Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust

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General Guidelines For The Use Of Hormone Treatment In Gender Dysphoria, Northern Region Gender Dysphoria Service, November 2020

Endocrine Guidelines For Treatment Of Gender Incongruence

Northern Region Gender Dysphoria Service

Treatment Specific Appendices – attached to policy	
1	Estradiol for Gender Incongruence in male assigned adults (18+)
2	Testosterone for gender incongruence in female assigned adults (18+)
3	GnRH Analogues for gender incongruence in male assigned adults (18+)
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Endocrine Guidelines For Treatment Of Gender Incongruence

1. Introduction and Background

Endocrine treatment is one of several evidence-based clinical interventions for the management of gender incongruence, recommended by NHS commissioned gender identity services. These guidelines set out the respective responsibilities of primary care and the Northern Region Gender Dysphoria Service (NRGDS) in the provision of endocrine treatment for this indication, for service users currently in care and treatment in the NRGDS and following discharge. This document is intended to outline the service's approach to treatment and provide sufficient information to support General Practitioners (GPs) to prescribe testosterone and estradiol preparations, GnRH analogues, and a small number of other suppressors of endogenous sex hormones, for transgender and non-binary adults, as recommended by a specialist in gender dysphoria.

At the time of writing, these guidelines aim to meet the requirements of NHS England's Service Specification No 1719: Gender Identity Services for Adults (Non-Surgical Interventions) (2019), in the provision of endocrine treatment to people over the age of 18, who have completed pubertal development. This service specification describes the clinical activities commissioned in NHS specialist gender identity clinic pathway. The respective roles of specialist services and primary care described herein are therefore primarily based on the way specialist services are commissioned. This document does not aim to outline the basis on which related primary care services and clinical activities are commissioned.

Please note that **this document is not intended to be used in the treatment of individuals under the age of 18 years of age.** At the time of writing, there are three nationally commissioned services providing care and treatment to trans people under the age of 18 years old. Further information regarding these services and how to make a referral is available here:
National Referral Support Service - AGEM_Gender_Services.

1.1 What are gender incongruence and gender dysphoria?

Gender incongruence, defined by ICD-11, is the primary diagnostic category used by NHS commissioned specialist gender identity clinics, as part of clinical assessment. It is a persistent and marked discrepancy between an individual's experienced gender and their assigned sex. It is core in understanding gender dysphoria. Gender dysphoria can be thought of as a syndrome comprising discomfort or distress caused by the discrepancy between a person's gender identity and their assigned sex at birth, as well as associated gender role(s) and/or primary and secondary sex characteristics. The term gender dysphoria is also a medical diagnosis codified in DSM-V, but this is not widely used in the UK. Identifying as trans or experiencing gender incongruence and gender dysphoria are not indicative of a mental health disorder.

There is evidence that failing to treat gender dysphoria can result in significant harm, including persistent distress, worsening mental health, self-harm and suicidality. For these reasons, the NRGDS aims to identify and manage gender dysphoria

appropriately, which may or may not include endocrine interventions for gender incongruence.

1.2 Endocrine treatment and gender incongruence

Most transgender and non-binary people who seek endocrine treatment do so to reduce existing sex characteristics and achieve varying degrees of feminisation or masculinisation. This is achieved through the administration of exogenous endocrine agents. Endocrine treatment of this type is a medically necessary intervention for many, but not all, transgender and non-binary people who experience gender dysphoria.

The aim of endocrine treatment is to reduce gender-related distress by making the individual's experience of their body more congruent with their gender identity, which may include the goal of modifying secondary sex characteristics. Sex hormones are administered, sometimes in conjunction with medication to suppress endogenous sex hormone production. Some effects of sex-steroids treatment are irreversible, but other effects may reverse if treatment is stopped. GnRH analogues can be used in order to achieve suppression of endogenous sex hormone production when this has not adequately been achieved by sex steroid treatment alone. Long-term treatment with sex-steroids is usually recommended if this is in keeping with the patient's goals, not only to manage gender dysphoria but also to prevent hypogonadism and associated health consequences, for those individuals who have gonadectomy as part of gender affirming surgery.

Endocrine treatment can provide significant comfort to transgender and non-binary people, including those who do not wish to transition to a different gender role or undergo surgery, or who are unable to do so for medical or personal reasons. For some, endocrine treatment alone may provide sufficient symptomatic relief to obviate the need for full-time social gender role transition or surgery. Endocrine treatment also has a role in preparing the individual and informing the decision-making process before surgery, particularly where surgical gonadectomy may form part of a management plan.

Alleviation of gender-related distress and physiological end organ response, where relevant, are the aim of endocrine treatments. These are achieved through careful holistic assessment, including consideration of health factors, the development of a patient-centred management plan and monitoring of circulating exogenous and endogenous sex hormone levels thereafter, to allow accurate and individual dose titration and appropriate suppression of endogenous sex hormone production. Supra-physiological levels of circulating sex hormones are undesirable. Treatment is flexible and led by the service user as far as is consistent with clinical safety and available guidance, while considering the individual's views of their needs.

Shared decisions regarding medication preparation, method of delivery and dosage are informed by current understanding of minimising health risks and maximising efficacy for each individual according to their goals, while managing change at a pace which is comfortable for the individual. Treatment specific guidance (see appendices) aims to deliver optimum results in the safest way and should be suitable for the majority of people. Where an individual has a medical condition that may

impact on endocrine treatment or vice versa, the specialist clinician may request that the GP refers the service user to a specialist endocrinology service.

1.3 Assigned sex and other terms in this guidance

Assigned sex (sometimes referred to as birth sex) refers to the sex an individual was determined to be at birth or in the first few weeks of their life. This is usually based on an assessment of genital appearance. Most male assigned people have a masculine gender identity in later life and most female assigned people have a feminine identity; they are known as cis men and cis women respectively. Trans people have a gender identity which is different from these expectations and many gender identities exist. In broad terms, transgender people identify with the opposite sex from that assigned to them at birth, while non-binary people do not identify as exclusively male or female.

From the perspective of considering endocrine interventions, assigned sex is the most relevant in terms of which general approach is used, which can then be tailored to an individual's experience of their gender identity and gender-related distress. Treatment specific guidance (see appendices) is labelled according to the medication in question and assigned sex for which each treatment is suitable.

2. Referral Criteria and Geography

The Northern Region Gender Dysphoria Service is based at Walkergate Park Hospital, Newcastle. It is a service for people aged 18 years and over, in England and Wales, who experience persistent unhappiness and/or discomfort with the sex they were assigned at birth; there is no upper age limit. This includes people who want to change physical aspects of their gender as well as those who do not. However, referral is not indicated simply because a person has a trans identity or a history of gender dysphoria. Referral should relate to an identified or suspected treatment need, whether psychological, medical and / or surgical.

Self-referral is available. Referrals are also accepted from GPs, mental health practitioners, and other medical and healthcare professionals. Referral information and relevant forms are available here:
Referral information - Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust

If a referral is received from a source other than the service user's GP, the GP will be informed. Supplementary information about the physical and mental health of the individual may also be requested from the GP. Some people who are distressed about their gender have other health problems such as physical disabilities or mental health difficulties. The service is open to all, however, people with more complex needs may require additional support from other services.

This guideline is used by the service to deliver endocrine care and treatment, irrespective of the service user's location. There may be specific arrangements or commissioned services for delivery of endocrine treatment for gender incongruence in primary care in an individual's locality. NRGDS staff will work with relevant services and clinicians to ensure the patient receives appropriate treatment, in

keeping with this document and the parameters of any local arrangements, as far as possible. In addition, drug formularies differ across England and Wales and this may mean that a product which is non-formulary or restricted in the service user's locality is recommended by the specialist clinician. If this causes any challenges in primary care, the team will endeavour to propose a suitable alternative.

3. Responsibilities for Endocrine Treatment

3.1 Placement of prescribing in primary care

Medications recommended for the treatment of gender incongruence are usually used outside the licensed indications approved by the Medicines and Healthcare Products Regulatory Agency. As is typically the case in respect of old drugs repurposed for new indications, these products are unlikely to be licenced for this indication in the future. However, they are widely used medicines in other contexts, with which GPs are generally familiar. 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 (see Section 7: Additional Resources).

The choice of specific drug preparation, formulation and dosage takes into consideration current understanding of health risks, efficacy, product characteristics and service user preference. Where relevant, cost and resource implications will also be considered.

Prescribing in this field, under the guidance of a specialist service, can be safely undertaken in primary care. This approach has been used by the NRGDS since its inception in 2006 and is utilised by all national gender identity services in England for prescribing endocrine treatment for gender incongruence.

Endocrine treatment is recommended for service users in the NRGDS following comprehensive assessment and in accordance with available UK and International guidance. A Multidisciplinary Team that includes a specialist clinical endocrinologist provides primary care support offered by the NRGDS.

NRGDS is not commissioned by NHS England to prescribe treatment or provide / arrange any investigations. Therefore, it is not possible to initiate or continue endocrine treatment without the support of primary care, to prescribe and monitor treatment, and, in some circumstances, send the results to NRGDS.

3.2 Primary care responsibilities

Some transgender and non-binary people never have contact with specialist gender identity clinics. For those who do, contact with specialist services represents a very small portion of their healthcare over their lifetime; most of their healthcare needs will be met and coordinated by primary care, which is consistent with the management of some other long-term endocrine conditions such as diabetes and thyroid disease. For some trans patients, primary care will be required to change an individual's name, use correct pronouns and / or change gender markers on medical records

and associated documentation, and update screening registers, none of which require endorsement by specialist services. See Section 7 for NHS advice regarding changing an individual's gender marker and health screening for trans people.

When endocrine treatment forms part of an individual's treatment plan, primary care is asked to work with specialist gender identity services in safety monitoring, by providing basic physical examinations. This includes arranging blood tests and other investigations as recommended by the specialist clinician, at baseline and intermittently thereafter. NRGDS staff have access to the Great North Care Record. For the most part, this allows staff to access results but there can be discrepancies, depending on patient consent, and, occasionally, how specific investigations have been processed. In the North East and North Cumbria it is rare for NRGDS staff to request investigation results from individual practices. However, in limited circumstances, especially if the patient resides outside this geographical area, NRGDS staff may not be able to access all clinical results through the digital platforms available to them and, where this is the case, primary care may be asked to provide results directly to NRGDS, for example, via email.

The NRGDS is not commissioned to prescribe any treatments, and a specialist clinician will make medication recommendations to primary care following a comprehensive assessment and consent process. Prescribing clinicians should ensure that they meet the competencies required as outlined in relevant GMC guidance.

NHS England's service specification clearly defines those interventions which are delivered by specialist pathways. However, there are a number of related interventions which may require referral. GPs may be asked to refer to local services, for adjunctive care, which supports patients through the care pathway, such as fertility preservation or mental health care. The GP has the most complete patient record available, although changes in practice and NHS number can complicate matters. Primary care also has access to local referral guidance, whereas the NRGDS covers a large geographical area, with many different service providers.

3.3 Joint working

Close liaison between the specialist clinical team and GP is essential, as are physical assessment and ongoing haematological, hormonal and biochemical monitoring in primary care.

The NRGDS will support primary care by providing specific, relevant information and support for prescribing and monitoring, including the interpretation of relevant investigations.

All service users receiving endocrine treatment are regularly reviewed by staff in NRGDS to assess the clinical benefits of treatment and identify any adverse effects, until they are discharged from the service.

If the GP has concerns regarding endocrine treatment or requires additional advice or information, they can contact the service (see Section 5). The patient's clinician or an appropriate colleague will respond to any queries.

3.4. NRGDS responsibilities

3.4.1 Assessment

The NRGDS will undertake a specialised assessment for people who may have gender incongruence; agree with them the most appropriate diagnostic coding; and develop a treatment plan. Clinicians making recommendations to prescribe endocrine treatment will meet training requirements outlined in relevant NHS England Specialised Services documents.

Most individuals will have two core assessment consultations, as per the current service specification at the time of writing. Assessments will be conducted according to individual need and circumstances. Specific attention will usually be given to gender identity and its development, psychosexual history and current functioning. Assessment will consider the service user's expectations and goals, early life experiences, body image, current and historic mental and physical health, medications, allergies, and family history, including health conditions relevant to hormone treatment, such as cardiovascular disease and venous thromboembolism. Screening programme participation will be checked and encouraged. Baseline laboratory investigations and physical measurements (height, weight, blood pressure) may be requested from primary care during the assessment.

At the conclusion of the assessment process, diagnostic coding will be discussed and agreed with the individual. The individual's treatment goals will be discussed and agreed.

If one of the agreed treatment goals is endocrine treatment for the alleviation of gender dysphoria, the clinician will ensure that that the individual meets the eligibility criteria set out in NHS England's service specification:

- Persistent, well-documented gender dysphoria
- Capacity to make a fully informed decision and to consent for treatment
- If significant medical or mental concerns are present, they must be reasonably well-controlled

The assessment process allows the clinician not only to identify gender incongruence and associated dysphoria but also facilitates the assessment of the risks, benefits, and limitations of endocrine treatment for the individual. These are explored in detail with the service user along with any investigation results. Data on the long-term health consequences of hormone treatment is highlighted, as is the importance of long-term monitoring. The irreversibility and / or reversibility of different aspects of treatment are discussed. There are detailed discussions of the implications for the individual's fertility and sexual functioning, including options for fertility preservation as appropriate.

The specialist team will consider the risks and benefits of the timing of initiation of endocrine treatment. Delay, perhaps to allow time for weight loss, smoking cessation or to start prescribed contraception, may cause distress to patients and increase psychosocial and behavioural risk, including risk of self-harm and / or suicidality.

There is no requirement for the patient to have commenced a social role transition before a recommendation is made for endocrine treatment, however, this is explored and supported if relevant. Treatments often have visible effects, and the consequences of physical change can be profound if the service user has not considered and addressed psychosocial aspects of transition.

The specialist clinician recommending treatment will obtain the service user's verbal and written informed consent to the hormone treatment under consideration and provide a copy of this to the individual and to their GP. Reasonable adjustments will be made, as required, to facilitate decision-making regarding treatment, as part of consent processes. If there are concerns that an impairment of mind or brain is affecting the individual's ability to consent to hormone treatment the service will undertake a capacity assessment. If capacity is lacking and a best interests decision is required, the specialist clinician will act according to the Mental Capacity Act 2005, which may mean the specialist clinician ("as decision-maker") contacts the GP to consult with them.

3.4.2 Providing a recommendation

Once assessment is complete, including formulation of a treatment plan, the specialist clinician will write to the GP. Where the treatment plan includes endocrine treatment, the specialist clinician will provide the GP with patient-specific "prescribing guidance"; a written treatment recommendation, which will include:

- Confirmation that the patient fulfils the necessary clinical criteria
- Adequately detailed information about necessary pre-treatment assessments
- Recommended preparations of medications
- Advice on dosage, administration, initiation, duration of treatment
- Physical and laboratory monitoring, including timing of blood sampling
- Interpretation of laboratory results
- Likely treatment effects.
- A clear follow up plan

The recommendation will also contain confirmation that the patient has been informed of:

- The potential risks and limitations of, and alternatives to endocrine therapy, as well as its potential benefits
- The likely impact of endocrine therapy on fertility and future reproductive options, and of the availability of potential solutions for fertility
- The need for effective contraception in users of endocrine therapy
- The importance of discussing pregnancy and pregnancy-related healthcare if parenthood is being considered.

A record of these discussions with the specialist service and their acknowledgement by the patient will be shared with the patient and GP to form part of an informed consent to treatment documentation.

Thereafter, GPs will be given advice on dose titration and the introduction of additional pharmacological interventions by the specialist clinical team, usually following further review by the specialist team, after initiation. Where it is desirable to

maintain serum hormone concentrations within a target range, such ranges will be clearly defined and advice given on dose adjustment.

3.4.3 Review by the NRGDS

The purpose of clinical monitoring during hormone treatment is to assess end organ response, review the degree of feminisation / masculinisation, discuss service user satisfaction with treatment and identify the presence of adverse effects of medication, if relevant. As part of ongoing care, the specialist team will request appropriate monitoring investigations. The results of monitoring investigations guide dosage of treatment and inform ongoing risk assessment and treatment planning.

Specialist clinician review will be provided according to clinical need and will usually be more frequent after initiation or significant changes in regimen. Reviews will be carried out by specialist medical staff, specialist non-medical prescribers and nursing staff, depending on where a service user is in their clinical pathway. Endocrine and other pharmacological interventions recommended by NRGDS will be reviewed by a medical practitioner from the specialist multi-disciplinary team at least once every twelve months, while the patient is under the care of the service.

3.4.4 Discharge from the NRGDS

When service users are discharged from the service on completion of care in the service, a detailed letter is sent to the GP and a copy provided to the service user, unless otherwise requested. Discharge information is tailored to the patient and will include information regarding long-term aspects of endocrine treatment. Whenever possible, specialist clinicians have detailed discussions regarding long-term treatment with the individual concerned. If this has not been possible because the service user disengaged from the service, the advice given to the GP might be limited by the lack of service user participation.

