

Men's health and the treatment of andropause

By Dr Alison Haywood and Professor Beverley Glass



Learning objectives

After reading this article you should be able to:

- Describe when compounding testosterone to meet specific requirements in men's health is necessary, and the precautions to be taken by pharmacists in undertaking this task
- Describe compounded transdermal gels and creams, including the components, methods of preparation, packaging, storage and labelling
- Counsel patients/carers on the appropriate use of and the precautions to be taken in using these compounded products.

Competencies addressed:

4.2.2, 5.1.2, 5.1.4, 5.1.5, 5.2.7

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Treatment of andropause: why and how?

Although andropause has been reported to affect about 25% of men,¹ this figure is a significantly higher estimate than the actual number of men treated by health professionals working in men's health. This can be attributed to men being reluctant to discuss andropause, not being willing to acknowledge the symptoms, or fear of the occurrence of side effects associated with treatment such as depression, loss of libido and particularly sexual dysfunction.² This gap between reported percentages and men currently treated provides an excellent opportunity for health professionals, both doctors and pharmacists, to work together collaboratively in the treatment of men with this condition. Because of some of the poorly understood aspects of andropause and the challenge in dosing patients, it is not surprising that this is an important area of interest for compounded products.³

The symptoms of andropause have been reported in clinical trials to be improved by testosterone therapy.⁴

Testosterone is available commercially in Australia in many different dosage forms including parenterals via intramuscular injection (*Primoteston Depot*, *Sustanon 100/250* and *Reandron 1000*), implants (*Testosterone Implant*), patches (*Androderm*), a soft gelatin capsule (*Andriol Testocaps*) and a gel (*Testogel*). Testosterone is also available internationally as a buccal patch (*Striant*).

Intramuscular testosterone enanthate or propionate (ester form) has been used for many years, however reduced symptomatic benefit may be seen towards the end of each dosing period due to fluctuating serum testosterone concentrations.⁵ Injectables and implants require administration by a health care professional, are invasive and, in the case of the occurrence of adverse effects, are not able to be immediately withdrawn. Although oral testosterone undecanoate has

been reported to have both variable bioavailability and short duration of action, it may be used when other routes of administration are poorly tolerated or not recommended.⁵ Another concern with oral administration is masking the bitter taste of testosterone.⁶

A transdermal gel (*Testogel*) has been recently introduced in Australia. The advantages of transdermal preparations include patient acceptance, ease of use, non-invasive thereby avoiding the inconvenience of parenteral therapy, and drug therapy may be terminated rapidly by removal of the application from the skin.⁷ The *Australian Medicines Handbook* states that skin irritation is very common with the patches and that the testosterone gel is less irritating than the patches.⁵

Rationale for compounding testosterone

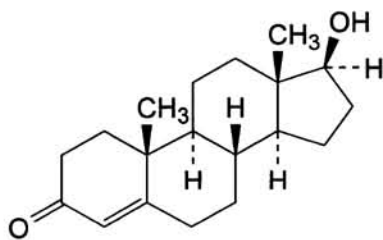
Compounding provides a solution when commercially available products are not suitable and no therapeutic alternatives are available. Allergies to excipients in the commercially available gel or ease of dose adjustments for compounded products are factors in favour of using these products. Since the commercial gel sachets are only available in a fixed size (5 g), this presents a challenge to patients requiring, for example, half (2.5 g) the dose.

Compounding transdermal testosterone

Active ingredient

Testosterone (Figure 1), a white or slightly creamy crystalline powder, is practically insoluble in water,

Figure 1. Chemical structure of testosterone (C₁₉H₂₈O₂, MW 288.4)



freely soluble in dehydrated alcohol and soluble in vegetable oils.⁸ Although testosterone is available commercially as a soft gelatin capsule (*Andriol Testocaps* contain 40 mg of testosterone undecanoate in castor oil and propylene glycol monolaurate), pharmacists wanting to compound testosterone should source this active pharmaceutical ingredient (API) as a *micronised powder* (raw material) since percutaneous absorption is enhanced with a smaller particle size (micronised) of the API. Other factors which facilitate percutaneous absorption include a low molecular weight (MW) for the API (ideally MW < 400),⁷ and drugs generally penetrate the skin better in their unionised (non-salt) form. Testosterone has a MW of 288.4, whereas testosterone undecanoate, present in *Andriol Testocaps*, is a salt of testosterone, and has a MW of 456.7).

