Cross-Sex Hormone Therapy for Transgender Female-to-Male (FtM) Patients

Criteria for Use

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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

The Product Information should be consulted for detailed prescribing information. The VA National PBM-MAP-VPE background document on Transgender Cross-sex Hormone Therapy Use can be found at www.pbm.va.gov or https://vaww.cmopnational.va.gov/cmop/PBM/default.aspx .

EXCLUSION CRITERIA (if ONE is checked, patient is not eligible)

For testosterone therapy:

- ❑ History of or active breast cancer or other hormonally-sensitive cancer
- ❑ Pregnancy (FDA Pregnancy Category X) or breast-feeding
- ❑ Severe renal or hepatic disease
- ❑ Unstable or severe cardiovascular disease (e.g., active or recent myocardial infarction (MI) or stroke, heart failure, etc.)

INCLUSION CRITERIA (ALL must be selected for patient to be eligible)

- ❑ Patient has had a medical and mental health evaluation by a specialist prior to provision of hormone therapy. Mental health evaluation should include:
  - Assessment for Gender Dysphoria (GD) (that is distinct from other co-existing conditions)
  - Eligibility and readiness for hormone therapy
  - Whether ongoing psychotherapy may or may not be indicated
- ❑ Patient fulfills diagnostic criteria for GD (DSM-5 or ICD-10) as made by mental health or other qualified provider with expertise in the treatment of transgender patients.
- ❑ Initial prescription(s) is (are) restricted to a VA provider experienced in the use of cross-sex hormone therapy (e.g., women's health specialist, endocrinologist, psychiatrist, or other local designee).
- ❑ Concurrent medical and psychiatric conditions and modifiable risk factors that could potentiate or be exacerbated by hormone therapy have been considered and addressed (e.g., recommending smoking cessation, weight control, erythrocytosis, liver or renal dysfunction, heart failure, hypertension, diabetes, dyslipidemia, depression, sleep apnea, anxiety, aggression, etc.).
- ❑ Patient has been fully informed of potential risks, benefits, and limitations of hormone treatments and expresses clear understanding.
- ❑ Patient understands and accepts the expectations of an ongoing monitoring plan.
- ❑ Patient agrees to adhere to the recommended treatment regimen and avoid the use of additional hormone treatment (to avoid intentional or unintentional supratherapeutic dosing).
- ❑ If patient is a smoker, smoking cessation has been recommended.

For biologic females of childbearing potential:

- ❑ Pregnancy must be excluded prior to receiving testosterone and patient provided contraceptive counseling on potential risk vs. benefit of taking testosterone if patient were to become pregnant

DOSAGE AND ADMINISTRATION

See PBM Transgender Cross-Sex Hormone Therapy Recommendations document for additional information (Link: VA PBM Intranet, Clinical Guidance, Clinical Recommendations)

Testosterone

- Several products are available (transdermal, injectable, buccal)
- FtM testosterone doses are typically within the usual dosing range for hypogonadal conditions in biologic males. Upon chronic use (2 yrs or more) or post oophorectomy, reduced doses may be used to aim for testosterone levels at the lower end of the physiologic male range.
- Use lowest effective dose, monitor serum testosterone levels for safety, and avoid supraphysiologic levels. Initiate at lower end of dosing range if co-morbid conditions are present.

Progestins

- Progestins are not routinely used but may be considered for short-term use (e.g., 3-6 months) when beginning cross-sex hormone therapy to aid in suppression of menses

MONITORING

See PBM Transgender Cross-Sex Hormone Therapy Recommendations document for additional information (Link: VA PBM Intranet, Clinical Guidance, Clinical Recommendations)

- Ongoing monitoring is needed (more frequent during initiation and titration of dose and then every 6-12 months once stable)
- Physical exam should include evaluation for signs of masculinization and adverse effects of hormone therapy
- Lab testing should include screening for conditions that could be exacerbated by hormone therapy, adverse effects, and hormone levels
- Hormone level goals: Testosterone - 320 – 1000 ng/dL for safety (normal male range) (see product information for recommendations on timing of testing); Estradiol <50 pg/mL, based on clinical response
- Health maintenance and screening should be completed as appropriate (e.g., routine cancer screening – breast, colon, ovarian, endometrial, and

bone mineral density screening for those at risk)