At discharge, advice is given on the individual's future need for endocrine and other pharmacological interventions, the anticipated duration of treatment (which may be life-long), the regimen recommended for on-going use, its intended effects and possible side-effects and long-term monitoring recommendations, including target ranges where relevant.

Guidance includes information on long-term health, including relevant screening. Advice is given regarding the action to take in response to common disorders and serious complications, including cessation of treatment in the rare circumstances where this would be indicated. Information is given on the situations in which specialist endocrine advice should be sought, as well as where to seek such advice. The circumstances in which direct referral back to the NRGDS would be appropriate are outlined. Re-referral to NRGDS is rarely indicated because of hormone treatment alone once a regimen has been established. Post-discharge, clinical queries can be submitted to the NRGDS and local specialist endocrinology is also available to advise (see Section 5).

Where patients are discharged from the NRGDS because of a request for transfer to another NHS commissioned gender identity clinic and endocrine treatment is

ongoing, information regarding treatment will include that required for transfer only and not detailed information about long-term management. This is a relatively infrequent reason for discharge.

4. General Health Concerns

4.1 Physical examination

Physical examination over and above measurement of height, weight and blood pressure is only recommended if the individual's clinical history suggests that it is likely to result in important benefit to the individual or is likely to reduce an important risk of harm. A physical examination may also be offered if specifically requested by the individual. Waiting times for gender dysphoria services are currently lengthy but early identification and management of obesity and hypertension can be beneficial in terms of patients' ability to access care and treatment for gender incongruence when seen. Physical examination over and above measurement of height and weight is not routinely undertaken by clinicians in the NRGDS.

Individuals must be told that they have the right to refuse physical examination and that refusal will not affect their care, unless omission of examination is likely to significantly and unreasonably compromise their safety. In rare circumstances, a refusal of examination may increase the clinically relevant risk to such a degree that it would be unethical to proceed.

4.2 Co-morbid health conditions

General health should be assessed and considered, throughout assessment and ongoing care and treatment. Should endocrine treatment be initiated, the ongoing health care needs of those receiving endocrine treatment will be managed in primary care. Nonetheless, the specialist team may also make suggestions regarding optimising treatment of underlying medical conditions where relevant to care and treatment of gender incongruence, for the consideration of the primary care team.

GPs need to be aware of pre-existing or pre-disposing conditions that might be exacerbated by treatment with or deficiency of estradiol and testosterone. These include cardiovascular disease, thrombophilia (thrombosis; pulmonary embolism), erythrocytosis (also known as polycythaemia) or, osteoporosis or osteopenia, hormone-dependent cancer, and metabolic disorders such as, dyslipidaemia and diabetes. See the treatment specific appendices at the end of this document for further information.

The presence of co-existing health concerns does not necessarily preclude access to hormone treatment; rather, these concerns need to be considered when assessing the risk of treatment, the appropriate medication and dose and during consent processes. Specialist endocrinological advice and / or treatment in secondary care may be required. Where a referral to specialist Endocrinology services is required, the GP may be asked to undertake this. In rare cases, a medical condition may be a contraindication to treatment.

If mental health concerns are present, this may require referral to local community mental health or psychological services. The GP, who is likely to be more aware of locally available services, may be asked to undertake this. The NRGDS does not provide advice and guidance on the management of general mental health disorders.

4.3 Interactions and standard treatments

In the absence of contraindications, cautionary conditions or specific drug interactions (see treatment specific appendices), treatment for co-morbid conditions should generally follow standard practice. In some instances, treatment can be offered to address side effects of treatment, such as acne secondary to testosterone therapy. If the patient is newly diagnosed with hypertension, dyslipidaemia, high blood pressure or diabetes, NICE guidance on management of these conditions should generally be followed. Dose reduction can be considered and advice sought from the NRGDS or specialist endocrinology in secondary care.

4.4 Obesity

Obesity increases the risk of adverse effects and complications related to hormone treatment. Service users with BMI ≥30 will have enhanced counselling about related risk, particularly with respect to cardiovascular disease, erythrocytosis, thrombosis, and diabetes, and are encouraged to seek help with weight reduction. The decision to recommend treatment will follow an individualised assessment and discussion of risk between the specialist clinician and patient. The NRGDS may ask for primary care support where weight reduction would reduce the risk of treatment. However, the provision of weight management services differs significantly in different areas and patients should be advised to make an enquiry with their practice regarding what is available before making an appointment. As obesity may also be a barrier to gender affirming surgery, or even hormone treatment in severe cases, weight loss early in the patient's care pathway in NRGDS is likely to have multiple benefits to delivery of care and treatment, as well as general health and wellbeing.

4.5 Smoking

Smoking increases the risks associated with hormone treatment, particularly the risk of thrombosis whilst taking estradiol and of erythrocytosis whilst taking testosterone. Smoking should be strongly discouraged and individuals who smoke should desist whilst using endocrine treatment, if possible. Whilst smoking is not an exclusion to access to endocrine interventions, treatment will only be recommended following an individualised discussion of risk, possible adverse effects and possible impacts on final treatment outcome. Moreover, ongoing smoking is likely to limit the possible doses and route of administration of any recommended hormone treatments. Those that choose to continue to smoke will be encouraged to seek help with smoking cessation and directed to seek out locally available support services. Changing from smoking to long-term nicotine replacement, including electronic cigarettes, does not eliminate risk, but may reduce it and, for some, this may be preferable to cigarette smoking.

4.6 Vitamin D

Expert consensus opinion recommends that all transgender and non-binary people should consider taking over-the-counter vitamin D supplements, because of the extremely high levels of deficiency within the population. Screening for deficiency is recommended at the outset of treatment, because many have extremely low levels.

4.7 End of life care

The role of endocrine treatment for trans and non-binary people as part of end-of-life care should, ideally, be discussed as part of their wishes when they can fully participate in decision making. It is possible that cessation of treatment may prolong life, due to the increased thromboembolic risk associated with treatment. However, endocrine treatment often has an important role in affirming a person's identity and cessation of treatment may be distressing and associated with unpleasant physical and emotional symptoms. Generally, treatment should not be stopped as part of end-of-life care, because of the symptomatic benefit of treatment, unless the risks are felt to outweigh benefit and this has been discussed and agreed with the individual. In some circumstances, end of life care may include a decision to increase the dose of sex steroids to offer greater relief of distress associated with gender incongruence.

5. Accessing Specialist Advice

If the GP requires specialist advice regarding endocrine treatment of current service users of the NRGDS, they can contact the service:
Northern Region Gender Dysphoria Service
Telephone number: 0191 287 6130
Opening hours: 9.15am-1pm / 2pm-4.30pm, Monday to Friday
Email address: NRGDS@cntw.nhs.uk
A system is in place to ensure that clinical queries will receive an initial response from a clinician in the team within 3 working days.

Following discharge, the GP can contact the NRGDS or specialist endocrinology for advice on endocrine treatment. However, the best course of action and source of advice depends on the clinical circumstances.

- If the GP is concerned about a medical emergency, they should seek urgent medical advice as per local arrangements.
- Advice regarding technical aspects of endocrine treatment, such as dose or preparation changes, abnormal or out of target range investigation results or newly diagnosed medical illnesses can be sought from the NRGDS clinical queries, via the contact information above. If specialist endocrinological advice is necessary, the response time may be delayed.
- Where there are complex identity-related difficulties, for example, if the patient's identity has changed and they are no longer happy with endocrine treatment, re-referral to NRGDS or another specialist gender identity service may be required. Please contact the service to discuss further.
- Enquiries related to complex physical health conditions are best directed to a specialist endocrinology service. GPs can make an advice and guidance request to specialist services or make a referral. In the North East and Cumbria specialist endocrinological input is available from the Royal Victoria Infirmary:
  Endocrinology and Metabolic Medicine
  Queen Victoria Road,

Newcastle upon Tyne,
NE1 4LP
Working hours telephone number: 0191 282 4636 / 4635
Advice and guidance can be accessed via e-Referrals, specifying for the attention of Dr Owain Leng (correct as of June 2025).

6. Excluded Medications

A number of medications may be prescribed for the management of gender incongruence in other settings or countries but are not part of routine NHS practice.

Please see appendix 6 for further information regarding the following:

- Progestogens, for the treatment of male assigned individuals
- Injectable estradiol
- Propecia® (Finasteride 1mg)

7. Additional Resources

- Service Specification No 1719: Gender Identity Services for Adults (Non-Surgical Interventions).
  NHS England » Service specification: Gender Identity Services for Adults (Non-Surgical Interventions)
- General Medical Council: Relevant guidance
  Prescribing unlicensed medicines - professional standards - GMC
  Trans healthcare - ethical topic - GMC
- The role of GPs in transgender care: RCGP position statement, March 2025
  https://www.rcgp.org.uk/representing-you/policy-areas/transgender-care
- How to change a patient's name and gender marker
  Adoptions and Gender Reassignment | PCSE
- NHS population screening: information for trans and non-binary people
  https://www.gov.uk/government/publications/nhs-population-screening-information-for-transgender-people/nhs-population-screening-information-for-trans-people
  Screening Gender Opt-in - NHS Cervical Screening Administration Service
- Faculty of Sexual and RH CEU Clinical Statement: Contraceptive Choices and Sexual Health for Transgender and Non-Binary People
  FSRH statement: Contraceptive Choices and Sexual Health for Transgender and Non-Binary People (2017) | FSRH

All resources / links are correct and accessible, as of June 2025. They will be updated on the service website, which also includes other relevant information and documentation, such as the service referral process and form(s).
https://www.cntw.nhs.uk/services/northern-region-gender-dysphoria-service-specialist-service-walkergate-park

Appendix 1: Estradiol for Gender Incongruence in male assigned adults (18+)

BACKGROUND

This information summary concerns the use of estradiol in the treatment of gender incongruence in adult male assigned individuals. It has been prepared with reference to the clinical approach adopted by the Northern Region Gender Dysphoria Service (NRGDS), but other NHS commissioned specialist gender identity services also recommend estradiol treatment for this indication and take a broadly similar clinical approach.

There are currently no estradiol preparations that are licensed for use outside the core indication of normal post-menopause. Thus, all prescriptions issued for the treatment of gender incongruence in individuals assigned male at birth lie outside marketing authorisations.

INDICATIONS

For the endocrine treatment of gender incongruence in individuals assigned male at birth, following specialist assessment and recommendation.

Criteria in NHSE's service specification apply to the use of estradiol for the treatment of gender incongruence in people assigned male at birth and include:

- Persistent, well-documented gender dysphoria.
- Capacity to make a fully informed decision and to consent for treatment
- If significant medical or mental concerns are present, they must be reasonably well-controlled

INITITATION

Medication is initiated by primary care, following specialist recommendation.

The specialist gender identity clinic is responsible for recommendations regarding:

- Dose titration and medication optimisation
- Duration and frequency of treatment based on clinical response and tolerability.
- Appropriate monitoring investigations and frequency.
- Dose or formulation adjustments unless directions have been discussed and agreed with the primary care clinician.

Termination of treatment will be the responsibility of the specialist clinical team while the patient is under the care of the specialist gender identity clinic, but the primary care clinician may equally choose to suspend or terminate treatment where there are reasonable concerns about ongoing safety, before seeking further advice from the specialist clinical team.

DOSE REGIMEN

Drug	Route/Formulation	Starting Dose	Titration (Usual increments)	Maintenance dose (following initial stabilisation)
Estradiol	Oral	0.5–1 mg daily	0.5–1 mg	2–6 mg once daily
Sandrena®	0.1% Gel	0.5 mg daily	0.5mg	1–3mg once daily
Oestrogel®	0.06 Gel	0.75–1.5 mg daily	0.75 mg	1.5–3 mg once daily
Estradiol	Transdermal patches	25–75 mcg/24hr	25–50 mcg/24hr	50–250 mcg/24hr
Lenzetto®	Spray	1.53 mg/day	1.53 mg	3.06–6.12 mg

BASELINE INVESTIGATIONS

Baseline investigations are requested by the specialist team following initial assessment and are undertaken by primary care; results are reviewed by the specialist gender identity clinician at second assessment and/or hormone counselling appointments. There is thus usually a delay of at least a few months between a request for investigations and further assessment / review of the results and specialist clinicians are not usually informed of availability of results. If investigations reveal abnormal results warranting action, primary care should respond accordingly and not assume that a specialist clinician has reviewed the results.

The results of these investigations inform personalised risk assessment, hormone counselling and shared decision making, which are undertaken by the specialist gender identity clinic in collaboration with the patient prior to a recommendation to initiate Estradiol treatment.

GENERAL INVESTIGATIONS

If abnormalities in general investigations are noted by the primary care team, these should broadly be approached by identifying potential reversible causes and investigating / treating as per local or NICE guidelines. However, the specialist team is also available to give advice, during the period between appointments.

Reversible causes may include treatments that patients are self-sourcing in order to attempt to manage gender incongruence, for example, abnormal U&Es may be due to the patient taking spironolactone and a high prolactin level may be due to excessive exogenous sex hormone exposure.

General investigations	**Action to be taken if abnormal**
Body mass index	Give advice regarding appropriate action.
Blood pressure	Recheck, identify reversible or secondary causes. If abnormal and sustained, manage as per local or NICE guidelines.
Full blood count	Identify reversible causes of abnormalities and investigate and manage as per local or NICE guidelines.
Urea and Electrolytes	
Liver function tests	
HbA1c (or Fasting blood glucose)	Investigate and manage as per local or NICE guidelines.
Lipid profile	Investigate and manage as per local or NICE guidelines.
Thyroid stimulating hormone	Treat as per local or NICE guidelines.
Vitamin D	Deficiency is very common in the UK, due to lack of sun exposure and this may be exacerbated in trans people because of the lifestyle measures that they often adopt to help manage gender dysphoria (e.g. covering large areas of the body), and that are often unlikely to change because of treatment. Long-term treatment with over-counter 1000 IU (25 mcg) daily is usually recommended, but an initial pharmacological dose may be prescribed if the level is very low as per local guidance.
PSA (in the over 40s not taking hormone treatment)*	If result is abnormal, refer to urology.

*While PSA has not been adopted as a screening test for prostate cancer in the UK, the result cannot be reliably interpreted once estradiol has been initiated. The rationale for measuring PSA prior to commencing estradiol treatment is to identify those with a raised PSA level that will require further investigations to exclude prostate cancer by a urologist prior to commencing treatment (the prostate is not removed during genital reconstructive surgery). There is a risk of both false-positive and false-

negative results, but this may be the last point at which a valid PSA can be checked. Once Estradiol is started and circulating testosterone falls, PSA results become uninterpretable. Furthermore, any cancer that does develop will be more likely to be hormone resistant and thus more refractory to treatment.

HORMONE SPECIFIC INVESTIGATIONS

Abnormal results may arise in individuals taking hormone and associated agents at the time of baseline assessment, whether prescribed or self-sourced. While it is not ideal for the patient to be taking hormones prior to assessment in the specialist gender identity clinic, there is probably little clinical utility in insisting that treatment is completely stopped, especially as this may increase mental distress and potentially risk.

Where hormone levels and other hormone specific investigations are abnormal, the specialist gender identity clinician will consider the possible causes, including underlying metabolic or developmental conditions, as well as the impact of any existing treatment. For the most part, no additional action is required on the part of the GP, other than in a limited set of circumstances outlined below.

Hormone specific investigations	Action to be taken if abnormal
Testosterone	No specific action required. Low level may be a consequence of taking estradiol or anti-androgens, including GnRH analogues*, or more rarely hypogonadism.
Estradiol	No specific action required, in the absence of additional treatment. High level may be a consequence of taking estradiol*. If the level is over 600pmol/L, reduce prescribed dose or advise patient to reduce / stop self-sourced treatment as soon as possible due to increased risk of a thrombotic event.
LH and FSH	No specific action required. High or low levels may be a consequence of endocrine interventions*, or more rarely hypogonadism.
Prolactin	Significantly high level may be due to a combination of spironolactone and estradiol therapy, especially at high doses, or another cause that warrants further investigations e.g. prolactinoma. Seek advice from the specialist gender identity team if levels are above 2,000 mIU/L.
Sex hormone binding globulin (SHBG)	Used as part of metabolic review and risk evaluation; no action usually required.

*When patients are self-sourcing treatment, they may not disclose this to their GP or, indeed, the specialist team. Where there is evidence of a patient taking endocrine interventions with no medical oversight, the patient's GP should check with the patient whether they have considered the impact of these interventions on their health and fertility. A period of more than a few months treatment with estradiol is likely to result in prolonged subfertility and may even result in permanent infertility. The patient should be advised of this and offered referral to fertility services in the region, which offer gamete storage.

ONGOING MONITORING

Monitoring

The specialist service will request appropriate monitoring investigations whilst the patient is under their care. The aim of monitoring is to detect adverse effects of hormonal treatment and guide dosage of treatment.

The specific investigations requested will differ depending on the stage of treatment and clinical need; the specialist team will advise the action to be taken based on results if flagged to the team or will review results at the next contact with the patient and advise accordingly. Details of appropriate long-term monitoring and relevant actions to be taken will be given at discharge.

