Grŵp Strategaeth Meddyginiaethau Cymru Gyfan
All Wales Medicines Strategy Group

Endocrine Management of Gender Incongruence in Adults

Prescribing Guidance for Non-specialist Practitioners

November 2019

(Updated in October 2025 – See 'Updates' section for details)

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All Wales Medicines Strategy Group. Endocrine Management of Gender Incongruence in Adults: Prescribing Guidance for Non-specialist Practitioners. November 2019 (Updated October 2025).

Contents

Glossary

BMI	Body mass index
CAMHS	Child and adolescent mental health services
Cisgender	A person whose gender identity corresponds with the sex assigned at birth.
DHT	Dihydrotestosterone
FBC	Full blood count
FSH	Follicle-stimulating hormone
GAHT	Gender affirming hormone therapy
GnRH	Gonadotrophin-releasing hormone agonists
Gender dysphoria	The discomfort or distress that some trans people experience because of the mismatch between their gender identity and sex assignment at birth.
Gender identity	A person's individual understanding of whether they are a man, woman, or something else.
Gender incongruence	The diagnostic term 'transsexualism' has been replaced with 'gender incongruence'[1]. (This refers to a marked and persistent incongruence between an individual's experienced gender and assignment at birth).
HbA_{1c}	Glycated haemaglobin
LFT	Liver function test
LGT	Local gender team
LH	Luteinizing hormone
Non-binary	A non-binary person has a gender identity that is neither (exclusively) male nor female.
NRT	Nicotine replacement therapy
Off Label	Use of medicines outside their licensed indications
SHBG	Sex hormone binding globulin
SLS	Selected list scheme
Transgender	A person whose gender identity does not correspond with the sex assigned at birth.
Trans men	Individuals assigned female at birth who have a male gender.
Trans women	Individuals assigned male at birth who have a female gender.
WCCG	Welsh Clinical Communications Gateway
WGS	Welsh Gender Service
WGT	Welsh Gender Team
U&E	Urea and electrolytes

1.0 Introduction

This document is intended for practitioners engaged in the prescribing and monitoring of medical therapies used in the management of gender incongruence in adults (over 18 years old). Guidance for people under 18 years old is typically provided by paediatric endocrinology services.

A treatment recommendation is currently made by a gender identity specialist* in the context of a diagnosis of gender incongruence (ICD-11 HA 60.0) and/or gender dysphoria (DSM-5 302.85)[1]. This document is also of utility for the purpose of harm reduction prescribing guided by a gender identity specialist (see Appendix 1).

In making a treatment recommendation, a suitably qualified clinician would be expected to have counselled the patient about the physical and psychological changes that can be anticipated, the risks and limitations of treatment, and the potential impact on their reproductive options. Gamete preservation, if desired, will ideally have been completed, and the patient offered appropriate sexual health and contraceptive advice.

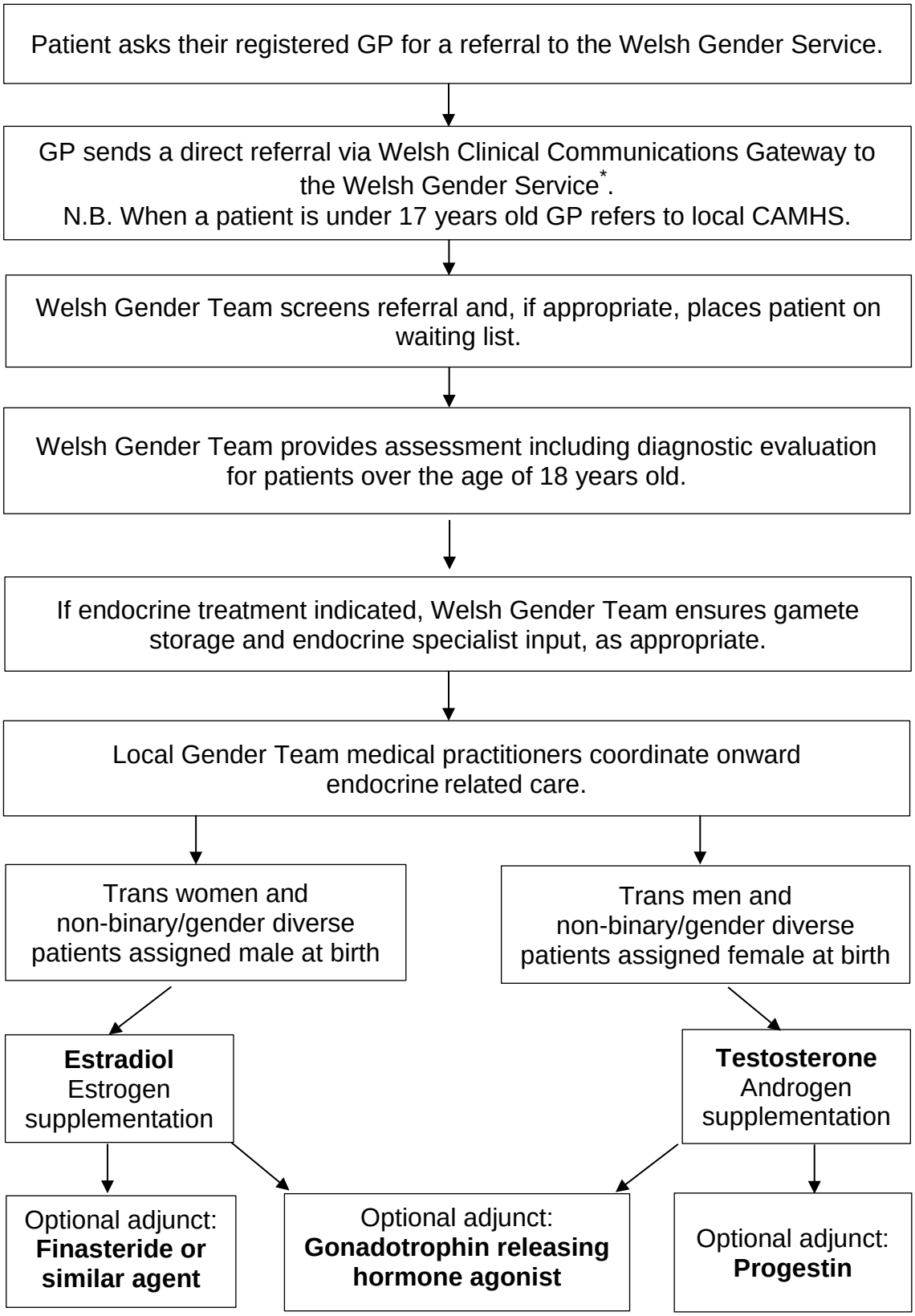
This document recommends some medicines for indications for which they do not have a UK marketing authorisation at the time of publication. For more information on the use of medicines outside their licensed indications ('off-label use'), see the General Medical Council's 'Good practice in prescribing and managing medicines and devices'. Also see AWMSG-endorsed resource 'Understanding unlicensed medicines'.

In Wales, each local health board hosts a Local Gender Team (LGT) comprised of medical practitioners and speech therapists. LGT medical practitioners are responsible for coordinating the initiation and optimisation of hormone therapies at a primary care level, guided by the Welsh Gender Team (WGT).

