

# **BSPED Guideline: Testosterone Therapy in Infancy and Adolescence**

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## **Scope**

This guideline is intended for general paediatricians and paediatric endocrinologists who are regularly managing boys with absent/delayed puberty requiring exogenous testosterone therapy. This includes boys with hypogonadotrophic hypogonadism (HH) of various aetiology, androgen deficiency secondary to testicular failure (hypergonadotrophic hypogonadism) of various aetiology, 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<sup>1</sup>. This guideline aims to provide the clinician with testosterone dosing regimens for pubertal induction, progression and post-pubertal maintenance, as well as for penile growth in infants with micropenis. It also discusses the various preparations of testosterone delivery that are available, and which are preferred based on evidence, risk-benefit balance and current practices. Where good quality evidence is unavailable to guide practice, consensus positions are provided.

## **Micropenis in infancy**

In 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<sup>2</sup>.

The two preferred modes of testosterone delivery in infants are intramuscular and topical<sup>2,3</sup> (regimes summarised in Table 1):

*Table 1: Testosterone delivery in infants with micropenis*

	<b>Intramuscular</b>	<b>Topical</b>
<b>Preparation</b>	Testosterone propionate	Testosterone 1-5% cream
<b>Dose</b>	25mg	1 application
<b>Frequency</b>	Monthly	Three times daily
<b>Duration</b>	3 months	3-6 weeks

See also notes within the text

### 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 reactions<sup>4</sup> and the safety profile of benzyl benzoate in infants is not known.

**Potential pitfall: Sustanon 250® (containing a mixture of testosterone esters) is contraindicated in infancy as it contains benzyl alcohol<sup>5</sup>, which carries the risk of a severe and potentially fatal toxic reaction<sup>6</sup>. Although the risk is highest in the neonatal period, decreasing with age up to 3 years, the European Medicine Agency recommendation is to avoid up to 3 years of age<sup>7</sup>.**

### Topical

- Preparation – Testosterone 1-5%\* cream
- Dose – 1 application
- Frequency – Three times daily
- Duration – 3-6\* weeks

\*Variability exists between centres in the concentration of testosterone cream and duration of treatment (i.e. longer treatment suggested for lower concentrations), because testosterone cream is a non-standard preparation

**Potential pitfall: There is the risk for inter-person transfer of testosterone cream preparations, therefore a female carer should wear gloves when applying.**

**Potential pitfall: 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.**

Dihydrotestosterone 2.5% gel (Adractim®) is not licensed in the UK, but has been shown to be of benefit in infants with 5-alpha reductase deficiency<sup>2</sup>. Dosing in studies have recommended 0.2-0.3mg/kg applied once daily for 3-4 months<sup>2</sup>. However, caution has to be applied as this gel contains 96% alcohol, which can be absorbed systemically and reach high levels in infants who have large surface area to mass ratios. Furthermore, high concentrations of alcohol can dehydrate and irritate the skin. Testosterone gels and patches are unsuitable for infants as they contain high alcohol contents and propylene glycol.

**Practical tip: Liaison with a local pharmacist is often required to calculate an easy measure of volume of gel to be applied when using dihydrotestosterone 2.5% gel (Adractim®)**

## Hypogonadism

For the purposes of this guideline, hypogonadism refers to both hypogonadotropic hypogonadism and testicular failure, as the management of both from a testosterone initiation and maintenance perspective is similar. In hypogonadism, the goals of testosterone treatment in puberty are to induce the development of secondary sexual characteristics, promote linear growth, promote normal accrual of muscle mass and bone mineral density, improve sexual function (libido, frequency of erections, masturbation and penetrative intercourse), improve energy levels and sense of well-being, whilst avoiding mistimed epiphyseal closure<sup>8-10</sup>. Testosterone replacement therapy does not increase testicular volume or improve the chances of fertility - other agents are available for these purposes, which are outside the scope of this guideline<sup>10</sup>. In children with suspected congenital HH, if there is evidence of testicular enlargement (suggesting gonadotrophin activity), the diagnosis of HH needs to be reviewed and a period off of testosterone treatment during induction is recommended. Similarly, a trial off testosterone treatment may be considered at some stage once full adult replacement doses have been reached, as 10% of cases show evidence of reversal of hypogonadism<sup>10</sup>.

