*Pharmacy Policy*

# Transgender Hormonal Treatment for Adults

**Line of Business:** Medicaid
**P & T Approval Date:** February 19, 2020 **Effective Date:** April 1, 2020

*This policy has been developed through review of medical literature, consideration of medical necessity, generally accepted medical practice standards, and approved by the IEHP Pharmacy and Therapeutics Subcommittee.*

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**Policy:**

II. Adult transgender hormonal therapy may be approved when all of the following criteria are met:
   1. Age 18 years or older;
   2. The individual must have a diagnosis of gender dysphoria.
   3. The individual must be able to provide informed consent. Feminizing/masculinizing hormone therapy may lead to irreversible physical changes and/or adverse effects. The individual must have the capacity to make a full informed decision to consent to treatment. This should include a discussion regarding options for fertility preservation.
   4. It is recommended that the individual be in therapy with a mental health professional.
   5. The medical provider prescribing the gender-affirming hormones may be a Primary Care Physician, an Obstetrician-Gynecologist, an Endocrinologist, or another medical professional with a license to prescribe hormones.

II. Transgender Females:
   1. Estrogen therapy (e.g. estradiol) is the preferred hormone therapeutic agent.
   2. Request for GnRH agonist requires trial of and inadequate response to estrogen therapy. **Zoladex** (goserelin) is the preferred GnRH product. Request is subject to clinical review by IEHP pharmacist, and exception may be granted with medical justification why preferred agent cannot be used.

III. Transgender Males:

   1. Testosterone therapy (e.g. testosterone cypionate or enanthate) is the preferred hormone therapeutic agent.
   2. Request for GnRH agonist requires trial of and inadequate response to testosterone therapy. **Zoladex** (goserelin) is the preferred GnRH product. Request is subject to clinical review by IEHP pharmacist, and exception may be granted with medical justification why preferred agent cannot be used.

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**Clinical Justification:**

***Department of Health Care Services All Plan Letter 16-013: Ensuring Access to Medi-Cal Services for Transgender Beneficiaries***

- MCPs shall use nationally recognized medical/clinical guidelines in reviewing requested services from transgender beneficiaries and shall apply those standards consistently across the population. One source of clinical guidance for the treatment of gender dysphoria is found in the most current "Standard of Care for the Health and Transsexual, Transgender, and Gender Nonconforming People," published by the World Professional Association for Transgender Health (WPATH).
- Nationally recognized medical experts in the field of transgender health care have identified the following core services in treating gender dysphoria: behavioral health services; psychotherapy; hormone therapy; and a variety of surgical procedures that bring primary and secondary gender characteristics into conformity with the individual's identified gender.
- MCPs are required to provide beneficiaries who have been diagnosed with gender dysphoria with all Medi-Cal covered services that are provided to non-transgender beneficiaries, so long as the services are medically necessary, or meet the definition of reconstructive surgery.
- The determination of whether a service requested by a transgender beneficiary is medically necessary and/or constitutes reconstructive surgery must be made by a qualified and licensed mental health professional and the treating surgeon, in collaboration with the beneficiary's primary care provider.
- MCPs must not categorically limit a service or the frequency of services available to a transgender beneficiary. Rather, MCPs must timely provide all medically necessary services and/or reconstructive surgery that are otherwise available to non-transgender beneficiaries.
- Medical necessity and/or reconstructive surgery determinations must be made on a case-by-case basis. MCPs may apply non-discriminatory limitations and exclusions, conduct medical necessity and reconstructive surgery determinations, and/or apply appropriate utilization management criteria that are non-discriminatory.

***Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People, The World Professional Association for Transgender Health 7$^{th}$ Version***

- Initiation of hormone therapy may be undertaken after a psychosocial assessment has been conducted and informed consent has been obtained by a qualified health professional
- A referral is required from the mental health professional who performed the assessment, unless the assessment was done by a hormone provider who is also qualified in this area
- The criteria for hormone therapy as follows: 1) Persistent, well-documented gender dysphoria; 2) Capacity to make a fully informed decision and to consent for treatment; 3) Age of majority in a given country; 4) If significant medical or mental health concerns are present, they must be reasonably well-controlled
- The presence of co-existing mental health concerns does not necessarily preclude access to feminizing/masculinizing hormones; rather, these concerns need to be managed prior to or concurrent with treatment of gender dysphoria
- Feminizing/masculinizing hormone therapy may lead to irreversible physical changes. Thus, hormone therapy should be provided to those who are legally able to provide informed consent. Providers should document in medical record that comprehensive information has been provided and understood about all relevant aspects of the hormone therapy, including both possible benefits and risks and the impact on reproductive capacity.