An enhanced service supports the prescribing and monitoring of endocrine treatments by GP surgeries[2]. The WGT offer advice via a dedicated clinical enquiries email (contact details under Section 10.0).

* This would be an individual with evidence of relevant training and at least **two years**' experience working in a specialised gender identity service.

2.0 Referral pathway to the Welsh Gender Service for patients aged 17 years and over.



*Guidance for people under 18 years old is typically provided by paediatric endocrinology services.

3.0 Testosterone therapy – prescribing recommendations

Testosterone gender affirming hormone therapy (GAHT) is used in trans men and non-binary or gender diverse people assigned female at birth seeking physical virilisation changes. For patients requiring full virilisation changes, the aim is to achieve a serum testosterone level equivalent to the mid-range for a cisgender male 15–20 nmol/L [3].

Physical changes are sequential and can take up to 5 years to complete. Some patients use a low dose testosterone therapy regimen under specialist guidance in which case changes can take longer and may be more limited.

Menstrual suppression/cessation of menstruation is typically achieved after 1–6 months of standard dose therapy[3,4] but for some patients, including those on a low dose regimen, additional treatments may be needed. Treatments used for menstrual suppression in this group are discussed in Section 7.0.

3.1 Summary recommendations:

1. Medical history and physical health including BMI, blood pressure and baseline blood investigations should be reviewed and clinical arising issues should be addressed prior to starting hormone therapy. Clinically significant abnormalities of the baseline test results should be reported to the WGT.

   Baseline blood investigations prior to starting testosterone therapy: FBC, U&E, LFT, HbA_{1c}*, fasting lipids, bone profile, prolactin, LH, FSH, serum testosterone, serum estradiol, SHBG, and vitamin D.

2. Smoking cessation should be discussed and strongly encouraged prior to starting testosterone therapy, since smoking further compounds the risk of polycythaemia and cardiovascular disease. Nicotine replacement therapy (NRT) is considered a safe alternative in this scenario. It is good practice to document smoking status at each clinical review. If a patient reports that they have resumed smoking, encourage cessation, offer NRT and contact the WGT for further guidance.

3. Testosterone is neither a contraceptive nor does it prevent sexually transmitted infections. Appropriate sexual and reproductive health advice should be provided when a treatment recommendation is made and at follow up review appointments where relevant[4].

4. Fertility preservation (gamete cryopreservation) and future fertility options should be discussed prior to initiation of gender affirming hormone therapy.

5. Testosterone therapy should ideally be started using transdermal gel. This offers a more stable testosterone level and has a short half-life so can be easily withdrawn should the need arise. Provided the first or subsequent titration test results are satisfactory, and the patient wishes to do so, they can move from gel treatment to the long-acting intramuscular testosterone undecanoate (Nebido®)[5]. Short-acting intramuscular testosterone is less commonly used in this setting (see Appendix 2).
   Titration blood tests for transdermal gel: FBC and serum testosterone.

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* Except in the case of a known haemoglobinopathy; request fasting glucose.

6. Testosterone therapy will cause a fall in HDL-cholesterol and an increase in triglycerides so can lead to an adverse lipid profile[6]. Lipid lowering therapy and/or specialist referral may be needed if significant hyperlipidemia is evident at baseline, particularly if there are other risk factors for cardiovascular disease. There is no need to routinely monitor liver function tests unless they were abnormal at baseline or there is a history of significant liver disease[7,8].

7. **Annual testosterone therapy blood tests:** serum testosterone, FBC, LFT, and fasting lipids.

3.2 Testosterone transdermal gel

Testogel® 16.2 mg/g gel[9] – 20.25 mg testosterone per pump actuation is the most commonly used testosterone gel on the market:

- Starting dose: 2 pumps daily (40.5 mg testosterone)
- Maximum dose: 4 pumps daily (81 mg testosterone)
- It is also available as Testogel® transdermal gel in 40.5 mg[10] and 50 mg[11] testosterone sachets.

Testavan® 20 mg/g transdermal gel[12] – 23 mg testosterone per pump actuation can be used as an alternative when Testogel® is unavailable. However, this would be off-label use[13] since the starting dose recommended is 2 pumps daily (46 mg) not 1 pump daily as recommended in the SPC.

Tostran® 2% gel[14] **– 10 mg testosterone per pump actuation**
Since the testosterone concentration is lower in Tostran®, it is generally not used for standard dose regimens except where other options are unavailable. Tostran® can also be useful where a lower dose regimen is required. This would however also be an off-label use[13] of this product.

All gels should be applied each morning to the skin of the inner thigh or abdomen (note - this differs from the recommendations for application sites stated in summary of product characteristics [SPC]) to avoid contamination during blood sampling. Patients should wash their hands thoroughly with soap after application and ensure the area is covered by clothes once the gel dries to avoid skin to skin transfer.

All blood tests, when indicated, should be performed 4–6 hours after the gel is applied. Care should be taken that no gel residue is present at the venepuncture site as this can contaminate the sample and cause a falsely elevated testosterone result.

During the titration phase, blood tests are typically performed every 10 weeks, with review each time (see Flowchart 1). It is advisable to repeat the test if an unexpectedly high or low testosterone result is observed and to check patient compliance with timing and administration before making a dose adjustment.

Increase the dose by 1 pump at each review until target range is reached. For patients on a standard dose regimen, if the target range of 15–20 nmol/l is not achieved at the maximal dose of gel, consider a switch to injectable testosterone, or seek specialist advice[9,14].

3.3 Short-acting injectable testosterone

Short-acting injectable testosterone is generally only recommended where gel therapy is not advised, e.g. in severe skin sensitivity, in circumstances where there is a significant risk of skin-to-skin transfer. This is partly due to the higher rates of polycythaemia observed[15]. See Appendix 2 for further information.

3.4 Moving to a long-acting injectable testosterone

Testosterone undecanoate (Nebido®) 1000 mg/4 ml solution for injection[5] is the most commonly used product on the market and must be administered in a healthcare setting. It is not associated with such wide variation in serum testosterone levels, has lower rates of polycythaemia than other injectable preparations, and only needs to be given approximately every 3 months. This makes it the long-term treatment of choice for most patients seeking full virilisation.

It is common practice for patients to spend time getting accustomed to a short-acting agent (usually transdermal gel) first to ensure they have not encountered unwanted side effects or titration blood abnormalities. If gel treatment is well tolerated, the patient may consider switching to the long-acting testosterone injection (Nebido®). To progress a patient from short-acting treatment to Nebido®, the loading schedule provided in Flowchart 2 is recommended.

In the loading schedule, only the dosing interval is adjusted. The dose (1000 mg/4 ml) remains fixed.

All blood tests, when indicated, should be performed on the day of, or up to 2 days before administration of the injection in order to capture a trough serum testosterone reading.

The frequency of Nebido® injections is set according to the trough serum testosterone reading taken before the final (fourth) loading injection. If it falls inside the target range of 15–20 nmol/L, the injection frequency will be 12-weekly. If it falls outside the target range, adjust the injection frequency by one week in either direction from the standard 12-week interval.