Certain laboratory results have gender-specific ranges, including haemoglobin, haematocrit and sex hormone levels. Therefore, it is important to change the patient's gender marker in their medical record if and when the patient requests this.

Timing of samples
Blood should ideally be taken 8–24 hr after a tablet, 24–48 hr after a patch has been applied, or 6–12 hr after application of a gel.

Monitoring – requests for advice
If monitoring results are forwarded to the specialist service, please include clear clinical information on the reason for sending, to inform action to be taken.

Frequency
The following should be monitored at least annually but potentially more frequently according to clinical need, as outlined by the specialist service:

- Body mass index
- Blood pressure
- Liver function tests
- HbA1c (or Fasting blood glucose)
- Lipid profile
- Estradiol
- Smoking status
- Alcohol intake

Supplementary investigations
The following may also be requested as part of monitoring, depending on the treatment(s) the patient is receiving, gonadal status and other clinical factors

- Testosterone
- LH
- FSH
- Additional investigations may be requested in limited circumstances, albeit infrequently, if a specific medical condition warrants this.

PHARMACEUTICAL ASPECTS			
ROUTE OF ADMINISTRATION:	**FORMULATION:**	**ADMINISTRATION DETAILS:**	**OTHER IMPORTANT INFORMATION:**
Oral	Estradiol / estradiol valerate and estradiol hemihydrate. A variety of brands are available, including generic products, in doses of 1 or 2 mg tablets.	Swallow the tablets with a drink of water. Try to take them at the same time each day.	Available data suggests that there is no clinical difference between oral estradiol, oral estradiol valerate and oral estradiol hemihydrate, although some patients may request one or the other, sometimes by brand name. They are all available as generic products and are fully interchangeable.
Topical	Oestrogel® Pump-Pack 0.06% gel (Estradiol 600 mcg per 1 gram) - 750 mcg per actuation Sandrena® (Estradiol hemihydrate) - available in 500 mcg or 1 gram sachets	**Oestrogel®**: Apply gel to clean, dry, intact skin such as arms, shoulders or inner thighs and allow to dry for 5 minutes before covering with clothing. Not to be applied on or near breasts or on genital region. Avoid skin contact with another person (particularly male) and avoid other skin products or washing the area for at least 1 hour after application. **Sandrena®**: Apply gel to intact areas of skin such as lower trunk or thighs, using right and left sides on alternate days. Wash hands after application. Not to be applied on the breasts or face and avoid contact with eyes. Allow area of application to dry for 5 minutes and do not wash area for at least 1 hour.	The prescribing of specific brands of gel is required, as different products differ in their pharmacokinetic properties and recommended doses. When blood tests are taken, it is essential the sample is not taken from the arm (if relevant) that had contact with gel on the day of testing.
Transdermal – patches	A variety of brands are available in doses of 25–100 mcg/24 hr	Patch should be removed after 3 to 4 days and replaced with a fresh patch on slightly different site. Recommended sites include clean, dry, unbroken areas of skin on trunk below waistline; not to be applied on or near breasts or under waistband. If patch falls off in warm water, allow skin to cool before applying a new patch.	Generic patches can be prescribed but this may not be suitable for some patients. Different patch preparations vary in their suitability for individuals, for example, in terms of skin reactions or effectiveness of adhesion.

Transdermal - spray	Lenzetto 1.53mg/dose transdermal spray - Estradiol (as Estradiol hemihydrate) 1.53 mg per 1 dose	Apply to dry, healthy skin of the inner forearm or alternatively the inner thigh and allow to dry for 2 minutes before covering with clothing. Do not allow sprays to overlap as this will reduce the overall absorption. Avoid skin contact with another person (particularly children) or pets and avoid washing the area for at least 1 hour after application. If a sunscreen is needed, apply at least 1 hour before Lenzetto®.	None

CAUTIONS AND CONTRADICTIONS Please see SmPC & BNF for comprehensive information.

This information does not replace the Summary of Product Characteristics (SmPC) and should be read in conjunction with it.

Contraindications

These are not equivalent to the use of estradiol for other indications in post-menopausal women, where alternative treatment strategies may be available. However, there are few, if any, alternatives to treatment with estradiol for gender incongruent male assigned individuals and these also confer risk.

Absolute contraindications include:	**Conditions that might be exacerbated by treatment with Estradiol:**	**Estradiol should be used with caution in the following conditions and dose and / or formulation will usually be adjusted (this list is not exhaustive):**
• History of estrogen dependent tumours • Recent arterial thromboembolic disease (e.g. new / unstable angina or recent myocardial infarction / stroke / TIA) • Some thrombophilic disorders	• Thromboembolic disease • Prolactinoma • Breast cancer • Coronary artery disease • Cerebrovascular disease • Cholelithiasis • Hypertriglyceridemia	• Obesity • Tobacco or other nicotine use • Venous thromboembolic disease • Family history of venous thromboembolic disease • Some thrombophilic disorders • Macroprolactinoma • Breast cancer • Coronary artery disease • Cerebrovascular disease, including most dementias • Increased cardiovascular event risk • Dyslipidemia, particularly raised triglycerides • Diabetes, particularly poorly controlled diabetes • Migraine with aura • Cholelithiasis • Severe liver disease • Hepatic porphyria

SIGNIFICANT DRUG INTERACTIONS

The following is not exhaustive. Please see BNF & SmPC for comprehensive information and recommended management.

Drugs which induce hepatic enzymes may have the following effects:	• They may decrease the bioavailability of estradiol, which is metabolised by those enzymes. • Long term alcohol abuse, rifampicin, anticonvulsants (particularly phenytoin, carbamazepine, phenobarbitone and primidone) and spironolactone. • If these drugs are being commenced and the aim is long-term use, dose adjustment of estradiol may be required.
Drugs which inhibit hepatic	• They may increase the bioavailability of estradiol, which is metabolised by those enzymes.

enzymes may have the following effects:	• Alcohol consumed during 'binges', SGL2-inhibitor drugs, antibiotics (isoniazid, erythromycin, sulphonamides, metronidazole, chloramphenicol), ketoconazole, anticonvulsants (particularly valproate), cimetidine, allopurinol, chlorpromazine, imipramine, propranolol, metoprolol and interferon. • If these drugs are being commenced and the aim is long-term use, dose adjustment of estradiol may be required.

ADVERSE EFFECTS / COMORBIDITIES AND MANAGEMENT

As well as responding to absolute values in laboratory tests, a rapid change or a consistent trend in any value should prompt caution and extra vigilance**.**
Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme. Visit www.mhra.gov.uk/yellowcard.
For information on incidence of ADRs see relevant SmPCs.

Adverse effect	**Management**
Estradiol under target range*	Check adherence to prescribed dose and consider increasing dose.
Estradiol above target range*	Check adherence to prescribed dose and consider reducing dose. Extremely high levels (e.g. >1000 pmol/L) may result from contamination of venepuncture site with a gel – consider rechecking before changing dose.
Increased frequency or severity of migraine	Identify reversible causes and investigate and manage as per local or NICE guidelines. Consider change to transdermal and dose reduction.
Skin reactions (topical treatments)	Change to alternative brand
Obesity	Body mass index 30–40, consider change to topical, if relevant. Body mass index >40, consider change to topical, if relevant, and dose reduction.
• Breast cancer • Other estrogen dependent tumour	Stop estradiol and seek specialist advice. Do not restart treatment.
• Deep vein thrombosis or pulmonary embolism • Cardiovascular event (e.g. acute coronary syndromes, ischaemic stroke and peripheral arterial occlusion)	Consider suspending treatment and seek specialist advice, as part of the acute management pathway. It is likely that transdermal estradiol treatment will be restarted following treatment of the acute event, depending on risk assessment. Advice should be sought from the specialist team or specialist endocrinology regarding recommencing treatment; dose or preparation changes may be advised.
• Hypertension • Adverse lipid profile • Diabetes • Abnormal liver enzymes	In the event of a new diagnosis of the following, follow NICE or local guidance regarding investigation and management, and consider a transdermal preparation and dose reduction.
• Unwanted erectile dysfunction	Phosphodiesterase-5 (PDE5) inhibitors can be used to support patients who wish to achieve erections in order to engage in sexual activity. The usual considerations, cautions and contraindications apply.

*Serum levels should be maintained in the upper half to third of the normal follicular range in otherwise young and healthy individuals, which would be 300–600 pmol/L in most laboratories in the North East and North Cumbria. Lower target ranges may be advised by the specialist team where there are co-morbid conditions.

DISCHARGE

Treatment with estradiol is usually life long, in the absence of serious complications. At discharge from specialist gender identity services, the specialist team will provide detailed information regarding many aspects of long-term treatment and associated healthcare to support long-term endocrine treatment in primary care:

- Long term goals and monitoring of hormone treatment (at least annually), including target ranges for serum hormone levels
- Chest / breast self-examination
- Breast and other health screening, as relevant
- Consideration of DEXA scan in individuals who have had a significant break from sex steroid treatment (>12 months), after the age of 20 years.
- Action to take in response to common disorders and serious complications, including cessation of treatment
- How and when to contact or refer back to the Northern Region Gender Dysphoria Service or seek other specialist advice.

FURTHER INFORMATION: Estrogens and associated adverse effects

Thromboembolic disease

- The prevalence of deep venous thrombosis (DVT) in trans women on estradiol therapy is high (approximately 2.6%). Although the majority occur during the first 2 years of treatment, there is a subsequent ongoing incidence of 0.4% per year.
- The type of estrogen may be a factor in the level of risk conferred. Ethinylestradiol and, to a lesser extent, conjugated equine estrogens, result in a procoagulant haemostatic profile in transgender subjects and are therefore not recommended.

Managing venous thromboembolism risk pre and post planned surgery

- Consideration should be given to cessation of estradiol, prior to any surgery with a high risk of venous thromboembolism.
- The treating team should consider individual risk factors and strategies to reduce the risk of VTE.
- If cessation is recommended, estradiol should be stopped at least 4 weeks before surgery, but this recommendation should be balanced against the risks of experiencing vasomotor or mental health symptoms. Adjunctive treatment, such as GnRH analogues, do not need to be stopped.
- Estradiol should be resumed post-operatively if there are no complications.

Breast cancer

- Unlike estrogen + progesterone HRT in menopausal women with an intact uterus, Randomised Controlled Trial data have shown only a minor increased incidence of breast cancer with estrogen-only hormone replacement therapy (HRT) in post-menopausal hysterectomised women, even with prolonged HRT use for up to 10 years;
- Although observational data have found the risk of developing breast cancer to be much higher in trans women than in cis men, it is nevertheless much lower than in cis women (https://www.bmj.com/content/365/bmj.l1652).
- Therefore, estradiol use beyond 55 years old in trans women appears relatively safe from the point of view of breast health

Prostate cancer

- Prostate cancer has only been reported in a handful of trans women in the world literature, suggesting that its incidence is greatly reduced in trans women compared with cis men.

Abnormal liver function

- Abnormalities of liver function are rarely associated with the use of estradiol therapy.
- The risk of abnormal liver function tests is approximately 3% in trans women on feminising treatment. In half of these, the abnormalities persist for more than 3 months. However, the increases are mild and only rarely require discontinuation of treatment.
- Transdermal estradiol may be associated with lower rates of transaminase rise.

Osteoporosis

- Estradiol therapy at adequate dose maintains bone mineral density among trans women prior to orchiectomy, at least in the first three years of treatment.
- There may be an increased risk of bone density loss if patients opt for orchiectomy, but this is unlikely to be significant unless estradiol therapy is interrupted for 12 months or more, is prescribed at an inadequate dose long-term, or is stopped entirely, whether as a result of the patient's health or personal choice.
- Exposure to testosterone earlier in life is likely to protect trans women from developing osteoporosis, relative to cis women.
- Lifelong treatment with estradiol is likely to protect trans women from developing osteoporosis, compared with cis women, who will not usually take HRT for longer than a few years post-menopause, if at all.

Age and mortality

- The risk of adverse effects increases with age and thus target serum levels could be lower as an individual gets older, although trial evidence is lacking. Advice will be given on discharge if relevant.
- Current data suggests that long-term treatment with estradiol in trans women is associated with a slight increase in the standard mortality ratio, possibly due to an increase in cardiovascular deaths or self-harm among vulnerable individuals. However, the increased suicide data is historical and improvements in service provision in recent decades mean this may no longer be relevant. Meanwhile, the increased cardiovascular mortality may be related to historic use of ethinylestradiol rather than current recommended estradiol therapy.
- Lifelong treatment is considered safe, in the absence of serious conditions, although breast screening should continue beyond the age of 70, if estradiol is continued.

ADVICE TO PATIENTS AND CARERS

The specialist clinician will counsel the patient with regard to the benefits and risks of treatment and will provide the patient with any relevant information and advice, including information on individual drugs, as part of consent processes. Patients are also counselled on lifestyle factors they can ameliorate, to reduce the risk of estradiol treatment.

As part of consent processes, the patient is also advised to seek urgent advice in the event of any of the following signs or symptoms:

- Hot, swollen, painful tender calf
- Pleuritic chest pain, shortness of breath and haemoptysis

The service's information / consent form is available here: LINK

PREGNANCY, PARENTAL EXPOSURE AND BREASTFEEDING

It is the responsibility of the specialist to provide advice on the need for contraception to all patients on initiation and at each review, but the ongoing responsibility for providing this advice rests with both the primary care prescriber and the specialist team.

Advice regarding contraception for trans people can be found at:
https://www.fsrh.org/news/fsrh-ceu-clinical-statement-srh-transgender-nonbinary-people/

Pregnancy: Not applicable to the patient group

Breastfeeding: Not applicable to this patient group

Parental exposure:

Estradiol exposure is likely to cause infertility for individuals assigned male at birth, which may be irreversible. However, hormone treatment in this context is not a contraceptive. It is inadvisable to attempt to conceive during treatment with estradiol as sperm quality may be adversely affected.

Fertility
The impact of hormone treatment on fertility and reproduction is explained, in detail, by the specialist clinician prior to initiation. Initial prescribing guidance and / or consent documentation will contain confirmation that the patient has been informed of:

- The likely impact of endocrine treatment on fertility and future reproductive options.
- The availability of potential solutions for fertility, including gamete storage.
- The need for effective contraception in users of endocrine treatment.
- The importance of discussing pregnancy and pregnancy related healthcare if parenthood is being considered.

SPECIALIST CONTACT INFORMATION AND ARRANGEMENTS FOR REFERRAL

The contact details of all national NHS gender identity services can be found here:
How to find an NHS gender dysphoria clinic - NHS

This document has been developed with specific reference to the Northern Region Gender Dysphoria Services' clinical approach.
Clinical Lead: Dr Helen Greener, Consultant in Gender Dysphoria
Lead Specialist Nurse: Deborah Quinn
Daytime telephone number: *0191 2876130*
Email address: NRGDS@cntw.nhs.uk

ADDITIONAL INFORMATION

Accurate advice is essential when the patient's condition becomes less stable and should ideally be in a format that ensures it is not miscommunicated with the need to minimise misunderstanding. In addition, the potential complexity for restarting after a short cessation involving more intense monitoring for a given period may be challenging to convey accurately in a verbal format and ensure the recipient can retain the detail. Communication in writing is preferable so as to reduce the potential for misunderstandings and enable an audit trail.

During the course of care and treatment in the specialist gender identity team, specialist clinicians will provide recommendations regarding:

- If and when a dose change is required OR if the drug needs to be stopped and for how long.
- Need for repeat blood test(s) and when this should be carried out.
- When to seek further advice specialist advice.
- When estradiol may be restarted, at what dose, and any change in frequency of monitoring until patient stable and on a stable maintenance dose again.

At discharge, advice will be given regarding all these scenarios and the specialist team can be contacted in working hours for advice.

In the event of a medical emergency, such as venous thromboembolism, the specialist team will not advise any deviation from usual acute assessment, care and management and no out of hours advice is available from the specialist gender identity team. However, specialist advice is available during working hours and should be sought as part of the acute management pathway.

The following circumstances/ changes in the patient's condition require discussion with the specialist team:

- If non-compliance is suspected or the patient fails to attend monitoring appointments and the primary care prescriber considers it no longer safe to continue prescribing. (All appropriate steps must first be taken by primary care to reinforce the importance of attendance to the patient).
- The patient's clinical condition deteriorates such that the primary care prescriber feels a dose change is required/ the patient no longer appears to be benefiting from therapy.

To be read in conjunction with the following documents

- NHSE guidance – Responsibility for prescribing between primary & secondary/tertiary care. Available from https://www.england.nhs.uk/publication/responsibility-for-prescribing-between-primary-and-secondary-tertiary-care/
- General Medical Council. Good practice in prescribing and managing medicines and devices. Shared care. Available from https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-practice-in-prescribing-and-managing-medicines-and-devices/shared-care
- NICE NG197: Shared decision making. Last updated June 2021. https://www.nice.org.uk/guidance/ng197/.

