Feminising 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

Oestrogens
Medication for feminisation starts at treatment with oestrogens which also have the effect of suppressing testosterone. Estradiol preparations are used at doses necessary to achieve serum estradiol levels typical of a pre-menopausal woman.

An individual being significantly overweight increases their risk of adverse effects and complications related to treatment with estradiol and medications that block the effects of testosterone. There is strong evidence that an individual's risk of thrombosis increases as their Body Mass Index (BMI) increases. Whilst a BMI greater than 40 is not exclusion to this treatment, hormone therapy should only be recommended following an individualised discussion of risk, possible adverse effects, and possible impacts on final treatment outcome[1].

There is strong evidence that an individual's risk of thrombosis is increased if they smoke, particularly if they are treated with estradiol. Whilst smoking is not an exclusion to access to this treatment, hormone therapy should only be recommended following an individualised discussion of risk, possible adverse effects, and possible impacts on final treatment outcome[1].

Patients undergoing surgery will need to come off oestrogens approximately 6 weeks prior to a planned operation to reduce the risk of thromboembolic complications. After surgery, patients will go back onto oestrogens, typically 2 to 4 weeks after their operation,

Oestrogen preparations include oral estradiol tablets and transdermal estradiol as gel or patches. Transdermal estradiol preparations should be offered to people over 40[1].

Oestrogel® 0.75mg/actuation gel should be applied to clean, dry, intact areas of skin *e.g.* on the arms and shoulders, or inner thighs. The area of application should be at least 750 cm^2. Oestrogel® should be allowed to dry for 5 minutes before covering the skin with clothing. Skin contact with others should be avoided for one hour after application. Wash hands with soap and water after applying the gel. Washing the skin or contact with other skin products should be avoided until at least one hour after application of Oestrogel®[2].

Estradiol patches (Evorel® and Estradot®) should be applied twice weekly to clean, dry, healthy, and intact skin. It is recommended that patch application site is rotated. The patches should remain in place during bathing and showering. Should it fall off during bathing or showering the patient should wait until cutaneous vasodilation ceases before applying a replacement patch to avoid potential excessive absorption. Should a patch fall off at other times it should be replaced immediately[3].

GnRH analogues

For most patients the testosterone suppression of oestrogen treatment will not be enough to put the testosterone level into the female range. GnRH analogues are usually required to achieve maximum suppression of the secondary male sexual characteristics. They are introduced after or alongside oestrogen therapy. Treatment is usually started with a monthly GnRH injection for 2 months before moving to a 3-monthly dosing regimen. Triptorelin preparations are recommended in Nottinghamshire for cost effectiveness and convenience reasons. Some patients may experience symptoms associated with a transient increase in testosterone levels after the first injection of a GnRH analogue. This may cause mood change, increased libido and an increase in or reoccurrence of erections. It is self-limiting and last 1-2 weeks only; it does not recur with subsequent injections.

Triptorelin 3mg (Decapepyl SR®) is a 28-day preparation. It should be administered by intramuscular injection[5].

Triptorelin 11.25mg (Decapepyl SR®) is a 3-monthly preparation. It should be administered by intramuscular injection[6].

A summary of all available preparations is shown below:

1-month preparations

Dose and frequency	Every 28 days			
Drug and dose	Goserelin 3.6mg	Leuprorelin 3.75mg	Triptorelin 3mg	Triptorelin 3.75mg
Brand name	Zoladex	Prostap SR	Decapeptyl SR	Gonapeptyl Depot*
Form	Implant in prefilled syringe	Powder to reconstitute	Powder to reconstitute	Microcapsules to reconstitute
Injection route	s/c	s/c or i/m	i/m	s/c or i/m

*Non-formulary in Nottinghamshire but may be requested rarely when alternatives are not appropriate.

3-month preparations

Dose and frequency	Every 3 months		
Drug and dose	Goserelin 10.8mg	Leuprorelin 11.25mg	Triptorelin 11.25mg
Brand name	Zoladex LA	Prostap 3	Decapeptyl SR
Form	Implant in prefilled syringe	Powder to reconstitute	Powder to reconstitute
Injection route	s/c	s/c	i/m

Oestrogen Therapy Prescribing & Monitoring – Initiation

Dosage of oestrogen depends on circulating oestradiol levels and clinical effects. The dose will be gradually increased to achieve a maximum degree of feminisation.

