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This document supersedes:

- Guidelines For The Use Of Masculinising Hormone Therapy In Gender Dysphoria: Information for Primary Care November 2014
- Guidelines For The Use Of Feminising Hormone Therapy In Gender Dysphoria: Information for Primary Care July 2014 (Minor update November 2014)

General Guidelines For The Use Of Hormone Treatment In Gender Dysphoria

Northern Region Gender Dysphoria Service

Treatment Specific Appendices – attached to policy	
1	Estradiol for alleviation of gender dysphoria in male assigned adults
2	Testosterone for alleviation of gender dysphoria in female assigned adults
3	GnRH Analogues for alleviation of gender dysphoria in male assigned adults
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GENERAL GUIDELINES FOR THE USE OF HORMONE TREATMENT IN GENDER DYSPHORIA

1. **Introduction and Background**

Hormone treatment is one of several evidence-based clinical interventions for the management of gender dysphoria, recommended by NHS commissioned gender dysphoria clinics. These guidelines set out details of the respective responsibilities of primary care and the Northern Region Gender Dysphoria Service (NRGDS) in the provision of hormone treatment for this indication. They are intended to provide sufficient information to enable General Practitioners (GPs) to prescribe testosterone and estradiol preparations, and 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 within the NRGDS.

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 hormone treatment to people over the age of 17, who have completed pubertal development. NRGDS is developing its services with the goal of fully implementing the specification, after a successful bid to deliver gender dysphoria clinics services was confirmed in February 2020.

Please not that **this document is not intended to be used in the treatment of individuals under the age of 17 years of age.** At the time of writing, it is not clear whether widely accepted standards of assessment of capacity apply when treating trans youth aged 16 to 17 years of age and **prescribing to this age group, without the support of a specialist NHS service, may be inadvisable**. The only organisations in England commissioned to provide gender affirming medical care for trans people under the age of 17 years old are the Tavistock and Portman NHS Foundation Trust, and their partners. The nearest of their clinics is in Leeds. Further information, including how to refer, can be found on the Gender Identity Development Service website (see section 9).

1.1 What is gender dysphoria?

Gender dysphoria can be thought of as a syndrome comprising discomfort or distress caused by a discrepancy between a person's gender identity and their assigned sex at birth, as well as the associated gender role(s) and/or primary and secondary sex characteristics. The term gender dysphoria is also a medical diagnosis codified in DSM-V, while transsexualism is a diagnosis defined by ICD-10. However, identifying as trans or experiencing gender dysphoria are not indicative of a mental health disorder.

1.2 Hormone treatment and gender dysphoria

Most transgender and non-binary people who seek hormone treatment do so in order to reduce existing sex characteristics and achieve varying degrees of feminisation or masculinisation. This is achieved through the administration of exogenous endocrine agents. Hormone 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 hormone treatment is to reduce gender dysphoria 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. GnRH analogues are generally 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, 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.

Hormone treatment can provide significant comfort to people who experience gender dysphoria, 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, hormone treatment alone may provide sufficient symptomatic relief to obviate the need for full-time social gender role transition or surgery. Hormone treatment has a role in preparing the individual and informing the decision making process before surgery, particularly where surgical gonadectomy forms part of a management plan.

Alleviation of gender dysphoria 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 personalised 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 taking into account the individual's views of their needs.

Shared decisions regarding hormone preparation, method of delivery and dosage are informed by current understanding of minimising health risks and maximising efficacy for each 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 hormone treatment or vice versa, the specialist clinician may request that the GP refers the service user to a regional specialist endocrinology service (see section 7).

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 hormone 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. The treatment specific guidance (see appendices) is labelled according to the assigned sex for which each treatment is suitable.

2. Referral Criteria

The Northern Region Gender Dysphoria Service is based at Walkergate Park Hospital, Newcastle. It is a service for people who experience persistent unhappiness and/or discomfort with the sex they were assigned at birth. 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.

Referrals are currently accepted from GPs, mental health practitioners, and other medical and healthcare professionals. A self-referral route is currently in development. 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.

The service is available to people 17 years and over living in England and Wales. 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.

3. Responsibilities for Hormone Treatment

3.1 Placement of prescribing in primary care

Medications recommended for the treatment of gender dysphoria 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.

The choice of specific drug preparation, formulation and dosage takes into consideration current understanding of health risks, efficacy, product characteristics and patient preference. 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 find an alternative.

Hormone prescribing in this field, under the guidance of a specialist service, is safely undertaken in primary care. This approach has been used by the NRGDS since its

inception in 2006, and is the standard and widely accepted means of prescribing hormone treatment for gender dysphoria, throughout England.

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

NRGDS is not commissioned by NHS England to prescribe treatment or provide / arrange any investigations. Therefore, it is not possible to initiate or continue hormone treatment without the support of primary care. Existing GMC guidance is supportive of these arrangements for prescribing.

3.2 Primary care responsibilities

Some transgender and non-binary people never have contact with specialist gender dysphoria clinics. For those who do, the contact with specialist services represents a very small portion of their healthcare over their lifetime; the majority of their healthcare needs will be met and coordinated by primary care. Nonetheless, primary care services, like all healthcare services have a duty to treat their patients with respect and adhere to relevant legislation, such as the Equality Act, 2010, and Gender Recognition Act, 2004. 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 9 for NHS advice regarding health screening for trans people.

When hormone treatment forms part of an individual's treatment plan, primary care is expected to co-operate with specialist gender services in patient safety monitoring, by providing basic physical examinations, within their competence. This includes arranging blood tests and other investigations as recommended by the specialist clinician, at baseline and intermittently thereafter. NRGDS staff may not be able to access all clinical results through established digital platforms 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 primary care is expected to provide prescriptions of the medication recommended by specialist clinicians in NRGDS. Prescribing clinicians should ensure that they meet the necessary competencies outlined in relevant documents. The RCGP has developed relevant training modules (see section 9).

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. The GP has the complete patient record, as well as any 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. GPs should offer transgender and non-binary people the usual range of primary healthcare services available to other patients.

All service users receiving hormone 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 hormone treatment or requires additional advice or information, they can contact the service (see section 7). The patient's clinician or an appropriate colleague will respond to any queries.

4. General Health Concerns

4.1 Physical examination

Measurement of height, weight and blood pressure should be performed in all patients seeking assessment for gender dysphoria. Physical examination over and above this 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.

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.

The individual's views will be sought with regard to who shall examine them, which may include the GP, and their wishes with regard to the gender of the examining medical practitioner should be respected, if at all possible. The presence of a chaperone during examination should always be offered.

4.2 Co-morbid health conditions

General health should be assessed and considered, throughout assessment for and treatment with hormones.

GPs should seek out, identify and address pre-existing or pre-disposing conditions that might be exacerbated by treatment with or deficiency of estrogen and testosterone. These include cardiovascular disease, thrombophilia (thrombosis; pulmonary embolism), polycythaemia, 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 and specialist advice and / or treatment 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 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 follow standard practice, and trans and non-binary people should be offered the same full spectrum of healthcare services as any other patient. In some instances, treatment can be offered to address side effects of treatment, such as acne secondary to testosterone therapy; treatment of acne is not affected by testosterone therapy. If the patient is newly diagnosed with hypertension, dyslipidaemia, high blood pressure or diabetes, NICE guidance on management of these conditions should be followed. Dose reduction can be considered and advice sought form the NRGDS.

4.4 Obesity

Obesity increases the risk of adverse effects and complications related to hormone treatment. Although there is no upper limit as a condition of access, patients with BMI ≥30 will have enhanced counselling about related risk, particularly with respect to cardiovascular disease, polycythaemia, thrombosis and diabetes, and must be encouraged to seek help with weight reduction. The decision to prescribe should follow an individualised assessment and discussion of risk between the prescriber and patient. The NRGDS may ask for primary care support for patients who wish to lose weight. As obesity may also be a barrier to gender affirming surgery, weight loss early in the patient's care pathway in NRGDS may have multiple benefits.

4.5 Smoking

Smoking increases the risks associated with hormone treatment, particularly the risk of thrombosis whilst taking estradiol. Smoking should be strongly discouraged and individuals who smoke should desist whilst using hormone therapies, if possible. Whilst smoking is not an exclusion to access to this treatment, hormone therapy should only be recommended following an individualised discussion of risk, possible adverse effects and possible impacts on final treatment outcome. Those that choose to continue to smoke must be encouraged to seek help with smoking cessation and NRGDS staff may request support from primary care. Although changing from smoking to long-term nicotine replacement, including electronic cigarettes, does not

eliminate risk, it appears to reduce it significantly and this may be preferable to cigarette smoking.

4.6 Vitamin D

Expert consensus opinion recommends that all transgender and non-binary people should take over-the-counter vitamin D supplements, because of the extremely high levels of deficiency within the population.

4.7 End of life care

The role of hormone 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, hormone 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. As a general rule, treatment should not be stopped as part of end of life care, because of the symptomatic benefit of treatment, unless this has been discussed with the patient and the risks are felt to outweigh benefit.

5. NRGDS Responsibilities

5.1 Assessment

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

The majority of individuals will have two core assessment consultations. 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 compliance 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 hormone treatment for the alleviation of gender dysphoria, the clinician will ensure that that the individual meets the relevant eligibility criteria set out in the World Professional Association for Transgender Health Standards of Care (2011):

- 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 dysphoria but also facilitates the assessment of the risks, benefits and limitations of hormone treatment for the individual. These are explored in detail with the patient 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. In particular, there are detailed discussions of the implications for the individual's fertility and sexual functioning.

The specialist team will consider the risks and benefits of the timing of initiation of hormone therapy. Delay, perhaps to allow time for weight loss or smoking cessation, may cause distress to patients and increase risk psycho-social and behavioural risk, including risk from self-harm.

There is no requirement for the patient to have commenced a social role transition before a recommendation is made for hormone 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 clinician recommending treatment will obtain the service user's verbal and written consent to the hormone treatment under consideration, and provide a copy of this to the individual and their GP. 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 a best interests decision is required the specialist will contact the GP to discuss this.

5.2 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 hormone 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
- Interpretation of laboratory results
- Likely treatment effects.

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.

GPs will be given advice on dose titration and the introduction of additional pharmacological interventions by the specialist clinical team. 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.

5.3 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 patient satisfaction with treatment and identify the presence of adverse effects of medication, when relevant.

Review will be provided according to clinical need, and will be more frequent after initiation or significant changes in regimen. Reviews will be carried out by specialist medical staff and specialist non-medical prescribers. 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.

5.4 Discharge from the NRGDS

When service users are discharged from the service, a 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 hormone therapy. Whenever possible, specialist clinicians have detailed discussions regarding long term treatment with the individual concerned. If this has not been possible because the patient disengaged from the service, the advice given to the GP might be limited by the lack of patient 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. A request for telephone advice from the NRGDS can also be made following discharge. The circumstances in which direct referral back to the NRGDS would be appropriate are outlined. Re-referral to NRGDS is rarely indicated as a result of hormone treatment alone, once a regimen has been established.

6. Prescribing In Special Circumstances

GPs may be faced with difficult clinical decisions, when trans people request prescription of hormone treatment, out with NHS specialist pathways. There are a variety of circumstances in which this might happen, which will be considered in turn below. The main challenges arise when there is no documented specialist NHS assessment and gender dysphoria related diagnosis.

The General Medical Council's Good medical practice guidance states that "as a good doctor you will:

- make the care of your patient your first concern
- be competent and keep your professional knowledge and skills up to date"

However, if a patient is requesting hormone treatment for gender dysphoria, without documented NHS assessment, there is a difficult balance between the "care of your patient' and being "competent and keep professional knowledge and skills up to date". This section aims to offer some guidance to thinking and decision making around this ethical dilemma.