Appendix 2: Testosterone for Gender Incongruence in female assigned adults (18+)

BACKGROUND

This information summary concerns the use of testosterone in the treatment of gender incongruence in adult female assigned individuals. It has been prepared with reference to the clinical approach adopted by the Northern Region Gender Dysphoria Service (NRGDS), but other NHS commissioned specialist gender identity services also recommend testosterone treatment for this indication and take a broadly similar clinical approach.

The only preparation currently licensed for the treatment of gender incongruence is Sustanon. Other preparations are not licensed for use outside the core indication of hypogonadism due to androgen / testosterone deficiency in cis men. Thus, aside from Sustanon, all prescriptions issued for the treatment of gender incongruence in individuals assigned female at birth lie outside marketing authorisations.

INDICATIONS

For the endocrine treatment of gender incongruence in individuals assigned female at birth, following specialist assessment and recommendation.

Criteria in NHSE's service specification apply to the use of testosterone for the treatment of gender incongruence in people assigned female at birth and include:

- Persistent, well-documented gender dysphoria.
- Capacity to make a fully informed decision and to consent for treatment
- If significant medical or mental concerns are present, they must be reasonably well-controlled

INITITATION

Medication is initiated by primary care, following specialist recommendation.

The specialist gender identity clinic is responsible for recommendations regarding:

- Dose titration and medication optimisation
- Duration and frequency of treatment based on clinical response and tolerability.
- Appropriate monitoring investigations and frequency, including timing of sample.
- Dose or formulation adjustments unless directions have been discussed and agreed with the primary care clinician.

Termination of treatment will be the responsibility of the specialist clinical team while the patient is under the care of the specialist gender identity clinic, but the primary care clinician may equally choose to suspend or terminate treatment where there are reasonable concerns about ongoing safety, before seeking further advice from the specialist clinical team.

DOSE REGIMEN

Drug	Route/Formulation	Starting Dose	Titration (Usual increments)	Maintenance dose (following initial stabilisation)
Testosterone undecanoate	1 g / 4 ml oily injection Testosterone undecanoate	Initially give 1 g IM 8 weeks later 1 g IM 12 weeks later 1 g IM	Change dose interval by 1–2 weeks	4 ml (1 g) IM every 12–18 weeks

Sustanon 250®	1 ml injection Combined: Testosterone propionate 30 mg Testosterone phenylpropionate 60 mg Testosterone isocaproate 60 mg & Testosterone decanoate 10 0mg	1 ml IM every 3–4 weeks	Change dose interval by 0.5–1 week	1 ml (250 mg) IM every 2-4 weeks
Testosterone enantate	1 ml injection Testosterone enantate 25 0mg	1 ml every 3–4 weeks	Change dose interval by 0.5–1 week	1 ml (250 mg) IM every 2-4 weeks
Tostran®	20 mg/1g topical gel (10 mg per actuation)	50 mg once daily	25–50 mg	40–80 mg once daily
Testogel®	50 mg/5 g topical gel (50 mg per sachet)	50 mg once daily	25–50 mg	50–100 mg once daily
Testogel®	40.5 mg/2.5 g topical gel (40.5 mg per sachet)	40.5 mg once daily	20.25–40.5mg	40.5–81 mg once daily
Testogel®	16.2 mg/g topical gel (20.25 mg per actuation)	20.25–40.5 mg once daily	20.25 mg	40.5–81 mg once daily
Testavan®	23 mg/1.15 g topical gel (23 mg per actuation)	23 mg once daily	23 mg	23–69 mg once daily

BASELINE INVESTIGATIONS

Baseline investigations are requested by the specialist team following initial assessment and are undertaken by primary care; results are reviewed by the specialist gender identity clinician at second assessment and/or hormone counselling appointments. There is usually a delay of at least a few months between a request for investigations and further assessment / review of the results and specialist clinicians are not usually informed of availability of results. If investigations reveal abnormal results warranting action, primary care should respond accordingly and not assume that a specialist clinician has reviewed the results.

The results of these investigations inform personalised risk assessment, hormone counselling and shared decision making, which are undertaken by the specialist gender identity clinic in collaboration with the patient prior to a recommendation to initiate testosterone treatment.

GENERAL INVESTIGATIONS

If abnormalities in general investigations are noted by the primary care team, these should broadly be approached by identifying potential reversible causes and investigating / treating as per local or NICE

guidelines. However, the specialist team is also available to give advice, during the period between appointments.

Reversible causes may include treatments that patients are self-sourcing in order to attempt to manage gender incongruence, for example, raised haematocrit and / or haemoglobin may be due to the patient taking testosterone.

General investigations	Action to be taken if abnormal
Body mass index	Give advice regarding appropriate action.
Blood pressure	Recheck, identify reversible or secondary causes. If abnormal and sustained, manage as per local or NICE guidelines.
Full blood count	Identify reversible causes of abnormalities and investigate and manage as per local or NICE guidelines. If haemoglobin and haematocrit are raised (see below for details) consider that the patient may be self-sourcing androgen therapy, advise them of the risk of thrombosis and recommend cessation / reduction in dose (if the former is not acceptable).
Urea and Electrolytes	Identify reversible causes of abnormalities and investigate and manage as per local or NICE guidelines.
Liver function tests	
HbA1c (or Fasting blood glucose)	Investigate and manage as per local or NICE guidelines.
Lipid profile	Investigate and manage as per local or NICE guidelines.
Thyroid stimulating hormone	Treat as per local or NICE guidelines.
Vitamin D	Deficiency is very common in the UK, due to lack of sun exposure and this may be exacerbated in trans people because of the lifestyle measures that they often adopt to help manage gender dysphoria (e.g. covering large areas of the body), and that are often unlikely to change because of treatment. Long-term treatment with over-counter 1000 IU (25 mcg) daily is usually recommended, but an initial pharmacological dose may be prescribed as per local guidance if the level is very low.

HORMONE SPECIFIC INVESTIGATIONS

Abnormal results may arise in individuals taking hormone and associated agents at the time of baseline assessment, whether prescribed or self-sourced. While it is not ideal for the patient to be taking hormones prior to assessment in the specialist gender identity clinic, there is probably little clinical utility in insisting that treatment is completely stopped, especially as this may increase mental distress and potentially risk.

Where hormone levels and other hormone specific investigations are abnormal, the specialist gender identity clinician will consider the possible causes, including underlying metabolic or developmental conditions, as well as the impact of any existing treatment. For the most part, no additional action is required on the part of the GP, other than in a limited set of circumstances outlined below.

Hormone specific investigations	Action to be taken if abnormal
Serum testosterone	No specific action required. Where serum testosterone is above normal range the patient may be self-sourcing androgen therapy, advise them of the risk of thrombosis and recommend cessation / reduction in dose (if the former is not acceptable)*.

	A high level (for female range) may also be a consequence of a medical condition, such as polycystic ovarian syndrome or a difference in sexual differentiation (DSD).
Estradiol	No specific action required, in the absence of additional treatment. Low level may be a consequence of taking testosterone*, hormonal contraceptives, the menopause, or more rarely, other causes of hypogonadism.
LH and FSH	No specific action required. Abnormal levels may be a consequence of endocrine interventions*, menopause, hormonal contraceptives, or, more rarely, other causes of hypogonadism.
Prolactin	A significantly high level would be unexpected and, therefore, warrants further investigation (e.g. for prolactinoma), as per any other patient. Seek advice from the specialist gender identity team if levels are above 2,000 mIU/L. However, if menstrual cyclicity is preserved, then a high prolactin is most likely the result of venepuncture stress.
Sex hormone binding globulin (SHBG)	Used as part of metabolic review and risk evaluation at baseline; no action usually required.

*When patients are self-sourcing treatment, they may not disclose this to their GP or, indeed, the specialist team. Where there is evidence of a patient taking endocrine interventions with no medical oversight, the patient's GP should check with the patient whether they have considered the impact of these interventions on their health and fertility. The patient should be advised of this and offered referral to fertility services in the region, which offer gamete storage.

ONGOING MONITORING

Monitoring

The specialist service will request appropriate monitoring investigations whilst the patient is under their care. The aim of monitoring is to detect adverse effects of hormonal treatment and guide dosage of treatment.

The specific investigations requested will differ depending on the stage of treatment and clinical need; the specialist team will advise the action to be taken based on results if flagged to the team or will review results at the next contact with the patient and advise accordingly. Details of appropriate long-term monitoring and relevant actions to be taken will be given at discharge.

Certain laboratory results have gender-specific ranges, including haemoglobin, haematocrit and sex hormone levels. Therefore, it is important to change the patient's gender marker in their medical record if and when the patient requests this.

Timing of samples

It should be noted that the accuracy of a testosterone level is dependent upon obtaining an appropriately timed sample and the timing of the sample depends on the method of administration. Blood should be taken just before injection (on the same day the injection is due), or 6–12 hours after application of a topical treatment.

Monitoring – requests for advice

If monitoring results are forwarded to the specialist service, please include clear clinical information on the reason for sending and, especially in relation to injection treatment, its temporal relationship to the cycle of injections, to inform the action to be taken.

Frequency

The following should be monitored at least annually, but potentially more frequently according to clinical need as outlined by the specialist service:

- Body mass index
- Blood pressure
- Liver function tests
- HbA1c (or Fasting blood glucose)
- Lipid profile
- Serum testosterone
- SHGB (in order to calculate free testosterone along with albumin which is more useful than serum testosterone)
- Free testosterone (if the laboratory does not provide this many free tools are available, including http://www.issam.ch/freetesto.htm). This is not the same as the Free Androgen Index, which has no validity in males and very limited validity in females, whether cis-or trans-gender
- Smoking status
- Alcohol

Supplementary investigations

The following may also be requested as part of monitoring, depending on the treatment(s) the patient is receiving, gonadal status and other clinical factors

- Estradiol
- LH
- FSH
- Additional investigations may be requested in limited circumstances, albeit infrequently, if a specific medical condition warrants this.

PHARMACEUTICAL ASPECTS			
ROUTE OF ADMINISTRATION:	**FORMULATION:**	**ADMINISTRATION DETAILS:**	**OTHER IMPORTANT INFORMATION:**
Topical	Tostran® Pump Pack (Testosterone 20 mg/1 g) 10 mg per actuation Testogel® Sachets (Testosterone 50 mg/ 5 g) 50mg per sachet Testogel® Sachets (Testosterone 40.5 mg/2.5 g) 40.5 mg per sachet Testogel® (Testosterone 16.2 mg/ 1gm) 20.25mg per actuation Testavan® Pump Pack (Testosterone 20 mg/g) 23 mg per actuation	Specific advice regarding application differs from product to product and patients are advised to read the product information carefully and follow the instructions given. They are also given generic information regarding application of treatment, for all topical products: • Apply treatment at the same time each day, ideally in the morning. • Apply the product to clean, dry, intact skin, in area that will be covered by clothing, such as the shoulders or thighs. • If product comes with an applicator (eg Testavan), do use this to apply the gel so as to avoid all contact with hands. • Do not apply to the chest and genitals. • Allow the area to dry completely before dressing and keep the area covered, to avoid transfer to others, particularly to women and children. • Wash hands thoroughly after application. • Wait the recommended time before showering, bathing or swimming. • Washing the application site with soap and water (after the recommended time period) before physical contact with others. • Dispose of any devices / packets carefully, away from children and pets.	The prescribing of specific brands of gel is required, as different products differ in their pharmacokinetic properties and recommended doses. Information regarding broadly equivalent doses can be found on the NRGDS website. Patients are advised that repeated accidentally transfer to children can result in genital enlargement and premature puberty due to increased blood-testosterone levels. Repeated accidental exposure in adult females may also result in facial and/or body hair growth, deepening of voice, and menstrual cycle changes. Medical advice should be sought if repeated exposure is suspected. When blood tests are taken, it is essential the sample is not taken from the arm (if relevant) that had contact with gel on the day of testing

IM Injection	Testosterone undecanoate 1 g in 4ml oily injection	Administered by deep IM injection, into the gluteal muscle. It should be administered very slowly, over at least 2 minutes. The patient should lie flat or stand, bending at a 45 degree angle during administration. The specialist team advises warming the vial in hot water for several minutes before drawing up and administering, to reduce the discomfort of the injection.	Pulmonary oily microembolism is a rare injection based reaction and is pathophysiologically related to fat embolism syndrome. It can occur following direct vascular or lymphovascular delivery of oil-based preparations. In rare cases it can lead to signs and symptoms, such as cough, dyspnoea, malaise, chest pain, dizziness, paraesthesia or syncope. These reactions may occur during or immediately after the injection and are reversible. Treatment is usually supportive. These symptoms may be difficult to distinguish from an allergic reaction, which can occur with any injectable product. Suspected anaphylactic reactions have been reported. **Sustanon 250 contains Arachis (peanut)oil and should not be administered to individuals known to be allergic to peanuts or soya.**
	Sustanon 250® 1 ml injection Combined: Testosterone propionate 30 mg Testosterone phenylpropionate 60 mg Testosterone isocaproate 60mg & Testosterone decanoate 100 mg	Administer slowly by deep intramuscular injection	
	Testosterone enantate 250 mg in 1 ml injection	Administer slowly by deep intramuscular injection	

Notes:

- Systemic hypersensitivity, antibody formation, and / or acute anaphylactic reactions have been reported with the use of testosterone, particularly those containing benzyl benzoate.
- Injection site injury and vascular injury have been reported with intramuscular formulations.

CAUTIONS AND CONTRADICTIONS Please see SmPC & BNF for comprehensive information

This information does not replace the Summary of Product Characteristics (SmPC) and should be read in conjunction with it.

Contraindications

These are not equivalent to the use of testosterone for other indications in cis men, where alternative treatment strategies may be available. However, there are few, if any, alternatives to treatment with testosterone for gender incongruent female assigned individuals.

Absolute contraindications include:	**Conditions that might be exacerbated by treatment with Testosterone:**	**Testosterone should be used with caution in the following conditions and dose and / or formulation will usually be adjusted (this list is not exhaustive):**
• History of estrogen dependent tumours • Recent arterial thromboembolic disease (e.g. new / unstable angina or recent myocardial infarction / stroke / TIA) • Some thrombophilic disorders • Nut allergy for Sustanon which contains arachis oil.	• Thromboembolic disease • Erythrocytosis • Coronary artery disease • Cerebrovascular disease • Hypertension • Breast or uterine cancer	• Obesity • Tobacco smoking • Venous thromboembolic disease • Family history of venous thromboembolic disease • Some thrombophilic disorders • Breast cancer • Coronary artery disease • Cerebrovascular disease, including most dementias • Congestive cardiac failure • Increased cardiovascular event risk • Dyslipidemias, if uncontrolled • Hypertension, if uncontrolled • Migraine with aura • Sleep apnoea, if uncontrolled • Epilepsy • Alcohol induced liver disease

SIGNIFICANT DRUG INTERACTIONS

The following is not exhaustive. Please see BNF & SmPC for comprehensive information and recommended management.

Testosterone preparations have few significant drug interactions.

- Warfarin – testosterone can increase the anticoagulant effect of warfarin
- Somapacitan might decrease the concentration of testosterone. Manufacturer makes no recommendation.
- Leflunomide and its metabolite terifunomide – there is an increased risk of liver dysfunction and more frequent monitoring may be required.
- Use of drugs which cause hepatotoxicity in combination with testosterone may increase the risk of hepatotoxicity – see BNF for a full list. However, in reality, the BNF cautions in relation to testosterone and liver disease derive from historic experiences with synthetic androgens.

ADVERSE EFFECTS / COMORBIDITIES AND MANAGEMENT

As well as responding to absolute values in laboratory tests, a rapid change or a consistent trend in any value should prompt caution and extra vigilance**.**
Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme. Visit www.mhra.gov.uk/yellowcard.
For information on incidence of ADRs see relevant SmPCs.

