Testosterone (Sustanon® 250 injection and Tostran® 2% gel) Therapy* for Hypogonadism and Constitutional Delay in Growth and Puberty in male children and adolescent *information sheet		
V2.0	Last reviewed: January 2023	Review date: January 2026

Nottinghamshire Area Prescribing Committee

Testosterone (Sustanon® injection and Tostran® gel) for Hypogonadism and Constitutional Delay in Growth and Puberty *in male children and adolescents*

Part of the shared care protocol for treatment of Hypogonadism and Constitutional Delay in Growth and Puberty in male children and adolescents

Traffic light classification - Amber 1
Information sheet for Primary Care Prescribers

This guideline is for children and young people assigned male sex at birth who have delayed puberty and/or hypogonadotropic hypogonadism. It does NOT apply to children and young people with gender identity difficulties

Licensed Indications

Sustanon-250 injection is licensed in adults for testosterone replacement therapy but not licensed in children and should be used with caution in children.

Tostran 2% gel is licensed in adults for testosterone replacement therapy, but not licensed in children.

Although both Sustanon -250 injection and Tostran 2% gel are unlicensed in children, it is established therapy for treatment of hypogonadism and constitutional delay in growth and puberty in children and recommended by national guidelines.

The British Society for Paediatric Endocrinology and Diabetes (BSPED) recommend several licensed preparations for use off-label in children.

This information sheet covers use for the following indications

- Constitutional delay in growth and puberty (CDGP)
- Hypogonadism

Products should only be used when testosterone deficiency has been confirmed by clinical features and biochemical tests.

Exclusions

- Patients who have not completed a specialist assessment and evaluation to confirm diagnosis of CDGP or Hypogonadism
- Female patients
- Children under 12 years

Therapeutic Summary

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The aim of testosterone replacement therapy is to mimic the normal cadence of puberty and match requirements at different stages of pubertal development in patients with Hypogonadism and CDGP. Testosterone replacement therapy is used to induce development of secondary sexual characteristics and promote linear growth, normal accrual of muscle mass and bone density while avoiding premature epiphyseal plate closure. Testosterone replacement therapy is usually started from the age of 12-14 years and dose is reviewed 6 monthly increasing progressively over 24-36 months until adult maintenance dose is reached. The maintenance dose of testosterone replacement is continued into adult life. In the case of CDGP the testosterone is stopped when there is established endogenous puberty, as assessed by the specialist.

All boys with delayed puberty (absence of signs of secondary sexual development i.e. testicular volume less than 4 mL at 14 years of age) should be referred to paediatric endocrinology for assessment. CDGP is the most common cause but it can be extremely difficult in the early stages of puberty to differentiate CDGP from Hypogonadism. Boys with CDGP/Hypogonadism may manifest with psychological distress because of their lack of growth and pubertal progression, which can affect their school performance, social relationships and can affect their psychological wellbeing. A course of testosterone treatment should be offered in order to enhance growth rate and expedite the features of puberty. In those with CDGP who receive testosterone treatment, the intervention is well tolerated, highly effective and regarded as a standard therapeutic option.

Monitoring of growth and pubertal status is paramount in boys who receive testosterone replacement treatment. This is done by the paediatric endocrine specialist team every 6 months.

Medicines Initiation

- Testosterone replacement therapy for pubertal induction in children and adolescents will only be started following recommendation from paediatric consultant endocrinologist. The first dose can be given in either primary or secondary care, depending on the preferences of the family and the GP practice.

