

# An update on testosterone replacement therapies

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*Effective treatments for testosterone deficiency are available for men at all ages. The choice of testosterone preparation depends on several factors, including length and severity of testosterone deficiency, pharmacokinetic profiles of the available preparations and the patient's age, comorbidities and personal preference.*

## Key points

- **Testosterone deficiency is common in the male population.**
- **Several therapeutic options are available to treat men with testosterone deficiency.**
- **There have been recent changes in testosterone products available on the PBS with the addition of a metered pump applicator and the withdrawal of subcutaneous pellets.**
- **The modality of testosterone replacement should be individualised according to patient convenience, compliance and side effect profile.**
- **Patients need to be assessed for contraindications before commencing testosterone therapy and monitored during therapy for the development of adverse effects.**

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Testosterone deficiency is one of the most common hormonal deficiencies in men, affecting approximately one in 200 men aged less than 60 years. It is categorised as primary (a consequence of intrinsic testicular damage or failure) or secondary (as a result of hypothalamic–pituitary disorders) and may be either congenital or acquired throughout a man's life.[1]

The role of testosterone replacement in men with established testosterone deficiency is of proven clinical efficacy and safety; however, its role in other clinical settings (e.g. male ageing, systemic illness) requires further study.[2]

## Therapeutic options for testosterone prescribing

A number of modalities for testosterone replacement are currently approved for use in Australia (see Table). These include oral, transdermal, intramuscular and subdermal modalities. The available therapies have changed with the withdrawal of all testosterone implants and the delisting of an intramuscular preparation from the PBS. A new transdermal preparation with a novel mode of application has recently become available.

The PBS criteria for the prescription of testosterone in adult men are:

- androgen deficiency in men with established pituitary or testicular disorders
- androgen deficiency in men aged 40 years and older who do not have established pituitary or testicular disorders other than ageing, confirmed by at least two morning blood samples taken on different mornings. Androgen deficiency is confirmed by testosterone levels of less than 8 nmol/L, or 8 to 15 nmol/L with high levels of luteinising hormone (greater than 1.5 times the upper limit of the eugonadal reference range for young men).

The Figure demonstrates the changes in prescribing trends in Australia for androgen replacement therapy since 2000 according to PBS data.

### Oral therapy

Testosterone undecanoate (Andriol Testocaps; 40 mg capsules) are absorbed via the intestinal lymphatic system and should be taken with a meal containing fat.[3] Daily doses vary from 160 to 240 mg in two to three divided doses. Gastrointestinal intolerances and frequent dosing limit clinical use, although it may be appropriate for initiating therapy when endogenous

**Table. Summary of currently available testosterone preparations for use in men with testosterone deficiency**

| Trade name | Generic name | Route of administration | Preparation | Typical dose regimen |
|---|---|---|---|---|
| Andriol Testocaps | Testosterone undecanoate | Oral | 40 mg | 80 to 160 mg in 2 to 3 divided doses daily |
| Androderm | Testosterone patches | Transdermal | 2.5 mg per 24 hours<br>5.0 mg per 24 hours | 2.5 to 5.0 mg daily |
| Testogel | Testosterone gel | Transdermal | 1%, 50 mg per 24 hours (1 sachet) | 2.5 to 5.0 g daily |
| AndroForte* | Testosterone cream | Transdermal | 5%, 50 mg per mL<br>2%, 20 mg per mL | 20 to 50 mg daily |
| Axiron | Testosterone transdermal solution | Transdermal | 2%, 30 mg/1.5 mL (1 actuation) | 30 to 60 mg daily |
| Sustanon* | Mixed testosterone esters | Intramuscular | 250 mg per mL | 250 mg every 2 to 3 weeks |
| Primoteston | Testosterone enanthate | Intramuscular | 250 mg per mL | 250 mg every 2 to 3 weeks |
| Reandron 1000 | Testosterone undecanoate | Intramuscular | 1000 mg per 4 mL | 1000 mg every 12 weeks (additional loading dose at 6 weeks) |

*Not available on the PBS.

levels have been low for a prolonged period of time and/or when only modest elevations in serum testosterone levels are required (e.g. in elderly men). It is safe for use in men with bleeding disorders in whom injections or implants are not suitable.

### Transdermal therapies

Nonscrotal testosterone patches (Androderm) are applied nightly to the back, stomach, thighs or upper arms. They mimic normal circadian rhythms of testosterone concentrations, peaking in the morning and declining slowly to a nadir in the evening. They achieve stable serum levels over a few days, resulting in maintenance of relatively stable energy levels, mood and libido.[4] These patches are available in two strengths, 12.2 mg (releasing 2.5 mg/24 hours) and 24.3 mg (releasing 5 mg/24 hours). Application sites should be rotated daily to reduce skin irritation, avoiding sites with excessive hair and oil to promote adhesion. Showering and recreational water activities should not affect adherence; however, strenuous exercise and perspiration may result in loosening and detachment. Use of these patches may be limited by skin irritation due to the addition of permeation enhancers.[5] The skin irritation can be minimised by using corticosteroid creams on the skin beneath the patch.

A testosterone gel 1% preparation (Testogel) is also available and is formulated as 5 g sachets containing 50 mg testosterone. The gel is applied once daily to the shoulders and torso. Approximately 10% of the gel is absorbed into the skin where it remains in the stratum corneum as a reservoir that is slowly released over hours. Serum testosterone concentrations reach normal range within a month and remain in steady state throughout the 24-hour period.[6] The testosterone gel has been shown to have similar clinical efficacy to that achieved with the patches but produces less skin irritation.[7] For several hours after application, men using the gel need to avoid direct physical contact with others (to prevent interpersonal transfer) and to avoid washing.