TABLE 1A: EFFECTS AND EXPECTED TIME COURSE OF MASCULINIZING HORMONES [A]

| Effect | Expected Onset[B] | Expected Maximum Effect[B] |
|---|---|---|
| Skin oiliness/acne | 1-6 months | 1-2 years |
| Facial/body hair growth | 3-6 months | 3-5 years |
| Scalp hair loss | >12 months[C] | variable |
| Increased muscle mass/strength | 6-12 months | 2-5 years[D] |
| 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 |

[A] Adapted with permission from Hembree et al.(2009). *Copyright 2009, The Endocrine Society*.
[B] Estimates represent published and unpublished clinical observations.
[C] Highly dependent on age and inheritance; may be minimal.
[D] Significantly dependent on amount of exercise.

TABLE 1B: EFFECTS AND EXPECTED TIME COURSE OF FEMINIZING HORMONES [A]

| Effect | Expected Onset[B] | Expected Maximum Effect[B] |
|---|---|---|
| Body fat redistribution | 3-6 months | 2-5 years |
| Decreased muscle mass/ strength | 3-6 months | 1-2 years[C] |
| Softening of skin/decreased oiliness | 3-6 months | unknown |
| Decreased libido | 1-3 months | 1-2 years |
| Decreased spontaneous erections | 1-3 months | 3-6 months |
| Male sexual dysfunction | variable | variable |
| Breast growth | 3-6 months | 2-3 years |
| Decreased testicular volume | 3-6 months | 2-3 years |
| Decreased sperm production | variable | variable |
| Thinning and slowed growth of body and facial hair | 6-12 months | > 3 years[D] |
| Male pattern baldness | No regrowth, loss stops 1-3 months | 1-2 years |

[A] Adapted with permission from Hembree et al. (2009). *Copyright 2009, The Endocrine Society.*
[B] Estimates represent published and unpublished clinical observations.
[C] Significantly dependent on amount of exercise.
[D] Complete removal of male facial and body hair requires electrolysis, laser treatment, or both.

TABLE 2: RISKS ASSOCIATED WITH HORMONE THERAPY. BOLDED ITEMS ARE CLINICALLY SIGNIFICANT

| Risk Level | Feminizing hormones | Masculinizing hormones |
|---|---|---|
| Likely increased risk | **Venous thromboembolic disease**[A]<br>Gallstones<br>Elevated liver enzymes<br>Weight gain<br>**Hypertriglyceridemia** | **Polycythemia**<br>Weight gain<br>Acne<br>Androgenic alopecia (balding)<br>Sleep apnea |
| Likely increased risk with presence of additional risk factors[B] | Cardiovascular disease | |
| Possible increased risk | **Hypertension**<br>Hyperprolactinemia or prolactinom[A] | Elevated liver enzymes<br>**Hyperlipidemia** |
| Possible increased risk with presence of additional risk factors[B] | **Type 2 diabetes**[A] | **Destabilization of certain psychiatric disorders**[C]<br>**Cardiovascular disease**<br>**Hypertension**<br>**Type 2 diabetes** |
| No increased risk or inconclusive | **Breast cancer** | Loss of bone density<br>**Breast cancer**<br>**Cervical cancer**<br>**Ovarian cancer**<br>**Uterine cancer** |

[A] Risk is greater with oral estrogen administration than with transdermal estrogen administration.
[B] Additional risk factors include age.
[C] Includes bipolar, schizoaffective, and other disorders that may include manic or psychotic symptoms. This adverse event appears to be associated with higher doses or supraphysiologic blood levels of testosterone.

Responsibilities of Hormone-Prescribing Physicians

- Perform an initial evaluation that includes discussion of a patient's physical transition goals, health, physical examination, risk assessment and relevant laboratory tests
- Discuss with patients the expected effects of feminizing/masculinizing medications and the possible adverse health effects. These effects can include a reduction in fertility. Therefore, reproductive options should be discussed with patients before starting hormone therapy.
- Confirm that patients have the capacity to understand the risks and benefits of treatment and are capable of making an informed decision about medical care
- Provide ongoing medical monitoring, including regular physical and laboratory examination to monitor hormone effectiveness and side effects
- Communicate as needed with a patient's primary care provider, mental health professional and surgeon
- If needed, provide patients with a brief written statement indicating that they are under medical supervision and care that includes feminizing/masculinizing hormone therapy. Particularly during

the early phase of hormone treatment, a patient may wish to carry this statement at all times to help prevent difficulties with the police and other authorities.