Adverse effect	**Management**
Haemoglobin above the normal **male** reference range or haematocrit between 0.5 or 50% (which is the upper limit of normality in most labs) and 0.54%.	• Routine venesection is not recommended • Check adherence to prescribed dose and, if excessive, encourage patient to revert to the prescribed dose. • Lifestyle advice regarding smoking / nicotine use and weight management may be relevant and beneficial. • Identify and treat pulmonary disease, such as obstructive sleep apnoea. • Identify and, if necessary, treat essential hypertension with vasodilator drugs (ACE-inhibitors or angiotensin receptor blockers); diuretics are best avoided • Consider whether hypertension needs investigating for secondary causes. • Reduce dose: ○ Testosterone undecanoate: increase the injection interval by 1–2 weeks ○ Sustanon®/ testosterone enantate: increase the injection interval by 0.5–1 week ○ Topical: reduce the testosterone dose by 10–20 mg (depending on the product) • If on injections, consider switch to topical • Recheck as described below*.
Trough free testosterone level is above target: Injectable 150–300 pmol/L Topical 300–600 pmol/L	• Check adherence to prescribed dose, if excessive, encourage patient to revert to the prescribed dose. • Verify the timing of the blood sample. • Consider rechecking level. • Reduce dose: - Testosterone undecanoate: increase the injection interval by 1–2 weeks - Sustanon®/ testosterone enantate: increase the injection interval by 0.5–1 week - Topical: reduce the testosterone dose by 10–20 mg (depending on the product). • If on injections, consider switch to topical • Recheck as described below*.
Haemoglobin and haematocrit continue to rise despite dose reductions and diastolic hypertension (>75 mmHg)	• Routine venesection is not recommended • Consider whether hypertension needs investigating for secondary causes • Otherwise, consider introducing an ACE-inhibitor or ARB drug, both to control blood pressure and to mitigate erythrocytosis by expanding plasma volume. • If on injections, consider switch to topical • Recheck as described below*

	• Reduce dose further
Haematocrit or haemoglobin do not normalise, with a dose interval of over 18 weeks for testosterone undecanoate or 4 weeks for testosterone enantate,	• Routine venesection is not recommended. • Change to topical, in order to reduce the overall testosterone exposure. • If the patient is extremely unhappy with the proposal to change to topical, alternatives can be considered but seek specialist advice.
Erythrocytosis: Haematocrit above 0.54 or 54% on one occasion Haematocrit remains above 0.5 or 50% after 2 dose reductions (e. g. increased dose interval for injectable) Haemoglobin above 18g/L on one occasion Haemoglobin above normal **male** range after 2 dose reductions (e. g. increased dose interval for injectable)	• Routine venesection is not recommended • Suspend treatment and seek specialist advice regarding when and how to resume treatment
Severe erythrocytosis (haematocrit >0.58 or haemoglobin >20 g/L	In addition to suspending treatment, please seek specialist advice as to whether urgent venesection might be indicated as a one-off procedure.
Free testosterone under target range	• Check adherence to prescribed dose and timing of blood sample. Consider rechecking. • If Haematocrit and haemoglobin are comfortably within the normal **male** range consider increasing dose. - Testosterone undecanoate: reduce the injection interval by 1 week - Sustanon®/ testosterone enantate: reduce the injection interval by 0.5–1 week - Topical: increase the testosterone dose by 10–20 mg (depending on the product). • Recheck as described below*.
Anaemia, according to **male** range, with trough free testosterone under target range	• Identify reversible causes and manage as per local or NICE guidelines. Consider whether testosterone treatment has unmasked iron deficiency • If anaemia continues with no identifiable cause, consider increasing the dose as above. • Recheck as described below*.
Low SHBG	Advise patient of increased metabolic risk and give relevant lifestyle advice.
Increased frequency or severity of migraine	• Identify reversible causes and investigate and manage as per local or NICE guidelines. • Consider change to topical and / or dose reduction.
Skin reactions (topical treatments)	Change to alternative brand of gel
Systemic hypersensitivity / anaphylactic reactions / unanticipated acute drug reaction	Manage acute condition as per local or NICE guidance. Suspend GnRH analogue treatment and seek specialist advice. Investigate and consider other potential causes.
Mild injection site reactions	Ensure treatment is administered correctly.

Obesity	• Body mass index 30–40, consider change to topical, if relevant. • Body mass index >40, recommend change to topical, if relevant, and consider dose reduction.
Breast or other estrogen-dependent cancer	Stop testosterone permanently and seek specialist advice.
- Deep vein thrombosis or pulmonary embolism - Cardiovascular event (e.g. acute coronary syndromes, ischaemic stroke and peripheral arterial occlusion) - Cardiac failure	Consider suspending treatment and seek specialist advice, as part of the acute management pathway. It is likely that topical testosterone treatment will be restarted following treatment of the acute event and depending on risk assessment. Advice should be sought from the specialist team or specialist endocrinology regarding recommencing treatment; dose or preparation changes may be advised. Testosterone therapy is unlikely to be an aetiological factor in such events, unless associated with erythrocytosis. If the patient is on a topical preparation and there is no evidence of erythrocytosis, suspension of treatment is very unlikely to be necessary.
- Unexplained vaginal bleeding	Consider whether missed or changed dosing of testosterone, GnRH analogue or hormonal contraception may account for recurrence of menstrual bleeding. In the absence of one of these potential causes, refer to gynaecology.
- Vulvovaginal dryness	Optimise testosterone therapy and consider topical estradiol – see below.
- Hypertension - Adverse lipid profile - Diabetes - Abnormal liver enzymes	In the event of a new diagnosis of the following, follow NICE or local guidance regarding investigation and management, and consider a topical preparation and dose reduction.

*Repeat investigations after a dose change:
Testosterone undecanoate
After a dose change, recheck FBC, serum testosterone, SHBG and albumin on a trough sample, usually on the next-but-one injection for 12–16 week interval, but with the next injection if 17–18 week interval. Dose changes and repeat investigations are usually not recommended more frequently than every other injection, unless the injection-interval is longer than 16 weeks.

Sustanon®/ testosterone enantate
After a dose change, recheck FBC, serum testosterone, SHBG and albumin on a trough sample, 3–4 months later or at the fourth subsequent injection, whichever of these is longer. Dose changes and repeat investigations are usually not recommended more frequently than every 3–-4 months or once every fourth injection, whichever is longer.

Topical:
After a dose change, recheck FBC, serum testosterone, SHBG and albumin on a trough sample 3 months later.

DISCHARGE

Treatment with testosterone is usually life long, in the absence of serious complications. At discharge from specialist gender identity services, the specialist team will provide detailed information regarding

many aspects of long-term treatment and associated healthcare to support long-term endocrine treatment in primary care:

- Long term goals and monitoring of hormone treatment (at least annually), including target ranges for serum hormone levels
- Chest / breast self-examination
- Breast, cervical and other health screening, as relevant
- Consideration of DEXA scan in individuals who have had a significant break from sex steroid treatment (>12 months), after the age of 20 years.
- Action to take in response to common disorders and serious complications, including cessation of treatment
- How and when to contact or refer back to the Northern Region Gender Dysphoria Service or seek other specialist advice.

FURTHER INFORMATION: Testosterone, comorbidities and associated adverse effects / events

Cardiovascular disease

- Testosterone treatment at normal physiologic doses does not appear to increase the risk of cardiovascular events among otherwise healthy patients.
- However, it may increase the risk of cardiovascular disease in patients with underlying risks factors.

Venous thromboembolism

Testosterone therapy, is not in and of itself, a risk for venous thromboembolism. However, erythrocytosis can raise the risk of DVT and PE. Adherence to prescribed doses and regular monitoring can reduce the risk of these occurring.

Lipid Profile

- The administration of testosterone in trans men is associated with an increase in triglyceride and a decrease in plasma HDL cholesterol levels, both of which are proatherogenic. Total cholesterol and LDL cholesterol remain unchanged.
- However, these adverse changes in lipid profile do not appear to translate into an alteration in cardiovascular risk, as there is no increase in cardiovascular mortality in treated trans men. The myocardial infarction rate is approximately half that expected in the general male population.

Ovarian and Endometrial Malignancy (where relevant organs remain in situ)

- **Ovaries**
  Regarding the risk of developing ovarian carcinoma, personal history of pregnancy may be more significant than the presence of exogenous testosterone (nulliparous cis women have a slightly greater lifetime risk that cis women who have been pregnant).
- **Endometrium & Uterus**
  The administration of exogenous testosterone, which then undergoes aromatization to estrogen, as well as the possible anovulatory state induced by testosterone, may create a hormonal milieu of "unopposed" estrogen. This creates a theoretical risk of endometrial hyperplasia or cancer. Hysterectomy (within 5 years of commencing testosterone therapy) thus used to be recommended for all female assigned patients taking testosterone for primary prevention of endometrial cancer. Failing this, a number of sources recommended endometrial surveillance with periodic pelvic ultrasounds in amenorrheic individuals.
  However, despite these theoretical considerations, evidence for an increased risk of endometrial disease in female-assigned trans people who take testosterone and have not undergone resection of uterus and ovaries is lacking and, in practice, endometrial atrophy appears to be near-universal. Nevertheless, unexplained vaginal bleeding (in the absence of missed or changed dosing of

testosterone, GnRH analogue or hormonal contraception) in a female assigned trans patient, previously with treatment-induced amenorrhea, should be investigated (e.g. ultrasound scanning and endometrial biopsy) to rule out any neoplastic alteration in the endometrial epithelium.
See https://transcare.ucsf.edu/guidelines/ovarian-cancer for a summary.

- **Cervix**
  Testosterone therapy does not increase the risk of cervical cancer, although it may increase the risk of minimally abnormal cervical smears due to atrophic changes.

Breast Malignancy

- Many patients taking testosterone for this indication will have chest masculinising surgery. However, as not all breast tissue is removed, malignancy can develop in remaining breast tissue due to aromatisation of testosterone to estradiol, particularly where dosage of treatment results in supraphysiological exposure to testosterone.
- Patients who have not had chest masculinising surgery should engage with national breast screening programme as appropriate to their age and any other clinical factors.
- Post-surgery, breast screening is not possible due to the very small volumes of residual tissue and so patients are advised to examine their chest regularly for lumps and skin or nipple changes.
- Although testosterone therapy does not increase the risk of breast cancer, the persistence of residual breast tissue and the impossibility of radiological breast screening make breast awareness especially important.

Obstructive Sleep Apnoea

- Testosterone therapy may exacerbate the symptoms of obstructive sleep apnoea, which can in turn predispose to erythrocytosis.
- In a trans man who has symptoms of obstructive sleep apnoea, symptom scores should be assessed and referral made to a specialist in sleep disorders for treatment if the patient displays deterioration in their condition.

Abnormal Liver Function

- In one series transient increases in liver function enzymes was seen in 4.4% of trans men and this was prolonged (>6 months) in 6.8%, although causation was not ascribed.
- Abnormalities are usually minor and do not require cessation of treatment.
- In general, if liver function tests do become abnormal during testosterone treatment, it is very likely that another underlying cause will be found.
- Minor derangement of liver function, with increases in liver enzyme levels to less than twice the upper limit of normal do not require withdrawal of testosterone therapy.
- There have been no reports of liver tumours with testosterone esters.
- The incidence of hepatic dysfunction with alkylated steroid preparations such as methyl testosterone was high. These anabolic steroids are no longer used in routine testosterone replacement and so historic concerns about incidence of hepatic dysfunction associated with testosterones use may no longer be relevant.

Osteoporosis

- Testosterone therapy maintains or increases bone mineral density among trans men prior to oophorectomy, at least in the first three years of treatment.
- There may be an increased risk of bone density loss if patient opts for oophorectomy or long-term GnRH analogue therapy, but this is unlikely to be significant unless testosterone therapy is interrupted for 12 months or more, prescribed at an inadequate dose long-term or stopped, whether as a result of the patient's health or personal choice.

Vulvovaginal atrophy

- A minority of women develop dyspareunia and/or urinary symptoms as a result of estrogen deprivation to the urogenital epithelium. These symptoms can occur in female assigned trans people treated with testosterone
- These symptoms respond well to long-term standard topical estrogen products recommended for use in postmenopausal women.
- Patients can be reassure that systemic absorption is negligible and that these treatments pose no risk to masculinisation.

Ageing

- The risk of adverse effects increases with age; physiological changes will likely result in the dose requirement lowering over time, as an individual ages.

ADVICE TO PATIENTS AND CARERS

The specialist clinician will counsel the patient with regard to the benefits and risks of treatment and will provide the patient with any relevant information and advice, including information on individual drugs, as part of consent processes. Patients are also counselled on lifestyle factors they can ameliorate, to reduce the risk of testosterone treatment.

As part of consent processes, the patient is also advised to seek urgent advice in the event of any of the following signs or symptoms:

- Hot, swollen, painful tender calf
- Pleuritic chest pain, shortness of breath and haemoptysis

The service's information / consent form is available here: LINK

PREGNANCY, PARENTAL EXPOSURE AND BREASTFEEDING

It is the responsibility of the specialist to provide advice on the need for contraception to all patients on initiation and at each review, but the ongoing responsibility for providing this advice rests with both the primary care prescriber and the specialist team.

Advice regarding contraception for trans people can be found at:
FSRH statement: Contraceptive Choices and Sexual Health for Transgender and Non-Binary People (2017) | FSRH

Pregnancy

- Patients must not attempt to conceive during treatment with testosterone as there may be a teratogenic effect.

Breastfeeding

- Testosterone should not be used during breast feeding.

Parental exposure:

- Testosterone exposure is likely to result in subfertility in individuals assigned female at birth, and the degree of reversibility cannot be predicted.
- However, hormone treatment in this context is not a contraceptive and, therefore, robust alternative contraception should be used if the individual has penis-in-vagina sexual intercourse.

Fertility

The impact of hormone treatment on fertility and reproduction is explained, in detail, by the specialist clinician prior to initiation. Initial prescribing guidance and / or consent documentation will contain confirmation that the patient has been informed of:

- The likely impact of endocrine treatment on fertility and future reproductive options.
- The availability of potential solutions for fertility, including gamete storage.
- The need for effective contraception in users of endocrine treatment.
- The importance of discussing pregnancy and pregnancy related healthcare if parenthood is being considered.

SPECIALIST CONTACT INFORMATION AND ARRANGEMENTS FOR REFERRAL

The contact details of all national NHS gender identity services can be found here:
How to find an NHS gender dysphoria clinic - NHS

This document has been developed with specific reference to the Northern Region Gender Dysphoria Services' clinical approach.
Clinical Lead: Dr Helen Greener, Consultant in Gender Dysphoria
Lead Specialist Nurse: Deborah Quinn
Daytime telephone number: *0191 2876130*
Email address: NRGDS@cntw.nhs.uk

ADDITIONAL INFORMATION

Accurate advice is essential when the patient's condition becomes less stable and should ideally be in a format that ensures it is not miscommunicated with the need to minimise misunderstanding. In addition, the potential complexity for restarting after a short cessation involving more intense monitoring for a given period may be challenging to convey accurately in a verbal format and ensure the recipient can retain the detail. Communication in writing is preferable so as to reduce the potential for misunderstandings and enable an audit trail.

During the course of care and treatment in the specialist gender identity team, specialist clinicians will provide recommendations regarding:

- If and when a dose change is required OR if the drug needs to be stopped and for how long.
- Need for repeat blood test(s) and when this should be carried out.
- When to seek further advice specialist advice.
- When testosterone may be restarted, at what dose, and any change in frequency of monitoring until patient stable and on a stable maintenance dose again.

At discharge, advice will be given regarding all these scenarios and the specialist team can be contacted in working hours for advice.

In the event of a medical emergency, such as a cardiovascular event, the specialist team will not advise any deviation from usual acute assessment, care and management and no out of hours advice is available from the specialist gender identity team. However, specialist advice is available during working hours and should be sought as part of the acute management pathway.

The following circumstances/ changes in the patient's condition require discussion with the specialist team:

- If non-compliance is suspected or the patient fails to attend monitoring appointments and the primary care prescriber considers it no longer safe to continue prescribing. (All appropriate steps must first be taken by primary care to reinforce the importance of attendance to the patient).
- The patient's clinical condition deteriorates such that the primary care prescriber feels a dose change is required/ the patient no longer appears to be benefiting from therapy.

To be read in conjunction with the following documents

- NHSE guidance – Responsibility for prescribing between primary & secondary/tertiary care. Available from https://www.england.nhs.uk/publication/responsibility-for-prescribing-between-primary-and-secondary-tertiary-care/
- General Medical Council. Good practice in prescribing and managing medicines and devices. Shared care. Available from https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-practice-in-prescribing-and-managing-medicines-and-devices/shared-care
- NICE NG197: Shared decision making. Last updated June 2021. https://www.nice.org.uk/guidance/ng197/.

Appendix 3: Gonadotrophin-releasing hormone (GnRH) analogues for treatment of gender incongruence in male assigned adults (18+)

BACKGROUND

This information summary concerns the use of GnRH analogues in the treatment of gender incongruence in adult male assigned individuals. It has been prepared with reference to the clinical approach adopted by the Northern Region Gender Dysphoria Service (NRGDS), but other NHS commissioned specialist gender identity services also recommend GnRH analogue treatment for this indication and take a broadly similar clinical approach.

There are currently no GnRH analogue preparations that are licensed for use outside the core indications, which include treatment of endometriosis, breast cancer, reduction of uterine fibroids and to achieve endometrial thinning before intra-uterine surgery in cis women and, in cis men, treatment of prostate cancer and male hypersexuality with severe sexual deviancy. Thus, all prescriptions issued for the treatment of gender incongruence necessarily lie outside marketing authorisations even though there is extensive clinical experience with evidence for safety and efficacy.

GnRH analogues for the treatment of gender incongruence in male assigned adults are only commenced once treatment with estradiol has been established. Administration of GnRH analogues produces a brief initial phase of stimulation, but continued administration is followed by down-regulation of gonadotrophin-releasing hormone receptors, thereby reducing the release of gonadotrophins (follicle stimulating hormone and luteinising hormone) which in turn leads to inhibition of endogenous sex hormone production. A short period of increased testosterone levels can occur over the first 1-2 weeks of treatment, which may be clinically significant in some individuals.

Depending on the goals of the patient, other antiandrogen medication may offer possible alternatives to treatment with GnRH analogues. This is discussed as part of initiation.