A testosterone cream (AndroForte) is available in Western Australia, but does not have TGA approval for national use. This

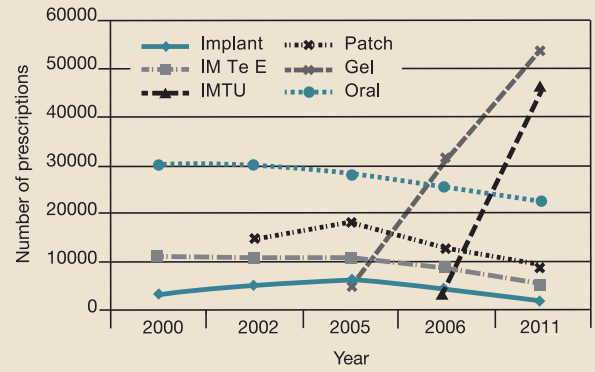


**Figure. Changes in testosterone replacement prescribing in Australia between 2000 and 2011.***

* Statistics from Medicare Australia Pharmaceutical Benefits Schedule.

Abbreviations: IM Te E = intramuscular testosterone esters; IMTU = intramuscular testosterone undecanoate.

testosterone cream contains 50 mg testosterone per 1 mL and is applied via a dose measuring applicator once daily to clean, dry scrotal skin. It is massaged into the scrotum until the cream is absorbed (usually 30 to 60 seconds). An alternative formulation containing 20 mg/mL testosterone is also available (see: http://www.lawleypharm.com.au/pharm/products/androforte.html).

A 2% testosterone formulation (Axiron) presented in a metered dose pump with an applicator is now available for use in Australia. Dosing is based on the amount of liquid pumped into the applicator (each depressed pump of 1.5 mL yields 30 mg testosterone). The preparation is applied once daily to the underarms in a similar fashion to roll-on deodorant. It has similar efficacy to other transdermal preparations with normalisation of serum testosterone levels.[8] It was well tolerated in an open-label trial, with few subjects discontinuing use because of side effects, the most common of which was application-site irritation including erythema.[9] The use of

deodorants and antiperspirants does not impede efficacy, but they should be applied before the testosterone preparation. This preparation became available on the PBS on 1 March 2013.

### Intramuscular therapies

Intramuscular injections (Sustanon and Primoteston depot) use esterified testosterone. Esterification renders testosterone less polar and more lipid soluble, thereby prolonging its duration of action. Although the esterification of testosterone provides a sustained release, nonlinear and different esters provide varying half-lives. Sustanon contains a combination of four different testosterone esters whereas Primoteston depot contains the single ester testosterone enanthate. The typical dose is 200 to 250 mg, which is administered as a depot every two to three weeks. The interval between injections may produce wide variations in testosterone levels over the weeks with initial supraphysiological levels followed by a gradual decline, which may result in fluctuations in energy, mood and libido in many patients.[10] A reduced dose of 100 mg administered more frequently, for example weekly, may ameliorate these fluctuations. This form of therapy requires a deep intramuscular injection; therefore, it is contraindicated in men who are taking anticoagulants and those with bleeding diatheses due to the risk of haematoma formation. Sustanon is no longer available on the PBS but is available on private prescription.

More recently, a longer-acting intramuscular injection (Reandron 1000) has become available.[11] This is administered initially at 0, 6, 18 and 30 weeks with the ongoing dosage interval determined by preinjection serum testosterone levels (commonly 10 to 14 weeks). Dependent on the patient's age, symptoms of androgen deficiency and comorbidities, a nadir serum testosterone level between 10 and 15 nmol/L is usually considered appropriate. Administered as a 4 mL injection with a castor oil vehicle into the buttock, it is usually well tolerated, requiring little analgesia and causing minimal interference in daily activities.[12] Although the extended dosing interval is appropriate in younger men, because of the long duration of action it should be used with caution in older men who may be at risk of developing clinically significant prostate disease, including carcinoma of the prostate. It is contraindicated in men who are taking anticoagulants or who have a bleeding diathesis.

### Subdermal therapies

Subcutaneous testosterone pellets, which were available in 100 mg and 200 mg strengths, were withdrawn from the Australian market at the end of 2012. Testosterone pellets (usual dose 600 to 800 mg) are inserted into the subdermal fat of the buttocks, abdomen or thigh under local anaesthetic every four to six months.[13] The infrequent administration of the implants is often suited to younger patients who are unlikely to need to terminate their therapy. Stable physiological levels of testosterone are achieved with a slow decline over four to six months. Dosing intervals should be individualised according to serum testosterone levels and symptoms of androgen deficiency.[14] Pellet extrusion (5 to 10%), infection and fibrosis are potential adverse events.

**Contraindications to prescribing testosterone[2]**

- Hormonally-dependent malignancies (prostate or breast)
- Abnormal prostate examination or an elevated prostate-specific antigen level (before urological review)
- Haematocrit value above 50%
- Untreated severe obstructive sleep apnoea
- Severe lower urinary tract symptoms
- Uncontrolled or poorly controlled heart failure
- Desire for fertility

## Contraindications to prescribing testosterone

Clinical assessment and relevant laboratory testing should be undertaken before prescribing testosterone. The box on this page lists the accepted contraindications to testosterone therapy.[2]

## Conclusion

Testosterone deficiency is important to recognise in men of all ages as treatments are available with long-term efficacy and safety that improve the clinical features of androgen deficiency.

The choice of testosterone preparation for an individual man depends on several factors, including duration and severity of testosterone deficiency, pharmacokinetic profiles of the available preparations and the patient's age, comorbidities and personal preference. **ET**

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