Efficacy and Risk Monitoring during Feminizing Hormone Therapy (MtF)

- The best assessment of hormone efficacy is clinical response consistent with the patient's gender goals. In order to more rapidly predict the hormone dosages that will achieve clinical response, one can measure testosterone levels for suppression below the upper limit of the normal female range, and estradiol levels within a premenopausal female range but well below supraphysiologic levels.
- Monitoring for adverse events should include both clinical and laboratory evaluation. Follow up should include careful assessment for signs of cardiovascular impairment and venous thromboembolism (VTE) through measurement of blood pressure, weight, and pulse; heart and lung exams; and examination of the extremities for peripheral edema, localized swelling or pain.

Efficacy and Risk Monitoring during Masculinzing Hormone Therapy (FtM)

- Clinicians can achieve a good clinical response with the least likelihood of adverse events by maintaining testosterone levels within the normal male range while avoiding supraphysiological levels. For patients using intramuscular testosterone cypionate or enanthate, some clinicians check trough levels while others prefer midcycle levels.
- Monitoring for adverse events should include both clinical and laboratory evaluation. Follow-up should include careful assessment for signs and symptoms of excessive weight gain, acne, uterine break-through bleeding and cardiovascular impairment, as well as psychiatric symptoms in at-risk patients. Physical examinations should include measurement of pressure, weight, pulse and skin; and heart and lung exams.

Regimens for Ferminizing Hormone Therapy (MtF)

- *Estrogen:*
    - Ethinyl estradiol is not recommended for feminizing hormone therapy due to the increased risk of VTE. Transdermal estrogen is recommended for those patients with risk factors for VTE. The risk of adverse events increases with higher doses, particularly those resulting in supraphysiologic levels. Patients with co-morbid conditions that can be affected by estrogen should avoid oral estrogen if possible and be started at lower levels.
- *Androgen reducing medications:*
    - Spironolactone, an antihypertensive agent, directly inhibits testosterone secretion and androgen binding to the androgen receptor. Blood pressure and electrolytes need to be monitored because of the potential for hyperkalemia.
    - GnRH agonists are neurohormones that block the gonadotropin releasing hormone receptor, thus blocking the release of follicle stimulating hormone and luteinizing hormone. This leads to highly effective gonadal blockade.
    - 5-alpha reductase inhibitor (finasteride and dutasteride) block the conversion of testosterone to the more active agent, 5-alpha-dihydrotestosterone. These medications have beneficial effects on scalp hair loss, body hair growth, sebaceous glands and skin consistency.
- *Progestins:*
    - Inclusion of progestins in feminizing hormone therapy is controversial. A clinical comparison of feminization regimens with and without progestins found that the addition of progestins neither enhanced breast growth nor lowered serum levels of free testosterone. Potential adverse effects include depression, weight gain, lipid changes, and possibly increased breast cancer risk and cardiovascular risk in women.

Regimens for Masculinizing Hormone Therapy (FtM)

- *Testosterone:*
    - Intramuscular testosterone may be associated with cyclic variation in effects (e.g. fatigue and irritability at the end of the injection cycle, aggression or expansive mood at the beginning of the injection cycle), and more time outside the normal physiologic level. This may be mitigated by using a lower but more frequent dosage schedule or by using a daily transdermal preparation.
    - There is evidence that transdermal and intramuscular testosterone achieve similar masculinizing results, although the timeframe may be somewhat slower than transdermal preparations. Especially as patient age, the goal is to use the lowest dose needed to maintain the desire clinical result, with appropriate precautions being made to maintain bone density.
- Other agents:
    - Progestin, most commonly medroxyprogesterone, can be used for a short period of time to assist with menstrual cessation early in hormone therapy. GnRH agonists can be used simiarly as well as for refractory uterine bleeding in patients without an underlying gynecological abnormality.