INDICATIONS

For the endocrine treatment of gender incongruence in individuals assigned male at birth, following specialist assessment and recommendation.

Criteria in NHSE's service specification apply to the use of GnRH analogue for the treatment of gender incongruence in people assigned male at birth and include:

- Persistent, well-documented gender dysphoria.
- Capacity to make a fully informed decision and to consent for treatment
- If significant medical or mental concerns are present, they must be reasonably well-controlled

INITITATION

Medication is initiated by primary care, following specialist recommendation.

The specialist gender identity clinic is responsible for recommendations regarding:

- Dose titration and medication optimisation
- Duration and frequency of treatment based on clinical response and tolerability.
- Appropriate monitoring investigations and frequency.
- Dose or formulation adjustments unless directions have been discussed and agreed with the primary care clinician.

Termination of treatment will be the responsibility of the specialist clinical team while the patient is under the care of the specialist gender identity clinic, but the primary care clinician may equally choose to

suspend or terminate treatment where there are reasonable concerns about ongoing safety, before seeking further advice from the specialist clinical team or terminate treatment when no longer required due to gonadectomy.

DOSE REGIMEN

Drug	Formulation	Dose/Route/Initial Dose/Maintenance dose
Leuprorelin	Propstap 3 DCS®	3.75 mg S/C or IM initial dose for one month 11.25 mg IM maintenance dose every 3 months
	Staladex	11.25 mg S/C maintenance dose every 3 months
Triptorelin	Decapeptyl® SR	3 mg IM initial dose for 4 weeks 11.25 mg IM maintenance dose every 3 months 22.25 mg IM maintenance dose every 6 months
	Gonapeptyl Depot®	3.75 mg S/C or IM initial dose for 4 weeks
	Salvacyl®	11.25 mg S/C maintenance dose every 12 weeks
Goserelin	Zoladex LA®	3.6 mg S/C implant initial dose for 28 days 10.8 mg S/C implant maintenance dose every 12 weeks
Nafarelin	200 mcg / dose nasal spray	200 mcg twice daily initial and / or maintenance dose 400 mcg twice daily maintenance dose

INVESTIGATIONS

Baseline investigations necessary for the initiation of estradiol therapy will already have been completed, prior to the initiation of GnRH analogues, and generally do not need to be repeated in this context. Investigations relevant to the initiation of GnRH analogues as specified by the specialist team, are part of ongoing monitoring of estradiol treatment and are undertaken by primary care. Results are reviewed by the specialist gender identity clinician at the next appointment, where GnRH analogue counselling will take place. There are no additional investigations required, over and above those detailed for the ongoing management of estradiol therapy and abnormal results warranting action should be managed, as outlined in Appendix 1.

The results of these investigations inform personalised risk assessment, counselling and shared decision making, which are undertaken by the specialist gender identity clinic in collaboration with the patient prior to a recommendation to initiate GnRH analogue treatment.

PHARMACEUTICAL ASPECTS			
DRUG:	**FORMULATION & ROUTE ADINSTRATION:**	**ADMINISTRATION DETAILS:**	**OTHER IMPORTANT INFORMATION:**
Leuprorelin	Propstap 3 DCS® SC or IM 3.75mg/month Propstap 3 DCS® SC or IM 11.25mg/3 months Staladex SC 11.25mg/ 3months	Administer by subcutaneous or intramuscular injection, depending on product. Where both are available for the same formulation, patient preference can take precedence. Rotate injection site to prevent atrophy and nodule formation. For Staladex® 11.25mg To be administered subcutaneously under the skin of the abdomen.	For Prostap 3 DCS® Patients and carers should be counselled on the signs and symptoms of severe cutaneous adverse reactions (SCARs) when starting treatment—treatment should be immediately discontinued if these occur.
Triptorelin	Decapeptyl® 3mg IM/ 4 weeks Decapeptyl® 11.25 IM/ 3 months Decapeptyl® 22.5mg IM/ 6 months Gonapeptyl Depot® 3.75mg SC or IM / 4weeks Salvacyl® 11.25mg every 12 weeks	Administer by subcutaneous or intramuscular injection, depending on product. Where both are available for the same formulation, patient preference can take precedence. Rotate injection site to prevent atrophy and nodule formation.	For Decapeptyl® SR Vials of all doses include an overage to allow accurate administration of the relevant dose.
Goserelin	Zoladex LA®	Insert the implant subcutaneously into the anterior abdominal skin, below the navel line. Rotate injection site to prevent atrophy and nodule formation. See manufacturer's instructions: https://www.zoladexhcp.co.uk/content/dam/open-digital/zoladex-hcp/en/pdf/zoladex-needle-admin.pdf	
Nafarelin	200 mcg / dose nasal spray	Start with one spray in one nostril in the morning, and one spray in the other nostril in the evening. If suppression of endogenous sex hormone axis is not achieved, increase to one spray in each nostril in the morning and in the evening. Patients are advised to carefully read the instructions regarding use of the spray as incorrect administration can affect treatment efficacy.	Manufacturer advises avoid use of nasal decongestants before and for at least 30 minutes after treatment; repeat dose if sneezing occurs during or immediately after administration.

Notes:

- Injectable preparations are first line treatment; spray preparations require multiple daily dosing and effectiveness is reliant on good adherence. Spray preparations are only used if injections cannot be tolerated.
- Systemic hypersensitivity, antibody formation, and / or acute anaphylactic reactions have been reported with the use of some GnRH analogues.
- Injection site injury and vascular injury have been reported with subcutaneous and intramuscular formulations.
- Nasal administration can cause rhinitis altered smell sensation, epistaxis, hoarseness, nasal irritation, altered taste.

CAUTIONS AND CONTRADICTIONS Please see SmPC & BNF for comprehensive information.

This information does not replace the Summary of Product Characteristics (SmPC) and should be read in conjunction with it.

Absolute contraindications

- None relevant to this indication.

Conditions that might be exacerbated by treatment with GnRH analogues:

- Metabolic bone disease (in the context of inadequate replacement with sex steroids)
- Diabetes (in the context of inadequate replacement with sex steroids)

Cautions:

For the most part cautions listed for the use of GnRH analogues relate to their use in the treatment of conditions where no "add-back" sex steroid treatment is given, and so these patients experience the full spectrum of negative effects of untreated hypogonadism.

SIGNIFICANT DRUG INTERACTIONS

The following is not exhaustive. Please see BNF & SmPC for comprehensive information and recommended management.

There are no clinically significant drugs interactions for GnRH analogues; please see SPC for comprehensive information and recommended management.

ADVERSE EFFECTS / COMORBIDITIES AND MANAGEMENT

Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme. Visit www.mhra.gov.uk/yellowcard.

For information on incidence of ADRs see relevant SmPCs.

For the most part the results of laboratory tests inform the overall management of endocrine care for gender incongruence in male assigned trans people, primarily estradiol, and do not impact directly on the delivery of GnRH analogues. Comorbidities relevant to endocrine care should be management as outlined in Appendix 1: Testosterone for gender incongruence in female assigned adults (18+).

Adverse effect / event	Management
Estradiol under target	Optimise estradiol therapy – see Appendix 1.
Estradiol under target, despite optimisation, for more than 9 months especially where there are menopausal symptoms	Consider cessation of GnRH analogues and alternative strategies to manage unwanted masculinisation, such as alternative antiandrogens.
Estradiol stopped because of safety concerns, adverse effects or non-adherence for more than 6 months	Seek specialist advice regarding ongoing treatment with GnRH analogues, potential cessation and possible alternative strategies for management of gender dysphoria, if relevant.
Systemic hypersensitivity / anaphylactic reactions / unanticipated acute drug reaction	Manage acute condition as per local or NICE guidance. Suspend GnRH analogue treatment and seek specialist advice. Investigate and consider other potential causes.
Mild injection site reactions	Ensure treatment is administered correctly.
Nasal irritation (nasal sprays)	Consider change to S/C or IM preparation

FURTHER INFORMATION: GnRH ANALOGUES and associated adverse effects

Information regarding side effects

- GnRH Analogues are usually well tolerated and are not generally associated with significant side effects in trans adults receiving sex steroid treatment at adequate dose.

- Many listed side effects in cis men (i.e. gynaecomastia), are, in fact, treatment goals in male assigned trans people.
- Other listed side effects are largely the result of the low levels of sex steroids in the body, as replacement with estradiol is not undertaken as part of treatment of the licenced indications. The introduction of GnRH analogues usually takes place after initiation of sex steroids (e.g. estradiol for male assigned people) so effects associated with the menopause or long-term hypogonadism, (e.g. hot flushes, depression and osteoporosis) are generally avoided or ameliorated by adequate estradiol levels.
- The timing of introduction (i.e. whether to wait for estradiol treatment to be established) is discussed with patients. Some patients' goals can be achieved without introduction of GnRH analogues. However, levels of estradiol may not be sufficiently high at initiation of GnRH analogues to completely avoid menopausal side effects. For some patients the risk level of estradiol means lower doses are prescribed and they will be more likely to experience menopausal effects and / or a degree of hypogonadism, long-term. The potential for these effects is discussed at initiation.

Gonadectomy

- Individuals taking estradiol who do not wish to have gonadectomy may wish to continue GnRH analogues long-term, in order to maximise feminisation and manage unwanted masculinisation. Continuation is not a requirement of endocrine care for gender incongruence but it is possible that cessation will result in unwanted effects, such as re-emergence of erectile function or increased growth of body hair.
- GnRH analogues have a role in preparing some individuals for gonadectomy by allowing them to experience the hormonal milieu associated with surgical treatment, prior to opting for this. Treatment with GnRH analogues should be stopped if the testicles are no longer present e.g. post orchidectomy. Patients should be treated up until the date of surgery and no further doses administered after the procedure.

Osteoporosis

- Estradiol therapy at adequate dose maintains bone mineral density among trans women prior to orchidectomy, at least in the first three years of treatment.
- There may be an increased risk of bone density loss if patients opt for orchidectomy or long-term GnRH therapy, but this is unlikely to be significant unless estradiol therapy is interrupted for 12 months or more, is prescribed at an inadequate dose long-term, or is stopped entirely, whether as a result of the patient's health or personal choice.
- Exposure to testosterone earlier in life is likely to protect trans women from developing osteoporosis, relative to cis women.
- Lifelong treatment with estradiol is likely to protect trans women from developing osteoporosis, compared with cis women, who will not usually take HRT for longer than a few years post-menopause, if at all.

ADVICE TO PATIENTS AND CARERS

The specialist clinician will counsel the patient with regard to the benefits and risks of treatment and will provide the patient with any relevant information and advice, including information on individual drugs, as part of consent processes.

As part of consent processes, the patient is advised of the importance of adhering to prescribed sex steroid doses and engaging with regular monitoring, to avoid the negative effects of potential hypogonadism.

The service's information / consent form is available here: LINK

PREGNANCY, PARENTAL EXPOSURE AND BREASTFEEDING

It is the responsibility of the specialist to provide advice on the need for contraception to all patients on initiation and at each review, but the ongoing responsibility for providing this advice rests with both the primary care prescriber and the specialist team.

Advice regarding contraception for trans people can be found at:
https://www.fsrh.org/news/fsrh-ceu-clinical-statement-srh-transgender-nonbinary-people/

Pregnancy: Not applicable to this group.

Breastfeeding: Not applicable to this group.

Parental exposure:

- Estradiol exposure is likely to cause infertility for individuals assigned male at birth, which may be irreversible. The additional impact of GnRH analogues on the fertility of individuals assigned male at birth in unlikely to be significant.
- However, hormone treatment in this context is not a contraceptive and it is inadvisable to attempt to conceive during treatment as sperm quality may be adversely affected.

Fertility

The impact of hormone treatment on fertility and reproduction is explained, in detail, by the specialist clinician prior to initiation. Initial prescribing guidance and / or consent documentation will contain confirmation that the patient has been informed of:

- The likely impact of endocrine treatment on fertility and future reproductive options.
- The availability of potential solutions for fertility, including gamete storage.
- The need for effective contraception in users of endocrine treatment.
- The importance of discussing pregnancy and pregnancy related healthcare if parenthood is being considered.

SPECIALIST CONTACT INFORMATION AND ARRANGEMENTS FOR REFERRAL

The contact details of all national NHS gender identity services can be found here:
How to find an NHS gender dysphoria clinic - NHS

This document has been developed with specific reference to the Northern Region Gender Dysphoria Services' clinical approach.
Clinical Lead: Dr Helen Greener, Consultant in Gender Dysphoria
Lead Specialist Nurse: Deborah Quinn
Daytime telephone number: *0191 2876130*
Email address: NRGDS@cntw.nhs.uk

ADDITIONAL INFORMATION

Accurate advice is essential when the patient's condition becomes less stable and should ideally be in a format that ensures it is not miscommunicated with the need to minimise misunderstanding. In addition, the potential complexity for restarting after a short cessation involving more intense monitoring for a given period may be challenging to convey accurately in a verbal format and ensure the recipient can retain the detail.

During the course of care and treatment in the specialist gender identity team, specialist clinicians will provide recommendations regarding:

- If and when a dose change is required OR if the drug needs to be stopped and for how long.
- Need for repeat blood test(s) and when this should be carried out.
- When to seek further advice specialist advice.
- When GnRH analogue may be restarted, at what dose, and any change in frequency of monitoring until patient stable and on a stable maintenance dose again.

At discharge, advice will be given regarding all these scenarios and the specialist team can be contacted in working hours for advice.

In the event of a medical emergency the specialist team will not advise any deviation from usual acute assessment, care and management and no out of hours advice is available from the specialist gender identity team. However, specialist advice is available during working hours and should be sought as part of the acute management pathway.

The following circumstances/ changes in the patient's condition require discussion with the specialist team:

- If non-compliance is suspected or the patient fails to attend monitoring appointments, and the primary care prescriber considers it no longer safe to continue prescribing. (All appropriate steps must first be taken by primary care to reinforce the importance of attendance to the patient).
- The patient's clinical condition deteriorates such that the primary care prescriber feels a dose change is required/ the patient no longer appears to be benefiting from therapy.

To be read in conjunction with the following documents

- NHSE guidance – Responsibility for prescribing between primary & secondary/tertiary care. Available from https://www.england.nhs.uk/publication/responsibility-for-prescribing-between-primary-and-secondary-tertiary-care/
- General Medical Council. Good practice in prescribing and managing medicines and devices. Shared care. Available from https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-practice-in-prescribing-and-managing-medicines-and-devices/shared-care
- NICE NG197: Shared decision making. Last updated June 2021. https://www.nice.org.uk/guidance/ng197/.

Appendix 4: Gonadotrophin-releasing hormone (GnRH) analogues for treatment of gender incongruence in female assigned adults (18+)

BACKGROUND

This information summary concerns the use of GnRH analogues in the treatment of gender incongruence in adult female assigned individuals. It has been prepared with reference to the clinical approach adopted by the Northern Region Gender Dysphoria Service (NRGDS), but other NHS commissioned specialist gender identity services also recommend GnRH analogue treatment for this indication and take a broadly similar clinical approach.

There are currently no GnRH analogue preparations that are licensed for use outside the core indications, which include treatment of endometriosis, breast cancer, reduction of uterine fibroids and to achieve endometrial thinning before intra-uterine surgery in cis women and, in cis men, treatment of prostate cancer and male hypersexuality with severe sexual deviancy. Thus, all prescriptions issued for the treatment of gender incongruence necessarily lie outside marketing authorisations even though there is extensive clinical experience with evidence of safety and efficacy.

GnRH analogues for the treatment of gender incongruence in female assigned adults are required in a minority of patients. They are only commenced once treatment with testosterone has been established and optimised and where endogenous hormone secretion has not been suppressed by testosterone monotherapy (high estradiol levels or persistence of menstruation or cyclical symptoms). Administration of GnRH analogues produces a brief initial phase of stimulation but continued administration is followed by down-regulation of gonadotrophin-releasing hormone receptors, thereby reducing the release of gonadotrophins (follicle stimulating hormone and luteinising hormone) which in turn leads to inhibition of endogenous sex hormone production.

Depending on the goals of the patient, progesterone only contraception may be a reasonable alternative to treatment with GnRH analogues. This is discussed as part of initiation.

INDICATIONS

For the endocrine treatment of gender incongruence in individuals assigned female at birth, following specialist assessment and recommendation.

Criteria in NHSE's service specification apply to the use of GnRH analogue for the treatment of gender incongruence in people assigned female at birth and include:

- Persistent, well-documented gender dysphoria.
- Capacity to make a fully informed decision and to consent for treatment
- If significant medical or mental concerns are present, they must be reasonably well-controlled

INITITATION

Medication is initiated by primary care, following specialist recommendation.

The specialist gender identity clinic is responsible for recommendations regarding:

- Dose titration and medication optimisation
- Duration and frequency of treatment based on clinical response and tolerability.
- Appropriate monitoring investigations and frequency.
- Dose or formulation adjustments unless directions have been discussed and agreed with the primary care clinician.