Excipients

Gels commonly include a gelling agent, water and a wetting agent for incorporating the API into the gel. Penetration enhancers, preservatives and fragrances may also be included.⁷ The commercially available gel, *Testogel*, contains testosterone (50 mg per 5 g gel), carbomer 980, isopropyl myristate, ethanol, sodium hydroxide and purified water. Carbomers are synthetic high molecular weight polymers. When dispersed in water, an acidic colloidal solution of low viscosity will form, which will thicken when an alkaline material, such as sodium hydroxide or triethanolamine, is added.⁹ Maximum viscosity can generally be obtained in a pH range of 6 to 11. Carbomer gels are required to be preserved, however some preservatives, such as benzalkonium chloride, benzoic acid and sodium benzoate, will decrease the viscosity of the dispersion.¹⁰ A high concentration of alcohol (above 15 % in acidic media and above 18 % in alkaline media) will make the formulation self-preserving.⁷ A formula and method of preparation for a Carbomer gel is shown in Figure 2, adapted from Allen.¹⁰

Common wetting agents include propylene glycol and glycerin. However, due to the sticky nature of glycerin, propylene glycol is preferred. If glycerin is used, dimethicone is often added to reduce the sticky feeling associated with glycerin.⁷

Figure 2. Carbomer gel formula and method of preparation.¹⁰

Carbomer gel 100 g	
API	qs
Isopropyl alcohol*	72 mL
Carbomer 940	500 mg
Triethanolamine	0.7 mL
Purified water to	100 g
Method	
1. Place about 28 mL purified water on a magnetic mixer and stir rapidly.	
2. Add the isopropyl alcohol containing the API and mix well.	
3. Sprinkle the Carbomer 940 slowly onto the surface and allow to hydrate.	
4. Add the triethanolamine slowly and mix to form the gel.	
5. Add sufficient purified water to final weight and mix well.	
6. Package and label.	

Tip: To facilitate the initial dispersion process, the Carbomer should be sprinkled on rapidly agitated water being careful to avoid the formation of lumps, and effort should be made to minimise the incorporation of air bubbles into the gel.^{9,10}

***Note:** As mentioned above, some excipients perform multiple roles. In this case isopropyl alcohol functions as a wetting agent, co-solvent and preservative. It also has penetration enhancing properties.⁹

Common penetration enhancers include acetone, azone, dimethyl sulphoxide, ethanol (alcohol), oleic acid, polyethylene glycol, propylene glycol and sodium lauryl sulphate.⁷ A requirement for these penetration enhancers is low dermal toxicity (i.e. not causing contact dermatitis) and compatibility with other excipients. Often excipients such as alcohol and propylene glycol, which are routinely included for their solvent, co-solvent, wetting and preservative properties, also play a role in enhancing the penetration of the API.^{7,9}

There are commercially available gel vehicles which contain a combination of excipients in one product (contact your local supplier for vehicle/base options). These products may provide a convenient resource, since it is not necessary for the pharmacy to hold a wide range of excipients. Vehicles other than gels (such as

creams) may also be suitable for transdermal application. Some cream options include commercially available bases such as *Lipoderm*, *Versabase cream* and, in Australia, macadamia-based creams for which there is anecdotal evidence of positive patient outcomes. It is important to note that pharmacists compound these products on prescription from a doctor who may request a specific base or change a cream/gel base depending on patient outcomes and, in some cases, costs. The benefits and limitations of these preparations are carefully assessed and followed up with appropriate testing to avoid under- or over-dosing. Therefore, the pharmacist in consultation with the prescriber may decide on the use of various cream/gel bases to meet the requirements of the patient.

