Barnsley, Rotherham & Sheffield
Clinical Commissioning Groups

Version 13 15-06-18

Prescribing Guidelines

Trans man medication (This applies to a person assigned female, cis-female, at birth undertaking gender transition to become a male)

These guidelines are to support GPs in the ongoing management of patients requiring life-long medication

Prescribing Guidelines developed by:

Stuart Lakin, Head of Medicines Management NHS Rotherham CCG on behalf of South Yorkshire & Bassetlaw CCGs
Dr Grainne Coakley Consultant Psychiatrist, Clinical lead, Gender Identity Clinic, SHSC NHS Foundation Trust

Date approved: 12th October 2017

Review Date: 3 years from approval

1. Transfer of Prescribing Responsibilities from Secondary to Primary Care

In March 2014 NHS England Specialist Services Circular SSC1417 was issued which described Primary Care responsibilities in relation to prescribing and monitoring of hormone therapy for patients undergoing or having undergone Gender Dysphoria treatments. In March 2016 the General Medical Council published *Guidance for Doctors Treating Transgender Patients.* This guidance reiterates the advice previously set out by NHS England in SSC 1417; and also explains the legal protection against discrimination and harassment given to trans people by The Equality Act 2010 and Gender Recognition Act 2004.

Those responsibilities include

- Prescribing hormone therapy,
- Patient safety monitoring,
- Provision of physical health examinations and blood tests under the guidance of a specialist Gender Identity Clinic.

The specialist Gender Identity Clinic will assist primary care by providing specific, relevant information and support for prescribing and monitoring, including the interpretation of blood test results. During and after a patient has completed the care pathway and has been discharged by the Specialist service, GPs should offer them the usual range of primary healthcare services that are available to other patients.

2. Roles and responsibilities

Responsibilities of the primary care clinician

- To refer appropriate patients to Gender Identity Clinics for assessment
- To agree to prescribe for patients in line with the prescribing guidelines
- To continue to prescribe for the patient as advised by the consultant
- To undertake monitoring as per prescribing guidelines.
- To adjust testosterone doses to maintain serum levels at the desired level (Appendix 1)
- To seek the advice of the consultant if there are any concerns with the patient's therapy.

Responsibilities of consultant clinician

- To discuss benefits and side effects of treatment with the patient/carer and obtain informed consent. This is particularly important for unlicensed products and when prescribing products outside of their licensed indications.
- To provide the details of the medication recommended and a copy\link to the prescribing guidelines.
- To contact patient's GP to request prescribing is commenced and continued and send a link to, or a copy of the prescribing guidelines.
- To discuss any concerns with the GP regarding the patient's therapy
- To provide the GP with clear instructions including referral criteria following the patients discharge from the specialist service.

3. Medication

All the medication in these guidelines are unlicensed for the indications for which they are being used.

Hormone treatment

It is anticipated that trans men (like hypogonadal cis gender men) will remain on lifelong hormone replacement therapy with testosterone. The goal is to avoid hypogonadism while reducing the potential impact of any negative effects of testosterone, the most serious of which are related to polycythaemia and erythrocytosis, and associated adverse thrombotic events.

Injectable preparations

Drug	Route/ Formulati	Dose	Comments
Nebido® (testosterone undecanoate)	IM injection	1g/4mls (250mg-1000mg) Every 10-20 weeks. (The gender identity clinic will advise on starting dose. This is usually nebido 1g IM every 12 weeks)	This is not suitable for self-administration. Trough level reached after steady state just before the fourth injection from initiation
Sustanon® 250® (testosterone propionate 30mg, testosterone phenylpropionate 60mg, testosterone isocaproate 60mg & testosterone decanoate 1OOmg)	IM injection	1ml every 2-6 weeks (The gender identity clinic will advise on starting dose/frequency. This is usually Sustanon 250 IM every 4 weeks).	The goal is for patients to self-administer. Practices may have to administer the initial injections and teach patients or a partner how to self-administer Contains peanut oil
Testosterone Enantate 250mg	IM Injection	1ml every 2-6 weeks (The gender identity clinic will advise on starting dose. This is usually testosterone enanthate 250mg IM every 4 weeks).	The goal is for patients to self-administer. Practices may have to administer the initial injections and teach patients or a partner how to self-administer