Termination of treatment will be the responsibility of the specialist clinical team while the patient is under the care of the specialist gender identity clinic, but the primary care clinician may equally choose to suspend or terminate treatment where there are reasonable concerns about ongoing safety, before seeking further advice from the specialist clinical team or terminate treatment when no longer required due to gonadectomy or menopause.

DOSE REGIMEN

Drug	Formulation	Dose/Route/Initial Dose/Maintenance dose
Leuprorelin	Propstap 3 DCS®	3.75 mg S/C or IM initial dose for one month 11.25 mg IM maintenance dose every 3 months
	Staladex	11.25 mg S/C maintenance dose every 3 months
Triptorelin	Decapeptyl® SR	3 mg IM initial dose for 4 weeks 11.25 mg IM maintenance dose every 3 months 22.25 mg IM maintenance dose every 6 months
	Gonapeptyl Depot®	3.75 mg S/C or IM initial dose for 4 weeks
	Salvacyl®	11.25 mg S/C maintenance dose every 12 weeks
Goserelin	Zoladex LA®	3.6 mg S/C implant initial dose for 28 days 10.8 mg S/C implant maintenance dose every 12 weeks
Nafarelin	200 mcg / dose nasal spray	200 mcg twice daily initial and / or maintenance dose 400 mcg twice daily maintenance dose
Buserelin	150 mcg / dose nasal spray	300 mcg three times daily maintenance dose

INVESTIGATIONS

Baseline investigations necessary for the initiation of testosterone therapy will already have been completed, prior to the initiation of GnRH analogues, and generally do not need to be repeated in this context. Investigations relevant to the initiation of GnRH analogues as specified by the specialist team, as part of ongoing monitoring of testosterone treatment and are undertaken by primary care. Results are reviewed by the specialist gender identity clinician at the next appointment, where GnRH analogue counselling will take place. There are no additional investigations required, over and above those detailed for the ongoing management of testosterone therapy and abnormal results warranting action should be managed, as outlined in Appendix 2.

The results of these investigations inform personalised risk assessment, counselling and shared decision making, which are undertaken by the specialist gender identity clinic in collaboration with the patient prior to a recommendation to initiate GnRH analogue treatment.

PHARMACEUTICAL ASPECTS			
DRUG:	**FORMULATION/ROUTE/ADMINSTRATION:**	**ADMINISTRATION DETAILS:**	**OTHER IMPORTANT INFORMATION:**
Leuprorelin	Propstap 3 DCS® SC or IM 3.75mg/month Propstap 3 DCS® SC or IM 11.25mg/3 months Staladex SC 11.25mg/ 3months	Administer by subcutaneous or intramuscular injection, depending on product. Where both are available for the same formulation, patient preference can take precedence. Rotate injection site to prevent atrophy and nodule formation. For Staladex® 11.25mg To be administered subcutaneously under the skin of the abdomen.	For Prostap 3 DCS® Patients and carers should be counselled on the signs and symptoms of severe cutaneous adverse reactions (SCARs) when starting treatment—treatment should be immediately discontinued if these occur.
Triptorelin	Decapeptyl® 3mg IM/ 4 weeks Decapeptyl® 11.25 IM/ 3 months Decapeptyl® 22.5mg IM/ 6 months Gonapeptyl Depot® 3.75mg SC or IM / 4weeks Salvacyl® 11.25mg every 12 weeks	Administer by subcutaneous or intramuscular injection, depending on product. Where both are available for the same formulation, patient preference can take precedence. Rotate injection site to prevent atrophy and nodule formation.	For Decapeptyl® SR Vials of all doses include an overage to allow accurate administration of the relevant dose.
Goserelin	Zoladex LA®	Insert the implant subcutaneously into the anterior abdominal skin, below the navel line. Rotate injection site to prevent atrophy and nodule formation. See manufacturer's instructions: https://www.zoladexhcp.co.uk/content/dam/open-digital/zoladex-hcp/en/pdf/zoladex-needle-admin.pdf	
Nafaerlin	200 mcg / dose nasal spray	Start with one spray in one nostril in the morning, and one spray in the other nostril in the evening. If suppression of endogenous sex hormone axis is not achieved, increase to one spray in each nostril in the morning and in the evening. Patients are advised to carefully read the instructions regarding use of the spray as incorrect administration can affect treatment efficacy.	Manufacturer advises avoid use of nasal decongestants before and for at least 30 minutes after treatment; repeat dose if sneezing occurs during or immediately after administration.

Buserelin	150 mcg / dose nasal spray	Administer one 150 microgram spray into each nostril. Patients are advised to carefully read the instructions regarding use of the spray as incorrect administration can affect treatment efficacy.	

Notes:

- Injectable preparations are first line treatment; spray preparations require multiple daily dosing and effectiveness is reliant on good adherence. Spray preparations are only used if injections cannot be tolerated.
- Systemic hypersensitivity, antibody formation, and / or acute anaphylactic reactions have been reported with the use of some GnRH analogues.
- Injection site injury and vascular injury have been reported with subcutaneous and intramuscular formulations.
- Nasal administration can cause rhinitis altered smell sensation, epistaxis, hoarseness, nasal irritation, altered taste.

CAUTIONS AND CONTRADICTIONS Please see SmPC & BNF for comprehensive information.

This information does not replace the Summary of Product Characteristics (SmPC) and should be read in conjunction with it.

Absolute contraindications

- Unexplained vaginal bleeding
- Pregnancy
- Breastfeeding

Conditions that might be exacerbated by treatment with GnRH analogues:

- Metabolic bone disease (in the context of inadequate replacement with sex steroids)
- Diabetes (in the context of inadequate replacement with sex steroids)

Cautions:

For the most part cautions listed for the use of GnRH analogues relate to their use in the treatment of conditions where no "add-back" sex steroid treatment is given, and so these patients experience the full spectrum of negative effects of untreated hypogonadism.

SIGNIFICANT DRUG INTERACTIONS

The following is not exhaustive. Please see BNF & SmPC for comprehensive information and recommended management.

There are no clinically significant drugs interactions for GnRH analogues; please see SPC for comprehensive information and recommended management.

ADVERSE EFFECTS / COMORBIDITIES AND MANAGEMENT

Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme. Visit www.mhra.gov.uk/yellowcard.

For information on incidence of ADRs see relevant SmPCs.

For the most part the results of laboratory tests inform the overall management of endocrine care for gender incongruence in female assigned trans people, primarily testosterone, and do not impact directly on the delivery of GnRH analogues. Comorbidities relevant to endocrine care should be management as outlined in Appendix 2: Testosterone for gender incongruence in female assigned adults (18+).

Adverse effect / event	Management
Testosterone under target	Optimise testosterone therapy – see Appendix 2
Testosterone under target, despite optimisation, for more than 9 months especially where there are menopausal symptoms	Consider cessation of GnRH analogues and alternative strategies to manage unwanted menstruation, if periods reemerge, such as progesterone only contraception.
Testosterone stopped because of safety concerns, adverse effects or non-adherence for more than 6 months	Seek specialist advice regarding ongoing treatment with GnRH analogues, potential cessation and possible alternative strategies for management of gender dysphoria, if relevant.
Systemic hypersensitivity / anaphylactic reactions / unanticipated acute drug reaction	Manage acute condition as per local or NICE guidance. Suspend GnRH analogue treatment and seek specialist advice. Investigate and consider other potential causes.
Mild injection site reactions	Ensure treatment is administered correctly.
Nasal irritation (nasal sprays)	Consider change to S/C or IM preparation
Vulvovaginal dryness or lower urinary tract symptoms	Investigate as per local or NICE guidance. Optimise testosterone therapy and prescribe topical estradiol, in the absence of other reversible causes – see Appendix 2.

Unexplained vaginal bleeding	Consider whether missed or changed dosing of testosterone, GnRH analogue or hormonal contraception may account for recurrence of menstrual bleeding. In the absence of one of these potential causes, refer to gynaecology.

FURTHER INFORMATION: GnRH ANALOGUES and associated adverse effects

Information regarding side effects

- GnRH Analogues are usually well tolerated and are not generally associated with significant side effects in trans adults receiving sex steroid treatment at adequate dose.
- Many listed side effects in cis women (i.e. cessation of menstruation), are, in fact, treatment goals in female assigned trans people.
- Other listed side effects are largely the result of the low levels of sex steroids in the body, as replacement with testosterone is not undertaken as part of treatment of the licenced indications. The introduction of GnRH analogues usually takes place after initiation of sex steroids (e.g. testosterone for female assigned people) so associated with the menopause or long-term hypogonadism, (e.g. hot flushes, depression and osteoporosis) are generally avoided or ameliorated by adequate testosterone levels.
- The timing of introduction (i.e. whether to wait for testosterone treatment to be established) is discussed with patients. Some patients' goals can be achieved without introduction of GnRH analogues. However, levels of testosterone may not be sufficiently high at initiation of GnRH analogues to completely avoid menopausal side effects. For some patients the risk level of testosterone means lower doses are prescribed and they will be more likely to experience menopausal effects and / or a degree of hypogonadism, long-term. The potential for these effects is discussed at initiation.

Menopause / gonadectomy

- Individuals taking testosterone who do not wish to have gonadectomy may wish to continue GnRH analogues long-term, in order to maximise masculinisation and manage unwanted feminisation, including menstruation. Continuation is not a requirement of endocrine care for gender incongruence, but it is possible that cessation will result in unwanted effects, particularly re-emergence of menstruation and / or associated symptoms, such as cramping prior to the onset of menopause.
- GnRH analogues should be stopped if the ovaries are no longer present or functional e.g. post oophorectomy or menopause. GnRH analogues have a role in preparing some individuals for gonadectomy by allowing them to experience the hormonal milieu associated with surgical treatment, prior to opting for this. Treatment with GnRH analogues should be stopped if the ovaries are no longer present e.g. post oophorectomy. Patients should be treated up until the date of surgery and no further doses administered after the procedure.
- Treatment can be continued until the age of 51–55 years in those individuals who retain their ovaries. Treatment can then be stopped. If unwanted menstrual symptoms emerge thereafter, treatment can be reinstated immediately. Trial cessation again every 1-2 years until amenorrhoea is achieved without treatment.

Osteoporosis

- Testosterone therapy at adequate dose maintains or increases bone mineral density among trans men prior to oophorectomy, at least in the first three years of treatment.

- There may be an increased risk of bone density loss if patient opts for oophorectomy or long-term GnRH analogue therapy, but this is unlikely to be significant unless testosterone therapy is interrupted for 12 months or more, prescribed at an inadequate dose long-term or stopped, whether as a result of the patient's health or personal choice.

ADVICE TO PATIENTS AND CARERS

The specialist clinician will counsel the patient with regard to the benefits and risks of treatment and will provide the patient with any relevant information and advice, including information on individual drugs, as part of consent processes.

As part of consent processes, the patient is advised of the importance of adhering to prescribed sex steroid doses and engaging with regular monitoring, to avoid the negative effects of potential hypogonadism.

The service's information / consent form is available here: LINK

PREGNANCY, PARENTAL EXPOSURE AND BREASTFEEDING

It is the responsibility of the specialist to provide advice on the need for contraception to all patients on initiation and at each review, but the ongoing responsibility for providing this advice rests with both the primary care prescriber and the specialist team.

Advice regarding contraception for trans people can be found at:
FSRH statement: Contraceptive Choices and Sexual Health for Transgender and Non-Binary People (2017) | FSRH

Pregnancy: Avoid – some agents have been found to be teratogenic in animal studies

Breastfeeding: Avoid

Parental exposure:

- GnRH analogues are likely to result in subfertility in individuals assigned female at birth, and the degree of reversibility cannot be predicted.
- However, hormone treatment in this context is not licenced for contraception and, therefore, robust alternative contraception should be used if the individual has penis-in-vagina sexual intercourse.

Fertility

The impact of hormone treatment on fertility and reproduction is explained, in detail, by the specialist clinician prior to initiation. Initial prescribing guidance and / or consent documentation will contain confirmation that the patient has been informed of:

- The likely impact of endocrine treatment on fertility and future reproductive options.
- The availability of potential solutions for fertility, including gamete storage.
- The need for effective contraception in users of endocrine treatment.
- The importance of discussing pregnancy and pregnancy related healthcare if parenthood is being considered.

SPECIALIST CONTACT INFORMATION AND ARRANGEMENTS FOR REFERRAL

The contact details of all national NHS gender identity services can be found here:
How to find an NHS gender dysphoria clinic - NHS

This document has been developed with specific reference to the Northern Region Gender Dysphoria Services' clinical approach.
Clinical Lead: Dr Helen Greener, Consultant in Gender Dysphoria
Lead Specialist Nurse: Deborah Quinn
Daytime telephone number: *0191 2876130*
Email address: NRGDS@cntw.nhs.uk

ADDITIONAL INFORMATION

Accurate advice is essential when the patient's condition becomes less stable and should ideally be in a format that ensures it is not miscommunicated with the need to minimise misunderstanding. In addition, the potential complexity for restarting after a short cessation involving more intense monitoring for a given period may be challenging to convey accurately in a verbal format and ensure the recipient can retain the detail.

During the course of care and treatment in the specialist gender identity team, specialist clinicians will provide recommendations regarding:

- If and when a dose change is required OR if the drug needs to be stopped and for how long.
- Need for repeat blood test(s) and when this should be carried out.
- When to seek further advice specialist advice.
- When GnRH analogue may be restarted, at what dose, and any change in frequency of monitoring until patient stable and on a stable maintenance dose again.

At discharge, advice will be given regarding all these scenarios and the specialist team can be contacted in working hours for advice.

In the event of a medical emergency the specialist team will not advise any deviation from usual acute assessment, care and management and no out of hours advice is available from the specialist gender identity team. However, specialist advice is available during working hours and should be sought as part of the acute management pathway.

The following circumstances/ changes in the patient's condition require discussion with the specialist team:

- If non-compliance is suspected or the patient fails to attend monitoring appointments and the primary care prescriber considers it no longer safe to continue prescribing. (All appropriate steps must first be taken by primary care to reinforce the importance of attendance to the patient).
- The patient's clinical condition deteriorates such that the primary care prescriber feels a dose change is required/ the patient no longer appears to be benefiting from therapy.

To be read in conjunction with the following documents

- NHSE guidance – Responsibility for prescribing between primary & secondary/tertiary care. Available from https://www.england.nhs.uk/publication/responsibility-for-prescribing-between-primary-and-secondary-tertiary-care/
- General Medical Council. Good practice in prescribing and managing medicines and devices. Shared care. Available from https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-practice-in-prescribing-and-managing-medicines-and-devices/shared-care
- NICE NG197: Shared decision making. Last updated June 2021. https://www.nice.org.uk/guidance/ng197/.

Appendix 5: Anti-androgens for treatment of gender incongruence in male assigned adults (18+)

BACKGROUND

This information summary concerns the use of a limited number of anti-androgens in the treatment of gender incongruence in adult male assigned individuals. It has been prepared with reference to the clinical approach adopted by the Northern Region Gender Dysphoria Service (NRGDS), but other NHS commissioned specialist gender identity services also recommend anti-androgen treatment for this indication and take a broadly similar clinical approach.

The vast majority of male assigned trans people receiving endocrine care for gender incongruence with receive treatment with estradiol alone or estradiol with a GnRH analogue. The latter is used to achieve maximum suppression of endogenous testosterone in individual with functioning testicles and, thereby attenuation of secondary male sexual characteristics. Their use is covered in Appendix 1 and 3 respectively. However, finasteride, cyproterone acetate and spironolactone are used in limited circumstances in the UK. The safety and side effect profile of these medications means that their use is limited. They may be appropriate, at low doses, where only mild anti-androgenic effects are desirable and profound suppression of testosterone is not wanted or tolerated by the patient.

These medications are used for the treatment of gender incongruence in many other countries. Thus they may used in the medium term as part of establishing treatment, especially if this has been initiated in another country or by the patient, using hormones purchased online. Long-term treatment, especially with cyproterone acetate and spironolactone is not desirable.

There are currently no preparations that are licensed for use outside the core indications for these medications. Thus, all prescriptions issued for the treatment of gender incongruence necessarily lie outside marketing authorisations.

INDICATIONS

For the endocrine treatment of gender incongruence in individuals assigned male at birth, following specialist assessment and recommendation.

Criteria in NHSE's service specification apply to the use of GnRH analogue for the treatment of gender incongruence in people assigned male at birth and include:

- Persistent, well-documented gender dysphoria.
- Capacity to make a fully informed decision and to consent for treatment
- If significant medical or mental concerns are present, they must be reasonably well-controlled

INITITATION

Medication is initiated by primary care, following specialist recommendation.

The specialist gender identity clinic is responsible for recommendations regarding:

- Dose titration and medication optimisation
- Duration and frequency of treatment based on clinical response and tolerability.
- Appropriate monitoring investigations and frequency.
- Dose or formulation adjustments unless directions have been discussed and agreed with the primary care clinician.

Termination of treatment will be the responsibility of the specialist clinical team while the patient is under the care of the specialist gender identity clinic, but the primary care clinician may equally choose to

suspend or terminate treatment where there are reasonable concerns about ongoing safety, before seeking further advice from the specialist clinical team or terminate treatment when no longer required due to gonadectomy.