***Endocrine Treatment of Gender-Dysphoria/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline 2017***

- We advise that only trained mental health professionals (MHPs) who meet the following criteria should diagnose gender dysphoria (GD)/gender incongruence in adults: (1) competence in using the Diagnostic and Statistical Manual of Mental Disorders (DSM) and/or the International Statistical Classification of Diseases and Related Health Problems (ICD) for diagnostic purposes, (2) the ability to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) training in diagnosing psychiatric conditions, (4) the ability to undertake or refer for appropriate treatment, (5) the ability to psychosocially assess the person's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) a practice of regularly attending relevant professional meetings
- We recommend that clinicians inform and counsel all individuals seeking gender-affirming medical treatment regarding options for fertility preservation prior to initiating puberty suppression in adolescents and prior to treating with hormonal therapy of the affirmed gender in both adolescents and adults
- We recommend that clinicians confirm the diagnostic criteria of GD/gender incongruence and the criteria for the endocrine phase of gender transition before beginning treatment
- We recommend that clinicians evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment
- We suggest that clinicians measure hormone levels during treatment to ensure that endogenous sex steroids are suppressed and administered sex steroids are maintained in the normal physiologic range for the affirmed gender
- We suggest that endocrinologists provide education to transgender individuals undergoing treatment about the onset and 3 months during the first year of hormone therapy for transgender males and females and then once or twice yearly
- We suggest periodically monitoring prolactin levels in transgender females treated with estrogens

- We suggest that clinicians evaluate transgender persons treated with hormones for cardiovascular risk factors using fasting lipid profiles, diabetes screening, and/or other diagnostic tools
- We recommend that clinicians obtain bone mineral density (BMD) measurements when risk factors for osteoporosis exist, specifically in those who stop sex hormone therapy after gonadectomy
- We suggest that transgender females with no known increased risk of breast cancer follow breast-screening guidelines recommended for non-transgender females
- We suggest that transgender females treated with estrogens follow individualized screening according to personal risk for prostatic disease and prostate cancer
- time course of physical changes induced by sex hormone treatment
- We suggest regular clinical evaluation for physical changes and potential adverse changes in response to sex steroid hormones and laboratory monitoring of sex steroid hormone levels every

**Table 2. DSM-5 Criteria for Gender Dysphoria in Adolescents and Adults**

A. A marked incongruence between one's experienced/expressed gender and natal gender of at least 6 mo in duration, as manifested by at least two of the following:
1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics)
2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics)
3. A strong desire for the primary and/or secondary sex characteristics of the other gender
4. A strong desire to be of the other gender (or some alternative gender different from one's designated gender)
5. A strong desire to be treated as the other gender (or some alternative gender different from one's designated gender)
6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's designated gender)

B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:
1. The condition exists with a disorder of sex development.
2. The condition is posttransitional, in that the individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one sex-related medical procedure or treatment regimen—namely, regular sex hormone treatment or gender reassignment surgery confirming the desired gender (*e.g.*, penectomy, vaginoplasty in natal males; mastectomy or phalloplasty in natal females).

Reference: American Psychiatric Association (14).

**Table 10. Medical Risks Associated With Sex Hormone Therapy**

| |
|---|
| Transgender female: estrogen |
| Very high risk of adverse outcomes: |
| •Thromboembolic disease |
| Moderate risk of adverse outcomes: |
| •Macroprolactinoma |
| •Breast cancer |
| •Coronary artery disease |
| •Cerebrovascular disease |
| •Cholelithiasis |
| •Hypertriglyceridemia |
| Transgender male: testosterone |
| Very high risk of adverse outcomes: |
| •Erythrocytosis (hematocrit > 50%) |
| Moderate risk of adverse outcomes: |
| •Severe liver dysfunction (transaminases > threefold upper limit of normal) |
| •Coronary artery disease |
| •Cerebrovascular disease |
| •Hypertension |
| •Breast or uterine cancer |

**Table 11. Hormone Regimens in Transgender Persons**

| | |
|---|---|
| Transgender females[a] | |
| Estrogen | |
| Oral | |
| Estradiol | 2.0–6.0 mg/d |
| Transdermal | |
| Estradiol transdermal patch (New patch placed every 3–5 d) | 0.025–0.2 mg/d |
| Parenteral | |
| Estradiol valerate or cypionate | 5–30 mg IM every 2 wk<br>2–10 mg IM every week |
| Anti-androgens | |
| Spironolactone | 100–300 mg/d |
| Cyproterone acetate[b] | 25–50 mg/d |
| GnRH agonist | 3.75 mg SQ (SC) monthly<br>11.25 mg SQ (SC) 3-monthly |
| Transgender males | |
| Testosterone | |
| Parenteral testosterone | |
| Testosterone enanthate or cypionate | 100–200 mg SQ (IM) every 2 wk or SQ (SC) 50% per week |
| Testosterone undecanoate[c] | 1000 mg every 12 wk |
| Transdermal testosterone | |
| Testosterone gel 1.6%[d] | 50–100 mg/d |
| Testosterone transdermal patch | 2.5–7.5 mg/d |

Abbreviations: IM, intramuscularly; SQ, sequentially; SC, subcutaneously.