In these circumstances, NRGDS staff cannot tell a GP if their patient has gender dysphoria, as diagnosis requires a lengthy, comprehensive holistic assessment and no swift diagnostic test exists. Without a clear diagnosis, it is impossible to offer a clinical opinion regarding whether proposed hormone treatment is needed. NRGDS staff cannot know if treatment would be likely to be beneficial or harmful. GP must make an assessment themselves, before deciding on treatment.

If a GP is considering prescribing in any of these circumstances the following factors are important, as they will be solely responsible for prescribing the treatment:

- Is the GP satisfied that the patient suffers from gender dysphoria?
- Is the GP satisfied that the prescription is needed and likely to be of benefit?
- Is the GP practicing within their competencies?

NRGDS staff can only give general advice and guidance in these circumstances, which will not be specific to a particular patient or constitute a recommendation. Such advice and guidance might relate to factors to consider in assessment and potential strategies but we cannot confirm a diagnosis, formulate a treatment plan for the patient or take any shared responsibility for interventions delivered in primary care in this way. These approaches lie outside specialist pathways and the treatment decisions lie entirely with the prescribing GP.

6.1 Prescribing on the recommendation of a private practitioner

The GMC states that "If you prescribe at the recommendation of another doctor, nurse or other healthcare professional, you must satisfy yourself that the prescription is needed, appropriate for the patient and within the limits of your competence," (Good practice in prescribing and managing medicines and devices, GMC, 2013). You will be responsible for the prescription for hormone treatment, if you decide to proceed.

When a GP receives a recommendation of hormone treatment for a trans person from a doctor in private practice it can be difficult for them to decide whether or not to prescribe. A formal training pathway for clinicians working in trans healthcare has

only been in place since 2019 and, aside from this, there are no educational, regulatory or registration processes specific to the field. However, the GMC also makes it clear that GPs should "collaborate with"…. "an experienced gender specialist to provide effective and timely treatment for your trans patients", including "prescribing medicines"… "for the treatment of gender dysphoria, and following recommendations for safety and treatment monitoring," (Trans Healthcare, GMC Website).

If you receive a written prescribing recommendation from a private practitioner, it may be worthwhile considering the following before deciding whether or not to prescribe the treatment (in addition to the factors outlined in section 6):

- Does the recommending clinician's assessment and your own knowledge of the patient support a diagnosis of gender dysphoria?
- Does correspondence make it clear that the prescription is needed and likely to be of benefit? Do you concur, based on your clinical knowledge of the patient?
- Does the correspondence list the full and correct demographic details for the patient concerned?
- Is the recommending clinician registered based in the UK? Is the clinic registered with the Care Quality Commission (or similar regulatory body, such as Healthcare Improvement Scotland)?
- Does the clinician have a licence to practice, or in the case of non-medical prescribers, are they registered with the Nursing and Midwifery Council, General Pharmaceutical Council or Health and Care Professions Council?
- Is the recommending clinician able to provide evidence of relevant training and at least two years' experience working in a specialised gender dysphoria practice, such as an NHS GIC?
- Are you confident that the patient has given their informed consent and is appropriately apprised of the likely benefits, risks and burdens, including serious and common side effects?
- Do you have adequate information about the likely duration of treatment, arrangements for monitoring, follow-up and review, relevant blood tests or other investigations, and processes for adjusting the medicine?

This is not an exhaustive list and further information can be found in Good practice in prescribing and managing medicines and devices (GMC, 2013) and the GMC's guidance on Trans Healthcare.

The GMC also makes clear that "if you are unsure whether a specialist working outside the NHS is suitably qualified, you are not obliged to follow their recommendations." Having said this, it goes on to state that it would not "be acceptable to simply refuse to treat the patient. Discuss your concerns with your patient, carefully assess their needs, seek to understand their concerns and preferences; consult more experienced colleagues and provide care in line with the guidance in Good medical practice."

GPs sometimes approach the NRGDS for advice as part of this. In these circumstances, it is very difficult for the NRGDS to comment on whether the specialist concerned is suitably qualified. We do not have access to additional professional information about other practitioners and cannot make an assessment of their clinical acumen.

6.2 Harm minimisation

GPs may be asked to prescribe hormones when a patient reports taking hormone treatment bought online and wants the GP to prescribe treatment instead. GPs may feel pressured to intervene, especially in light of lengthy waits for NHS assessment.

NRGDS strongly advises against "self-medication" of this type. There is no guarantee that the products obtained are the medication stated or that the dose is accurate, as the substances are not necessarily from regulated pharmaceutical suppliers. However, we recognise that patients may choose to continue taking these substances and thereby expose themselves to risks related to the following:

- Exposure to harmful chemicals, because the "medication" is tainted, poor quality or a different chemical.
- Exposure to hormone preparations that are not recommended for treatment for trans people, such as the combined oral contraceptive pill or nandrolone.
- Unidentified adverse effects of "standard" hormone treatment.
- Excessive dosing with otherwise legitimate hormone preparations.
- Hypogonadism.
- Exacerbation of existing health conditions.
- Incurring unwanted effects of treatment, which they may not be aware of and may be irreversible, such as infertility.

In the first instance, we would recommend exploring the individual's understanding of hormone treatment. Psychoeducation regarding potential unwanted effects of legitimate hormone treatment and the risks of taking unregulated products may be helpful. The patient may not be aware of the risks, as the information available regarding hormone therapy for trans people is often inaccurate or of poor quality. (Further information regarding treatment specific effects is available in the appendices.) After discussion, some patients may agree to stop or reduce the dose or number of different agents.

If a patient is not willing to stop taking unregulated treatment entirely, the GP may wish to take harm minimisation approach. The options are:

- Harm minimisation, basic monitoring only.
- Harm minimisation, restricted prescribing and monitoring.

NRGDS staff can discuss these approaches and give limited advice and guidance, in general terms only. They cannot advise the GP of the likely presence of gender dysphoria, and benefits and risks of treatment to a particular patient. In these circumstances, the GP must provide care independently and monitor / prescribe in line with GMC guidance and without shared specialist responsibility.

6.2a) Harm minimisation, monitoring only

Here, the GP does not provide a prescription for treatment but provides monitoring only, with the aim of supporting the patient to make an informed decision about continuing to source unregulated hormones. The GP can check the parameters outlined in the service documentation, approximately 6 monthly, but may wish to avoid checking serum hormone levels. Thus the GP and patient are able to identify some of the serious side effects or harm that can arise from treatment. However, as

serum levels are not checked, the GP cannot comment on dosing or make recommendations about sourcing other illicit products.

6.2b) Harm minimisation, prescribing and monitoring

In this approach, the GP assesses for gender dysphoria and the need for hormone treatment and balances this against the risks of the patient continuing to take unregulated hormones. The assessment of gender dysphoria being made is not specialist, may be incorrect and could lead to harm secondary to prescribing hormone treatment but these challenges should be acknowledged by the GP and the patient. This approach can also be used for the GP to prescribe, if they feel the risks of the patient taking no treatment are intolerable and likely to cause greater harm than prescribing in the way outlined here.

The uncertainty inherent in this approach should be explained to the patient. They should be informed of the following:

- They will be prescribed a treatment, out with recommended prescribing pathways.
- Treatment will be provided without a specialist assessment; there is a greater chance of such an assessment being incorrect.
- They may be unhappy with the effects of treatment in the future, which may be irreversible.
- Although the risks and burdens of treatment will be explored, including side effects, the GP is unlikely to be as familiar with the use of hormone for the indication and therefore the quality of the information the patient is basing their decision on may be of lesser quality.

In order to reduce the risk of inappropriate treatment, adverse effects and irreversible physical changes that may not be beneficial or desirable in the future, the GP may wish to follow the prescribing schedules outlined in the treatment specific appendices, with minor adjustments. They may wish to consider the following:
Before treatment

- Explain that this approach is dependent on the patient not taking any unregulated hormone treatment in addition to prescribed treatment.
- Explore the risks and benefits of treatment, as far as possible
- Discuss fertility, both the risk of infertility (which may be irreversible) and the importance of contraception due to potential teratogenicity.
- Consider referral to a fertility clinic.
- Consider any pre-existing conditions that may complicate treatment.
- Check baseline investigations as outlined in treatment specific appendices.

Treatment considerations

- Use the agents with the least risk, in term of adverse effects.
- Prescribe a low, starting dose of a transdermal preparation of testosterone or estradiol. The GP may wish to provide limited or no dose titration upwards thereafter, which should be explained to the patient beforehand.
- Consider alternatives to GnRH analogues; without titration these are likely to cause unpleasant side effects but their effects may be priorities for the patient. Finasteride can be used, for male assigned people and due to its milder anti-androgenic effect and protective effect on hair. Progesterone only

contraception can be used for female assigned people, to achieve amenorrhoea and provide contraceptive protection.
- Check monitoring investigations, as outlined in treatment specific appendices.

6.3 "Bridging" prescriptions

Although frequently cited, the concept of bridging is ill-defined in the field of gender dysphoria and may mean different things to different patients, and prescribers. Sometimes it refers to a primary care harm minimisation approach, or a full range of prescribing in primary care, without specialist support, or it can refer to a specialist recommendation to prescribe hormones, before an assessment process is complete. As the term lacks clarity, it can be unhelpful.

6.4 Continuing a prescription when a patient changes practice

When patient care is transferred from one specialist service or GP practice to another, including from other countries within the United Kingdom (UK), hormone medication that has been initiated by a specialist service should be continued by the GP. Hormones prescribed for the management of gender dysphoria should not be stopped abruptly; there are likely to be wide ranging and significant negative consequences for the individual's wellbeing, both psychologically and physically. Cessation could also result in avoidable use of NHS resources. For example, patients may require referral to mental health services to manage the impact of cessation or they may acquire unwanted secondary sex characteristics of their birth assigned gender, which were being supressed by treatment and then require additional NHS expenditure to manage these. Potential outcomes of cessation are irreversible and / or devastating, such as completed suicide.

When a patient transfers from another practice, it may be difficult to establish whether an assessment in a specialist service has been completed and what recommendations, if any, were made in relation to hormone treatment. It may take time to trace related correspondence; treatment should not be stopped while liaising with specialist services. Many specialist services insist on written consent from the patient before disclosing their gender history; an email statement from the patient is often adequate and may help primary care to access the documentation needed. If the relevant information is forthcoming, the GP can continue to prescribe and may wish to access advice from NRGDS or specialist endocrinology thereafter.

6.5 When a patient moves to England from outside the UK on treatment

Trans healthcare and practice in the field of gender dysphoria varies considerably from country to country. With this in mind, when a patient transfers from a country outside the UK, the approach depends on a number of factors, including the available paperwork and the language it is written in, the stage of treatment the individual is at and their circumstances.

For patients who have been assessed, have a diagnosis and are established on treatment in another location, it is likely to be harmful to withdraw or make significant changes to their treatment, as outlined above. With this in mind, GPs should continue the patient's hormone treatment but may wish to consider the following:
- Contacting the gender dysphoria service for further advice.

- Contact / refer to specialist endocrinology for advice regarding the most appropriate treatment, as the patient may present requesting products, doses or delivery methods that are outside accepted UK practice.
- Referral to NRGDS for a one off assessment, to confirm a diagnosis and establish suitability for hormone treatment.