Products available, dosages, route of administration and duration

Table 1: Testosterone delivery for constitutional delay in growth and puberty

	Intramuscular (preferred option)	**Metered-dose gel (secondary option)**
Preparation	Sustanon-250® (250mg/ml ampoule for injection)	Tostran® (2%; 10mg testosterone per metered application)
Initial dose	50mg-100mg (0.2ml - 0.4ml)	10-20mg
Frequency	Monthly	Once daily
Duration	3-6 months	3-6 months

Table 2: Testosterone delivery for pubertal induction in boys with hypogonadism:

	Intramuscular (preferred option)	Metered-dose gel (secondary option)
Preparation	Sustanon-250® (250mg/ml ampoule for injection)	Tostran® (2%; 10mg testosterone per metered application)
Initial dose	50mg-100mg (0.2ml-0.4ml)	10-20mg
Initial Frequency	Monthly	Once daily
Titration	Increase by 50mg (0.2ml) every 6-12 months, increasing frequency to 2-3 weekly once 250mg reached	Increase by 10mg every 6 months
Adult dosing	200-250mg 2-4 weekly	60-80mg once daily

In the treatment of hypogonadism, dose escalation to achieve adult dosing of 250mg every 3 weeks may take 2.5 years to 3 years to be established. This group of boys will be reviewed in the transitional clinic for joint review with adult endocrinologist. Information will be provided on other testosterone preparations once maintenance dose is established.
Testosterone replacement information sheet for male hypogonadism in adults can be located here

Duration of treatment

Patients with a diagnosis of CDGP will mostly complete the course at 6 months, rarely requiring treatment beyond 12 months.

Patients with a diagnosis of hypogonadism will require life-long treatment with testosterone replacement therapy.

Monitoring Requirements and Responsibilities

All monitoring will be done in secondary care.

Table 3: Assessments to be taken in secondary care specialist clinic.

	3-6 monthly	12 monthly
Pubertal development and staging	✓	
Height and weight	✓	
Bone age		✓

The local specialist team have advised that further monitoring will not be required by primary care as the doses for pubertal induction are so much lower than the normal doses used for testosterone replacement.

Explicit criteria for review and discontinuation of the medicine

In patients with CDGP, keep under specialist review until testicular volumes are 10mL or more. If during treatment for hypogonadism, an increase in testicular volume is noticed, treatment must be discontinued immediately, and diagnosis reviewed. Treatment can be recommenced once diagnosis of hypogonadism due to testicular failure is reconfirmed.

Contraindications

Sustanon 250 and Tostran 2% gel

- Hypersensitivity to the active substance or to any of the excipients in any of the testosterone formulations i.e. Arachis oil in Sustanon-250
- Known or suspected carcinoma of the prostate or breast

For Sustanon-250 only

- Hypercalcaemia
- Past and present liver tumors
- Nephrosis

Precautions

- Sustanon®-250 contains arachis oil and therefore should be used with caution in those with peanut allergy (and soya allergy, due to cross sensitivity). The arachis oil does not contain peanut protein and therefore most individuals with peanut allergy will tolerate the preparation, unless their sensitivity is high.
- Care and clarity must be taken when prescribing volumes of testosterone intramuscular injection. The recommendation is to write dose and volume on prescriptions e.g. "Sustanon® 250mg/ml injection: administer 50mg (0.2ml of 250mg/ml vial) IM monthly". This dosage direction must also be clear on the written communication to primary care practitioners.
- With topical formulations men should avoid skin to skin contact with pregnant or breastfeeding women. During application, female carers should be advised to wear gloves. In the event of contact the area of the skin should be washed with warm soapy water as soon as possible.
  See MHRA drug safety update on risk of harm to children following accidental exposure to topical testosterone.
- Topical formulations must specify form i.e. gel to avoid prescriptions for cream, which can cause variations in dosing.

Side-effects

Local discomfort at injection site due can occur due to the oily formulation. The injection site should be varied periodically to minimise this.

Other possible side-effects in childhood include: priapism, polycythaemia, electrolyte imbalance, fluid retention, depression, altered mood, nervousness, pruritus, acne, weight gain, sleep apnoea, hypertension, cholestatic jaundice, gynecostamia.