### Timing

Unless a boy with hypogonadism also has growth hormone deficiency (multiple pituitary hormone deficiency), and therefore pubertal induction may be delayed to maximise height with growth hormone treatment, puberty is induced in boys with hypogonadism at 12-13 years of age<sup>8,11</sup>. In boys with hypergonadotropic hypogonadism, some clinicians choose to start testosterone replacement when serum testosterone falls below the normal range and serum LH rises to >2.5 SD above the mean normal value<sup>8</sup>.

Low doses are initiated and gradually increased to adult dosage over time. This is to mimic testosterone levels during the natural pubertal process and maximise growth, while allowing psychosexual development and minimising the risk of precocious sexual activity<sup>10,12</sup>. Intramuscular testosterone remains the most popular preparation for induction of puberty, however recent studies have suggested a possible role for transdermal and oral preparations<sup>13-15</sup> (regimes summarised in Table 2).

### Intramuscular

The mode of delivery most commonly utilised by clinicians to induce puberty is intramuscular<sup>16</sup>. This is due to much greater experience with these regimens over time, with a greater evidence-base and better known side-effect profile<sup>11,16</sup>. Furthermore, doses can be easily titrated to match the various stages and requirements through puberty<sup>1,16</sup>.

### *Intramuscular testosterone regime*<sup>1,8,10,12,13</sup>

- Preparation – Testosterone enantate, testosterone propionate, or mixture of esters (Sustanon 250®) are all licensed in the UK<sup>3</sup>
- Dose – 50-100mg, increasing by 50mg every 6 months until 200-250mg reached
- Frequency – Monthly, reducing in frequency to 2-3 weekly 6 months after 250mg is reached

**Potential pitfall: Sustanon 250® contains arachis oil, and therefore should be used with caution in those with peanut allergy (and soya allergy, due to cross-reactivity)<sup>5</sup>. 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.**

**Potential pitfall: Great care and clarity must be taken when prescribing volumes of Testosterone for intramuscular injections to avoid dosage errors – both testosterone enantate and Sustanon 250® come as 250mg per 1ml ampoules. For example: when prescribing 50mg of testosterone enantate, wording should read “Testosterone enantate at a dose of 50mg (0.2ml of 250mg/1ml vial) IM monthly”.**

### *Post-pubertal maintenance intramuscular testosterone regime*

After 2-3 years, adult doses can be used for post-pubertal maintenance - these vary in the adult literature from 100-250mg 2-4 weekly, though mostly 200-250mg 2-3 weekly in clinical practice<sup>10,17-21</sup>. Dosing for adult maintenance needs to be guided by monitoring of trough morning serum testosterone concentrations - aiming to maintain these at the lower end of the normal range<sup>10,18</sup>.

**Potential pitfall: Intramuscular testosterone undecionate (Nebido®) is a longer acting intramuscular testosterone preparation, but should only be used for post-pubertal maintenance rather than induction, and is only licensed in males over 18 years old<sup>22</sup>.**

Dosing for Nebido® is 1g every 10-14 weeks (with the second dose given after 6 weeks to achieve rapid steady state plasma testosterone levels). Again, dosing needs to be adjusted according to trough serum testosterone concentrations. Nebido® needs to be administered very slowly (over 1-2 minutes).

### Transdermal

Transdermal testosterone gels are available, though are as yet unlicensed in the UK<sup>3</sup>. Although popular amongst patients (due to lack of injections and ease of application), there is virtually no good-quality evidence of efficacy in the adolescent population, with dosing regimes also extrapolated from adult doses<sup>1,8,10</sup>.

### *Transdermal testosterone gel regimes*<sup>1,10,13</sup>

- 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®, Testim®), 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

There is plenty of evidence supporting use of transdermal testosterone gels within the adult setting, with the key advantage of sustained drug plasma levels that most closely resemble the natural diurnal variation in serum testosterone concentrations<sup>18,23</sup>. Therefore, they may have more of a place in post-pubertal maintenance regimes, following induction through puberty with intramuscular testosterone, and switching to an equivalent adult dose of the gel preparation.

**Potential pitfall: There are concerns and reports of inter-person transfer of testosterone gel preparations from contact to women and children, therefore care is needed in application, with female carers ensuring they wear gloves<sup>18,23</sup>.**

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

Current advice is to apply the gel to areas of the skin which are not likely to come in contact with others, but also avoiding the genital and under-arm areas due to local irritation (shoulders and arms recommended). The gel should be allowed to dry before covering with clothing, and hands washed after application. Bathing and swimming should be avoided for at least 6 hours following application.