7. Accessing Specialist Advice

If the GP requires specialist advice regarding current patients of the NRGDS, they can contact the service:
Northern Region Gender Dysphoria Service
Daytime telephone number: 0191 287 6130 or 6110
The service can be contacted by telephone between 0930 and 1630, Monday to Friday
Email address: NRGDS@cntw.nhs.uk
A system is in place to ensure that enquiries will receive an initial response from a clinician in the team within 3 working days.

The service receives specialist advice from a consultant endocrinologist, with experience in the hormone treatment for transgender and non-binary adults. Service users can be referred to him where there is greater complexity, for additional guidance regarding initiation of treatment and for ongoing monitoring and advice. This is particularly relevant to treatment with Nebido® (Testosterone undecanoate).
Dr Richard Quinton
Consultant Endocrinologist,
Royal Victoria Infirmary,
Queen Victoria Road,
Newcastle upon Tyne,
NE1 4LP
Working hours telephone number: 0191 282 4635

Following discharge, the GP can also contact the NRGDS or specialist endocrinology for advice on hormone treatment. The best source of advice or course of action depends on the circumstances

- Enquiries related to complex identity-related difficulties, for example, if the patient's identity has changed and they are no longer happy with hormone treatment, may require re-referral to NRGDS.
- Enquiries related to complex physical health conditions are best directed to the specialist endocrinologist.
- Where review is requested, solely in relation to technical or physical aspects of hormone treatment, the patient should be referred to a specialist endocrinology service, rather than the NRGDS. The NRGDS can advise the GP regarding how to access such specialist endocrine input, if required.

If the GP is concerned about a medical emergency out of hours, they should seek urgent medical advice as per local arrangements.

8. Excluded Medications

There are a number of treatments which may be prescribed for the management of gender dysphoria in other settings or countries, which are not part of accepted UK practice.

Please seen appendix 6 for further information regarding the following:

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

9. Relevant Resources

Gender Identity Development Service, Tavistock and Portman NHS Foundation Trust
https://gids.nhs.uk/

Service Specification No 1719: Gender Identity Services for Adults (Non-Surgical Interventions). Available at:
https://www.england.nhs.uk/wp-content/uploads/2019/07/service-specification-gender-dysphoria-services-non-surgical-june-2019.pdf

Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People, The World Professional Association for Transgender Health
https://wpath.org/publications/soc

RCGP Gender Variance E-learning Modules
https://elearning.rcgp.org.uk/course/info.php?id=341&_ga=2.190361835.1993976877.1605541895-1347867039.1603287235

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

Faculty of Sexual and RH CEU Clinical Statement: Contraceptive Choices and Sexual Health for Transgender and Non-Binary People
https://www.fsrh.org/news/fsrh-ceu-clinical-statement-srh-transgender-nonbinary-people/

Good practice in prescribing and managing medicines and devices, General Medical Council, 2013. Available at:
https://www.gmc-uk.org/-/media/documents/prescribing-guidance_pdf-59055247.pdf?la=en&hash=958C4EED51E3D145EA8798A1AFD85887D3A577B2

General Medical Council
https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-medical-practice

Trans Healthcare, General Medical Council. Available at:
https://www.gmc-uk.org/ethical-guidance/ethical-hub/trans-healthcare

All resources / links are correct and accessible, as of November 2020. 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

TREATMENT SPECIFIC APPENDICES

Appendix 1 – Estradiol for alleviation of gender dysphoria in male assigned adults (17 years and over)

1. Background /Introduction

Doses and products covered by this primary care guidance

Drug	Route/ Formulation	Typical Dose
Estradiol	Oral (1mg or 2mg tablets)	1-6mg once daily
Sandrena®	0.1% gel (0.5mg or 1mg sachets)	1-3mg once daily
Oestrogel®	0.06% gel (0.75mg per actuation)	1.5mg-3mg once daily
Estradiol	Transdermal patches (various doses available from 25-100 micrograms)	50-250 micrograms in 24 hours, to be changed twice weekly

Choice of product and dose:

- The choice of hormone preparation, formulation and dosage takes into consideration current understanding of health risks, efficacy and patient preference.
- Transdermal preparations probably confer less risk and are usually advised for patients over 40 years, in obesity, smokers or those with liver disease due to lower risk of thrombosis and liver dysfunction.
- Patients will be counselled on the use of transdermal preparations.
- Maximum doses apply to licences for use in older, post-menopausal cis women and are therefore of limited applicability to male assigned trans people, especially younger patients. Higher doses than those quoted above may be recommended, albeit rarely.
- At times, the availability of products is also influential; there have been numerous supply issues with estradiol products in recent years.

Notes on prescribing:

- Estradiol is an estrogen steroid hormone and the major naturally occurring female sex hormone. Only estradiol and its esters are recommended for treatment of gender dysphoria.
- 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 we consider them

	interchangeable. • The prescribing of specific brands of gel is required, as different products differ in their pharmacokinetic properties and recommended doses. • 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. • We do not recommend synthetic derivatives, such as ethinylestradiol, and conjugated estrogens (please see appendix 6).
2. Indications (Please state whether licensed or unlicensed)	The eligibility criteria for hormone treatment for gender dysphoria are set out in the World Professional Association for Transgender Health Standards of Care (2011) and are echoed by NHS England. These apply to the use estradiol for the alleviation of gender dysphoria in people assigned male at birth and are: • 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 Estradiol is not licensed for this indication.
3. Contraindications and cautions Please note this does not replace the Summary of Product Characteristics (SPC) and should be read in conjunction with it.	**Contraindications:** These are not equivalent to the use of estradiol for other indications in cis women, where alternative treatment strategies may be available. However, there are few, if any, alternatives to treatment with estradiol for male assigned individuals who experience gender dysphoria and those available also confer risk. **Absolute contraindications include:** • History of estrogen dependent tumours • Recent arterial thromboembolic disease (e.g. new / unstable angina or recent myocardial infarction / stroke / TIA) • Some thrombophilic disorders **Conditions that might be exacerbated by treatment with estradiol:** • Thromboembolic disease • Prolactinoma • Breast cancer • Coronary artery disease • Cerebrovascular disease • Cholelithiasis • Hypertriglyceridemia **Estradiol should be used with caution in the following**

conditions and dose will usually be adjusted (this list is not exhaustive):

- Obesity
- Tobacco smoking
- 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
- Raised triglycerides
- Poorly controlled diabetes
- Severe migraine
- Cholelithiasis
- Hypertriglyceridemia
- Severe liver disease
- Hepatic porphyria

Please see SPC for comprehensive information.

4. Initiation and ongoing dose regime

The specialist team will provide the GP with recommendations regarding starting doses, titration and maintenance doses of treatment.
All prescribing is undertaken by the GP.

Drug	Route/ Formulation	Starting Dose	Usual increments
Estradiol	Oral	0.5-1mg daily	0.5-1mg
Sandrena®	0.1% gel	0.5mg daily	0.5mg
Oestrogel®	0.06% gel	0.75-1.5mg daily	0.75mg
Estradiol	Transdermal patches	25-75 micrograms in 24 hours	25-50 micrograms

General principles:

- Dosage of estradiol therapy largely depends on circulating serum estradiol levels, end organ response and patient goals.
- The dose is usually gradually increased to achieve the desired degree of feminisation, within agreed target ranges. High estradiol levels are associated with an increased risk of adverse effects.
- Dose changes are usually not recommended more frequently than once every 3-4 months, during titration. Slower, gradual titration may be particularly important in order to achieve maximum breast development, in terms of both size and fullness.

	• If feminisation is well-established dose changes can be made more frequently, for example, in order to reach target levels and eliminate menopausal symptoms. Estradiol levels stabilise within a week of changing dose or preparation. • If maximum feminisation is the goal, serum levels should be maintained in the upper half – third of the normal follicular range (300–750 pmol/l depending on the laboratory), in young otherwise healthy individuals. • LH and FSH levels may provide additional information on whether to increase or decrease dosage.
5. Significant medicine interactions For a comprehensive list consult the BNF or Summary of Product Characteristics. SPC	**The following list is not exhaustive; please see SPC 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. • Examples include 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 enzymes may have the following effects:** • They may increase the bioavailability of estradiol, which is metabolised by those enzymes. • Examples include alcohol consumed during 'binges', 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.
6. Initiation requirements and clinical monitoring to be undertaken by specialist	**Prior to initiation the specialist team will undertake:** • Diagnosis of gender dysphoria • Assessment of suitability of treatment with hormones, against nationally agreed clinical criteria • Formulation of individualised risks associated with treatment • Recommendations regarding any pre-treatment referrals • Detailed discussion of treatment and its implications with the patient • Consent for hormone treatment • Recommendation of pharmacological agent and dose. **At initiation the specialist team will provide the GP with**

	patient-specific "prescribing guidance", including: • Confirmation that the patient fulfils the necessary clinical criteria • Information about necessary pre-treatment assessments • Recommended preparation(s) of medications • Advice on dosage, administration, initiation, duration of treatment • Advice on physical and laboratory monitoring and interpretation of laboratory results • Likely treatment effects • Confirmation that the patient has been informed of the potential risks and limitations of, and alternatives to endocrine therapy, as well as of its potential benefits, including a signed copy of the relevant consent form. **Following initiation, the specialist team will:** • Review the patient, at least 6 monthly • Review the psychological and physical effects of treatment • Give advice to GPs regarding dose titration and the introduction of additional pharmacological interventions. • Give information on desirable target ranges and dose adjustment to maintain serum hormone concentrations within a target range. **Treatment with estradiol is usually life long, in the absence of serious complications. Therefore the specialist team will provide detailed information regarding many aspects of long-term treatment and associated healthcare, at discharge, including:** • Long term goals and monitoring of hormone treatment (at least annually), including target ranges for serum hormone levels • Reducing the dose and circulating levels as the patient ages • Breast, prostate and other health screening • 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.
7. Investigation and monitoring requirements to be undertaken by primary care. See section 10 for further guidance on management of adverse effects/ responding	**All investigations, at baseline, during treatment in the gender dysphoria service and following discharge, are the responsibility of the general practitioner.** **Baseline investigations:** Body mass index Blood pressure

to monitoring results.	Full blood count Urea and electrolytes Liver function tests HbA1C (or Fasting blood glucose) Lipid profile Thyroid function Serum testosterone Serum estradiol Serum prolactin LH FSH Serum vitamin D Prostate specific antigen (PSA) (in the over 40s) 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). Pre-test counselling should be undertaken and the patient informed that by itself it is not an approved cancer screening tool and there is a risk of both false-positive and false-negative results. Once estradiol is started the circulating testosterone reduces and PSA results become uninterpretable. Furthermore, any cancer which does develop will be likely to be hormone resistant and very difficult to treat. **Monitoring thereafter** The specific investigations requested will differ depending on the stage of treatment and clinical need. Body mass index Blood pressure Liver function tests HbA1C (or Fasting blood glucose) Lipid profile Serum testosterone Serum estradiol LH FSH **Timing of samples** Tests should ideally be taken 8-24 h after a tablet, 24-48 h after a patch has been applied or 4-12 hours after application of a gel. **Monitoring** The aim of monitoring is to detect major side effects of hormonal treatment and guide dosage of treatment. It should be carried out 4-12 monthly, for 3 years, and then at least annually, or according to clinical need, thereafter. The risks of estradiol exposure appear to be related to the duration of treatment in cis females but it is not known whether

<table>
<tr><td></td><td>this can be assumed in male assigned individuals.