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

Clinically relevant medicine interactions and their management

Sustanon 250 and Tostran 2% gel (as per SPC)

- Testosterone may enhance the activity of coumarin anticoagulants.Close monitoring of INR especially when the androgen treatment is started, stopped or the dose is changed is recommended
- Testosterone may decrease concentrations of thyroxine-binding globulin, resulting in decreased T4 serum concentrations and increased uptake of T3 and T4. .Free thyroid hormone levels remain unchanged, and there is no clinical evidence of thyroid dysfunction.
- The concurrent administration of testosterone with ACTH or corticosteroids may enhance oedema formation therefore these active substances should be administered cautiously, particularly in patients with cardiac or hepatic disease or in patients predisposed to oedema

For Sustanon only (as per SPC)

- Androgens may improve glucose tolerance and decrease the need for insulin or other anti-diabetic medicines in diabetic patients. Patients with diabetes mellitus should therefore be monitored especially at the beginning or end of treatment and at periodic intervals during Sustanon 250 treatment.
- Enzyme-inducing agents may decrease, and enzyme-inhibiting drugs may increase testosterone levels. Therefore, adjustment of the dose of Sustanon 250 may be required.

For a full list of contraindications, precautions and medication interactions refer to the Summary Product Characteristics (SPC) and BNFC

Information given to patient

Advice to patients/carers:

- Female carers must be advised to wear gloves to avoid cross transfer of Tostran® gel.
- See MHRA drug safety update on risk of harm to children following accidental exposure to topical testosterone.
- Attend all follow-up appointments and participate in monitoring requirements.
- An information leaflet for patients or parents and carers can be found here.

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Further advice and support – this information is not inclusive of all prescribing information
Summary of products characteristics via electronic Medicines Compendium (eMC) British National Formulary for children via www.medicinescomplete.com Consultant Paediatric Endocrinologists Secretary Telephone Number: 0115 924 9924 Ext 82336 Paediatric Endocrine Specialist Nurse Telephone number: 0115 924 9924 Ext 85123 Paediatric Pharmacy Team Telephone Number: 0115 924 9924 Ext 84410 **Specialist Contact Details (out of hours)** For Medical Professionals – Ring 0115 924 9924 and ask to speak to the Paediatric Endocrinology Consultant on call. For Patients – Ring 0115 924 9924 and ask to speak to on call paediatric medical registrar.

Acknowledgements

Adapted from Leicestershire medicines strategy group shared care agreement for children and adolescents for induction of and progression through puberty in hypo-gonadotrophic hypogonadism (HH), hypogonadism due to primary testicular failure (PTF) and in constitutional delay of growth and puberty (CDGP).

Version Control- Testosterone Therapy for Hypogonadism and Constitutional Delay in Growth and Puberty in children and adolescents – Sustanon 250 and Tostran 2 % gel information sheet

Version	Author(s)	Date	Changes
2.0	Vimbayi Mushayi, Specialist Interface Medicine Optimisation Pharmacist, Nottingham and Nottinghamshire ICB In consultation with Dr Tabitha Randell Consultant Paediatric Endocrinologists, Nottingham University Hospitals (NUH)	January 2023	• Added standard header and version control • Removed footer • Added information about the guidance being for children and adolescences assigned male at birth • Amended information about Sustanon licencing as it is unlicensed in children - used off label • Amended exclusion criteria from children under 3 years to under 12 years • Added information about GPs being able to give first injection

			• Deleted Testosterone Proprionate injection preparation as non-formulary and has to be ordered as a special. • Deleted Sustanon administration guide as it is the same as giving any other IM injection • Added contraindications for Sustanon 250 as per SPC • Added some side effects listed in BSPED guideline • Deleted specific interaction with phenobarbitone not in SPC or BNFC of either Sustanon or Tostran but general point about enzyme inducers and inhibitors which has been added in the information sheet as per Sustanon SPC • Updated interactions as per current Sustanon 250 and Tostran SPC • Added link to SPC and BNC • Added link to MHRA drug safety update on topical testosterone • Statement added: Link to PIL to be added to document once approved • Updated references and contact details