Transdermal testosterone patches (Andropatch® and Intrinsa®) are available (though unlicensed in the UK), but evidence of their use and dosing regimens in pubertal induction are very scarce in the literature. In the absence of even consensus on regimes, its use is not recommended for pubertal induction. There may still be a role

for its use in post-pubertal maintenance therapy (with evidence from adult studies available), and readers may wish to consult the adult literature<sup>17,24</sup>.

### Oral

Oral testosterone undecanoate (Restandol® Testocaps) is licensed for use in children to induce puberty. However, they are less commonly used than intramuscular preparations because of evidence of variable absorption and hepatic first-pass metabolism leading to chaotic drug levels, with a relatively large degree of inter-person and intra-person variability<sup>21</sup>. It must be taken with food for satisfactory absorption, and can be 5-alpha reduced to dihydrotestosterone in the gut<sup>1</sup>.

### *Oral testosterone regime*<sup>3,13,22</sup>

- Preparation – Testosterone undecanoate (Restandol® Testocaps)
- Dose – 40mg (can be increased to 80mg)
- Frequency – Once daily, increasing every 6 months to twice daily and then thrice daily
- Adult dosing – Up to 120mg daily<sup>22</sup>

In the absence of common use, with evidence lacking and no clear dosing regimes available for pubertal induction, buccal testosterone (Striant® SR) and subcutaneous implanted pellets of testosterone (Testopel®) are not discussed in this guideline.

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

	<b>Intramuscular (preferred option)</b>	<b>Metered-dose gel (secondary option)</b>	<b>Gel sachet (secondary option)</b>	<b>Oral (secondary option)</b>
<b>Preparation</b>	Testosterone enantate, Testosterone propionate, Sustanon 250®	Tostran® (2%; 10mg testosterone per metered application)	Testogel®, Testim® (1%; 50mg testosterone per 5g sachet)	Testosterone undecanoate (Restandol® Testocaps)
<b>Initial dose</b>	50-100mg	10-20mg	One third of sachet	40mg
<b>Initial frequency</b>	Monthly	Once daily	Once daily/ alternate days	Once daily
<b>Titration</b>	Increase by 50mg every 6-12 months, reducing frequency to 2-3 weekly once 250mg reached	Increase by 10mg every 6 months	Increase by one third of a sachet yearly until full sachet daily achieved	Increase every 6 months to twice daily, then three times a day
<b>Adult dosing</b>	200-250mg 2-4 weekly	60-80mg once daily	1-2 sachets daily	Up to 120mg daily

See also notes within the text

50mg intramuscular testosterone monthly = 40mg oral testosterone (Restandol® Testocaps) daily = 10mg topical testosterone (Tostran® gel) daily

## **Constitutional delay in growth and puberty (CDGP)**

In boys with CDGP, testosterone therapy is initiated to induce pubertal development, with the body being able to progress itself through puberty (should the diagnosis be accurate) following a short course of testosterone. Although it is accepted that boys with CDGP will eventually induce themselves into puberty, testosterone is given to alleviate the distress boys often suffer because of their lack of growth and pubertal progression, which can affect school performance, social relationships and psychological well-being<sup>8,12</sup>. Testosterone treatment in boys with CDGP is usually initiated around 13-14 years of age. Low doses are used to avoid premature epiphyseal maturation and minimise suppression of the endogenous hypothalamic-pituitary-testicular axis. A one-off course of 3-6 months is usually given, with review 1-2 months after - if there has been no increase in testicular volume, a further 3-6 month course of testosterone can be given<sup>8</sup>.

**Potential pitfall: If there is no progress in testicular volumes and serum testosterone after two courses of testosterone treatment, then a diagnosis of HH must be considered and investigated<sup>8</sup>.**

Intramuscular testosterone remains the most popular preparation for induction of puberty, however recent studies have suggested a possible role for transdermal and oral preparations<sup>13-15</sup> (regimes summarised in Table 3).

