optimisation team.

Indications for referral back to Specialist

- Refer back to the specialist if the patient's condition deteriorates, or if there are other concerns or adverse effects of treatment.
- Report to and seek advice from the specialist on any aspect of patient care that is of concern and may affect treatment.
- Refer back to the specialist if any patient/parent concerns or non-adherence.

Further information and supporting documents

References:

BSPED Guideline: Testosterone Therapy in Infancy and Adolescence R El-Khairi, N Shaw, EC Crowne (November 2016) Revision: A Chinoy, EC Crowne, M Skae (January 2018). Available at; https://www.bsped.org.uk/media/1659/revised-bsped-testosterone-guideline-4th-draft-30072019.pdf accessed 10/09/2024

Corona G et al. 2014 Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis. Expert Opin Drug Saf. 13(10):1327-51.

Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press <http://www.medicinescomplete.com> [Accessed on 25.6.20]

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5.0	Nov 2023	SN/JC MO Team NWICB	Final	Transferred to new template and formatted ready for publication on new KNoW website
6.0	Nov 2024	JC – MO Team NWICB	Final	Reviewed by Paediatric Endocrinology Nurse Specialist and supported by TAG. Amendments to available preparations and addition of micrppenis indication