[a]Estrogens used with or without antiandrogens or GnRH agonist.

[b]Not available in the United States.

[c]One thousand milligrams initially followed by an injection at 6 wk then at 12-wk intervals.

[d]Avoid cutaneous transfer to other individuals.

**Table 14. Monitoring of Transgender Persons on Gender-Affirming Hormone Therapy: Transgender Male**

1. Evaluate patient every 3 mo in the first year and then one to two times per year to monitor for appropriate signs of virilization and for development of adverse reactions.
2. Measure serum testosterone every 3 mo until levels are in the normal physiologic male range:[a]
   a. For testosterone enanthate/cypionate injections, the testosterone level should be measured midway between injections. The target level is 400–700 ng/dL to 400 ng/dL. Alternatively, measure peak and trough levels to ensure levels remain in the normal male range.
   b. For parenteral testosterone undecanoate, testosterone should be measured just before the following injection. If the level is <400 ng/dL, adjust dosing interval.
   c. For transdermal testosterone, the testosterone level can be measured no sooner than after 1 wk of daily application (at least 2 h after application).
3. Measure hematocrit or hemoglobin at baseline and every 3 mo for the first year and then one to two times a year. Monitor weight, blood pressure, and lipids at regular intervals.
4. Screening for osteoporosis should be conducted in those who stop testosterone treatment, are not compliant with hormone therapy, or who develop risks for bone loss.
5. If cervical tissue is present, monitoring as recommended by the American College of Obstetricians and Gynecologists.
6. Ovariectomy can be considered after completion of hormone transition.
7. Conduct sub- and periareolar annual breast examinations if mastectomy performed. If mastectomy is not performed, then consider mammograms as recommended by the American Cancer Society.

[a]Adapted from Lapauw *et al.* (154) and Ott *et al.* (159).

**Table 15. Monitoring of Transgender Persons on Gender-Affirming Hormone Therapy: Transgender Female**

1. Evaluate patient every 3 mo in the first year and then one to two times per year to monitor for appropriate signs of feminization and for development of adverse reactions.
2. Measure serum testosterone and estradiol every 3 mo.
   a. Serum testosterone levels should be <50 ng/dL.
   b. Serum estradiol should not exceed the peak physiologic range: 100–200 pg/mL.
3. For individuals on spironolactone, serum electrolytes, particularly potassium, should be monitored every 3 mo in the first year and annually thereafter.
4. Routine cancer screening is recommended, as in nontransgender individuals (all tissues present).
5. Consider BMD testing at baseline (160). In individuals at low risk, screening for osteoporosis should be conducted at age 60 years or in those who are not compliant with hormone therapy.

This table presents strong recommendations and does not include lower level recommendations.

***Suggested Medical Monitoring for MTF patients on cross-hormone therapy***

| Timeframe | Monitoring |
|---|---|
| Baseline, pre-screening | ▪ Routine health screening and physical exam including general health screening for biologic males, blood pressure, weight, medication history, etc.<br>▪ Fasting blood glucose (hemoglobin A1C for patients with diabetes), lipid profile, LFTs, testosterone, prolactin<br>▪ Additional lab tests as clinically indicated (e.g., electrolytes and renal function for spironolactone, thyroid function tests in patients on thyroid replacement) |
| Regular Monitoring<br>Q1-3 months after initiation or after change in regimen (unless otherwise noted), then q6-12 months once stable | ▪ Physical exam for signs of feminization and adverse effects of hormone therapy<br>▪ Weight, blood pressure<br>▪ Fasting blood glucose (hemoglobin A1C for patients with diabetes), lipid profile, LFTs<br>▪ Prolactin levels q6-12 months<br>▪ Additional lab tests as clinically indicated, for example:<br>  ▪ Electrolytes and renal function for spironolactone (1 wk after initiation and dose change)<br>  ▪ Thyroid function tests in patients on thyroid replacement |