Referrals to local services
The specialist team may request that the GP makes referrals to services local to the patient, for additional investigations or treatment, for example, endocrinology, fertility services or mental health services.</td></tr>
<tr><td>8. Adverse effects and managements
Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme
www.mhra.gov.uk/yellowcard</td><td>Relevant risks, adverse effects and consequences of this treatment, not only for patients in this group but also for the individual based on a patient-specific assessment, are explained by the specialist team prior to initiation.

Risk level of feminising hormones
<table>
<tr><th>Risk Level</th><th>Condition</th></tr>
<tr><td>Likely increased risk</td><td>Venous thromboembolic disease*
Gallstones
Elevated liver enzymes
Hypertriglyceridemia*</td></tr>
<tr><td>Likely increased risk with presence of additional risk factors (including age)</td><td>Cardiovascular disease</td></tr>
<tr><td>Possible increased risk</td><td>Breast Cancer
Hyperprolactinemia</td></tr>
<tr><td>Possible increased risk with presence of additional risk factors (including age)</td><td>Type 2 diabetes*
Hypertension</td></tr>
</table>
*Risk is greater with oral estradiol than with transdermal preparations

In the event of the following, stop estradiol and seek specialist advice:
• Breast cancer
• Other estrogen dependent tumour

In the event of the following seek specialist advice, as part of the acute management pathway:
• Deep vein thrombosis
• Pulmonary embolism
• Cardiovascular event (e.g. acute coronary syndromes, ischaemic stroke and peripheral arterial occlusion)

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:
• Hypertension
• Adverse lipid profile
• Diabetes
• Abnormal liver enzymes</td></tr>
</table>

Further information: Estrogens and associated adverse effects

Thromboembolic disease

- The incidence of deep venous thrombosis (DVT) in trans women on estradiol therapy is raised at approximately 2.6%. The majority occur during the first 2 years of treatment. An ongoing risk of 0.4% per year continues.
- The type of estradiol 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 not recommended.

Managing venous thromboembolism risk pre and post planned surgery

- It is recommended that consideration 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. Adjunctive treatment, such as GnRH analogues, do not need to be stopped.
- Estradiol can be resumed post-operatively if there are no complications, usually at discharge.

Breast cancer

- Randomised Controlled Trial data have not shown an increased incidence of breast cancer with estrogen-only hormone replacement therapy (HRT) in post-menopausal hysterectomised cis women, even with prolonged HRT use for up to 10 years; unlike with estrogen + progesterone HRT in cis women with an intact uterus.
- 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

Hyperprolactinaemia

- Estradiol therapy to excess can result in hyperprolactinaemia and lactotroph hyperplasia.
- The incidence of significant hyperprolactinaemia was reported to be up to 15% in historical studies, where the estrogen dose was not always adjusted to physiological target range and synthetic deriatives were more commonly used. However, it appears to be very much rarer with

	modern, physiologically-dosed treatment (https://journals.aace.com/doi/abs/10.4158/EP-2018-0101). • Moreover, there have only a handful of case reports of prolactinomas in trans women and none have needed withdrawal of estradiol treatment (https://www.fertstert.org/article/S0015-0282%2810%2900151-2/fulltext). **Prostate cancer** • Prostate cancer has only been reported in a handful of trans women in the world literature, suggesting that its incidence of prostate cancer 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 patient opts for orchiectomy, but this is unlikely to be significant unless estradiol 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. • Exposure to testosterone earlier in life may protect trans women from developing osteoporosis, relative to cis women. **Age and mortality** • The risk of adverse effects increases with age and target serum levels should 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, increased cardiovascular mortality may be related to the past use of

<table>
<tr><td></td><td>ethinylestradiol rather than current recommended estradiol therapy.
• Life long treatment is considered safe, in the absence of serious conditions, although breast screening should continue beyond the age of 70, if estradiol is continued.</td></tr>
<tr><td>9. Advice to patients and carers
The specialist 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 patient information leaflets on individual medicines.</td><td>Patients are informed of the effects of treatment, both positive and negative.
Detailed information is given at the outset of treatment.

Effects and expected time course of feminising hormones (This is a general guide and the timing of introduction of GnRH analogues may influence timescales)

<table>
<tr><th>Effect</th><th>Expected onset</th><th>Expected maximum effect</th></tr>
<tr><td>Body fat redistribution</td><td>3–6 months</td><td>2–5 years</td></tr>
<tr><td>Decreased muscle mass/ strength</td><td>3–6 months</td><td>1–2 years</td></tr>
<tr><td>Softening of skin/ decreased oiliness</td><td>3–6 months</td><td>Unknown</td></tr>
<tr><td>Decreased libido</td><td>1–3 months</td><td>1–2 years</td></tr>
<tr><td>Decreased spontaneous erections</td><td>1–3 months</td><td>3–6 months</td></tr>
<tr><td>Male sexual dysfunction</td><td>Variable</td><td>Variable</td></tr>
<tr><td>Breast growth</td><td>3–6 months</td><td>2–3 years</td></tr>
<tr><td>Decreased testicular volume</td><td>3–6 months</td><td>2–3 years</td></tr>
<tr><td>Decreased sperm production</td><td>Variable</td><td>Variable</td></tr>
<tr><td>Thinning and slowed growth of body and facial hair</td><td>6–12 months</td><td>> 3 years</td></tr>
<tr><td>Male pattern baldness</td><td>Loss stops 1–3 months, no regrowth</td><td>1–2 years</td></tr>
</table>
Patients are counselled on lifestyle factors they can ameliorate, in order to reduce the risk of estradiol treatment.

The patient should be advised to seek urgent advice in the event of any of the following signs or symptoms:
• Hot, swollen, painful tender calf</td></tr>
</table>

	• Pleuritic chest pain, shortness of breath and haemoptysis
10. Pregnancy, parental exposure and breast feeding It is the responsibility of the specialist to provide advice on the need for contraception to patients on initiation and at each review but the ongoing responsibility for providing this advice rests with both the GP and the specialist.	**Fertility and parental exposure** Estradiol exposure may 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. The impact of hormone treatment on fertility and reproduction is explained, in detail, by the specialist clinician at initiation. Initial prescribing guidance will contain confirmation that the patient has been informed of: • The likely impact of endocrine therapy on fertility and future reproductive options, and of the availability of potential solutions for fertility, including gamete storage • The need for effective contraception in users of endocrine therapy • The importance of discussing pregnancy and pregnancy-related healthcare if parenthood is being considered. Advice regarding contraception for trans people can be found at: https://www.fsrh.org/news/fsrh-ceu-clinical-statement-srh-transgender-nonbinary-people/

Appendix 2 – Testosterone for alleviation of gender dysphoria in female assigned adults (17 years and over)

1. Background /Introduction

Doses and products covered by this primary care guidance

Drug	Route/ Formulation	Typical Dose
Nebido®	4ml oily injection Testosterone undecanoate 1g	4ml (1g) IM Every 12-20 weeks
Sustanon 250®	1ml injection Combined: Testosterone propionate 30mg Testosterone phenylpropionate 60mg Testosterone isocaproate 60mg & Testosterone decanoate 100mg	1ml (250mg) IM Every 2-6 weeks
Testosterone enantate	1ml injection Testosterone enantate 250mg	1ml (250mg) IM Every 2-6 weeks
Tostran®	20 mg/1g topical gel (10 mg per actuation)	40-80mg once daily
Testogel®	50mg/5g topical gel (50mg per sachet)	50-100mg once daily
Testogel®	16.2mg/g topical gel (20.25 mg per actuation)	40.5-81mg once daily
Testavan®	23 mg/1.15 g topical gel (23 mg per actuation)	23-69mg once daily
Testim®	50 mg/5 g topical cream (50mg per tube)	50-100mg once daily

Choice of product:

- The choice of hormone preparation, formulation and dosage takes into consideration current understanding of health risks, efficacy and patient preference.
- Transdermal preparations should be considered in older patients, obesity and smokers, because they may confer lower risk of polycythaemia, thrombosis and liver dysfunction. They also allow smaller doses and increments and should be used when these are desirable.
- Patients will be counselled on the use of transdermal preparations.
- At times, the availability of products is also influential; there has been disruption in availability of some testosterone products in recent years.

Notes on prescribing:

- The prescribing of specific brands of gel is required, as different products differ in their pharmacokinetic properties and recommended doses.
- Sustanon® contains arachis (peanut) oil and should not

	prescribed for patients known to be allergic to peanut. As there is a possible relationship between allergy to peanut and allergy to soya, patients with soya allergy should also avoid Sustanon®.
2. Indications (Please state whether licensed or unlicensed)	The eligibility criteria for hormone treatment for gender dysphoria are set out in the World Professional Association for Transgender Health Standards of Care (2011) and are echoed by NHS England. These apply to the use of testosterone for the alleviation of gender dysphoria in people assigned female at birth and are: • 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 Sustanon® is the only licenced testosterone product for this indication.
3. Contraindications and cautions Please note this does not replace the Summary of Product Characteristics (SPC) and should be read in conjunction with it.	**Contraindications:** These are not equivalent to the use of testosterone for other indications in cis men. There are few, if any, alternatives to treatment with testosterone for female assigned individuals who experience gender dysphoria. **Absolute contraindications include:** • History of estrogen dependent tumours • Recent arterial thromboembolic disease (e.g. new / unstable angina or recent myocardial infarction / stroke / TIA) • Some thrombophilic disorders **Conditions that might be exacerbated by treatment with testosterone:** • Polycythaemia • Coronary artery disease • Cerebrovascular disease • Hypertension • Breast or uterine cancer **Testosterone should be used with caution in the following conditions and dose will usually be adjusted (this list is not exhaustive):** • 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

- Dyslipidaemias, if uncontrolled
- Hypertension
- Severe migraine
- Sleep apnoea
- Epilepsy

Please see SPC for comprehensive information.

4. Initiation and ongoing dose regime

The specialist team will provide the GP with recommendations regarding starting doses, titration and maintenance doses of treatment.
All prescribing is undertaken by the GP.

Drug	Route/ Formulation	Starting dose(s)	Increments
Nebido®	1g in 4ml injection	Initially give 1g IM 8 weeks later 1g IM 12 weeks later 1g IM	Change dose interval by 1-2 weeks
Sustanon 250®	250mg in 1ml injection	1ml IM every 3-4 weeks	Change dose interval by 1-2 weeks
Testosterone enantate	250mg 1ml injection	1ml every 3-4weeks	Change dose interval by 1-2 weeks
Tostran®	20 mg/1g gel	50mg once daily	25-50mg
Testogel®	50mg/5g gel	50mg once daily	25-50mg
Testogel®	16.2mg/g gel	20.25-40.5 mg once daily	20.25mg
Testavan®	23 mg/1.15 g gel	23 mg once daily	23mg
Testim®	50 mg/5 g	50mg once daily	25-50mg