If an interval adjustment is required, blood tests (FBC, LFT, fasting lipids and serum testosterone)[7,8] * are re-checked on the day of, or up to two days before, the **third** scheduled injection at this new interval to allow time for settling. **Report a trough serum testosterone level greater than 25 nmol/L to the Welsh Gender Team and instigate the reset plan (see Flowchart 2).**

3.5 Long-term monitoring

Regardless of which type of treatment is used, a patient's testosterone therapy can be considered optimised when two consecutive serum testosterone levels are in target range approximately 6 months apart. At this stage, annual blood monitoring is sufficient.

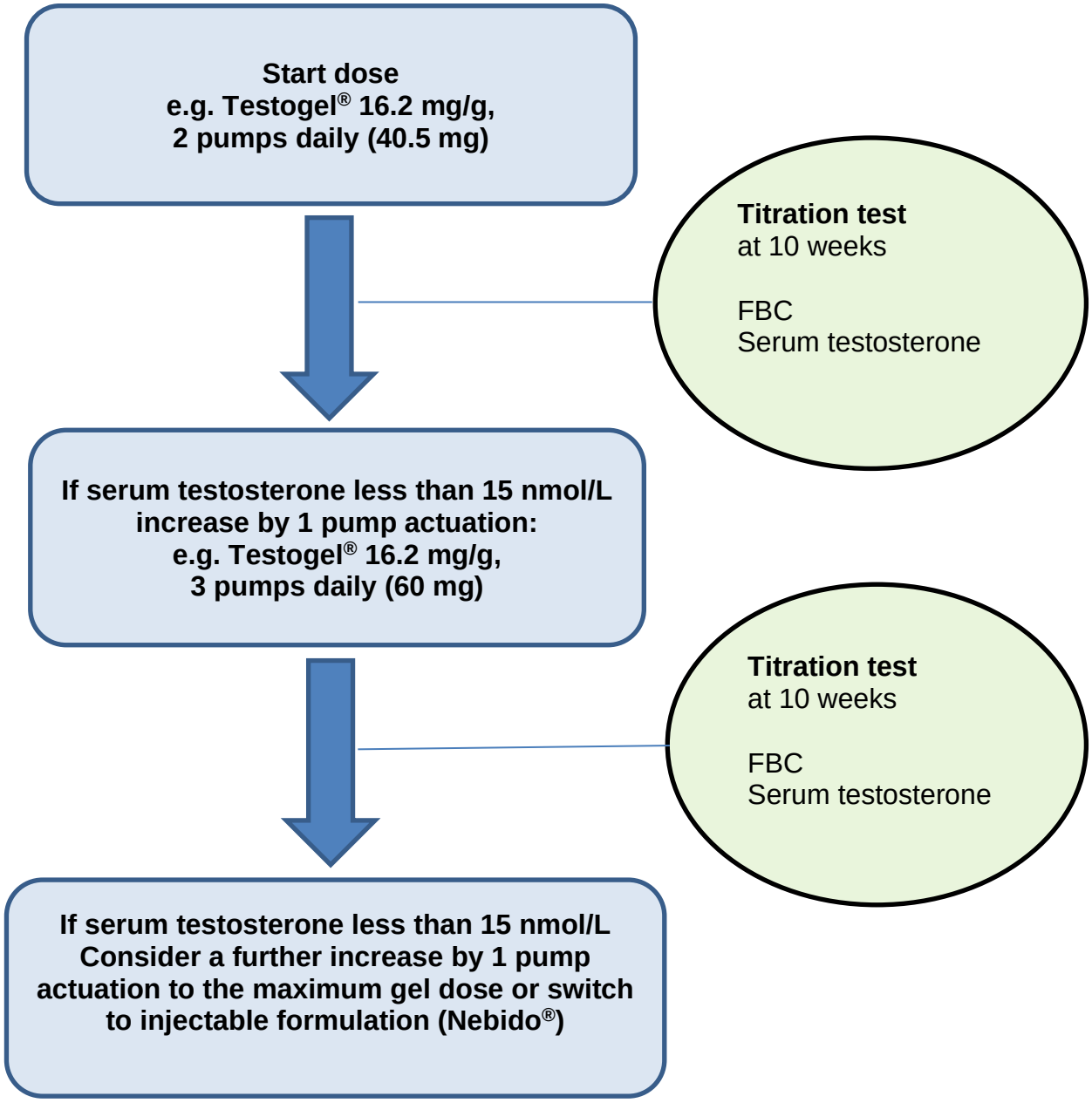
Treatment with testosterone is usually continued life-long unless medical contraindications arise. The decision to discontinue therapy should be made in collaboration with the patient and the WGT.

* LFT and fasting lipids should be included. This is because by the time the third injection occurs this will be close to 12 months (when the annual bloods are recommended).

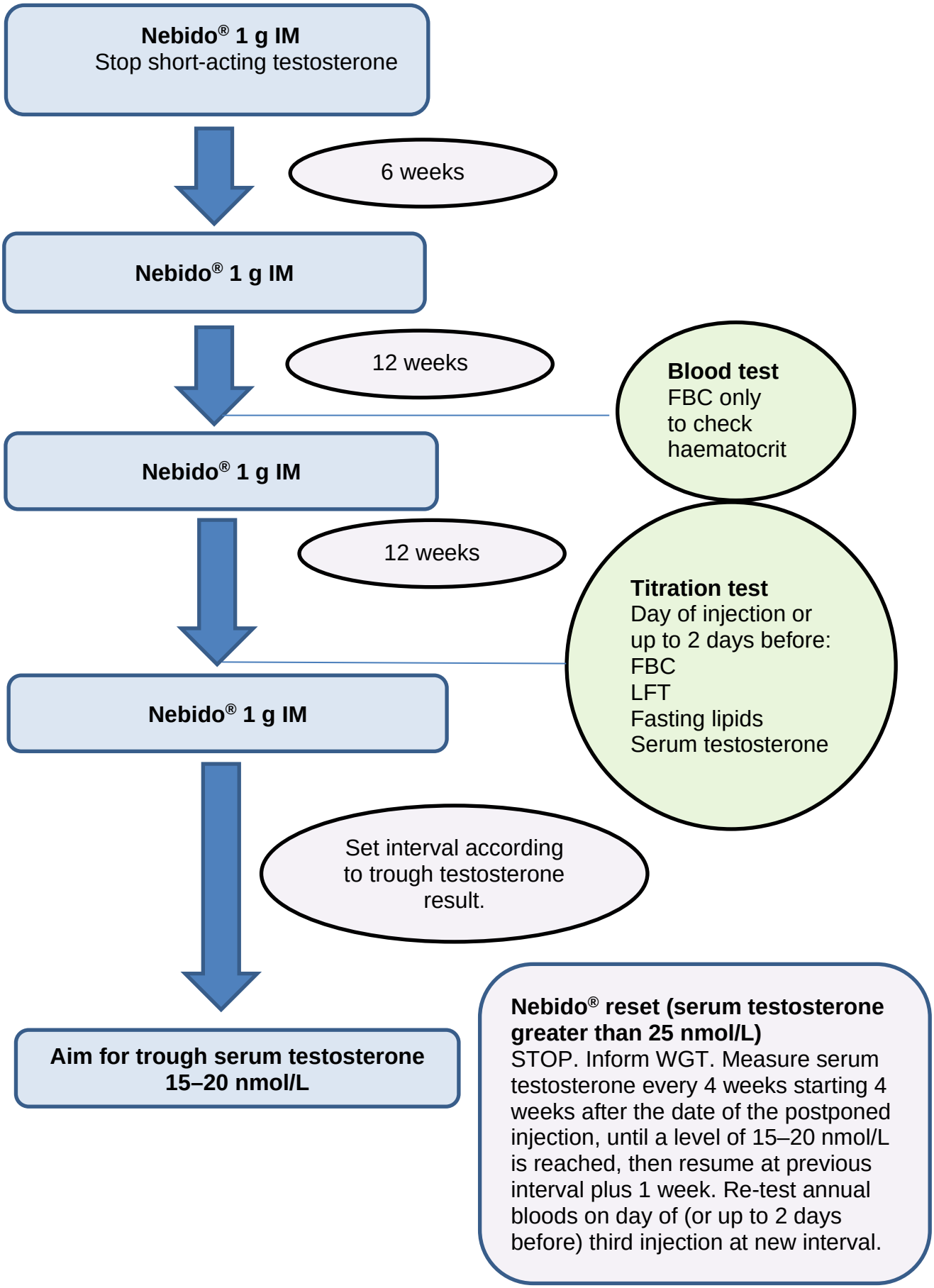
Table 1. Testosterone therapy – summary of precautions