Product	Starting dose	Oestradiol level monitoring	Target oestradiol level
Tablets **First line:** Elleste solo® (estradiol hemihydrate) 1mg and 2mg tablets. **Second line (only when Elleste Solo® are not available):** Progynova® (estradiol valerate) 1mg and 2mg tablets.	1mg twice daily	Trough sample prior **to morning tablet** Titrate dose every 3 months if trough levels not at target *Option for blood test 2-4 hrs after morning tablet if trough levels are not achieved on highest dose to confirm absorption/adherence*	400-600 pmol/l
Gel **First line:** Oestrogel® pump pack (1 measure 1.25g = 0.75 mg)	0.75 mg once daily *Consider higher starting dose if switching from higher dose tablet regimen to gel*	After 3 months Sample 4-6 hrs **after** gel application *(early afternoon typically)* Titrate dose every 3 months if trough levels not at target	400-600 pmol/l
Gel **Second line (only when Oestrogel® is not available):** Sandrena® 0.5mg and 1mg sachets	0.5-1 mg once daily	After 3 months Sample 4-6 hrs **after** gel application *(early afternoon typically)* Titrate dose every 3 months if trough levels not at target	400-600 pmol/l

Patches Evorel® (25, 50, 75 and 100 microgram/24hr patches) Estradot® (25, 37.5, 50, 75 and 100 microgram/24hr patches)	50 microgram/24hr patch *Consider higher starting dose if switching from tablet to patch e.g.2mg bd or greater start 100 microgram/24hr patch*	After 3 months Sample 2 days after patch application Titrate dose every 3 months if trough levels not at target to 400microgram/24hr max patch dose	400-600 pmol/l

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

Oestrogen therapy Prescribing & Monitoring – Maintenance

Product	Dose range	Oestradiol level monitoring	Target oestradiol level
Tablets **First line:** Elleste solo® (estradiol hemihydrate) 1mg and 2mg tablets. **Second line (only when Elleste Solo® are not available):** Progynova® (estradiol valerate) 1mg and 2mg tablets.	1 mg – 4 mg twice daily	Trough sample prior **to morning tablet** *Option to blood test 2-4 hrs after morning tablet if trough levels are not achieved on highest dose to confirm absorption/ adherence*	400-600 pmol/l
Gel **First line:** Oestrogel® pump pack (1 measure 1.25g = 0.75 mg) **Second line (only when Oestrogel® is not available):** Sandrena® 0.5mg and 1mg sachets	0.75mg – 6 mg once daily	Sample 4-6 hrs **after** gel application *(early afternoon typically)*	400-600 pmol/l
Patches Evorel® (25, 50, 75 and 100 microgram/24 hr patches)	50 micrograms - 400 micrograms/24hr	Sample 2 days after patch application (steady state)	400-600 pmol/l

Estradot® (25, 37.5, 50, 75 and 100 microgram/24 hr patches)	Apply twice weekly		

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 oestrogen titration, monitoring will be performed by the GP on advice of the specialist. The results should be communicated to the specialist for review.
- 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.

Timing of monitoring	**Blood tests to be done**								
	Oestradiol levels	LH/FSH	SHBG	Prolactin	LFTs	Lipids	HbA1C	U&Es	FBC
Baseline	✓	✓	✓	✓	✓	✓	✓	✓	✓
At 3 months and before each dose titration	✓	✓	✓	✓	✓				
At 12 months	✓	✓	✓	✓	✓	✓			
Annually (on going)	✓	✓	✓	✓	✓	✓			

Screening	**Frequency**
Cervical screening	A transgender woman or non-binary person assigned male at birth, will not need to be screened as they do not have a cervix. Transgender women with a neovagina will not need screening as the neovagina is typically lined with keratinized penile skin. For transgender females, registered with the GP as female, the GP can contact the screening programme to inform that the patient isn't eligible.
Breast screening	Transgender women aged 50-71 and registered with their GP as female will be invited for routine breast screening. Long-term hormone therapy can increase risk of breast cancer so transgender women should consider attending for the screening when invited.

	Transgender women aged 50-71 and registered with their GP as male will not be invited for breast screening. Long-term hormone therapy can increase risk of breast cancer. Discuss with patients and consider referral for mammograms.
AAA screening	Any transgender woman or non-binary person assigned male at birth are likely to have the same AAA risk as a man and should consider accessing screening.
Prostate cancer	Risk of prostate cancer in transgender women is probably low but the data are lacking. Prostate cancer screening may be considered after discussion with the patient. In transgender women PSA level can be spuriously low.

Duration of treatment
Oestrogen hormone treatment may be life-long. Details of anticipated treatment duration will be communicated to primary care at the point of discharge from the transgender health clinic.
GnRH analogues are no longer required after testes removal.