Topical Preparations

Drug	Route/ Formulation	Dose	Comments
Testogel®	50mg/5g 1% sachets	50-100mg daily (1-2 sachets)	Apply to clean dry skin
Tostran®	10mg/0.5ml 2% metered dose pump	30-80mg daily One application = 10mg testosterone	Apply to clean dry skin

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. Thus, the most

important parameters are haemoglobin and haematocrit. 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.

Although it is important to monitor serum testosterone level, the finding of haemoglobin and/or haematocrit above male reference range should prompt an overall reduction in dose, almost irrespective of the serum testosterone level and/ or patient symptoms. This is because polycythaemia and erythrocytosis are associated with significantly increased risk of both venous and arterial thrombosis.

If a patient becomes significantly polycythaemic (Hb>175g/L, or Hct >0.52 or 52%), or experiences a thrombotic event, we would recommend that testosterone treatment be temporarily suspended and a haematology referral made. If the patient is still attending clinic seek advice from the gender identity clinic.

Ovarian Suppression

Achieving maximum suppression of female secondary sexual characteristics sometimes requires treatment with GnRH analogues. This is especially the case where introduction of testosterone has not led to suppression of the ovarian axis and cessation of the menstrual cycle. The goal is to achieve equivalent male levels of estradiol. They are usually introduced after testosterone.

- Leuproelin, 3.75mg-11.25mg every month, 2 months or 3 months.
- Triptorelin 3mg -11.25mg every month, 2 months or 3 months

(Occasionally these are given every 10 weeks)

These medications inhibit the secretion of pituitary gonadotrophins, leading to low circulating levels of estradiol and cessation of the menstrual cycle.

They are effective, well tolerated and generally are not associated with significant side effects.

- Many side effects, such as hot flushes, depression and loss of libido do not occur as testosterone is co-administered and thus the effects of hypogonadism avoided. However, vaginal dryness can be a problem.
- The use of gonadorelin analogues in pregnancy is contra-indicated.

Pregnancy should be excluded before treatment; the first injection should be given during menstruation (if this continues) or shortly afterwards or use barrier contraception for 1 month beforehand.

Drug	Route/ Formulation	Dose	Comments
Leuprorelin	Subcutaneous or IM injection (Depending on formulation)	3.75mg-11.25mg every month, 2 months or 3 months (The gender identity clinic will stipulate the frequency. This is usually 3.75mg injection monthly for 2 months and if well tolerated change to 11.25mg subcutaneous injection every 3 months thereafter).	The goal is for patients to self-administer. Practices may have to administer the initial injections and teach patients or partner how to self-administer
Triptorelin	Subcutaneous or IM injection (Depending on formulation)	3mg -11.25mg every month, 2 months or 3 months (The gender identity clinic will stipulate the frequency. This is usually 3mg injection monthly for 2 months and if well tolerated change to 11.25mg subcutaneous injection every 3 months thereafter).	Self-administer may not be possible due to the volume of the injection.