Contraindications	Cautions
Breast cancer Pregnancy Breast feeding Primary liver tumour Hypercalcaemia Acute or recent arterial disease	Epilepsy Migraine Hypertension Predisposition to oedema Liver disease Renal insufficiency Obstructive sleep apnoea Ischaemic heart disease
Drug interactions For a comprehensive list consult the British National Formulary (BNF) or the SPC [5,9,12,14]	
Warfarin – testosterone may enhance anticoagulant effect.	
Adverse drug reactions For a comprehensive list (including rare and very rare adverse effects), or if significance of possible adverse event is uncertain, consult the Summary of Product Characteristics or BNF.	
The side effect profile and safety of testosterone in trans men is identical to that seen in cisgender males undergoing testosterone replacement for hypogonadism. If you suspect an adverse reaction has occurred, report this to the specialist team. Any serious adverse reactions should also be reported to the MHRA through the "Yellow Card" scheme.	
Clinical condition	**Management**
Local irritation	Rotate application/injection sites.
Mood fluctuations	Particularly with the short-acting injectable formulation given the more pronounced peaks and troughs.
Polycythaemia	Testosterone therapy stimulates erythropoietin production[15] Seek advice from Welsh Gender Team if the haematocrit value is greater than 52%. Suspend treatment and seek urgent advice from a haematologist if the value is greater than 60%.
Obstructive sleep apnoea	Testosterone therapy may exacerbate the symptoms of obstructive sleep apnea. Refer to a specialist in sleep disorders if the patient's condition deteriorates.
Abnormal lipid profile	Testosterone replacement in trans-men is associated with an increase in triglycerides and a decrease in plasma high density lipoprotein (HDL) cholesterol levels. However, these changes do not appear to alter cardiovascular mortality[16]. Normal cardiovascular risk assessment applies.
Future fertility	Patients are informed that treatment with testosterone may temporarily or permanently impair fertility and counselled about their future reproductive options.
Liver dysfunction	LFT abnormalities are usually minor and do not require treatment to be stopped[7,8]. An increase in liver enzymes to more than three times the upper limit of normal requires suspension of treatment; contact the Welsh Gender Team.

Flowchart 1. Titration: Initiation of transdermal testosterone to standard target 15–20 nmol/L



Flowchart 2. Initiation/loading of long-acting intramuscular testosterone (Nebido®)



4.0 Estrogen therapy – prescribing recommendations

Estrogen gender affirming hormone therapy (GAHT) is used in trans women and non-binary or gender diverse people assigned male at birth seeking physical feminisation changes. The aim of treatment for most patients is to establish a serum estradiol level equivalent to the mid-follicular range 350–750 pmol/L [3].

Physical changes are sequential and can take up to 3 years to complete. Some patients may use a low dose regimen under specialist guidance in which case physical changes will take longer and may be more limited[17]. For patients seeking full feminisation, titrating towards the upper limit of this range for the first 2–3 years of treatment tends to ensure optimal breast growth, guided by patient-reported breast shape (Tanner stages[18]) and tissue sensitivity.

Venous thromboembolism (VTE) is the most significant risk associated with estrogen therapy especially in older people and those on estrogen therapy for long durations[19]. In the population overall, age, smoking and high BMI have been consistently associated with a higher VTE risk[20].

Transdermal estrogen has been shown to have a lower risk of VTE in cisgender post-menopausal women using it for hormone replacement compared to oral estradiol[21]. Hence transdermal estrogen is recommended as first line, although patient choice is an important factor to consider.

Synthetic estrogens (e.g. ethinylestradiol) or conjugated equine estrogens should not be prescribed as there is an unacceptably high risk of venous thromboembolism. Patients using these treatments should be advised to switch to one of the formulations recommended in this guidance document[3].

Although endogenous testosterone release is suppressed, estrogen therapy alone is not usually sufficient to do so fully if the patient requires it. The use of GnRH agonists and other anti-androgen treatment are covered in Section 5.0.

4.1 Summary recommendations:

1. Medical history and physical health including BMI, blood pressure and baseline blood investigations should be reviewed and clinical issues arising addressed prior to starting hormone therapy. Clinically significant abnormalities of the baseline test results should be reported to the WGT.

   Baseline blood investigations before starting treatment: FBC, U&E, LFT, HbA_{1c}*, fasting lipids, bone profile, prolactin, LH, FSH, testosterone, estradiol, SHBG, and vitamin D. Add prostate-specific antigen (PSA) in patients aged 50 years and older[22].

2. Smoking cessation should be discussed and strongly encouraged prior to starting estrogen therapy, as the risk of venous thromboembolism and cardiovascular disease is increased[23]. Nicotine replacement therapy (NRT) is considered a safe alternative in this scenario. It is good practice to document smoking status at each clinical review. If a patient reports that they have resumed smoking, encourage cessation, offer NRT and contact the WGT for further guidance.

* Except in the case of a known haemoglobinopathy; request fasting glucose.

3. Estradiol is neither a contraceptive nor does it prevent sexually transmitted infections. Appropriate sexual and reproductive health advice should be provided when a treatment recommendation is made and at follow up review appointments where relevant[4].

4. Fertility preservation (gamete cryopreservation) and future fertility options should be discussed prior to initiation of gender affirming hormone therapy[24].

5. Estrogen therapy should be started using transdermal gel or patches and should be guided by patient preference. Oral estradiol can be offered as an alternative except in patients who are over 40 years old, BMI over 35, smokers, or where there is an otherwise higher risk of venous thromboembolism, cardiovascular disease, or a history of pre-existing liver disease[25].

6. **Titration blood tests for estrogen therapy:** serum estradiol, serum testosterone and prolactin.

   For all types of estrogen, titration blood tests are performed every 10 weeks, with review each time (see Flowchart 3). It is advisable to repeat the test if an unexpectedly high or low estradiol result is observed and check patient compliance with timing and administration before making a dose adjustment. There is no need to routinely monitor liver function tests unless they were abnormal at baseline or there is a history of significant liver disease[7,8].