Explicit criteria for review of feminising 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	Actions
Persistently raised LH/FSH	Seek specialist advice.
Persistently raised SHBG	Oral oestrogen will raise SHBG levels which may interfere with feminisation. Raised levels don't have any clinical significance (except some other conditions may also raise SHBG e.g. thyrotoxicosis). Seek specialist advice.
Venous thromboembolism	Discontinue oestrogen and seek an urgent advice and guidance from Nottingham Centre for Transgender Health
Breast cancer	Discontinue oestrogen and seek an urgent advice and guidance from Nottingham Centre for Transgender Health
Hyperprolactinaemia	Repeat prolactin level to confirm persistent hyperprolactinemia. Elevated prolactin levels can be due to physiological situations (e.g. stress), or due to other medical comorbidities and medications. If there is no obvious trigger for persistently elevated prolactin levels, refer to endocrinology clinic for further investigations.
Impact on fertility	Oestradiol may cause an irreversible reduction in fertility up to and including, infertility. Patients will have been counselled on the

	potential impact on fertility and will have been offered the opportunity to gain individual funding for gamete storage. If a patient wishes to explore their fertility after having estradiol, seek advice and guidance from Nottingham Centre for Transgender Health. Also consider early referral to obstetric services.
Abnormal liver function	Transient rise in liver enzyme levels can be observed in the initial period (usually up to 6 months) from starting estradiol. For persistently abnormal liver function tests, please follow adult liver disease risk stratification pathway.

Clinically Relevant Medicine Interactions and their Management

Oestrogens[2,3,4]

- The metabolism of oestrogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz). An increased metabolism of oestrogens may lead to decreased effect.
- Ritonavir and nelfinavir, although known as strong inhibitors, exhibit inducing properties when used concomitantly with steroid hormones.
- Herbal preparations containing St John's Wort (Hypericum Perforatum) may induce the metabolism of oestrogens.

GnRH analogues[5,6]

- Drugs which raise prolactin levels should not be prescribed concomitantly if possible as they reduce the level of GnRH receptors in the pituitary.
- Androgen deprivation treatment may prolong the QT interval. Concomitant use with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated.

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

Information Given to Patient

- A feminising hormone treatment information sheet (Appendix 1) is available.
- 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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Version Control – **Adult Transgender – Feminising Hormones Information Sheet**			
Version	Author(s)	Date	Changes
1.0	Hannah Godden, Specialist Mental Health Interface Pharmacist, NHS Nottingham and Nottinghamshire ICB Dr Derek Glidden, Transgender Healthcare Consultant (psychiatrist), Nottingham Centre for Transgender Health. Dr Kaustubh Nisal, Consultant Endocrinologist, Nottingham Centre for Transgender Health.	July 2022	

Appendix One
Patient Information Leaflet – Feminising Hormone Treatment

Feminising hormone treatment for people assigned male at birth may involve the use of oestrogen (female hormone) and testosterone blocking medication. This sheet gives some information about the expected changes and the risks of this treatment.

The effects of taking hormones may include breast growth and body fat redistribution to give a more feminine body shape. You may become less muscular. Body hair may grow more slowly and become softer, but facial hair growth may not change much. NHS funded facial hair removal treatment is available. Mood changes, both positive and negative, may happen but these don't often require treatment. Female hormones will not change your voice. Speech and Language Therapy is available.

Female hormone treatment may affect sex drive. You will probably also be unable to get a full erection after some time on treatment. You are likely to become infertile (not able to have children) and even if you stop treatment you may still be infertile. You need to consider storing gametes (sperm) before treatment if you wish to have biologically related children in the future. Although hormones are likely to make you infertile, there is a possibility that if you engage in penile-vaginal intercourse your sexual partner could become pregnant so you should use contraception if this is a possibility.

Research on the treatment with hormones of people assigned male at birth is limited. More evidence may be found in future about the benefits and risks. It is important to have regular blood tests as there may be changes to things like liver function and prolactin which could require more investigation. For this reason, we recommend that you have your blood tested regularly so that we know if there have been any changes.

There is a risk of developing DVT (also called 'deep vein thrombosis' or 'blood clots') on this treatment. This is important as it may result in serious illness or even death, particularly if it is not treated quickly. If you develop unexpected pain or swelling (usually in your leg), sudden chest pain, shortness of breath and cough you should see a doctor very quickly. For example, you should go to the Accident & Emergency Department (A&E), a Walk-in Centre, or see your GP as an emergency on that day. The chance of getting a DVT is greater if you smoke or if you are overweight.

There may be long-term risks in taking feminising hormone treatment. These are not fully known but include cardiovascular risks such as heart attack and strokes which can make you very ill or even cause death. These risks will be increased if you are overweight, smoke, have high blood pressure, high cholesterol levels, or diabetes.

If you are on a testosterone blocker or have had surgery to remove your testicles then your testosterone levels will be low. If your testosterone level is low you must take oestrogen treatment regularly. You must also have blood tests to make sure you are taking enough oestrogen. Otherwise there is a risk that you could develop osteoporosis (also called thinning of the bones) which may increase the risk of breaking your bones.

The risk of breast cancer in people assigned male at birth is low but may be higher than that of cisgender (non-trans/non-binary) men. You should go for regular breast screening when asked

to. The risk of prostate cancer may be less than for cisgender men, but your GP should be aware that it is still a risk and should screen or investigate you as usual.

You may stop this treatment at any time but some of the effects such as breast growth and infertility may not be reversed if you do. 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 all the information above.

I confirm I understand feminising hormones are not licensed for the treatment of Gender Incongruence; however, I am happy to receive this treatment.

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