Masculinising Hormone Treatment for Adults

Part of the collaborative care protocol for prescribing hormone treatment for transgender adults.
Information sheet for Primary Care Prescribers

Indications
Gender incongruence in adults who are under the care of a transgender health clinic as part of a comprehensive treatment programme.

Any patient groups to be excluded from collaborative care
- Children and young people under 18 years of age
- Adult patients who are not under the care of a transgender health clinic

Off-label prescribing
Most recommendations will be for medications to be used outside the indications approved by the Medicines and Healthcare Products Regulatory Agency. The General Medical Council advises GPs that they may prescribe 'unlicensed medicines' where this is necessary to meet the specific needs of the patient and where there is no suitably licensed medicine that will meet the patient's need. The specialist will obtain written consent from the patient to the unlicensed/off-label prescribing and provide a copy of this to the patient and the GP.

Therapeutic Summary
Medication for masculinisation involves testosterone preparations[1]. This can be given by intramuscular injection or by a gel which is applied to the skin each day. Testosterone products should be prescribed by brand as they are not bioequivalent.

Testogel® 16.2mg/g gel should be applied onto clean, dry, healthy skin over the right and left upper arms and shoulders[2]. The gel should be spread on the skin gently as a thin layer. It is not necessary to rub it on the skin. Allow to dry for at least 3-5 minutes before dressing. Wash hands with soap and water after application and cover the application site(s) with clothing after the gel has dried. Wash the application site thoroughly with soap and water prior to any situation where skin-to-skin contact of the application site with another person is anticipated[2].

Tostran® 2% gel can be applied to the abdomen (entire dose over an area of at least 10 by 30 cm), or to **both** inner thighs (one half of the dose over an area of at least 10 by 15 cm for each inner thigh)[3]. Daily rotation between the abdomen and inner thighs is recommended to minimise application site reactions. The gel should be applied to clean, dry, intact skin. It should be rubbed in gently with one finger until dry, then the application site should be covered, preferably with loose clothing. Hands should then be washed with soap and water[3].

Sustanon 250® 250mg/mL solution for injection is administered by deep intramuscular injection[4]. The dosing interval is adjusted based on individual patient response. **It includes arachis oil as an excipient and therefore should not be used in patients with a peanut or soya allergy.**

Nebido® 1000mg/4mL solution for injection is administered by deep intramuscular injection into the gluteal muscle. The injections must be administered very slowly (over two minutes)[5].

In some cases where testosterone alone does not suppress oestradiol production and/or the patient is experiencing related symptoms, a GnRH analogue may be considered. The specialist will provide guidance on an individual case basis.

Testosterone Therapy Prescribing and Monitoring – Initiation

Product	Dose range	Testosterone level monitoring	Target testosterone levels
Gel Testogel® (1 actuation = 20.25mg) Tostran® (1 actuation = 10mg)	Start 40 mg once daily and titrate monthly depending on blood results Dose range 50-100mg daily	Sample after 3 months. Take sample 4-6 hours **after** gel application *(early afternoon typically)*	Mid-range of local reference range (14-19nmol/L)
IM Injection **Sustanon 250®** If switching from gel stop gel with 1st injection Contains arachis oil as an excipient. Do not use in patients with a peanut or soya allergy.	250 mg every 4 weeks	Sample before 4th injection (3 months). Trough level. If dose interval is changed, repeat trough level after 3 further injections	Lower 1/3 of local reference range (8-14nmol/L) *If lower than 8nmol/L reduce injection interval* *If higher than 14nmol/L increase injection interval*
IM Injection **Nebido®** If switching from gel – continue gel for 1 week after 1st injection If switching from Sustanon®, give Nebido® instead of Susanton® and continue with standard Nebido® loading regimen	1000 mg stat 1000 mg at 6 weeks 1000 mg at 18 weeks 12 weekly thereafter	Sample before 4th injection (30 weeks). Trough level.	Lower 1/3 of local reference range (8-14nmol/L) *If lower than 8nmol/L reduce injection interval* *If higher than 14nmol/L increase injection interval*

Adapted from: Hembree, W. C., Cohen-Kettenis, P. T., Gooren, L., Hannema, S. E., Meyer, W. J., Murad, M. H., T'Sjoen, G. (2017). Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society* Clinical Practice Guideline. Journal of Clinical Endocrinology & Metabolism. doi: 10.1210/jc.2017-01658

Testosterone Therapy Prescribing and Monitoring – Maintenance

Product	Dose range	Testosterone level monitoring	Target testosterone levels
Gel Testogel® (1 actuation = 20.25mg) Tostran® (1 actuation = 10mg)	Typical dose range is 50-100 mg once daily	Sample 4-6 hrs **after** gel application *(early afternoon typically)*	Middle of local reference range (14-19nmol/L)
IM Injection **Sustanon 250®**	250 mg every 2-4 weeks	Sample prior to next planned injection – trough level *Option to blood test 5-7 days after injection to check peak level.*	Lower 1/3 of local reference range (8-14nmol/L) *If lower than 8nmol/L reduce injection interval* *If higher than 14nmol/L increase injection interval*
IM Injection **Nebido® 1000mg/4mL**	1000 mg every 10-14 weeks	Sample prior to next planned injection – trough level *Option to blood test 3-4 weeks after injection to check peak level.*	Lower 1/3 of local reference range (8-14nmol/L) *If lower than 8nmol/L reduce injection interval* *If higher than 14nmol/L increase injection interval*