8. **Annual blood tests for estrogen therapy:** serum estradiol, serum testosterone, LFT and prolactin.

4.2 Estradiol gel

Estradiol hemihydrate (Sandrena®)[26] – 1 mg estradiol per sachet

- Starting dose: 1 sachet daily
- Maximum dose: 5 sachets daily

Estradiol 0.06% (Oestrogel®)[27] – 0.75 mg estradiol per pump

- Starting dose: 2 pumps daily (1.5 mg estradiol)
- Maximum dose: 6 pumps daily (4.5 mg estradiol)

Estradiol gel should be applied each morning to the skin of the inner thigh or abdomen (note - this differs from the SPC recommendations for application sites to avoid contamination when blood sampling). Patients should wash their hands thoroughly with soap after application and ensure the area is covered by clothes once the gel dries to avoid skin to skin transfer.

All blood tests, when indicated, should be performed 4–6 hours after the gel is applied. Care should be taken that no gel residue is present at the venepuncture site as this can contaminate the sample and cause a falsely elevated estradiol result.

Increase the dose by 1 sachet or 1 pump at each review until target serum estradiol range is reached. If target range of 350–750 pmol/L is not achieved at the maximum dose of gel, consider a switch to estradiol patches, or seek specialist advice.

4.3 Estradiol patches

Estradot®[28] or Evorel®[29] *

- Starting dose: 50 micrograms/24 hours twice weekly
- Maximum dose: 200 micrograms/24 hours twice weekly

Patches can be applied anywhere below the waist. It is worth noting that some brands are affected by exposure to sunlight, and application to the waistline may also risk patches being rubbed off by clothing.

All blood tests, when indicated, should be performed 48 hours after a new patch is applied.

Increase the dose by 50 micrograms/24 hours twice weekly at each review until target serum estradiol range is reached. If target range 350–750 pmol/L is not achieved at the maximum dose of patches, consider a switch to estradiol gel, or seek specialist advice.

4.4 Oral estradiol

Estradiol valerate (Progynova®)[30]
Estradiol hemihydrate (Elleste Solo®[31], Zumenon®[32])

- Starting dose: 2 mg daily
- Maximum dose: 8 mg daily

Patients are advised to take the full daily dose in the morning, swallowed whole.

All blood tests, when indicated, should be performed 4–6 hours after tablet(s) are taken.

Increase the dose by 2 mg at each review until target serum estradiol range is reached. If target range 350–750 pmol/L is not achieved at the maximum dose, consider a switch to a transdermal agent or seek specialist advice.

4.5 Switching from oral estradiol to transdermal therapy

When switching from oral to transdermal treatment, patients should be moved to the equivalent dose as per the table below:

Table 2. Dose equivalence when switching from oral to transdermal estradiol

Oral Dose	Transdermal Gel*	Transdermal Patches
2 mg	1 mg	50 mcg
4 mg	2 mg	100 mcg
6 mg	3 mg	150 mcg
8 mg	4 mg	200 mcg

* For **Oestrogel®** the closest equivalent dose should be used

Perform a titration blood test at 10 weeks, reviewing the result to see if further dose titration is needed.

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* Anecdotal data suggests some brands are preferred for their small size and adhesive quality.

4.6 Long-term monitoring

Regardless of which type of treatment is used, a patient's estrogen therapy can be considered optimised when two consecutive serum estradiol tests are in range approximately 6 months apart. At this stage, annual blood monitoring is sufficient.

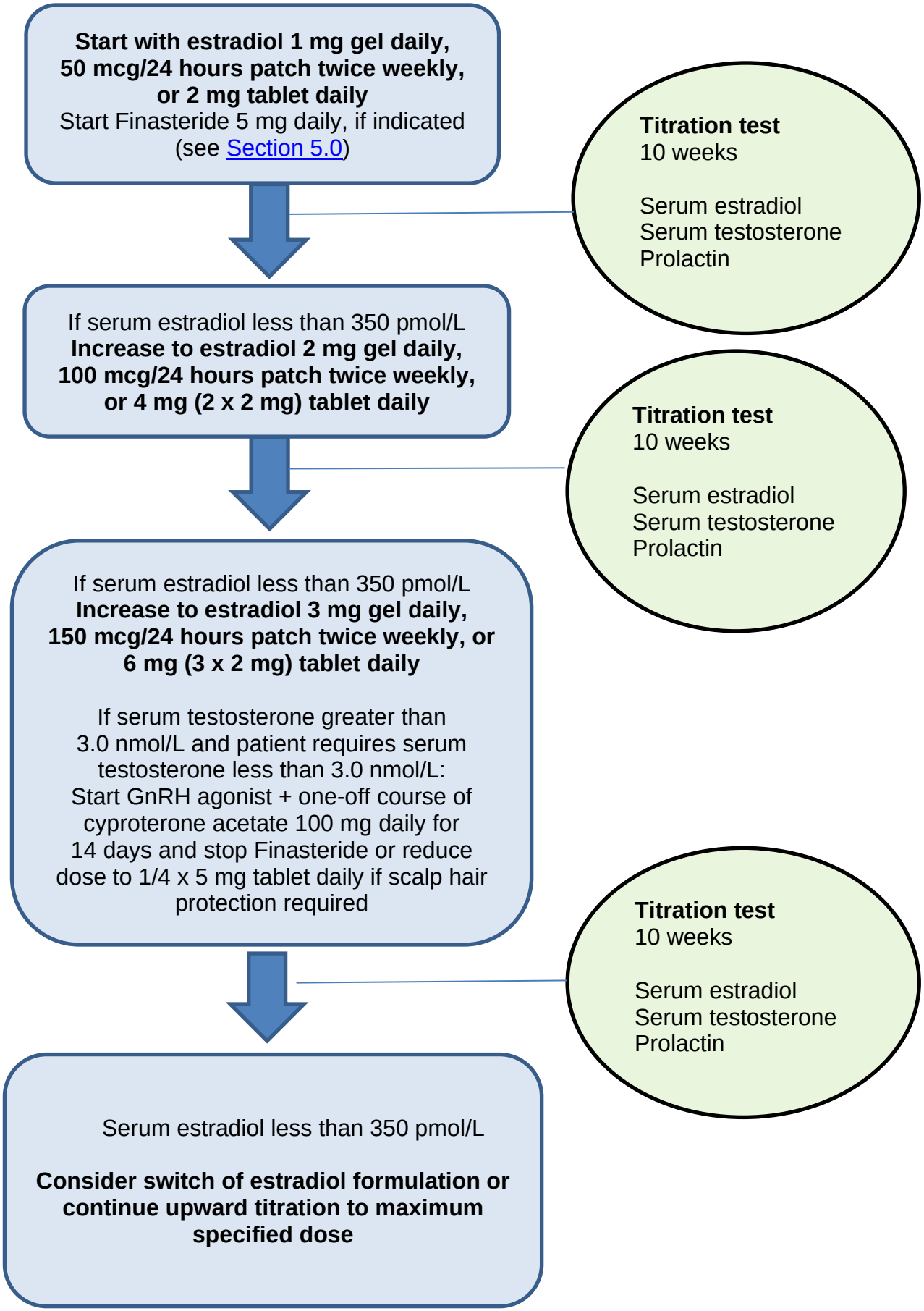
Treatment with estrogen is usually continued life-long unless medical contraindications arise. Older patients using oral estradiol are advised to switch to a transdermal formulation due to the increased risk with age of thromboembolism and cardiovascular disease[33]. Patients who underwent orchiectomy wanting to reduce their estradiol dose require a serum estradiol level of at least 200 pmol/L to maintain bone density[34],[35]. The decision to discontinue therapy should be made in collaboration with the patient and the WGT.