General principles – Nebido®

- First trough investigations should be checked prior to giving the third dose of Nebido®.
- Dosing of Nebido® can be complex and referral to specialist endocrinology service is usually recommended, because the dose is fixed and so overall exposure to testosterone can only be adjusted through altering the injection-interval.
- The goal is to achieve a steady state, that is to say unchanged injection interval with similar trough haemoglobin and haematocrit over 3 successive Nebido® injections, which can take several years, due to the long acting nature of the treatment.
- After initiation, the specialist team will recommend the ongoing

	treatment dose interval based on the first trough investigations. • The goal is trough serum levels in the lower half of the male reference range, subject to any concomitant issues of age, sexual function and bone health. However, if haematocrit or haemoglobin is raised, this should take precedence and a lower testosterone level may need to be accepted. **General principles – other injectable preparations** • First trough investigations should be checked prior to giving the fourth injection. • The goal is to achieve trough serum testosterone levels in the lower third of the male reference range, subject to any concomitant issues of age, sexual function and bone health. However, if haematocrit or haemoglobin is raised, this should take precedence and a lower testosterone level may need to be accepted. **General principles – topical treatments** • First trough investigations should be checked after 12 weeks of treatment as, even though stable testosterone levels will be achieved within days, the new steady-state haematocrit takes much longer to be established. • The goal is to achieve trough serum testosterone levels in the middle third of the male reference range, subject to any concomitant issues of age, sexual function and bone health. However, if haematocrit or haemoglobin is raised, this should take precedence and a lower testosterone level may need to be accepted. **Dose adjustment** • Dose changes are usually not recommended more frequently than once every 3-4 months. • If haemoglobin and haematocrit are with the normal male reference range, serum testosterone is in target range and patient is happy, then the existing dosing maintained. • If haemoglobin is above the normal male reference range, haematocrit is above 0.5 or serum testosterone level is above target extend the injection interval by an extra 1-2 weeks OR by the increments stated above for topical treatments. • If trough testosterone is below target and/ or the patient is unhappy, reduce interval before next injection by 1 week OR by the increments stated above for topical treatments, but only if haemoglobin & haematocrit are normal and stable. • If the patient is anaemic and no other cause is identified, this may indicate that a dose increase is required. • After a dose change, recheck dosing (FBC, serum testosterone +/- SHBG and albumin on a trough sample) at least 12 weeks later or on the next but one injection for Nebido®. • Thereafter, monitoring is usually recommended at least annually and usually not more often than:

	○ Every other injection for Nebido®. ○ Every 4 doses for other injectables ○ Every 12 weeks for topical treatments.
5. Significant medicine interactions For a comprehensive list consult the BNF or Summary of Product Characteristics. SPC	**The following list is not exhaustive; please see SPC for comprehensive information and recommended management.** **Testosterone preparations have few significant drug interactions.** • Warfarin – testosterone can increase the anticoagulant effect of warfarin • Leflunomide and its metabolite terifunomide – there is an increased risk of liver dysfunction and more frequent monitoring may be required.
6. Initiation requirements and clinical monitoring to be undertaken by specialist	**Prior to initiation the specialist team will undertake:** • Diagnosis of gender dysphoria • Assessment of suitability of treatment with hormones, against nationally agreed clinical criteria • Formulation of individualised risks associated with treatment • Recommendations regarding any pre-treatment referrals • Detailed discussion of treatment and its implications with the patient • Consent for hormone treatment • Recommendation of pharmacological agent and dose. **At initiation the specialist team will provide the GP with patient-specific "prescribing guidance", including:** • Confirmation that the patient fulfils the necessary clinical criteria • Information about necessary pre-treatment assessments • Recommended preparation(s) of medications • Advice on dosage, administration, initiation, duration of treatment • Advice on physical and laboratory monitoring and interpretation of laboratory results • Likely treatment effects • Confirmation that the patient has been informed of the potential risks and limitations of, and alternatives to endocrine therapy, as well as of its potential benefits, including a signed copy of the relevant consent form. **Following initiation, the specialist team will:** • Review the patient, at least 6 monthly • Review the psychological and physical effects of treatment • Give advice to GPs will regarding dose titration and the introduction of additional pharmacological interventions by the specialist clinical team. • Give information on desirable target ranges and dose adjustment to maintain serum hormone concentrations within a target range. **Treatment with testosterone is usually life long, in the absence**

	of serious complications. Therefore the specialist team will provide detailed information regarding many aspects of long-term treatment and associated healthcare, at discharge, including: • 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.
7. Investigation and monitoring requirements to be undertaken by primary care. See section 10 for further guidance on management of adverse effects/ responding to monitoring results.	**All investigations, at baseline, during treatment in the gender dysphoria service and following discharge, are the responsibility of the general practitioner.** **Baseline investigations:** Body mass index Blood pressure Full blood count Urea and electrolytes Liver function tests HbA1C (or Fasting blood glucose) Lipid profile Thyroid function Serum testosterone Serum sex hormone binding globulin Serum estradiol LH FSH **Immediately prior to initiation:** A pregnancy test is recommended if the patient may be pregnant. **Timing of samples** Tests should ideally be taken immediately prior to administration of an injection, or 4-12 hours after application of a gel. **Monitoring thereafter** The specific investigations requested will differ depending on the agent, stage of treatment and clinical need. Body mass index Blood pressure Full blood count Liver function tests, including albumin HbA1C (or Fasting blood glucose) Lipid profile

Serum testosterone
Serum sex hormone binding globulin
Serum estradiol
LH
FSH

Free testosterone

Serum testosterone equates to total testosterone, which is adequate for dosing for 90% of patients. However, most circulating testosterone is bound to plasma proteins and is biologically largely inactive. Checking sex hormone binding globulin (SHBG) allows the calculation of free testosterone level, which gives a more accurate guide to treatment. This should be considered in the following circumstances:

- Anticonvulsant therapy – tends to high SHBG, so lower calculated free testosterone
- Underweight / slim individuals (as above)
- Metabolic syndrome (obesity/ diabetes/ hypertension/ dyslipidaemia) – tends to low SHBG, so higher calculated free testosterone)

In these patients, consider calculated free testosterone. Many laboratories will perform the calculation automatically and provide a normal range. However, where the result is not provided it can be calculated using SHBG, albumin and serum total testosterone. Many free tools are available, including:
http://www.issam.ch/freetesto.htm
The normal range is 0.22-0.76nmol/L or 220-760pmol/L. The same targets should be used using free rather than serum testosterone, as outlined for each of the different preparations.

Monitoring

The aim of monitoring is to detect major side effects of hormonal treatment and guide dosage of treatment. It should be carried out 4-12 monthly, for 3 years, and then at least annually, or according to clinical need, thereafter.

Referrals to local services

The specialist team may request that the GP makes referrals to services local to the patient, for additional investigations or treatment, for example, endocrinology, fertility services or mental health services.

8. Adverse effects and managements
Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme
www.mhra.gov.uk/yellowcard

Relevant risks, adverse effects and consequences of this treatment, not only for patients in this group but also for the individual based on a patient-specific assessment, are explained by the specialist team prior to initiation.

Risk level of masculinising hormones

Risk Level	Condition
Likely increased risk	Polycythaemia* Weight gain / increased visceral fat

	Acne Androgenic alopecia (balding) Sleep apnoea
Possible increased risk	Altered lipid profiles* ** Liver dysfunction
Possible increased risk with presence of additional risk factors	Type 2 diabetes** Hypertension** Mood disorders (in patients with predisposition and supraphysiologic blood levels of testosterone) Cardiovascular disease
No increased risk or inconclusive	Breast Cancer Osteoporosis Cervical cancer Ovarian cancer Uterine cancer

*Risk is greater with supraphysiologic (beyond normal male range) serum levels of testosterone, which are more likely to be found with extended intramuscular dosing, than transdermal administration
** Patients with Polycystic Ovarian Syndrome may be at greater risk

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

- Thrombotic event
- Polycythaemia
    - Haematocrit above 0.53 or 53 % on one occasion
    - Haemoglobin above normal male range on 2 consecutive samples, despite reduction in dose (e.g. increased dose interval for injectable)
    - Haematocrit above 0.5 or 50% on more that 2 consecutive samples, despite reduction in dose (e.g. increase dose interval for injectable)
- Breast or uterine cancer
- Other estrogen dependent tumour

In the event of the following seek specialist advice, as part of the acute management pathway:

- Deep vein thrombosis
- Pulmonary embolism
- Cardiovascular event

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:

- Hypertension
- Adverse lipid profile
- Diabetes
- Abnormal liver enzymes

Further information: androgens and associated adverse effects.

Polycythaemia

- The commonest serious adverse effect of testosterone is polycythaemia and erythrocytosis, because of the associated risk of venous and arterial thrombotic events.
- The adult male red blood cell mass is around 30g/L greater than that of women and children, reflecting the erythropoeisis-stimulating action of testosterone.
- Although both anaemia and polycythaemia or erythrocytosis have multiple causes, in a patient on testosterone these findings could likely reflect under- and over- replacement, respectively.
- In those that have a haematocrit above reference range, there may be an increased risk of myocardial infarction and stroke. This can occur even in young subject as both stroke and myocardial infarction have been reported in athletes who abuse testosterone.
- Polycythaemia may be seen more when injectable testosterone is used and appears to be proportional to the degree of supraphysiological testosterone.
- Polycythaemia usually responds to an increase in dose interval or reduction in dose. If this is inadequate, urgent referral to specialist endocrinology is advised.

Liver Dysfunction

- In one series transient increases in liver function enzymes was seen in 4.4% of trans men and this was prolonged (>6months) in 6.8%.
- 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 the incidence of hepatic dysfunction associated with testosterones use has lessened.

Lipid Profile

- The administration of testosterone in trans men is associated with an increase in triglyceride and a decrease in plasma HDL levels both of which are proatherogenic. However total

cholesterol and LDL cholesterol remain unchanged.

- These 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.

Gynaecological Malignancy

- **Ovaries**
  The risk of developing ovarian carcinoma (if the ovaries remain in situ), is unlikely to be different to that of nulliparous women (whose lifetime risk is slightly greater than that of women who have been pregnant).
- **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.
- **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) used to be recommended for all female assigned patients taking testosterone, for primary prevention of endometrial cancer but there is little evidence for an increased risk of either in female assigned trans people who take testosterone.
  Failing this, a number of sources recommended endometrial surveillance with periodic pelvic ultrasounds in amenorrheic individuals. However, evidence for this is lacking and, in practice endometrial atrophy appears to be near universal in this group of people.
- Despite these theoretical considerations, there is little evidence for an increased risk of any gynaecological cancer in female-assigned trans people who take testosterone and have not undergone resection of uterus and ovaries.
- Nonetheless, unexplained vaginal bleeding (in the absence of missed or changed dosing of testosterone) in a female assigned trans patient, previously with testosterone-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.

Breast Malignancy

- The majority of female assigned patients taking testosterone for this indication will have mastectomy. However, as not all breast tissue is removed, malignancy can develop in remaining breast

tissue due to aromatisation of testosterone to estradiol. 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.

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, 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.

Cardiovascular disease
- Masculinising hormone therapy at normal physiologic doses does not appear to increase the risk of cardiovascular events among healthy patients.
- Masculinising hormone therapy may increase the risk of cardiovascular disease in patients with underlying risks factors.

Obstructive Sleep Apnoea
- Testosterone therapy may exacerbate the symptoms of obstructive sleep apnoea. 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.

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

9. Advice to patients and carers
The specialist 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 patient information leaflets on individual medicines.

Patients are informed of the effects of treatment, both positive and negative.
Detailed information is given at the outset of treatment.

Effects and expected time course of masculinising hormones (This is a general guide and the timing of introduction of GnRH analogues may influence timescales. Other factors including age, genetics and amount of exercise are also of significance.)

Effect	Expected onset	Expected maximum effect

	Skin oiliness/acne	1–6 months	1–2 years
	Facial/body hair growth	3–6 months	3–5 years
	Scalp hair loss	>12 months	Variable
	Increased muscle mass/strength	6–12 months	2–5 years
	Body fat redistribution	3–6 months	2–5 years
	Cessation of menses	2–6 months	n/a
	Clitoral enlargement	3–6 months	1–2 years
	Vaginal atrophy	3–6 months	1–2 years
	Deepened voice	3–12 months	1–2 years

Patients are counselled on lifestyle factors they can ameliorate, in order to reduce the risk of testosterone treatment.