*Intramuscular testosterone regime* (licensed in UK)<sup>3,8,12,13</sup>

- Preparation – Testosterone enantate, testosterone propionate, or mixture of esters (Sustanon 250®)
- Dose – 50-100mg,
- Frequency – Monthly
- Duration – 3-6 months

**Potential pitfall: Sustanon 250® contains arachis oil, and therefore should be used with caution in those with peanut allergy (and soya allergy, due to cross-reactivity)<sup>5</sup>. 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.**

**Potential pitfall: Great care and clarity must be taken when prescribing volumes of Testosterone for intramuscular injections to avoid dosage errors – both testosterone enantate and Sustanon 250® come as 250mg per 1ml ampoules. For**

**example: when prescribing 50mg of testosterone enantate, wording should read “Testosterone enantate at a dose of 50mg (0.2ml of 250mg/1ml vial) IM monthly”.**

*Transdermal testosterone regime (unlicensed in UK)<sup>13</sup>*

- Preparation – 2% metered-dose testosterone gel (Tostran®), containing approximately 10mg per metered application
- Dose – 10-20mg (1-2 metered applications)
- Frequency – Once daily
- Duration – 3-6 months

**Potential pitfall: There are concerns and reports of inter-person transfer of testosterone gel preparations from contact to women and children, therefore care is needed in application, with female carers ensuring they wear gloves<sup>18,23</sup>.**

**Potential pitfall: Care must be taken to specify gel rather than cream when prescribing topical testosterone preparations for induction of puberty in CDGP, as the testosterone content of each per application varies significantly.**

*Oral testosterone regime (licensed in UK)<sup>3,13</sup>*

- Preparation – Testosterone undecanoate (Restandol® Testocaps)
- Dose – 40mg
- Frequency – Once daily
- Duration – 3-6 months

Oral preparations are not commonly used, though licensed, due to concerns about variable absorption and hepatic first-pass metabolism<sup>21</sup>.

Table 3: Testosterone delivery for pubertal induction in boys with constitutional delay in growth and puberty

	Intramuscular (preferred option)	Transdermal (secondary option)	Oral (secondary option)
Preparation	Testosterone enantate, Testosterone propionate, Sustanon 250®	2% metered-dose testosterone gel (Tostran®; 10mg per metered application)	Testosterone undecanoate (Restandol® Testocaps)
Dose	50-100g	10-20mg	40mg
Frequency	Monthly	Once daily	Once daily
Duration	3-6 months	3-6 months	3-6 months

See also notes within the text

50mg intramuscular testosterone monthly = 40mg oral testosterone (Restandol® Testocaps) daily = 10mg topical testosterone (Tostran® gel) daily



## Advantages and disadvantages of preparations<sup>12,17,21</sup>

	Advantages	Disadvantages
<b>Intramuscular</b>	<ul style="list-style-type: none"> <li>- Cheap</li> <li>- Known efficacy</li> <li>- Lots of experience of use</li> <li>- Long-acting</li> <li>- Easy dose titration</li> <li>- Licensed in UK</li> <li>- Can monitor compliance</li> </ul>	<ul style="list-style-type: none"> <li>- Fluctuating drug levels resulting in fluctuating symptoms (mood and libido – which may be an issue in boys with learning difficulties)</li> <li>- Local problems with injections (pain, inflammation, sterile abscess)</li> <li>- Attending to healthcare services</li> <li>- Priapism potentially if excess administered</li> <li>- Potential paroxysms of coughing and dyspnoea from lipid embolism (Nebido®)</li> </ul>
<b>Transdermal</b>	<ul style="list-style-type: none"> <li>- Pharmacokinetics most closely replicate natural diurnal variation - Convenient</li> </ul>	<ul style="list-style-type: none"> <li>- Evidence of efficacy lacking</li> <li>- Doses extrapolated from adults</li> <li>- More expensive</li> <li>- Transfer to other persons</li> <li>- Skin irritation</li> <li>- Not licensed in UK</li> </ul>
<b>Oral</b>	<ul style="list-style-type: none"> <li>- Convenient</li> <li>- Easy dose titration</li> <li>- Licensed in UK</li> </ul>	<ul style="list-style-type: none"> <li>- Evidence of efficacy lacking</li> <li>- Variable absorption and metabolism</li> <li>- Gastrointestinal side effects</li> <li>- Frequent dosing</li> </ul>

## Side effects<sup>3,18,22</sup>

### 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<sup>25</sup>

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