Table 3. Estradiol therapy – summary of precautions

Contraindications	Cautions
Breast cancer Thromboembolism ● active ● recurrent Thrombophilic disorders Dubin-Johnston and Rotor syndromes Acute liver disease Acute or recent arterial disease Acute porphyria	Obesity Hypertension Ischaemic heart disease Single DVT Family history of thromboembolism and breast cancer Migraine with focal neurology SLE Sickle cell disease Gallstones and liver disorders
Drug interactions For a comprehensive list consult the BNF or SPC[26-32].	
There are no drug interactions with transdermal estradiol. The metabolism of oral estradiol can be affected by drugs which act on liver enzymes, such as cytochrome P450. Both enzyme inducers and inhibitors have been shown to have enzyme-inducing properties when used concomitantly with steroid hormones.	
Adverse drug reactions For a comprehensive list (including rare and very rare adverse effects), or if the significance of a possible adverse event is uncertain, consult the SPC or BNF.	
Although higher doses are used, estrogen is usually very well tolerated. If you suspect an adverse reaction has occurred this should be reported to the specialist team. Any serious reaction should also be reported to the MHRA through the "Yellow Card" scheme.	
Clinical condition	**Management**
Thromboembolic disease	DVT risk is dramatically reduced with newer estrogen formulations[3,19]. Advise patients to report symptoms urgently.
Breast cancer	Risk of breast cancer secondary to estrogen therapy in this patient group* is thought to be lower than for cisgender women[36]. However, uptake of the National Breast Screening program is strongly advised.
Prostate cancer	Incidence is likely reduced secondary to estrogen therapy[37], but symptoms should be investigated.
Fertility impairment	Estrogen therapy can lead to a reduction in spermatogenesis. Patients are counselled that treatment might affect their fertility and are offered sperm storage before starting treatment[24].
Liver dysfunction	LFT abnormalities are usually minor and do not require stopping treatment[7,8]. An increase in liver enzymes to more than three times the upper limit of normal should prompt advice to be sought from the WGT.
Hyperprolactinaemia	Serum prolactin may rise with the introduction of estradiol therapy[38]. If there is a new rise of greater than 750 mIU/L, repeat the test. If there is a new rise of greater than 1,000 mIU/L, repeat the test and inform the WGT.

* Trans women and non-binary or gender diverse people assigned male at birth.

Flowchart 3. Initiation of estrogen to standard target 350–750 pmol/L and introduction of anti-androgen therapies or GnHR agonist therapies



5.0 Gonadotrophin-releasing hormone agonist and anti-androgen treatments – prescribing recommendations

These treatments are particularly helpful for trans women or non-binary/gender diverse patients assigned male at birth who require further androgen suppression when estrogen treatment alone is not sufficient. Some patients use anti-androgen monotherapy under specialist guidance, while others have no requirements and opt for estrogen monotherapy.

5.1 Gonadotrophin-releasing hormone agonists

GnRH agonist medications bind to the GnRH receptor on the pituitary gland, initially stimulating, then downregulating the release of gonadotrophins (luteinizing hormone, follicle-stimulating hormone). With the hypothalamic-pituitary-gonadal (HPG) axis switched off, sex hormone production from the gonads falls significantly.

Patients intending to undergo feminising genital surgery involving orchiectomy are required to achieve prior suppression of testosterone less than 3.0 nmol/L[39]. For some this can only reliably be achieved through GnRH agonist administration. Post-operatively, this treatment can be stopped.

To avoid triggering menopausal symptoms, GnRH agonist treatment is introduced once the serum estradiol level is greater than 250 pmol/L (see Flowchart 3).

The first GnRH agonist injection will trigger an initial testosterone flare as GnRH receptors (and production of LH and FSH) are stimulated. Symptoms of this flare are counteracted by the co-administration of cyproterone acetate 100 mg taken once-daily for 14 days. Thereafter, gonadal testosterone production is switched off and remains so for the duration of treatment.

Recommended GnRH agonists:

- **Leuprorelin (Prostap 3 DCS®)[40]** 11.25 mg intramuscularly every 12 weeks.
- **Triptorelin (Decapeptyl SR®)[41]** 11.25 mg intramuscularly every 12 weeks.

Alternative GnRH agonist:

- **Goserelin (Zoladex LA®)[42]** 10.8 mg subcutaneously every 12 weeks.

Please note – When prescribing GnRH agonists, the prescriber must endorse the prescription with the reference ‘SLS’.

Available as monthly preparations (Leuprorelin and Triprorelin 3.75 mg every 4 weeks) or (Goserelin 3.6 mg every 4 weeks), if indicated or preferred.

Triptorelin is also available as a 6-monthly preparation (22.5 mg every 24 weeks).

Once testosterone suppression has been confirmed, or after feminising genital surgery involving orchiectomy is completed, routine monitoring of serum testosterone is not necessary as it will reliably be less than 3.0 nmol/L.

With guidance from the WGT, GnRH agonist treatment can be offered to trans men or non-binary/gender diverse patients assigned female at birth if progestin and/or testosterone treatment fails to abolish menstruation/cyclical symptoms (see Section 7.0 Menstrual suppression).

Table 4. GnRH agonist therapy – summary of precautions

Contraindications
Hypersensitivity to GnRH agonists, its analogues or any other component of the medicinal product
Drug interactions For a comprehensive list consult the BNF or the Summary of Product Characteristics[40-42]
Androgen suppression can prolong QT interval therefore concomitant use of medication known to prolong the QT interval should be used with care. An ECG should be undertaken to assess baseline QT interval.
Adverse drug reactions For a comprehensive list (including rare and very rare adverse effects), or if significance of possible adverse event uncertain, consult the Summary of Product Characteristics or BNF.
This treatment is well tolerated and generally not associated with significant side effects. The use of GnRH agonists in conjunction with cross-sex hormone therapy mitigates menopausal symptoms, cardiovascular risk and bone demineralisation. Some patients report short-lived musculoskeletal aching immediately after each injection which resolves after one or two days. Low energy, drive, or sexual desire should be reported to the Welsh Gender Team. If you suspect an adverse reaction has occurred this should be reported to the registered GP. Any serious reaction should also be reported to the MHRA through the "Yellow Card" scheme.

5.2 5-Alpha reductase inhibitors (Finasteride and Dutasteride)

Finasteride[43] and Dutasteride[44] are oral alternatives to a GnRH agonist for use in trans women or non-binary/gender diverse patients assigned male at birth who do not require their testosterone to be fully suppressed. They also help to minimise scalp hair loss, offering long-term protection for those at risk. Treatment can start at the same time as the commencement of estrogen therapy (see Flowchart 3).