10. Pregnancy, parental exposure and breast feeding

It is the responsibility of the specialist to provide advice on the need for contraception to patients on initiation and at each review but the ongoing responsibility for providing this advice rests with both the GP and the specialist.

Fertility and parental exposure

Testosterone exposure may cause infertility 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 alternative contraception should be used.

Patients must not attempt to conceive during treatment with testosterone as there may be a teratogenic effect. Testosterone should not be used during breast feeding.

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

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

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

	transgender-nonbinary-people/

Appendix 3 – GnRH Analogues for alleviation of gender dysphoria in male assigned adults (17 years and over)

1. Background /Introduction

Doses and products covered by this primary care guidance

Drug	Route/ Formulations	Typical Doses
Goserelin	3.6mg S/C implant 10.8 S/C implant	10.8mg every 12 weeks
Leuprorelin	3.75mg IM or SC injection 11.25mg IM or SC injection	11.25mg every 3 months
Triptorelin	3mg IM injection 3.75mg IM or S/C injection 11.25mg IM injection 22.5mg IM injection	11.25mg every 3 months 22.5 mg every 6 months.
Nafarelin	Intranasal 200 micrograms per 1 dose	400 micrograms, twice daily
Buserelin	Intranasal 100 micrograms per 1 dose 150 micrograms per 1 dose	300 micrograms three times daily

Role of GnRH analogues

- GnRH analogues are used to achieve maximum suppression of endogenous testosterone and, thereby, attenuation of secondary male sexual characteristics.
- They inhibit the secretion of pituitary gonadotrophins leading to low circulating levels of testosterone
- These drugs are effective, well tolerated and generally not associated with significant side effects for this indication.
- The treatment goal is to achieve equivalent female levels of testosterone.
- This maximises masculinisation achieved by estradiol and allows patients to experience a post surgical hormonal milieu, in advance of gonadectomy, if this forms part of their treatment plan.
- For a minority, estradiol alone supresses testosterone sufficiently without the introduction of these agents. However, estradiol may have to be stopped temporarily for these patients to access surgery. If this is the case, short acting GnRH analogues can be used prior to surgery to prevent masculinisation caused by the withdrawal of estradiol.

Choice of product and dose:

- The choice of preparation is largely related to patient

<table>
<tr><td></td><td>preference, as different injectable GnRH analogues are similar in their side effect profiles and cost.
• 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.

Notes on prescribing:
• GnRH analogues can have an initial stimulating action, causing a transient increase in serum testosterone before the sustained drop. This occurs during the first 10 days after initiation. Some patients opt for a short course of cyproterone acetate (50mg once daily for 2 weeks) to prevent this “flare-effect”. See appendix 5 for further information.</td></tr>
<tr><td>2. Indications
(Please state whether licensed or unlicensed)</td><td>The eligibility criteria for hormone treatment for gender dysphoria are set out in the World Professional Association for Transgender Health Standards of Care (2011) and are echoed by NHS England. These apply to the use of GnRH analogues for the alleviation of gender dysphoria in people assigned male at birth and are:
• 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
None of the listed preparations are licensed for this indication.</td></tr>
<tr><td>3. Contraindications and cautions
Please note this does not replace the Summary of Product Characteristics (SPC) and should be read in conjunction with it.</td><td>Contraindications:
• None

Conditions that might be exacerbated by treatment with GnRH analogues:
• Metabolic bone disease (in the context of inadequate replacement with sex steroids)
• Diabetes

Please see SPC for comprehensive information.</td></tr>
<tr><td>4. Initiation and ongoing dose regime</td><td>The specialist team will provide the GP with recommendations regarding initiation and maintenance doses of treatment.
All prescribing is undertaken by the GP.

<table>
<tr><th>Drug</th><th>Initiation</th><th>Maintenance</th></tr>
<tr><td>Goserelin</td><td>3.6mg
Wait 4 weeks to administer first maintenance dose</td><td>10.8mg every 12 weeks</td></tr>
<tr><td>Leuprorelin</td><td>3.75mg</td><td>11.25mg every 3</td></tr>
</table>
</td></tr>
</table>

	Wait 4 weeks to administer first maintenance dose	months
Triptorelin	3mg or 3.75mg Wait 4 weeks to administer first maintenance dose	11.25mg every 3 months 22.5 mg every 6 months
Nafarelin	None needed	400 micrograms, twice daily
Buserelin	None needed	300 micrograms three times daily

General principles:

- If the first dose is well tolerated, maintenance doses can be given thereafter.
- These drugs are most often initiated and prescribed in line with their licenced uses. However, some male assigned people who experience gender dysphoria experience escalation in gender dysphoria towards the end of the dose interval of long-acting injectable preparations. This can be remedied by reducing the dose interval by 1-2 weeks.

5. Significant medicine interactions
For a comprehensive list consult the BNF or Summary of Product Characteristics.
SPC

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

6. Initiation requirements and clinical monitoring to be undertaken by specialist

Prior to initiation the specialist team will undertake:

- Diagnosis of gender dysphoria
- Assessment of suitability of treatment with hormones, against nationally agreed clinical criteria
- Formulation of individualised risks associated with treatment
- Recommendations regarding any pre-treatment referrals
- Detailed discussion of treatment and its implications with the patient
- Consent for hormone treatment
- Recommendation of pharmacological agent and dose.

At initiation the specialist team will provide the GP with patient-specific "prescribing guidance", including:

- Confirmation that the patient fulfils the necessary clinical criteria
- Information about necessary pre-treatment assessments
- Recommended preparation(s) of medications
- Advice on dosage, administration, initiation, duration of treatment
- Advice on physical and laboratory monitoring and interpretation of laboratory results

	• Likely treatment effects • Confirmation that the patient has been informed of the potential risks and limitations of, and alternatives to endocrine therapy, as well as of its potential benefits, including a signed copy of the relevant consent form. **Following initiation, the specialist team will:** • Review the patient, at least 6 monthly • Review the psychological and physical effects of treatment • Give advice to GPs regarding dose titration and the introduction of additional pharmacological interventions. • Give information on desirable target ranges and dose adjustment to maintain serum hormone concentrations within a target range. **The duration of treatment with GnRH analogues largely depends on whether the individual is referred for gonadectomy. Medication can be stopped after orchiectomy. If GnRH analogues are continued long-term, the specialist team will provide detailed information regarding many aspects of long-term treatment and associated healthcare, at discharge, including:** • Long term goals and monitoring of hormone treatment (at least annually) • Breast, prostate and other health screening • 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 • How and when to contact or refer back to the Northern Region Gender Dysphoria Service or seek other specialist advice.
7. Investigation and monitoring requirements to be undertaken by primary care. See section 10 for further guidance on management of adverse effects/ responding to monitoring results.	**All investigations, at baseline, during treatment in the gender dysphoria service and following discharge, are the responsibility of the general practitioner.** **Baseline investigations:** Body mass index Blood pressure Full blood count Urea and electrolytes Liver function tests HbA1C (or Fasting blood glucose) Lipid profile Thyroid function Serum testosterone Serum estradiol Serum prolactin

	LH FSH Prostate specific antigen (in the over 40s) **Monitoring thereafter** The specific investigations requested will differ depending on the stage of treatment and clinical need. Body mass index Blood pressure Liver function tests HbA1C (or Fasting blood glucose) Lipid profile Serum testosterone Serum estradiol LH FSH Note: once effective treatment with a GnRH analogue is established, monitoring of serum testosterone, LH and FSH usually becomes unnecessary. **Timing of samples** There is usually no need to consider timing of administration of GnRH analogue when taking samples of blood. **Monitoring** The aim of monitoring is to detect major side effects of hormonal treatment and guide dosage of treatment. It should be carried out 4-12 monthly, for 3 years, and then at least annually, or according to clinical need, thereafter. **Referrals to local services** The specialist team may request that the GP makes referrals to services local to the patient, for additional investigations or treatment, for example, endocrinology, fertility services or mental health services.
8. Adverse effects and managements **Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme** www.mhra.gov.uk/yellowcard	**Relevant risks, adverse effects and consequences of this treatment, not only for patients in this group but also for the individual based on a patient-specific assessment, are explained by the specialist team prior to initiation.** **Risk level of GnRH Analogues** • GnRH Analogues are usually well tolerated and are not generally associated with significant side effects. • Many listed side effects in cis men (i.e. feminising effects such as gynaecomastia and erectile dysfunction), are treatment goals in male assigned trans people. • Other listed side effects of the GnRH analogues are largely the result of the low levels of sex steroids in the body, namely symptoms associated with the menopause or long-term hypogonadism. The introduction of GnRH analogues usually

	takes place after initiation of sex steroids (e.g. estradiol for male assigned people) so the risk of such side effects, i.e. hot flushes, depression and osteoporosis, is significantly reduced. • The timing of introduction (i.e. whether to wait for higher levels of estradiol) is discussed with patients. Some patients' goals can be achieved without introduction of GnRH analogues. 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 a degree of hypogonadism, long-term. • Commoner side effects include: Injection site reactions Headaches, dizziness or nausea Mood changes Lower energy levels Loss of libido and changes in sexual functioning Joint or muscle pain • Genitalia may be smaller as a result of treatment with GnRH analogues, if initiated at a young age or given over a long period. This can have implications for genital reconstructive surgery, as vaginal depth is related to the quantity of genital skin. **In the event of the following, stop GnRH analogues and seek specialist advice:** • Anaphylaxis or unanticipated acute drug reaction.
9. Advice to patients and carers The specialist 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 patient information leaflets on individual medicines.	**Patients are informed of the effects of treatment, both positive and negative.** **Detailed information is given at the outset of treatment, including discussion of:** • Role and duration of treatment • Risks of treatment and associated hypogonadism • The importance of replacement sex steroid therapy, alongside GnRH analogues • The potential impact of treatment on surgical outcomes, if relevant • The effects of GnRH Analogue on fertility • The degree of reversibility. A copy of the service's signed consent form for GnRH analogues will be sent to the GP.
10. Pregnancy, parental exposure and breast feeding It is the responsibility of the specialist to provide advice	**Fertility and parental exposure** GnRH exposure is likely to cause infertility, and the degree of reversibility cannot be predicted. However, this treatment is not licensed as a contraceptive and alternative contraception should be used.

on the need for contraception to patients on initiation and at each review but the ongoing responsibility for providing this advice rests with both the GP and the specialist.	Patients must not attempt to conceive during treatment with GnRH analogues, due to their disruptive effects on endogenous sex steroid production. The impact of hormone treatment on fertility and reproduction is explained, in detail, by the specialist clinician at initiation. Initial prescribing guidance will contain confirmation that the patient has been informed of: • The likely impact of endocrine therapy on fertility and future reproductive options, and of the availability of potential solutions for fertility, including gamete storage • The need for effective contraception in users of endocrine therapy • The importance of discussing pregnancy and pregnancy-related healthcare if parenthood is being considered. Advice regarding contraception for trans people can be found at: https://www.fsrh.org/news/fsrh-ceu-clinical-statement-srh-transgender-nonbinary-people/

Appendix 4 – GnRH Analogues for alleviation of gender dysphoria in female assigned adults (17 years and over)

1. Background /Introduction

Doses and products covered by this primary care guidance

Drug	Route/ Formulations	Typical Doses
Goserelin	3.6mg S/C implant 10.8 S/C implant	10.8mg every 12 weeks
Leuprorelin	3.75mg IM or SC injection 11.25mg IM or SC injection	11.25mg every 3 months
Triptorelin	3mg IM injection 3.75mg IM or S/C injection 11.25mg IM injection 22.5mg IM injection	11.25mg every 3 months 22.5 mg every 6 months.
Nafarelin	Intranasal 200 micrograms per 1 dose	400 micrograms, twice daily
Buserelin	Intranasal 100 micrograms per 1 dose 150 micrograms per 1 dose	300 micrograms three times daily

Role of GnRH analogues

- GnRH analogues are used to achieve suppression of endogenous sex steroid production and, thereby, attenuation of secondary female sexual characteristics.
- They inhibit the secretion of pituitary gonadotrophins leading to low circulating levels of ovarian hormones.
- These drugs are effective, well tolerated and generally not associated with significant side effects for this indication.
- The treatment goal is to achieve symptomatic attenuation of unwanted feminine characteristics, such as menstruation.
- This maximises masculinisation achieved by testosterone and allows patients to experience a post surgical hormonal milieu, in advance of gonadectomy, if this forms part of their treatment plan.
- For some, testosterone alone supresses endogenous hormones sufficiently without the introduction of these agents.