DOSE REGIMEN

Drug	Route/ Formulation	Starting Dose	Titration (Usual increments)	Maintenance dose (following initial stabilisation)
Finasteride	Oral	5 mg once daily	None	5 mg once daily
Cyproterone acetate	Oral	12.5–25mg once daily	12.5 mg	12.5–50 mg once daily
Spironolactone	Oral	25–50 mg once daily	25 mg	50–200 mg daily, in divided doses, above 100mg daily

BASELINE INVESTIGATIONS

All baseline investigations as specified by the specialist team are undertaken by primary care; results are reviewed by the specialist gender identity clinician at second assessment and/or hormone counselling appointments. There is thus usually a delay of at least a few months between a request for investigations and further assessment / review of the results.

The results of these investigations inform personalised risk assessment, hormone counselling and shared decision making, which are undertaken by the specialist gender identity clinic in collaboration with the patient prior to a recommendation to initiate endocrine treatment, including anti-androgen therapy.

The general approach to initiating treatment with anti-androgens reflects that of treatment with estradiol and is outlined in Appendix 1. In addition, U&Es should be checked before initiation of treatment with spironolactone.

ONGOING MONITORING

Monitoring

The specialist service will request appropriate monitoring investigations whilst the patient is under their care. The aim of monitoring is to detect adverse effects of treatment and guide dosage of treatment.

The specific investigations requested will differ depending on the stage of treatment and clinical need; the specialist team will advise the action to be taken based on results if flagged to the team or will review results at the next contact with the patient and advise accordingly. Details of appropriate long-term monitoring and relevant actions to be taken will be given at discharge.

Certain laboratory results have gender-specific ranges, including haemoglobin, haematocrit and sex hormone levels. Therefore, it is important to request a change to the patient's gender marker in their medical record if and when the patient requests this.

Monitoring – requests for advice

If monitoring results are forwarded to the specialist service, please include clear clinical information on the reason for sending, to inform action to be taken.

Frequency

The following should be monitored at least annually but potentially more frequently according to clinical need, as outlined by the specialist team. Requests will be tailored to the medication the patient is prescribed.

- Body mass index
- Blood pressure
- Liver function tests
- U&Es (check once month after initiation of spironolactone as well as annually to monitor potassium)
- HbA1c (or Fasting blood glucose)
- Lipid profile
- Testosterone
- Estradiol
- LH
- FSH
- Supplementary investigations may be requested in limited circumstances, albeit infrequently, if a specific medical condition warrants this.

PHARMACEUTICAL ASPECTS			
DRUG/ROUTE OF ADMINISTRATION:	**FORMULATION:**	**ADMINISTRATION DETAILS:**	**OTHER IMPORTANT INFORMATION:**
Finasteride/ oral	5 mg tablets	Swallow tablet with or without food. Take treatment around the same time each day.	Patients must use condoms when having penetrative sex if their partner is or is likely to become pregnant, as Finasteride is excreted in ejaculate.
Cyproterone acetate / oral	Available in 50 mg or 100 mg tablets	Swallow tablets with a drink after meals. Take them at evenly spaced times during the day. A tablet cutter will be needed for smaller doses	Direct dose-dependent hepatotoxicity reported (see below)
Spironolactone	Available in 12.5 mg, 25 mg, 50 mg and 100 mg tablets.	Swallow tablet with or without food. Take treatment around the same time each day.	

CAUTIONS AND CONTRADICTIONS Please see SmPC & BNF for comprehensive information.

This information does not replace the Summary of Product Characteristics (SmPC) and should be read in conjunction with it.

Contraindications

- Finasteride: none
- Cyproterone acetate: Dubin-Johnson syndrome; existing or history of thromboembolic disorders; malignant diseases (except for carcinoma of the prostate); meningioma or history of meningioma; previous or existing liver tumours (not due to metastases from carcinoma of the prostate); Rotor syndrome; wasting diseases (except for inoperable carcinoma of the prostate)
- Spironolactone: Addison's disease, anuria, hyperkalaemia.

Conditions that might be exacerbated by treatment with GnRH analogues:
See drug-specific information

Cautions:
Finasteride:obstructive uropathy
Cyproterone acetate: diabetes
Spironolactone. acute porphyrias

SIGNIFICANT DRUG INTERACTIONS

The following is not exhaustive. Please see BNF & SmPC for comprehensive information and recommended management.

See BNF for drug specific information.

ADVERSE EFFECTS / COMORBIDITIES AND MANAGEMENT

Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme. Visit www.mhra.gov.uk/yellowcard.
For information on incidence of ADRs see relevant SmPCs.

As these drugs are used in limited circumstances, any concerns about significant adverse effects or events should prompt the prescriber to consider suspending treatment and seeking specialist advice. See further information below. Comorbidities relevant to endocrine care should be management as outlined in Appendix 1: Estradiol for gender incongruence in male assigned adults (18+).

Finasteride: side effects
Depression, breast abnormalities, breast cancer, sexual dysfunction, testicular pain, skin reactions.

Cyproterone acetate: side effects
Depressed mood; dyspnoea; fatigue; gynaecomastia; hepatic disorders; hot flush; hyperhidrosis; nipple pain; restlessness; weight change, skin reactions, galactorrhoea; meningioma (increased risk with increasing cumulative dose); neoplasms, subfertility, adrenocortical suppression; anaemia; azoospermia; hair changes; hypotrichosis; osteoporosis; sebaceous gland underactivity (may clear acne); thromboembolism.
Direct hepatic toxicity including jaundice, hepatitis and hepatic failure have been reported (fatalities reported, usually after several months, at dosages of 100 mg and above). If hepatotoxicity is confirmed, cyproterone should normally be withdrawn unless the hepatotoxicity can be explained by another cause such as metastatic disease

Spironolactone: side effects
Acidosis hyperchloraemic; acute kidney injury; agranulocytosis; alopecia; breast neoplasm benign; breast pain; confusion; dizziness; electrolyte imbalance; gastrointestinal disorder; gynaecomastia; hepatic function abnormal; hyperkalaemia (discontinue); hypertrichosis; leg cramps; leucopenia; libido

disorder; malaise; menstrual disorder; nausea; severe cutaneous adverse reactions (SCARs); skin reactions; thrombocytopenia

FURTHER INFORMATION: ANTI-ANDROGENS and associated adverse effects

Finasteride

- Some side effects of treatment may be desirable in for male assigned people who experience gender incongruence (e.g. breast changes).
- Cases of male breast cancer have been reported. Patients should be told to promptly report to their doctor any changes in breast tissue such as lumps, pain, or nipple discharge.

In the event of the following, stop Finasteride and seek specialist advice:

- Breast cancer

Cyproterone acetate

- Some side effects of treatment may be desirable for male assigned people who experience gender incongruence (e.g. gynaecomastia).
- Some side effects listed in drug information may be related to hypogonadism and therefore less common when estradiol is administered at the same time.

In the event of the following, stop Cyproterone acetate and seek specialist advice:

- Hepatic impairment
- Meningioma

Spironolactone

- Some side effects of treatment may be desirable for male assigned people who experience gender incongruence (e.g. gynecomastia, reduced libido)

In the event of the following, stop Spironolactone and seek specialist advice:

- Hyperkalaemia
- Renal impairment
- Hepatic impairment

Gonadectomy

Treatment should be stopped following orchidectomy.

ADVICE TO PATIENTS AND CARERS

The specialist clinician will counsel the patient with regard to the benefits and risks of treatment and will provide the patient with any relevant information and advice, including information on individual drugs, as part of consent processes.

As part of consent processes, the patient is advised of the importance of adhering to prescribed doses and engaging with regular monitoring, to avoid the negative effects of treatment.

Drug specific information is discussed with patients prior to initiation.

The service's information / consent form is available here: LINK

PREGNANCY, PARENTAL EXPOSURE AND BREASTFEEDING

It is the responsibility of the specialist to provide advice on the need for contraception to all patients on initiation and at each review, but the ongoing responsibility for providing this advice rests with both the primary care prescriber and the specialist team.

Advice regarding contraception for trans people can be found at:
FSRH statement: Contraceptive Choices and Sexual Health for Transgender and Non-Binary People (2017) | FSRH

Pregnancy: Not applicable to this group.

Breastfeeding: Not applicable to this group.

Parental exposure:

- Anti-androgen exposure is likely to cause subfertility for individuals assigned male at birth, and the degree of reversibility cannot be guaranteed.
- Anti-androgens can affect sperm quality and may be teratogenic. Conception is strongly inadvisable and patients should use effective contraception throughout treatment.
- Finasteride is excreted in ejaculate; thus barrier contraception must be used during penetrative sex.

Fertility

The impact of treatment on fertility and reproduction is explained, in detail, by the specialist clinician prior to initiation. Initial prescribing guidance and / or consent documentation will contain confirmation that the patient has been informed of:

- The likely impact of endocrine treatment on fertility and future reproductive options.
- The availability of potential solutions for fertility, including gamete storage.
- The need for effective contraception in users of endocrine treatment.
- The importance of discussing pregnancy and pregnancy related healthcare if parenthood is being considered.

SPECIALIST CONTACT INFORMATION AND ARRANGEMENTS FOR REFERRAL

The contact details of all national NHS gender identity services can be found here:
How to find an NHS gender dysphoria clinic - NHS

This document has been developed with specific reference to the Northern Region Gender Dysphoria Services' clinical approach.
Clinical Lead: Dr Helen Greener, Consultant in Gender Dysphoria
Lead Specialist Nurse: Deborah Quinn
Daytime telephone number: *0191 2876130*
Email address: NRGDS@cntw.nhs.uk

ADDITIONAL INFORMATION

Accurate advice is essential when the patient's condition becomes less stable and should ideally be in a format that ensures it is not miscommunicated with the need to minimise misunderstanding. In addition, the potential complexity for restarting after a short cessation involving more intense monitoring for a given period may be challenging to convey accurately in a verbal format and ensure the recipient can retain the detail.

During the course of care and treatment in the specialist gender identity team, specialist clinicians will provide recommendations regarding:

- If and when a dose change is required OR if the drug needs to be stopped and for how long.
- Need for repeat blood test(s) and when this should be carried out.
- When to seek further advice specialist advice.
- When GnRH analogue may be restarted, at what dose, and any change in frequency of monitoring until patient stable and on a stable maintenance dose again.

At discharge, advice will be given regarding all these scenarios and the specialist team can be contacted in working hours for advice.

In the event of a medical emergency the specialist team will not advise any deviation from usual acute assessment, care and management and no out of hours advice is available from the specialist gender identity team. However, specialist advice is available during working hours and should be sought as part of the acute management pathway.

The following circumstances/ changes in the patient's condition require discussion with the specialist team:

- If non-compliance is suspected or the patient fails to attend monitoring appointments and the primary care prescriber considers it no longer safe to continue prescribing. (All appropriate steps must first be taken by primary care to reinforce the importance of attendance to the patient).
- The patient's clinical condition deteriorates such that the primary care prescriber feels a dose change is required/ the patient no longer appears to be benefiting from therapy.

To be read in conjunction with the following documents

- NHSE guidance – Responsibility for prescribing between primary & secondary/tertiary care. Available from https://www.england.nhs.uk/publication/responsibility-for-prescribing-between-primary-and-secondary-tertiary-care/
- General Medical Council. Good practice in prescribing and managing medicines and devices. Shared care. Available from https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-practice-in-prescribing-and-managing-medicines-and-devices/shared-care
- NICE NG197: Shared decision making. Last updated June 2021. https://www.nice.org.uk/guidance/ng197/.

Appendix 6 – Excluded Medications

It is impossible to provide an exhaustive list of drugs that are generally not recommended for the treatment of gender incongruence by NHS commissioned specialist gender identity clinics, including the NRGDS. However, patients may present to their GP in the following circumstances:

- To request the prescription of medications that are not available in the UK or are definitively not recommended for the treatment of gender incongruence in the UK.
- To request the prescription of medications recommended by other NHS specialist clinicians or private providers, which would not usually be recommended by NRGDS.
- To request the prescription of off-formulary medications.

NOT AVAILABLE / NOT RECOMMENDED

Injectable estrogens

- Injectable estradiol is used in some other countries. Patients may purchase these preparations online but they are not available in the UK.
- Preparations have very long half-lives and their use often results in excessively high serum levels and, hence, an increased risk of adverse effects.

Synthetic derivatives and conjugated estrogens

- Only estradiol is recommended for the treatment of gender incongruence as laid out elsewhere in this document (see appendix 1).
- Synthetic derivatives include ethinylestradiol and some other estrogens in combined preparations, and Premarin is a conjugated form of estrogen.
- Synthetic derivatives and conjugated estrogens are generally associated with more side effects and greater risk of adverse effects. They should not be prescribed in the treatment of gender incongruence.
- Serum tests for estradiol only detect bioidentical estrogens, such as estradiol; serum levels are meaningless if synthetic or conjugated forms are used, which compounds the risks.

Combined contraceptive and HRT products

- These medications usually contain synthetic derivatives of estrogen and / or prostagens and should not be used in the treatment of gender incongruence.

NOT RECOMMENDED BY THE NRGDS

Progestogens – various formulations and doses

- These medications purportedly increase breast development and support feminisation in the treatment of male assigned people who experience gender incongruence.
- There is little evidence to confirm this reported benefit, which may largely be secondary to side effects of water retention and weight gain.
- Almost all breast growth in cis women occurs before they start to produce progesterone, so it plays almost no part in breast development in cis women. Indeed, early exposure to progestogens in hypogonadal girls and adolescents during pubertal induction can irrevocably compromise final breast development.
- Progestogens can reduce the effectiveness of estradiol and progesterone is a precursor of testosterone; treatments of this type are associated with masculinising side effects such as increase in body hair growth, acne and weight gain.
- In postmenopausal cis women, estrogen + progestogens combined hormone replacement treatment (HRT) is associated with increased risk of breast cancer and increased cardiovascular risk. Meanwhile, estrogen-only HRT in postmenopausal cis-women without a uterus is associated with a far smaller increased risk of breast cancer. The cardiovascular risk of estrogen-only HRT is also less

that of combined HRT, for this group. The only benefit of adding progesterone is to prevent endometrial cancer in this post-menopausal group, which is not relevant endocrine care for gender incongruence.

- Progestogens may compound the risks of taking estradiol; taking them in combination with estradiol can increase the overall risk and, for some individuals, it is not possible to recommend estradiol if patient continues to take progestogens.
- Although micronised progesterone may be safer than synthetic progestogens, there is no evidence of benefit of these agents in terms of feminisation.
- During treatment planning and consent processes in the NRGDS, patients are counselled on the potential negative effects of progesterone. Cessation is discussed where this is relevant to the risk that would be associated with estradiol.

ESTRADIOL CONSENT FORM LINK

While progestogens are not part of routine clinical practice in any of the nationally commissioned NHS speciality gender identity clinics, a small number of clinics may recommend progestogens for individual patients on a case by case basis. Similarly, private providers may recommend these medications. As this lies out with the clinical practice of the NRGDS, it is not possible to give details regarding initiation, relevant investigations, ongoing monitoring, adverse effects etc. GPs may wish to consult the clinician recommending these agents before making a decision regarding prescribing.

Please note:
Progestogens can be used appropriately in the treatment of female assigned trans people, as contraception, including alongside testosterone and GnRH analogues.

Propecia® (Finasteride 1mg)

- Low dose finasteride has a licence for the treatment of male pattern hair loss in cis men. It is most often used at this low dose in cis men to try to prevent male-pattern hair loss,
- Finasteride 1mg is not on the North East and North Cumbria formulary.
- Female assigned trans people may request this drug or it may be recommended by private providers to address side effects of testosterone, specifically head hair loss; the risks and benefit in this group are not known and Propecia® may be detrimental to masculinisation.
- Meanwhile, finasteride 5mg is recommended by NRGDS and other specialist gender identity clinics as part of adjunctive treatment for treatment of gender incongruence in male assigned trans people. When used in the treatment of this group, it is more cost-effective and possibly clinically effective when used at the higher dose; feminisation is usually desirable in this context.
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To be read in conjunction with the following documents

- NHSE guidance – Responsibility for prescribing between primary & secondary/tertiary care. Available from https://www.england.nhs.uk/publication/responsibility-for-prescribing-between-primary-and-secondary-tertiary-care/
- General Medical Council. Good practice in prescribing and managing medicines and devices. Shared care. Available from https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-practice-in-prescribing-and-managing-medicines-and-devices/shared-care
- General Medical Council. Good practice in deciding if it is safe to propose, prescribe or provide medicines, treatment and devices. https://www.gmc-uk.org/professional-standards/the-professional-standards/good-practice-in-prescribing-and-managing-medicines-and-devices/deciding-if-it-is-safe-to-prescribe?
- NICE NG197: Shared decision making. Last updated June 2021. https://www.nice.org.uk/guidance/ng197/.

- BMA: General practice responsibility in responding to private healthcare. Last updated August 2023. https://www.bma.org.uk/advice-and-support/gp-practices/managing-workload/general-practice-responsibility-in-responding-to-private-healthcare