These medicines inhibit 5-alpha reductase, preventing conversion of testosterone into the more potent dihydrotestosterone (DHT).

The serum testosterone level can increase on treatment, but patients should be counselled that this does not mean it is ineffective, as DHT levels will fall. There is no justification for monitoring DHT as the test is not routinely available.

Treatment can be continued with concomitant GnRH agonist administration or after orchiectomy at a reduced dose of ¼ x 5 mg daily for patients wanting to protect against scalp hair loss as a small amount of testosterone is secreted by the adrenal glands.

5-alpha reductase inhibitor treatment can be used by trans men or non-binary / gender diverse patients assigned female at birth as part of a bespoke regimen under direction from the WGT.

6.0 Self-medication and private care

A significant proportion of patients waiting for NHS gender services are known to self-medicate with treatments purchased from online pharmacies outside the UK, shared with friends or obtained on the 'grey market'[45].

The WGT offer specialist review and advice around this area. This includes evaluation of a self-medicating patient in support of a general practitioner seeking to meet GMC criteria for harm reduction prescribing (See Appendix 1).

Some patients will also seek private specialist care. General practitioners may not wish to take responsibility for a patient who is seen by a private specialist. If this is the case then care should remain with the specialist. WGT advice can be requested, if needed, via the dedicated WGS clinical advice email (Contact details under Section 10.0).

7.0 Menstrual suppression

Menstrual suppression (amenorrhoea) is typically achieved for patients starting testosterone at standard doses within 1–6 months[4]. However, some patients may wish to start a low dose regimen or may not want to have any testosterone at all but still would like menstrual suppression as part of their treatment for gender incongruence.

Moreover, a minority of patients on therapeutic testosterone may still experience menstrual bleeding/cyclical symptoms despite appropriate therapeutic levels. The WGT offers advice to GPs on menstrual suppression for patients via the dedicated clinical advice email (contact details under Section 10.0).

The use of high dose norethisterone®[46] is *not* recommended as a long-term measure for menstrual suppression as this is metabolised to ethinylestradiol and will result in higher estrogen levels than would result from standard combined hormonal contraception.

Options for menstrual suppression include:

7.1 Continuous combined hormonal contraception

This can be effective at suppressing menstrual bleeding but there is still a possibility of breakthrough bleeding requiring an occasional withdrawal bleed. Low estrogen options can be more successful for this indication. As estrogens will cause an increase in SHBG and fall in free testosterone, this is not recommended for patients on testosterone therapy.

Patients may find some side effects unacceptable, particularly breast tenderness and fullness. This can be particularly problematic for patients who bind their chest. Combined hormonal contraception should not be used in those who have medical conditions that would otherwise contraindicate its use[47].

7.2 Systemic progesterone-based hormonal contraception methods

Breakthrough bleeding can occur with these methods but in patients taking testosterone as well, this is less likely to occur.

7.2.1 Oral medroxyprogesterone acetate (MPA) - Provera®[48.]

With specialist guidance, a dose of 10 mg twice or three times daily is often effective in suppressing menstrual bleeding even in patients who are not taking testosterone therapy. High dose oral MPA will cause a fall in endogenous estradiol and can lead to bone mineral density loss with long term use in patients who do not use testosterone therapy. Patients should have adequate calcium and Vitamin D intake (with supplementation if necessary). Oral MPA is *not* licensed as a method of contraception so if this is needed additional methods should be used.

7.2.2 Injectable Medroxyprogesterone acetate (MPA) - Depo Provera®[49] or Sayana Press®[50]

This treatment also provides effective contraception if used correctly. If menstruation is not fully suppressed, the dose interval of this treatment can be shortened to 8–10 weeks to achieve higher drug levels (off-label recommendation).

7.3 Intrauterine systems

Amenorrhea commonly occurs with the Levonorgestrel Intrauterine System (LNG-IUS), but some people may still experience breakthrough bleeding. It can be a good option for patients who do not wish to have systemic hormone therapy. However, many patients consider the insertion and removal procedure too invasive.

7.4 Gonadotrophin-releasing hormone agonist

Recommendation of a GnRH agonist for menstrual suppression would typically be made by a specialist following specialist evaluation. Ideally patients should be established on testosterone therapy, as GnRH agonist monotherapy will inevitably lead to bone density loss. Patients who do not have adequate sex hormone replacement may also develop menopausal type symptoms. GnRH agonists are *not* licensed as a method of contraception so if this is needed additional methods should be used.

8.0 Other hormone therapy agents

Other hormone therapy agents not included in this guidance document may be prescribed following specialist review from the WGT on a case-by-case basis or as part of a clinical trial. For non-standard therapies used through self-medication or recommended by a private or non-UK specialist, seek advice from the WGT (see Section 6.0 and Appendix 1).

9.0 Long-term health screening

Patients and their registered GP should be aware that automatic call-up to National Screening Programs is linked to the gender marker on the primary care record.

It is advised that GP surgeries apply an alert to the primary care record at the time a gender marker is changed. This should provide a prompt for surgery staff to organise only appropriate screening invitations.

Long-term health screening should include self-examination for chest lumps (even after bilateral mastectomy and chest reconstruction surgery), breast screening if breasts are present, bowel screening, and cervical screening if the cervix is present. Trans men on long term testosterone therapy and people who underwent a prior male puberty are advised to attend abdominal aortic aneurysm (AAA) screening[51].

Routine biennial endometrial ultrasound screening is no longer recommended[52]. Current evidence shows that there is no increased risk of endometrial malignancies or pre-malignant changes in trans people using testosterone GAHT compared to the cisgender population[53]. However, if there is a recurrence of vaginal bleeding after a period of amenorrhoea in patients using testosterone, ultrasound evaluation of the endometrium should be part of a comprehensive assessment of the underlying cause. This should include a pregnancy test if relevant, and testing for sexually transmitted infections if appropriate, as well as a review of medication adherence and check of serum testosterone levels.

Public Health Wales information for transgender service users can be accessed here.

10.0 Welsh Gender Service contact information

Postal Address:
Welsh Gender Service
St David's Hospital (Ysbyty Dewi Sant)
Cowbridge Road East,
Cardiff
CF11 9XB
Telephone: 02921 836612
General enquiries email: cav.wgs_enquiries@wales.nhs.uk
Clinical advice email: cav.wgs@wales.nhs.uk

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Updates

Date of update	Update details
August 2023 update	
Title	• Updated from ‘Endocrine management of gender dysphoria’ to ‘Endocrine management of gender incongruence’.
Throughout	• References updated as required. • Based on feedback received, the order of information in each section has been altered to improve ease of use. For example, general aims of treatment are grouped together, followed by the prescribing recommendations that apply to all forms of the relevant therapy. The flowcharts (previously located at the back of the document) are now presented within the relevant sections.
Glossary	• Expanded to include additional terms.
1.0 Introduction	• Added clarification that this document only refers to treatment of patients aged 18 years and over. • Added signpost to current direct enhanced service details.
2.0 Pathway	• Updated to reflect current service specification, including amending the referral age from ‘17.5 years and over’ to ‘17 years and over’.
3.0 Testosterone therapy	• Blood test requirements updated (baseline tests now include U&E plus bone profiling; titration tests no longer include liver function and lipids unless indicated; annual tests no longer include HbA_{1c}). • More information provided on transdermal gel dosages. • Information on short-acting intramuscular testosterone injection now separated out into Appendix 2. • Recommended application site(s) for transdermal gel have been updated. • Calculation examples have been removed. • Information regarding national screening programmes and long-term health screening have been moved to Section 9.0.