Choice of product and dose:

- The choice of preparation is largely related to patient preference, as different injectable GnRH analogues are similar in their side effect profiles and cost.
- Injectable preparations are first line treatment; spray

<table>
<tr><td></td><td>preparations require multiple daily dosing and effectiveness is reliant on good adherence. Spray preparations are only used if injections cannot be tolerated.</td></tr>
<tr><td>2. Indications
(Please state whether licensed or unlicensed)</td><td>The eligibility criteria for hormone treatment for gender dysphoria are set out in the World Professional Association for Transgender Health Standards of Care (2011) and are echoed by NHS England. These apply to the use of GnRH analogues for the alleviation of gender dysphoria in people assigned female at birth and are:
• 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
None of the listed preparations are licensed for this indication.</td></tr>
<tr><td>3. Contraindications and cautions
Please note this does not replace the Summary of Product Characteristics (SPC) and should be read in conjunction with it.</td><td>Contraindications:
• Pregnancy
• Undiagnosed vaginal bleeding
• Breastfeeding

Conditions that might be exacerbated by treatment with GnRH analogues:
• Metabolic bone disease (in the context of inadequate replacement with sex steroids)
• Diabetes

Please see SPC for comprehensive information.</td></tr>
<tr><td>4. Initiation and ongoing dose regime</td><td>The specialist team will provide the GP with recommendations regarding initiation and maintenance doses of treatment.
All prescribing is undertaken by the GP.

<table>
<tr><th>Drug</th><th>Initiation</th><th>Maintenance</th></tr>
<tr><td>Goserelin</td><td>3.6mg
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<tr><td>Leuprorelin</td><td>3.75mg
Wait 4 weeks to administer first maintenance dose</td><td>11.25mg every 3 months</td></tr>
<tr><td>Triptorelin</td><td>3mg or 3.75mg
Wait 4 weeks to administer first maintenance dose</td><td>11.25mg or 3 months
22.5 mg every 6 months</td></tr>
<tr><td>Nafarelin</td><td>None needed</td><td>400 micrograms, twice daily</td></tr>
</table>
</td></tr>
</table>

Buserelin	None needed	300 micrograms three times daily

General principles:

- If the first dose is well tolerated, maintenance doses can be given thereafter.
- The maintenance intervals are indicative. For patients receiving Nebido® testosterone treatment, it is almost always acceptable to allow the interval between GnRH analogue injections to coincide with that between Nebido® injections.

5. Significant medicine interactions

For a comprehensive list consult the BNF or Summary of Product Characteristics.

SPC

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

6. Initiation requirements and clinical monitoring to be undertaken by specialist

Prior to initiation the specialist team will undertake:

- Diagnosis of gender dysphoria
- Assessment of suitability of treatment with hormones, against nationally agreed clinical criteria
- Formulation of individualised risks associated with treatment
- Recommendations regarding any pre-treatment referrals
- Detailed discussion of treatment and its implications with the patient
- Consent for hormone treatment
- Recommendation of pharmacological agent and dose.

At initiation the specialist team will provide the GP with patient-specific "prescribing guidance", including:

- Confirmation that the patient fulfils the necessary clinical criteria
- Information about necessary pre-treatment assessments
- Recommended preparation(s) of medications
- Advice on dosage, administration, initiation, duration of treatment
- Advice on physical and laboratory monitoring and interpretation of laboratory results
- Likely treatment effects
- Confirmation that the patient has been informed of the potential risks and limitations of, and alternatives to endocrine therapy, as well as of its potential benefits, including a signed copy of the relevant consent form.

Following initiation, the specialist team will:

- Review the patient, at least 6 monthly
- Review the psychological and physical effects of treatment
- Give advice to GPs regarding dose titration and the introduction of additional pharmacological interventions.

	• Give information on desirable target ranges and dose adjustment to maintain serum hormone concentrations within a target range. **The duration of treatment will be discussed and agreed.** • Once testosterone therapy is well-established and serum testosterone is maintained within a treatment target range (see relevant treatment specific appendix) for 6-9 months, GnRH analogues can usually be withdrawn with a low risk of resumption. • Concerns about distress caused by menstruation means many patients will continue treatment until gonadectomy or long-term. Medication is stopped after oophorectomy. **If GnRH analogues are continued long-term, the specialist team will provide detailed information regarding many aspects of long-term treatment and associated healthcare, at discharge, including:** • Long term goals and monitoring of hormone treatment (at least annually) • Breast, cervical and other health screening • 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 • How and when to contact or refer back to the Northern Region Gender Dysphoria Service or seek other specialist advice.
7. Investigation and monitoring requirements to be undertaken by primary care. See section 10 for further guidance on management of adverse effects/ responding to monitoring results.	**All investigations, at baseline, during treatment in the gender dysphoria service and following discharge, are the responsibility of the general practitioner.** **Baseline investigations:** Body mass index Blood pressure Full blood count Urea and electrolytes Liver function tests HbA1C (or Fasting blood glucose) Lipid profile Thyroid function Serum testosterone Serum estradiol Serum prolactin LH FSH **Immediately prior to initiation:**

	A pregnancy test is recommended if the patient may be pregnant. **Monitoring thereafter** The specific investigations requested will differ depending on the stage of treatment and clinical need. Body mass index Blood pressure Liver function tests HbA1C (or Fasting blood glucose) Lipid profile Serum testosterone Serum estradiol LH FSH Note: once effective treatment with a GnRH analogue is established, monitoring of serum estradiol, LH and FSH usually becomes unnecessary. **Timing of samples** There is usually no need to consider timing of administration of GnRH analogue when taking samples of blood. **Monitoring** The aim of monitoring is to detect major side effects of hormonal treatment and guide dosage of treatment. It should be carried out 4-12 monthly, for 3 years, and then at least annually, or according to clinical need, thereafter. **Referrals to local services** The specialist team may request that the GP makes referrals to services local to the patient, for additional investigations or treatment, for example, endocrinology, fertility services or mental health services.
8. Adverse effects and managements **Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme** www.mhra.gov.uk/yellowcard	**Relevant risks, adverse effects and consequences of this treatment, not only for patients in this group but also for the individual based on a patient-specific assessment, are explained by the specialist team prior to initiation.** **Risk level of GnRH Analogues** • GnRH Analogues are usually well tolerated and are not generally associated with significant side effects. • Many listed side effects in cis women (i.e. cessation of menstruation), are treatment goals in female assigned trans people. • Other listed side effects of the GnRH analogues are largely the result of the low levels of sex steroids in the body, namely symptoms associated with the menopause or long-term hypogonadism. The introduction of GnRH analogues usually takes place after initiation of sex steroids (e.g. testosterone

	for female assigned people) so the risk of such side effects, i.e. hot flushes, depression and osteoporosis, is significantly reduced. • 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 a degree of hypogonadism, long-term. • Commoner side effects include: Injection site reactions Headaches, dizziness or nausea Mood changes Lower energy levels Loss of libido and changes in sexual functioning Joint or muscle pain **In the event of the following, stop GnRH analogues and seek specialist advice:** • Anaphylaxis or unanticipated acute drug reaction.
9. Advice to patients and carers The specialist 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 patient information leaflets on individual medicines.	**Patients are informed of the effects of treatment, both positive and negative.** **Detailed information is given at the outset of treatment, including discussion of:** • Role and duration of treatment • Risks of treatment and associated hypogonadism • The importance of replacement sex steroid therapy, alongside GnRH analogues • The potential impact of treatment on surgical outcomes, if relevant • The effects of GnRH Analogue on fertility • The degree of reversibility. A copy of the service's signed consent form for GnRH analogues will be sent to the GP.
10. Pregnancy, parental exposure and breast feeding It is the responsibility of the specialist to provide advice on the need for contraception to patients on initiation and at each review but the ongoing responsibility for providing	**Fertility and parental exposure** GnRH exposure is likely to cause infertility, and the degree of reversibility cannot be predicted. However, this treatment is not licensed as a contraceptive and alternative contraception should be used. Patients must not attempt to conceive during treatment with GnRH analogues, due to their disruptive effects on endogenous sex steroid production. GnRH analogues should not be used during breast feeding.

this advice rests with both the GP and the specialist.	The impact of hormone treatment on fertility and reproduction is explained, in detail, by the specialist clinician at initiation. Initial prescribing guidance will contain confirmation that the patient has been informed of: • The likely impact of endocrine therapy on fertility and future reproductive options, and of the availability of potential solutions for fertility, including gamete storage • The need for effective contraception in users of endocrine therapy • The importance of discussing pregnancy and pregnancy-related healthcare if parenthood is being considered. Advice regarding contraception for trans people can be found at: https://www.fsrh.org/news/fsrh-ceu-clinical-statement-srh-transgender-nonbinary-people/

Appendix 5 –Anti-androgens for alleviation of gender dysphoria in male assigned adults

1. Background /Introduction

Doses and products covered by this primary care guidance

Drug	Route/ Formulation	Typical Doses
Finasteride	Oral	5mg once daily
Cyproterone acetate	Oral	25-100mg once daily
Spironolactone	Oral	50-200mg once daily

Role of anti-androgens

- For the vast majority of male assigned trans people receiving treatment, GnRH analogues are used to achieve maximum suppression of endogenous testosterone and, thereby attenuation of secondary male sexual characteristics.
- The oral preparations listed above are used across the world in the treatment of male assigned trans people but are used in the UK in limited circumstances.
- They may be appropriate, at low doses, where only mild anti-androgenic effects are needed and profound suppression of testosterone is not desirable for the patient.
- Anti-androgens are sometimes 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.

Finasteride

- Has relatively mild anti-androgenic properties; it prevents the action of 5-alpha reductase, thereby preventing the conversion of testosterone into dihydrotestosterone (DHT), which is a potent androgen.
- Can be used when mild anti-androgen effects are desirable, for example, when this is requested by the patient or if prevention of male-pattern baldness is especially important but the patient does not wish to commence GnRH analogues.
- Is relatively well tolerated and can be used on a long-term basis, in such circumstances.