Packaging and storage

Testosterone undergoes photodegradation when exposed to light. It is important that the packaging provides adequate protection from light. A variety of packaging options are available including amber glass ointment jars or plastic tubes combined with an appropriate measuring device. Amber coloured syringes may be useful for dispensing small quantities and accurately measuring a dose. Contact your local supplier for packaging options. Patients may also have a preference for a particular packaging type. It is important that patients are counselled on the use, accurate measurement of dose and appropriate disposal of the packaging. The formulation should be stored in a cool, dry place out of reach of children and pets.

Labelling

Compounded products are to be labelled according to regulatory requirements¹⁹ and should include the approved pharmacopoeial name (where applicable) and the name and strength of any preservatives used. The label must also be in accordance with the relevant state law.⁷ A complete list of ingredients and their amounts/proportions should be included when non-pharmacopoeial products are prepared. Ancillary labels should be used to indicate specific storage conditions, provide an expiry date and indicate specific usage conditions.

Quality control and self-inspection

The pharmacist is responsible for ensuring the quality of compounded products and should verify that products are prepared according to documented procedures and meet product specifications before release to the patient.⁷ Self-inspections should also be conducted at regular intervals to identify areas for improvement and the resulting actions should be documented.⁷

Counselling and instructions for patients/carers

In the preparation of compounded products, the pharmacist should be guided by the professional standards,¹¹ the prescriber and the needs of the patient. Patient counselling and education may be adapted from CMI's available for commercially available products. Essential information would include:

Directions for use

- Spread a thin layer onto clean, dry healthy skin over the upper arms, shoulders or stomach. Do not apply to the testes, scrotum or penis since certain ingredients may cause local irritation.^{5,12} You don't need to rub it in but allow to dry for at least 3–5 minutes before dressing.⁵
- Wash your hands thoroughly with soap and water after application.^{5,12}
- Cover the application area with clothing once dried.¹² Do not allow others to touch the application area.⁵
- Do not shower for at least six hours after application.¹²
- Application at approximately the same time each day, preferably in the morning, helps maintain a steady level of testosterone in the blood and will help you to remember when to apply the product.¹²

Special precautions

- It is important to emphasise to the patient/carer that others should avoid contact with the application area, especially children, since enough testosterone to cause virilisation can be absorbed by children from skin contact with patients using transdermal testosterone products.⁵

Testosterone may be transferred to another person during close and relatively prolonged skin contact with the gel application area. This can cause the other person to show signs of increased testosterone such as more hair on the face and body and a deepened voice and changes in the menstrual cycle in women.¹²

- Athletes should note that testosterone may produce a positive reaction in anti-doping tests.¹²

Key learning points

- Pharmacists should use a micronised form of testosterone in the compounding of creams/gels for the treatment of andropause in men.
- Pharmacists in consultation with doctors may decide on the use of various cream/gel bases to meet the specific requirements of the patient.
- Due to the potential for interactions of multiple ingredients and adverse effects in patients such as contact dermatitis, KEEP IT SIMPLE and limit the number of ingredients in compounded testosterone.

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Questions

A score of 3 out of 4 attracts three quarters of a credit point.

1. Testosterone is **not** available commercially in Australia in the following dosage form(s):
 - a) Soft gelatin capsule.
 - b) Buccal patch.
 - c) Transdermal cream.
 - d) b and c.
 - e) a, b and c.
2. The reason(s) for compounding testosterone for transdermal delivery is/are as follows:
 - a) Lack of availability of a commercial product in a semi-solid dosage form.
 - b) Inability to adjust the dose in a compounded transdermal product.
 - c) Bitter taste of oral testosterone resulting in the potential for patient non-compliance.
 - d) a and b.
 - e) a, b and c.
3. Which of the following excipients are essential components in formulating a gel for transdermal delivery?
 - a) Co-solvent.
 - b) Gelling agent.
 - c) Alcohol.
 - d) a and b
 - e) a, b and c
4. Counselling and instructions for patients/carers in respect of transdermal testosterone in a semi-solid dosage form should include the following:
 - a) Spread a thin layer of the gel or cream on clean, wet skin over the upper arms, shoulders or stomach.
 - b) Take a shower within six hours of application.
 - c) Application need not be at the same time every day.
 - d) There is no need to avoid contact with other family members especially children as testosterone cannot be transferred to another person during close and prolonged contact.
 - e) Wash hands thoroughly with soap and water after application.