4. Monitoring Requirements

- Every 6 months for 3 years after starting therapy
- Yearly thereafter

Test/Measurement	**Recommended action if results outside of the normal range**	
Body Mass Index	Offer to refer to local weight loss services if BMI increases to over 30.	Only necessary if the patient is considering surgery. Surgery may be declined if BMI over 30.
Blood Pressure	Treat in accordance with local hypertension guidelines if BP greater than 140/90mmHg	All patients
Haemoglobin 140-175 g/L	If a patients becomes significantly polycythaemic (Hb>175g/L, or Hct >0.52 or 52%), or experiences a thrombotic event, testosterone treatment be should temporarily suspended and a haematology referral made. If the patient is still attending clinic seek advice from Porterbrook or the patients original gender identity clinic.	All patients
Haematocrit 0.40-0.52 (52%)		
Urea and electrolytes	Long term use of gondotrophins can cause U&E's to fall outside of usual ranges seek advice from Porterbrook or the patients original gender identity clinic.	All patients
Liver function tests	Refer to gastroenterology if elevated (see section 6)	All patients Risk of elevated LFT's
HbA1c	Treat in accordance with local diabetes guidelines	All patients Increased diabetes risk with hormonal treatment
Lipid profile	Treat in accordance with local lipid management guidelines	Increased CVS risk with hormonal therapy
Serum testosterone < 8 – 12 nmol\L trough level for injectables 25 – 30nmol/L peak level for injectables 15 – 20nmol/L for gel preparation measured 4 – 6 hours after application	Serum testosterone should be at the lower end of the normal range.	Testosterone levels should be a trough measurement for injectables. The blood sample should be taken immediately before the next dose. For gel preparations blood tests are to be taken 4 – 6 hours after application.
Serum estradiol < 70pmol/L	Seek advice from Porterbrook or the patients original gender identity clinic.	
Serum prolactin < 400mU/L		

5. **Risk and adverse effects of masculinising hormones**

Risk Level	**Condition**
Likely increased risk	Polycythaemia *(see below for further details) 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** Mania and psychosis in patients with pre-existing disorders (this is associated with 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

6. Hormone therapies and associated adverse effects

Adverse effects	Comments
Polycythaemia	Testosterone replacement can be associated with polycythaemia and this increase in blood viscosity can lead to an increased incidence of stroke. In those that have a haematocrit above 48% there appears to be an increased risk of stroke. This can occur even in young subjects, both stroke and myocardial infarction have been reported athletes that abuse testosterone This is seen more when injectable testosterone is used and appears to be proportional to the amount of supraphysiological testosterone that is administered. For this reason haematocrit takes precedence over serum trough levels of testosterone during injectable treatments. • Polycythaemia usually responds to an increase in dose interval or reduction in dose. • Referral to specialist gender identity clinic is advised.
Liver Dysfunction	• In one study transient increases in liver function enzymes was seen in 4.4% of trans-men and this was prolonged (>6months) in 6.8%. • These are usually minor and do not require cessation of treatment. Routine monitoring of the liver function in patients on testosterone replacement is recommended. • 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. Screening for other causes of hepatic dysfunction should be performed and ultrasound scanning of the liver to exclude any hepatic lesion or the presence of gall stones. • There have been no reports of liver tumours with testosterone esters
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 transmen. The myocardial infarction rate is approximately half that expected in the general male population.

Gynaecological Malignancy	The risk of developing ovarian carcinoma if the ovaries remain in situ once testosterone therapy commences is unlikely to be different to that of a cis women whose lifetime risk is slightly greater than that of women who have been pregnant. • Testosterone therapy does not increase the risk of cervical cancer, although it may increase the risk of minimally abnormal Pap smears due to atrophic changes. • Testosterone can be aromatised to oestradiol. The reported risk of endometrial hyperplasia is 15% in transmen. • Endometrial cancer may be of higher risk in trans men who have a uterus while their body is aromatising 'unopposed oestrogen' derived from testosterone. In this respect it is assumed that they will have the same negative response as cis woman with a uterus who have the same 'unopposed' oestrogen exposure. • Hysterectomy is recommended within 5 years of commencing testosterone therapy but some patients may elect to retain their uterus. • If irregular bleeding occurs then the patient should undergo ultrasound scanning and endometrial biopsy to rule out any neoplastic alteration in the endometrial epithelium.It is not necessary to routinely monitor endometrial thickness.
Breast Malignancy	**Trans man** *Registered with a GP as a female* A trans man aged 50 to 70 who is registered with a GP as female, will be routinely invited for screening. Patients on long-term hormone therapy may be at increased risk of developing breast cancer and should consider going for breast screening. Patients should strongly consider breast screening if they have not had chest reconstruction surgery or still have breast tissue *Registered with a GP as male* A trans man aged 50 to 70 who is registered with a GP as male, won't be invited for breast screening. Patients on long-term hormone therapy may be at increased risk of developing breast cancer and should consider asking for breast screening. Patients that have had chest reconstruction will still have breast tissue; discuss with the patient

	whether they wish referring to a breast screening service.
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 after oophorectomy, but this is unlikely to be significant unless testosterone therapy is interrupted or insufficient
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 exacerbates the symptoms of obstructive sleep apnoea. In a transman 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

7. Treatment Outcomes

The effects of masculinising hormones and the time to realise the desired outcomes are shown below.