Adapted from: Hembree, W. C., Cohen-Kettenis, P. T., Gooren, L., Hannema, S. E., Meyer, W. J., Murad, M. H., T'Sjoen, G. (2017). Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society* Clinical Practice Guideline. Journal of Clinical Endocrinology & Metabolism. doi: 10.1210/jc.2017-01658

Monitoring Requirements and Responsibilities

- Baseline physical health assessments to be performed by the GP with specialist guidance. This usually includes blood pressure, height, weight, and blood tests as below.
- Results of baseline monitoring should be sent to the specialist for review.
- During testosterone titration, monitoring will be performed by the GP on advice of the specialist. The results should be communicated to the specialist for review. Frequency of monitoring during the titration period depends on the product used (gel or injection).
- Ongoing monitoring will be performed by the GP, as advised by the specialist and information contained in this document. Any abnormal monitoring results should be communicated to the specialist urgently.
- **Testosterone levels are required 6-monthly long term.**

Timing of monitoring	**Blood tests to be done**									
	Testosterone level*	FBC	LFTs	FSH and LH**	Oestradiol level	Lipids	SHBG	U&Es	HbA1C	Prolactin
Baseline	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
At 3 months (gel and Sustanon)	✔	✔	✔	✔						
At 30 weeks (Nebido)	✔	✔	✔	✔						
Six monthly (all) on going	✔			✔						
Annually (all) on going	✔	✔	✔	✔	✔	✔				

*Additional testosterone level monitoring may be required during dose titration; the specialist will advise on an individual patient basis.
**FSH/LH are required each time a testosterone level is checked.

Screening	**Frequency**
Cervical screening	A transgender male who is registered with the GP as male will not automatically be invited for screening. Screening should be considered. Discuss with the patient and contact the NHS cervical screening programme if the patient wishes to be invited for screening.
Breast screening	A transgender male, who is registered with the GP as male, will not automatically be invited for breast screening. If a transgender male has not had chest reconstruction (top surgery), and is ≥50 years of age, discuss with the patient and consider referral for mammograms. If a transgender male has had chest reconstruction but still has breast tissue, discuss with the patient and consider referral for mammograms.
AAA screening	A transgender male aged 65, who is registered with the GP as male, will be sent an appointment to attend for AAA screening. A transgender male can have AAA screening even though risk is lower.

Diabetes screening	Consider offering as part of metabolic screening for transgender men with previous history of PCOS.

Duration of treatment
Transgender males will most likely remain on lifelong hormone replacement therapy with testosterone.

Explicit criteria for review of masculinising hormone treatments
These recommendations do not replace the need for medical assessments that would be undertaken in response to these signs/symptoms. In any case of withholding/reducing doses, please discuss with the specialist first and assess the need for a risk management plan and follow up appointments.

Adverse effect	Action
Polycythaemia	Ensure patient is not dehydrated. Smoking will increase the risk of erythrocytosis. Please ensure the patient is not continuing to smoke. In case of persistent polycythemia please seek specialist advice and guidance from Nottingham Centre for Transgender Health and local Haematology services concurrently. Although, in majority of the cases polycythemia will have been triggered by use testosterone, the patient may need investigations via haematology service
Significant rise in LFTs or worsening lipid profile	Seek advice from specialist. Management of dyslipidemia - use risk calculators cautiously as they are not validated in transgender population.
Persistently raised LH/FSH	Seek specialist advice.
Application site reaction with gel formulation	Usually mild to moderate in severity and improves with continued application. Seek advice from specialist regarding alternative formulation if persists.
Injection related reactions such as cough, fluctuation in mood or libido, dyspnoea, malaise, hyperhidrosis, chest pain, dizziness, paraesthesia, or syncope with injection formulation	Ensure injection is administered slowly. Observe patient during and immediately after each injection to allow for early recognition of possible signs and symptoms of pulmonary oily microembolism. Treatment is usually supportive, e.g. by administration of supplemental oxygen.

Clinically Relevant Medicine Interactions and their Management

Testosterone[2,3]

- Warfarin - testosterone may increase the anticoagulant effect. Monitor INR especially when the treatment is started, stopped or the dose adjusted.
- ACTH or corticosteroids- increased likelihood of oedema; use with caution, particularly in patients with cardiac, renal or hepatic disease.

- Anti-diabetic medicines - androgens may improve glucose tolerance and decrease the need for insulin or other anti-diabetic medicines. Monitor patients at the beginning or end of treatment and at periodic intervals during.

For a full list of contraindications, precautions and drug interactions refer to the BNF/product SPC.