Date of update	Update details
4.0 Estrogen therapy	• Added further information regarding venous thromboembolism risk. • Transdermal estrogens are now recommended first line, rather than oral therapy. • Blood test requirements updated (baseline tests now include U&E plus bone profiling; titration tests no longer include liver function and lipids unless indicated; annual tests no longer include HbA_{1c}). • Recommended application site(s) for transdermal gel have been updated. • Added Table 2 to aid calculating switching from oral to transdermal estradiol therapy. • Information regarding national screening programmes and long-term health screening have been moved to Section 9.0.
5.0 Gonadotrophin-releasing hormone agonist and anti-androgen treatments	• Table 4 has been updated to reflect current guidelines. • Added dutasteride as an alternative preparation to finasteride.
6.0 Self-medication and private care	• Added in response to the increasing number of GP enquiries about self-medication and the request for endocrine input in relation to recommendations from private specialist providers.
7.0 Menstrual suppression	• Pre-existing information included and expanded on in standalone section, in response to GP enquiries and in line with current Welsh Gender Team (WGT) pathways regarding offering support with menstrual suppression.
8.0 Other hormone therapy agents	• Added to ensure this document acknowledges the other compounds used in self-medicated and private care.
9.0 Long-term health screening	• Pre-existing information included and expanded on in standalone section, in response to GP enquiries. Including breast cancer screening, ascending aortic aneurysm (AAA) screening.
10.0 Contact information	• Information updated.
Appendix 1 Harm reduction prescribing	• Added in response to GP enquiries and in line with current WGT pathways regarding offering harm reduction support.
Appendix 2 Short-acting intramuscular testosterone	• Information moved out of the Section 3.0, to reflect this treatment being less commonly recommended or used.
July 2024 update	
Appendix 1 Harm reduction prescribing	• Wording on fertility preservation removed to align with the specifications of commissioned services as determined by **NHS Wales Joint Commissioning Committee.**

Date of update	Update details
October 2024 update	
5.0 Gonadotrophin-releasing hormone agonist and anti-androgen treatments – prescribing recommendations	• Wording on GnRH added: **Please note** – When prescribing GnRH agonists, the prescriber must endorse the prescription with the reference 'SLS'. • SLS added to glossary
October 2025 update	
9.0 Long-term health screening	• Wording has been updated to reflect that routine biennial endometrial ultrasound screening is no longer recommended.

Appendix 1. Harm reduction prescribing

Trans, non-binary, and gender diverse people sometimes self-medicate with prescription-only medicines or other compounds obtained without a prescription, often from an unregulated website. They usually do this because they have been unable to have timely access to NHS specialist care. However, some of the physical changes that can result from use of hormone therapy may be permanent, and some people are at risk of serious harm or even death from their misuse. Consequently, it is important that patients who are self-medicating engage in medical care, so that the Welsh Gender Team (WGT), in collaboration with their GP, can consider if substituting a harm-reduction prescription is in their best interests.

'Harm reduction' is a set of practical strategies intended to substitute the patients from self-medication, over to drug therapy of known quality, with appropriate medical monitoring, until the patient who is on an NHS Gender Identity Clinic waiting list receives diagnostic evaluation and definitive advice about long-term treatment.

Around half of internet sites offering medication without prescription sell counterfeit medicines. Counterfeit medicines may:

- Contain a different active ingredient from that indicated in the package labelling;
- Contain a different dose from that indicated in the package labelling;
- Not contain any active ingredient;
- Contain contaminants that constitute a serious toxicity or infection risk.

The extent and risks to patients from self-medication with counterfeit medicines are well-described by international law enforcement agencies[54]. The sale of counterfeit prescription-only drugs medicines is a criminal offence. Their use constitutes a serious risk to health, including risk of permanent disability and death. Doctors should never encourage or condone the use of irregularly sourced prescription-only medication. Doctors and patient with information that could help the MHRA track down people responsible for counterfeit medicines and devices can e-mail their concerns to the Medicines and Healthcare products Regulatory Agency (MHRA) at counterfeit@mhra.gsi.gov.uk or ring their 24-hour hotline on 020 3080 6701.

In the circumstances specified in the relevant GMC guidance, and with specialist guidance, GPs may substitute an NHS prescription for patients already self-medicating with hormone and other endocrine agents obtained without a doctor's prescription. The aim being to reduce potentially serious harm related to self-medicating with prescription only medicines, where there is no monitoring, or guaranteed content and quality of the medication.

Doctors approached by patients seeking a prescription for hormone and other endocrine agents in this context, but who have not received a treatment recommendation from an experienced gender specialist*, should refer to the Welsh Gender Service via Welsh Clinical Communications Gateway (WCCG) for advice.

* The GMC defines 'an experienced gender specialist' as someone who will have evidence of relevant training and at least two years' experience working in specialised practice

The WGT will screen the GP request with a view to offering a one-off appointment with a specialist clinician to the patient, in parallel with placing them on the main waiting list, if not already undertaken. The registered GP might be asked to support the undertaking of baseline blood tests in preparation.

Following consultation, the WGT will provide a comprehensive letter, including an outline of prescribing recommendations on a case-by-case basis with details of further monitoring requirements, as appropriate. NHS-prescribed harm reduction regimens are almost exclusively fixed dose. In harm-reduction prescribing, the purpose of blood tests is to monitor safety parameters and not to inform adjustments in hormone dose.

The WGT will not at this stage undertake a diagnostic assessment or recommendation regarding the appropriateness of long-term hormone therapy in the context of the patient's gender identity-related concerns. The WGT will provide appropriate signposting for support.

Follow-up

The WGT will remain active in providing clinical oversight until such time as the patient reaches the top of the main waiting list for the Welsh Gender Service or equivalent NHS Gender Identity Clinic. The clinical advice email service (cav.wgs@wales.nhs.uk) can also be used for reporting any psychological difficulties encountered by the patient in relation to the new regimen. Patient review by the WGT will be tailored to the specific needs of the individual patient. Changes to the patient's circumstances relevant to this care pathway should be reported by the GP.

Appendix 2. Short-acting intramuscular testosterone

Short-acting injectable preparations are associated with a larger variation in serum testosterone levels over the cycle of administration and are therefore less preferred to the long-acting injectable preparation. Higher rates of polycythaemia are also observed[55] so it tends not to be recommended for long term use.

Short-acting injectable testosterone might be recommended as a starting point where gel therapy is not advised, e.g., in severe skin sensitivity, in circumstances where there is a significant risk of skin-to-skin transfer.

The most commonly used product on the market is **Sustanon®**[55], which has a licence for use in this context and is the preparation of choice.

Testosterone enantate[56] is used ‘off-label’ at an equivalent dose for patients with allergy to nut or soya.

For non-specialist prescribers wanting support and guidance with management of a patient already established on this treatment, contact the WGT. Self-administration of short acting intramuscular, if feasible, reduces the demand on primary care resources.