Effects and expected time course of masculinising hormones

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

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.

8. Follow up and Discharge Arrangements

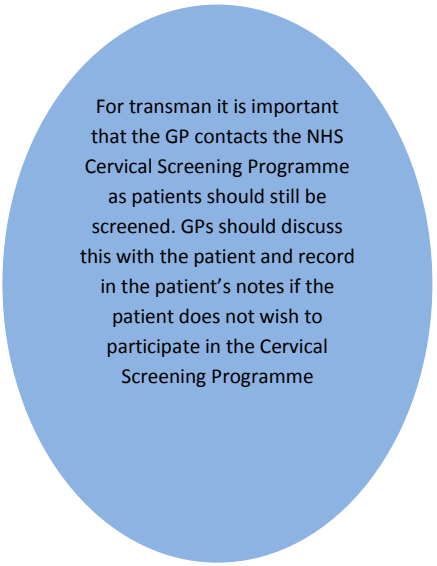
When service users are discharged from the service, detailed information is sent to the GP and service user. Guidance includes:

- Breast screening
- Ongoing treatment testosterone is usually life long, in the absence of serious complications,
- Long term goals and monitoring of hormone treatment, including target ranges for hormone levels
- Monitoring tests are needed for life on 6 monthly basis for 3 years, then yearly thereafter if the patient remains well
- Action to take in response to common disorders and serious complications, including cessation of treatment
- When and where to seek specialist advice
- How to refer back or contact the Sheffield Gender Identity Clinic.

9. Screening

Which screening is necessary Trans-man

Trans Man	
Breast Screening or patient is made breast aware	√
Cervical Screening	√
Abdominal aortic aneurysm screening	√
Bowel screening	√
Monitoring of the endometrial thickness by ultrasound scanning every two years is recommended in patients who retain their uterus	X



10. For advice on on-going management contact;

Porterbrook Clinic, Michael Carlisle Centre, 75 Osborne Road, Sheffield, S11 9BF, 01142716671

Appendix 1

Gender Identity Clinic usually recommends starting at lowest dose i.e. Testogel 50mg/5g 1 sachet per day; or Tostran 3 measures per day and a testosterone serum check 6 – 8 weeks after commencement. Once satisfactory serum levels are reached then 6 monthly checks, for first 3 years and annually thereafter.

Titration of Testosterone – Gels

Serum testosterone levels should be in the middle of adult range 15 – 20nmol/L

	Testogel 50-100 mg/day	**Tostran 30-80mg daily**
If testosterone above - Above 20nmol/l	Decrease dose to 1/2 sachet (or consider change to Tostran)	Decrease dose by one measure.
If testosterone below 15nmol/L	Increase to 2 sachets per day.	Increase by one measure and re-test in 8 weeks.
	One sachet contains 50mg testosterone *need to recheck in 8 weeks	An application = 10mg of testosterone *need to recheck in 8 weeks

Titration of Testosterone – Injectables (Sustanon/Enanthate)

Serum testosterone levels should be <8 - 12nmol/L trough serum level. I.e. blood tests should be taken day of next injection – before the injection is given

If above 12nmol/l , decrease frequency of injections i.e. if on a 3 weekly injection change this to a 4 weekly injection and then retake bloods in 3 months time.

If below 8nmol/L, increase frequency of injections.

* Note: peak levels can also be checked. Peak levels should be within 25 – 30nmol/L and blood tests taken one week after injection has been given.