Information Given to Patient

- A masculinising hormone treatment information sheet (Appendix 1) is available.
- Athletes should be informed that testosterone treatment, may give positive results in a doping test.
- Testosterone gels leave a testosterone residue on the skin that can be transferred to a woman or child who might come in close contact. If a testosterone gel is used, advise patients to cover the application sites with a shirt and to wash the skin with soap and water before having skin-to-skin contact. Serum testosterone levels are maintained when the application site is washed 4–6 h after application of the testosterone gel.
- Provide information on NHS population screening.
  Available from: https://www.gov.uk/government/publications/nhs-population-screening-information-for-transgender-people

Contacts

The Nottingham Centre for Transgender Health
12 Broad Street, Nottingham, NG1 3AL
Telephone: 0115 8760160
Email (for referrals): ReferralsNCTH@nottshc.nhs.uk
Email (for healthcare professionals and blood results): ClinicalNCTH@nottshc.nhs.uk
Email (for patients): NCTHGeneral@nottshc.nhs.uk

References

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2. Testogel 16.2mg/g gel – Besins Healthcare UK Ltd. Summary of product characteristics (last updated 02/03/2021). https://www.medicines.org.uk/emc/product/8919/smpc [Accessed 01/03/2022].
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5. Sustanon 250, 250mg/mL solution for injection – Aspen. Summary of product characteristics (last updated 09/07/2020). https://www.medicines.org.uk/emc/product/5373/smpc [Accessed 17/02/2022].

Version Control – **Adult Transgender – Masculinising Hormones Information Sheet**			
Version	Author(s)	Date	Changes
1.0	Hannah Godden, Specialist Mental Health Interface Pharmacist, NHS Nottingham and	July 2022	

	Nottinghamshire ICB Dr Derek Glidden, Transgender Healthcare Consultant (psychiatrist), Nottingham Centre for Transgender Health. Dr Kaustubh Nisal, Consultant Endocrinologist, Nottingham Centre for Transgender Health		

Appendix One
Patient Information Leaflet – Masculinising Hormone Treatment

Information about masculinising hormone treatment

Hormone treatment for people assigned female at birth involves the use of testosterone. This can be given by intramuscular injection or by a gel which is applied to the skin each day. This sheet provides information about what changes can be expected as well as the risks of this treatment.

Testosterone treatment will increase the growth of body and facial hair. There is a risk of developing male pattern baldness on your head. There may be redistribution of body fat and an increase in muscles giving a more masculine body shape. Acne can be a problem but should be treated as usual. Mood changes, both positive and negative, may happen but these don't often require treatment. Over time it is likely that your voice will deepen into the male range. There may be a small amount of bone thickening which may help masculinisation.

Taking testosterone causes your clitoris to get bigger which can be uncomfortable at first. You are likely to feel an increase in your sexual drive. Your vagina may also not get lubricated so easily. This may cause pain and discomfort on penetration, but you can buy a personal lubricant (lube) to help with this. Note that oil-based lubes can't be used with latex condoms as they can break down the latex.

Your periods will stop but this can take many months. Some people have a problem with light bleeding which is sometimes called spotting. You are likely to become infertile (not able to have children) and this might still be the case even if you stop taking male hormones. Although hormones are likely to make you infertile, there is still a possibility that, if you engage in penile-vaginal intercourse, you could become pregnant so you should use contraception (e.g. condoms) if this is a possibility. There are risks to the baby if you become pregnant whilst taking testosterone treatment. You need to think about storing gametes (eggs) if you wish to have biologically related children in the future.

Research on the treatment of people assigned female at birth with testosterone is currently limited. More evidence may be found in future about the benefits and risks. Male hormone treatment may cause changes to liver function, haematocrit (a measure of the thickness of the blood), and haemoglobin levels which could require more investigation and could be an indication of a serious illness. For this reason, it is important for you to have your blood tested regularly so that we know if there have been any changes.

There may be long-term risks in taking masculinising hormone treatment. These are not fully known but include higher risks of cancers of the uterus (womb) and ovaries. After 2-3 years of hormone treatment you should think about monitoring for any problems that may occur or having an operation to remove the uterus and ovaries; if you choose to have monitoring you will need to have scans to check the womb and ovaries are healthy - which may include a scan from inside your vagina.

You can stop this treatment at any time. There will be effects such as body hair growth, baldness, a deeper voice and the loss of ability to have children, which may not be reversed if you do stop treatment.

It is important to have regular blood tests and to attend appointments at our clinic to reduce the chances of unwanted effects. If you are unable to attend appointments regularly, we may no longer support your treatment and your GP may decide to stop your treatment.

Declaration

I confirm that I have read and understood the information above.

I confirm I understand that all testosterone treatment apart from Sustanon® is not licensed for the treatment of Gender Incongruence. I understand that if I receive testosterone in the form of gel or Nebido® injection this would be off license; however, I agree to receive this medication.

Signed…….

Patient name…… (DOB……)

Date.....

Further information about national NHS screening Programmes available to transgender and non-binary people can be found at: https://www.gov.uk/government/publications/nhs-population-screening-information-for-transgender-people

It is important that you return both side/pages of this document with your signature, if not it can cause delays.