Cyproterone Acetate

- Directly binds to and blocks the androgen receptor (it is a weak partial agonist) and has potent antigonadotropic effects.
- It is generally not recommended for long-term use in the treatment of male assigned people who experience gender dysphoria, because of its adverse effects.
- Its use is limited to specific roles as outlined above and as a short course (50mg daily for 2 weeks) at initiation of GnRH analogues (see treatment specific appendix)
- The BNF states that “treatment with high doses of cyproterone acetate for any indication, except prostate cancer, should be restricted to when alternative treatments or interventions are

	unavailable or considered inappropriate." With this in mind, if long-term effective suppression of testosterone is indicated, treatment should be changed to a GnRH analogue. **Spironolactone** • Spironolactone is a weak diuretic, which also has anti-androgenic activity. • High doses of spironolactone are often needed to achieve potent anti-androgenic effects, meaning it is not generally recommended for male assigned trans people, as GnRH analogues have a better side effect profile. • If long-term, effective suppression of testosterone is indicated, treatment should be changed to a GnRH analogue.
2. Indications (Please state whether licensed or unlicensed)	The eligibility criteria for hormone treatment for gender dysphoria are set out in the World Professional Association for Transgender Health Standards of Care (2011) and are echoed by NHS England. These apply to the use of anti-androgens for the alleviation of gender dysphoria in people assigned male at birth and are: • 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 None of the listed preparations are licensed for this indication.
3. Contraindications and cautions Please note this does not replace the Summary of Product Characteristics (SPC) and should be read in conjunction with it.	**Contraindications and cautions apply, as when these drugs are used for other indications. Important considerations are:** **Finasteride** **There are no relevant contradictions or cautions to Finasteride treatment.** **Cyproterone acetate** **Contraindications** • 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) • Severe depression • Severe diabetes (with vascular changes) • Sickle cell anaemia • Hepatic impairment **Cautions** • Diabetes mellitus

<table>
<tr><td></td><td>
Spironolactone
Contraindications
• Addison's disease
• Anuria
• Hyperkalaemia
• Acute renal insufficiency
• Renal impairment
• Acute porphyrias
Cautions
• Elderly
Please see SPC for comprehensive information.
</td></tr>
<tr><td>4. Initiation and ongoing dose regime</td><td>
The specialist team will provide the GP with recommendations regarding initiation and maintenance doses of treatment.
All prescribing is undertaken by the GP.
<table>
<tr><th>Drug</th><th>Route/ Formulation</th><th>Typical Doses</th></tr>
<tr><td>Finasteride</td><td>Oral</td><td>5mg once daily</td></tr>
<tr><td>Cyproterone acetate</td><td>Oral</td><td>25-100mg once daily
(do not exceed 100mg daily as risks of treatment increase above this dose)</td></tr>
<tr><td>Spironolactone</td><td>Oral</td><td>50-200mg once daily</td></tr>
</table>
General principles:
• The minimum effective dose is used.
• The goal is usually transfer to a GnRH analogue. Depending on timescales, treatment may be continued and then stopped after gonadectomy.
• Long-term treatment is undesirable but can be tolerated for Finasteride.
</td></tr>
<tr><td>5. Significant medicine interactions
For a comprehensive list consult the BNF or Summary of Product Characteristics.
SPC</td><td>Please see SPC for comprehensive information and recommended management for these agents. In addition potassium-conserving drugs should not be used concurrently with Spironolactone.</td></tr>
<tr><td>6. Initiation requirements and clinical monitoring to be undertaken by specialist</td><td>
Prior to initiation the specialist team will undertake:
• Diagnosis of gender dysphoria
• Assessment of suitability of treatment with hormones, against nationally agreed clinical criteria
• Formulation of individualised risks associated with treatment
• Recommendations regarding any pre-treatment referrals
• Detailed discussion of treatment and its implications with the patient
• Consent for treatment
</td></tr>
</table>

	• Recommendation of pharmacological agent and dose. **At initiation the specialist team will provide the GP with patient-specific "prescribing guidance", including:** • Confirmation that the patient fulfils the necessary clinical criteria • Information about necessary pre-treatment assessments • Recommended preparation(s) of medications • Advice on dosage, administration, initiation, duration of treatment • Advice on physical and laboratory monitoring and interpretation of laboratory results • Likely treatment effects • Confirmation that the patient has been informed of the potential risks and limitations of, and alternatives to endocrine therapy, as well as of its potential benefits, including a signed copy of the relevant consent form. **Following initiation, the specialist team will:** • Review the patient, at least 6 monthly • Review the psychological and physical effects of treatment • Give advice to GPs regarding dose titration and the introduction of additional pharmacological interventions. • Give information on desirable target ranges and dose adjustment to maintain serum hormone concentrations within a target range. **The duration of treatment with anti-androgens should, ideally, be kept to a minimum. In rare cases where treatment is continued long-term, the reasons for this will be communicated to the GP and the specialist team will provide detailed information regarding many aspects of long-term treatment and associated healthcare, at discharge, including:** • Long term goals and monitoring of treatment (at least annually) • Breast, prostate and other health screening • Action to take in response to common disorders and serious complications • How and when to contact or refer back to the Northern Region Gender Dysphoria Service or seek other specialist advice.
7. Investigation and monitoring requirements to be undertaken by primary care. See section 10 for further guidance on management of adverse effects/ responding to monitoring results.	**All investigations, at baseline, during treatment in the gender dysphoria service and following discharge, are the responsibility of the general practitioner.** **Baseline investigations:** Body mass index Blood pressure Full blood count Urea and electrolytes Liver function tests HbA1C (or Fasting blood glucose) Lipid profile Thyroid function

	Serum testosterone Serum estradiol Serum prolactin LH FSH Prostate specific antigen (in the over 40s but levels are not reliable while taking finasteride) **Monitoring thereafter** The specific investigations requested will differ depending on the stage of treatment and clinical need. Body mass index Blood pressure Liver function tests (essential for cyproterone acetate) UEs (for spironolactone) HbA1C (or Fasting blood glucose) Lipid profile Serum testosterone Serum estradiol LH FSH **Timing of samples** There is usually no need to consider timing of administration of anti-androgens when taking samples of blood. **Monitoring** The aim of monitoring is to detect major side effects of anti-androgen treatment and guide dosage of treatment, where relevant. It should be carried out 4-12 monthly, for 3 years, and then at least annually, or according to clinical need, thereafter. **Referrals to local services** The specialist team may request that the GP makes referrals to services local to the patient, for additional investigations or treatment, for example, endocrinology, fertility services or mental health services.
8. Adverse effects and managements **Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme** www.mhra.gov.uk/yellowcard	**Relevant risks, side effects and consequences of these treatments, not only for patients in this group but also for the individual based on a patient-specific assessment, are explained by the specialist team prior to initiation.** **Finasteride** • Some side effects of treatment may be desirable in for male assigned people who experience gender dysphoria (e.g. sexual dysfunction, breast changes). • Other possible side effects include: Skin reactions, angioedema, depression, infertility, palpitations, testicular pain • 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 dysphoria (e.g. gynaecomastia). • Common side effects include: Depressed mood, dyspnoea, fatigue, hepatic disorders, hot flush, hyperhidrosis, nipple pain, restlessness, weight change. • Fatigue and lassitude caused by Cyproterone acetate may be sufficient to impair performance of skilled tasks (e.g. driving). • Some side effects listed in drug information may be related to hypogonadism and therefore less common when estradiol is administered at the same time. • Other listed side effects include: Skin reactions, galactorrhoea, meningioma (increased risk with increasing cumulative dose), neoplasms, anaemia, hair changes, hypotrichosis, sebaceous gland underactivity, 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). **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 dysphoria (e.g. gynecomastia, reduced libido) • Side-effects of spironolactone include Electrolyte abnormalities (particularly high potassium) acute kidney injury, alopecia, benign breast neoplasm, breast pain, confusion, gastrointestinal disturbance, nausea, dizziness, hepatic impairment, hypertrichosis, leg cramps, malaise, skin reactions (including severe cutaneous adverse reactions) **In the event of the following, stop Spironolactone and seek specialist advice:** • Hyperkalaemia • Renal impairment • Hepatic impairment
9. Advice to patients and carers The specialist will counsel the patient with regard to the	**Patients are informed of the effects of treatment, both positive and negative.** **Detailed information is given at the outset of treatment, including discussion of:**

benefits and risks of treatment and will provide the patient with any relevant information and advice, including patient information leaflets on individual medicines.	• Role and duration of treatment • Risks of treatment • The importance of considering alternative treatment strategies, to reduce testosterone • The importance of replacement sex steroid therapy, where relevant • The effects of anti-androgens on fertility • The degree of reversibility. A copy of the service's signed consent form for anti-androgens (if recommended for more than 2 weeks) will be sent to the GP.
10. Pregnancy, parental exposure and breast feeding It is the responsibility of the specialist to provide advice on the need for contraception to patients on initiation and at each review but the ongoing responsibility for providing this advice rests with both the GP and the specialist.	**Fertility and parental exposure** Anti-androgen exposure is likely to cause infertility, and the degree of reversibility cannot be predicted. However, these products are not licenced contraceptives and alternative contraception should be used. It is inadvisable to attempt to conceive during treatment with any of the listed medication. In addition: • Finasteride is excreted in semen and use of a condom is specifically recommended if the patient's sexual partner is pregnant or likely to become pregnant. • Conception while taking Sprironolactone conveys nigh risk of major fetal malformation. The impact of hormone treatment on fertility and reproduction is explained, in detail, by the specialist clinician at initiation. Initial prescribing guidance will contain confirmation that the patient has been informed of: • The likely impact of endocrine therapy on fertility and future reproductive options, and of the availability of potential solutions for fertility, including gamete storage • The need for effective contraception in users of endocrine therapy • The importance of discussing pregnancy and pregnancy-related healthcare if parenthood is being considered. Advice regarding contraception for trans people can be found at: https://www.fsrh.org/news/fsrh-ceu-clinical-statement-srh-transgender-nonbinary-people/

Appendix 6 – Excluded Medications

It is impossible to provide an exhaustive list of drugs that we do not, as a general rule, recommend for the treatment of gender dysphoria. However, the following are requested and / or purchased by patients frequently enough to document why they do not form part of treatment regimens recommended by the service.

Progestagens – various formulations and doses

- These medications purportedly increase breast development and support feminisation in the treatment of male assigned people who experience gender dysphoria.
- 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. Indeed early exposure to progestagens in hypogonadal girls during pubertal induction can irrevocably compromise final breast development.
- Progestagens 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 + progestagens combined hormone replacement treatment (HRT) is associated with increased risk of breast cancer and increased cardiovascular risk. Meanwhile, estrogen-only HRT is not associated with an increased risk of breast cancer in cis-women, without a uterus. The cardiovascular risk of estrogen-only HRT is less that of combined HRT, for this group.
- Although micronised progesterone may be safer than synthetic progestogens, there is no evidence of benefit of these agents in terms of feminisation.
- *Progestagens can be used appropriately in the treatment of female assigned people, as contraception, including alongside testosterone therapy*.

Injectable estrogens

- Injectable estradiol is used in some other countries. Patients may purchase these preparations online but they are not prescribed 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 dysphoria as laid out elsewhere in this document (see appendix 1).
- Synthetic derivatives include ethinylestradiol and some other estrogens in combined preparations, such as mestranol, which is found in a combined contraceptive pill. 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 dysphoria.
- Serum tests for estradiol only detect bioidentical estrogens, such as estradiol; serum levels are meaningless if synthetic / 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 dysphoria.

-

Propecia® (Finasteride 1mg)

- Low dose finasteride has a licence for the treatment of male pattern hair loss in cis men. It is used at this low dose to try to prevent side effects associated with feminisation.
- When used in the treatment of gender dysphoria in male assigned individuals, it is more cost-effective and possibly clinically effective (depending on the desired outcome) when used at the higher dose (e.g. 5mg once daily); feminisation is usually desirable in this context.
- Female assigned trans people may request this drug to address side effects of testosterone; the risks and benefit in this group are not known and Propecia® may be detrimental to masculinisation.