Cross-Sex Hormone Therapy for Transgender Male-to-Female (MtF) 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 OUTSIDE THE RECOMMENDATIONS 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 http://vaww.pbm.va.gov.

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

For estrogen therapy:

- ❑ History of or active venous thromboembolic event (VTE)
- ❑ History of or active breast cancer or other hormonally-sensitive cancer

For spironolactone therapy:

- ❑ Acute renal failure or significant renal impairment
- ❑ Hyperkalemia

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 and other risk factors for VTE, hypertension, diabetes, dyslipidemia, migraines, depression, anxiety, 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.

DOSAGE AND ADMINISTRATION

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

Estrogen

- Several products are available (transdermal, oral, injectable)
- Estradiol (also known as 17-β estradiol) products preferred over ethinyl estradiol (e.g., as in contraceptive products) and conjugated estrogens (e.g., Premarin) due to ability to monitor serum levels, and these products may be associated with a lower risk of VTE
- MtF estrogen doses are often higher than usual doses for hypogonadal conditions in biologic females. Doses required post-orchiectomy are lower, and if used, anti-androgen therapy may be discontinued after surgery.
- Use lowest effective dose, monitor serum estradiol levels for safety avoiding supraphysiologic levels.

Androgen suppression agents

- Spironolactone
- GnRH agonist (goserelin has been studied)
- Progestin (not routinely recommended in recent guidelines)
- Finasteride (not specifically studied in transgender patients)

MONITORING

See PBM Transgender Cross-Sex Hormone Therapy background 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 feminization 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 - <55 ng/dL (normal female range, based on clinical response); Estradiol – not to exceed 200 pg/mL for safety (mean premenopausal female level)
- Health maintenance and screening should be completed as appropriate (e.g., routine cancer screening – prostate, breast, colon, and bone mineral density screening for those at risk)

ISSUES FOR CONSIDERATION

- **Individualized therapy:** Patient-specific goals (e.g., desired extent of masculine suppression and feminine 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 estrogen therapy:** Established risks include VTE, hyperprolactinemia, cholelithiasis, elevations in liver function tests, weight gain, fluid retention, hypertension, elevated triglycerides, migraines, fertility impairment (may be permanent). It is likely that estrogen is associated with an increased risk of cardiovascular/cerebrovascular events. It is not known if estrogen is associated with an increased risk of hormone-sensitive tumors or increased insulin resistance.
- **Androgen suppression therapy:** Additional agents are commonly used along with estrogen with the goal of enhanced effects and use of lower doses of estrogen. Progestins are not routinely recommended in recent guidelines due to unclear benefit and potential harm.
- **Spironolactone precautions:** Consider risk of hyperkalemia and use of concomitant meds that may increase risk (e.g., angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, non-steroidal anti-inflammatory drugs, potassium-sparing diuretics)
- **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

MtF Estrogen Therapy

Drug	Dosing Guidance†	Issues for Consideration
Estradiol, oral* (17-β estradiol)	Initiate at 1-2 mg/day; gradually increase Usual (oral): 2-4 mg/day, up to 6 mg/day noted	Contraindications: breast cancer or estrogen-dependent neoplasm, VTE (active or past), active or recent stroke or MI Consider factors that increase risk for AEs including increased age, smoking, obesity, hypercholesterolemia, hypertension, diabetes, cardiovascular disease, etc. Consider holding estrogen therapy 4 wks prior to surgery and restarting when patient is mobile to reduce risk of VTE Choice of product: ▪ Estradiol (also known as 17-β estradiol) products are preferred over ethinyl estradiol (as in contraceptive products) and conjugated estrogens (e.g., Premarin) due to ability to monitor serum levels and potentially lower risk of VTE. ▪ Transdermal estradiol may be preferred in patients with increased risk of VTE including age >35-40 yrs, smoking, etc. ▪ IM estradiol products may cause cyclical fluctuations in hormone levels and adverse effects Dosing considerations: ▪ Use lowest effective dose ▪ Monitor serum levels ▪ Avoid supraphysiologic levels Hormone level goals: ▪ Testosterone levels goal <55 ng/dL ▪ Estradiol level NTE physiologic range for pre-menopausal females, 200 pg/mL
Estradiol, transdermal* (17- β estradiol) Products available for weekly or twice weekly admin	Initiate at 0.1 mg/24h; gradually increase Usual (transdermal): 0.1-0.2 mg/24h, up to 0.4 mg/24h noted	
Estradiol, injectable* (17- β estradiol) Valerate or cypionate	Usual injectable (valerate) 5-20 mg IM q2 wks; up to 40 mg noted Usual injectable (cypionate): 2-10 mg IM qwk	

*Drug is on VA National Formulary;
†Note: MtF estrogen doses are often higher than usual doses for hypogonadal conditions in biologic females. Doses required post-orchiectomy are lower, and anti-androgen therapy may be discontinued. Patients using reduced doses should be monitored for osteoporosis.
AE=adverse effects; MI=myocardial infarction; NTE=not to exceed; VTE=venous thromboembolism

MtF Androgen Suppression Therapy

Drug/Class	MOA	Dosing Guidance†	Adverse Effects	Monitoring Parameters	Issues for consideration
Spironolactone*	Decreases testosterone synthesis; inhibits androgen binding at the receptor site; may increase estrogen levels	Usual: 100-200 mg/day Initiate at 50/day (or 25 mg/day if low BP) Use lowest effective dose Max 400-600 mg/day has been used but little info on long term safety Max 400 mg/day	Hyperkalemia, gynecomastia (may be irreversible), dehydration, hypotension, renal impairment, possibly tumirogenic	Serum electrolytes, BUN/SCr, BP Check periodically and after increase in dose	Hyperkalemia: Concomitant use of meds that increase potassium (e.g., ACEI/ARB, NSAIDs, potassium-sparing diuretics) may increase risk of hyperkalemia; low doses and careful monitoring required
GnRH agonists	Decrease gonadotropin and testosterone levels	Studied: goserelin 3.6 mg SQ monthly Duration: up to 2 years has been reported to be well tolerated	Not well reported in TG; in general, peripheral edema, headache, mood change, depression, site reaction	BMD, although BMD was not shown to be adversely affected when used in MtF in combination with estrogen	None
Progestin	Suppress GnRH production	Medroxyprogesterone*: 5-30 mg/day (divide higher doses) Micronized progesterone: 100-400 mg/day	Mood changes, depression, fluid retention, headache In combo with estrogen, concern for increased risk of MI, stroke, PE, breast cancer from WHI	BP, weight, lipids, blood glucose, LFTs	*Not routinely recommended for use due to lack of clear benefit and concerns for harm*
Finasteride*	Blocks conversion of testosterone to 5-alpha dihydrotestosterone	Usual: 2.5-5 mg/day Lower doses, 2.5 mg every other day, have been used for alopecia only	Not reported in TG; in general decreased libido, sexual dysfunction, breast tenderness, breast enlargement	None required when not used for BPH	No studies have been published in TG patients; use is extrapolated from alopecia indication in biologic males, hirsute non-TG females Teratogenic drug; should not be crushed or handled by women

*Drug is on VA National Formulary;
†Note: doses required post-orchiectomy are lower, and anti-androgen therapy may be discontinued;
BMD=bone mineral density; BP=blood pressure; LFT=liver function tests; MI=myocardial infarction; TG=transgender; VTE=venous thromboembolism; WHI=Women's Health Initiative

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.