ISSUES FOR CONSIDERATION

- **Individualized therapy:** Patient-specific goals (e.g., desired extent of feminine suppression and masculine induction) and co-existing medical conditions should be considered in determining the appropriate approach to treatment.
- **Coordination of care:** Effective clinical care of transgender patients receiving cross-sex hormone therapy requires an interdisciplinary, coordinated treatment approach with collaboration among multiple specialties including gynecology, mental health, primary and specialty care, women's health, pharmacy, and urology.
- **Risks of cross-sex testosterone therapy:** Established risks include erythrocytosis, liver dysfunction, hypertension, salt retention/edema, weight gain, adverse psychological changes, lipid changes (reduced HDL and elevated triglycerides), hypoglycemia, induction or worsening of sleep apnea, fertility impairment (may be permanent), and teratogenicity during pregnancy. It is unclear whether testosterone is associated with an increased risk of hormone-sensitive cancers or increased cardiovascular risk.
- **Secondary exposure with testosterone gel, solution:** There is risk of secondary exposure to others (concerns with women and children) via unclothed application site or unwashed clothing. Special precautions are necessary (see Prescribing Information).
- **Drug interactions:** Testosterone may potentiate the actions of anticoagulants.
- **Dual care patients***:* All patients receiving medications from VA should be managed according to the same standards (e.g., eligibility, monitoring, follow-up), consistent with the VHA National Dual Care Directive 2009-038.
- **VHA Directive 2013-003:** Providing Health Care for Transgender and Intersex Veterans

Note: The use of cross-sex hormones for transgender patients is non-FDA approved, or off-label. See PBM Guidance on off-label use for more information: https://vaww.cmopnational.va.gov/cmop/PBM/Directives%20Policies%20and%20Information%20Letters/Guidance%20on%20Off%20Label%20Prescribing.doc

Table: FtM Testosterone Therapy

Drug	Dosing Guidance†	Issues for Consideration
Testosterone, injection in oil* (cypionate or enanthate)	Initiate at 50-80 mg q2 wks (or 50% weekly); gradually increase monthly Usual dose: 100-200 mg q2 wks (or 50% weekly) Older, higher dose regimens of 250 mg IM q2 wks noted	Contraindications: breast cancer, prostate cancer, pregnancy, breast-feeding Precautions: lung disease (sleep apnea), heart failure, hypertension, cardiovascular disease Consider factors that increase risk for AEs including increased age, smoking, obesity, hypercholesterolemia, hypertension, diabetes, cardiovascular disease, etc. Drug interactions: warfarin Choice of product: ▪ IM testosterone products may cause cyclical fluctuations in hormone levels and adverse effects ; transdermal products produce more consistent hormone levels ▪ Transdermal patches commonly cause skin irritation ▪ Secondary exposure with transdermal gel/solution: Risks of secondary exposure to women and children via unclothed application site or unwashed clothing. Special precautions necessary. See product information for details. ▪ Buccal system may cause mouth and gum irritation; clinical and safety data are limited Dosing considerations: ▪ Initiate at lower end of dosing range if co-morbid conditions are present ▪ Use lowest effective dose ▪ Monitor serum levels ▪ Avoid supraphysiologic levels Hormone level goals: ▪ Testosterone levels goal: 320 – 1000 ng/dL ▪ See specific product information for recommendations on timing of testing
Testosterone, transdermal patch*	Usual dose 2.5-7.5 mg q24 hrs Doses up to 10 mg/day noted	
Testosterone, transdermal gel*, solution	Several products available with varying dosing; check specific product information for dosing instructions	
Testosterone, buccal system	Usual dose (non TG): 30 mg (one) q12 hr	

*Drug on VA National Formulary;
†Note: FtM testosterone doses are typically within the usual dosing range for hypogonadal conditions in biologic males. Upon chronic use (2 yrs or more) or post-oophorectomy, reduced doses may be used to keep testosterone levels at lower end of physiologic male range. Patients using reduced doses should be monitored for osteoporosis.
AE=adverse effects

References:

1. Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, et al. Endocrine treatment of transsexual persons: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2009;94(9):3132-54.

2. Dahl M, Feldman JL, Goldberg JM, et al. Physical aspects of transgender endocrine therapy. International Journal of Transgenderism. 2006;9:111-34.