| | |
|---|---|
| | ▪ Testosterone and estradiol levels q3 months until stable<br>▪ Testosterone levels goal: <55 ng/dL (normal female range)<br>▪ Estradiol levels: not to exceed 200 pg/mL (mean level for premenopausal females)<br>▪ Health maintenance and screening as clinically appropriate, including:<br>▪ Routine cancer screening (i.e., prostate, breast, testicular, colon)<br>▪ Bone mineral density (BMD) testing if at risk for osteoporotic fracture, age 60 and older, or those who stop hormone therapy (i.e., noncompliance, after sex-reassignment surgery) |

Department of Veterans Affairs Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives: Transgender Cross-Sex Hormone Therapy Use Recommendations 2012.

***Suggested Medical Monitoring for FTM patients on cross-hormone therapy***

| **Timeframe** | **Monitoring** |
|---|---|
| Baseline, pre-screening | ▪ Routine health screening and physical exam including general health screening for females, blood pressure, weight, medication history, etc.<br>▪ Complete blood count, LFTs, lipid profile, fasting blood glucose (hemoglobin A1C for patients with diabetes), may consider baseline testosterone level<br>▪ Additional lab tests as clinically indicated<br>▪ Pregnancy must be excluded prior to receiving testosterone and contraceptive counseling should be provided |
| Regular Monitoring<br>Q1-3 months after initiation or after change in regimen (unless otherwise noted), then q6-12 months once stable | ▪ Physical exam for signs of virilization and adverse effects of hormone therapy<br>▪ Weight, blood pressure<br>▪ Fasting blood glucose (hemoglobin A1C for patients with diabetes), lipid profile, LFTs<br>▪ Testosterone levels until stable<br>▪ Testosterone level goal: normal male range - 320-1000 ng/dL<br>▪ Issues for consideration in checking testosterone levels:<br>▪ IM injection (cypionate or enanthate) – check level mid-way between injections<br>▪ Transdermal – check level at any time after one week of treatment<br>▪ Total testosterone level may be elevated in some patients due to high levels of sex hormone binding globulin, but free testosterone levels are normal (for first 3-9 months of treatment)<br>▪ Estradiol levels during first 6 months or until there has been no uterine bleeding for 6 months<br>▪ Estradiol level goal: <50 pg/mL<br>▪ Health maintenance and screening as clinically appropriate, including: |

| | |
|---|---|
| | ▪ Routine cancer screening (i.e., breast, cervical, colon); additional cancer screening as appropriate: endometrial, ovarian<br>▪ BMD testing if at risk for osteoporotic fracture, age 60 and older, or those who stop or reduce hormone therapy (i.e., noncompliance, after sex-reassignment surgery) |

Department of Veterans Affairs Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives: Transgender Cross-Sex Hormone Therapy Use Recommendations 2012.

***Transsexual Female (MTF) Estrogen Therapy***

| Drug | Formulary Status | Dosing Guidance† | Issues for consideration |
|---|---|---|---|
| Estradiol, oral (17-β estradiol) | F | Initiate at 1-2 mg/day; gradually increase<br><br>Usual (oral): 2-4 mg/day, up to 6 mg/day noted | <u>Contraindications</u>: breast cancer or estrogen-dependent neoplasm, VTE (active or past), active or recent stroke or MI<br><br>Consider factors that increase risk for AEs including increased age, smoking, obesity, hypercholesterolemia, hypertension, diabetes, cardiovascular disease, etc.<br><br>Consider holding estrogen therapy 4 wks prior to surgery and restarting when patient is mobile to reduce risk of VTE<br><br><u>Choice of product</u>:<br>▪ 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<br>▪ Transdermal estradiol may be preferred in patients with increased risk of VTE including age >35-40 yrs, smoking, etc.<br>▪ IM estradiol products may cause cyclical fluctuations in hormone levels and adverse effects<br><br><u>Dosing considerations</u>:<br>▪ Use lowest effective dose<br>▪ Monitor serum levels |
| Estradiol, transdermal (17- β estradiol)<br><br>Products available for weekly or twice weekly admin | F | Initiate at 0.1 mg/24h; gradually increase<br><br>Usual (transdermal): 0.1-0.2 mg/24h, up to 0.4 mg/24h noted | |
| Estradiol, injectable* (17- β estradiol)<br><br>Valerate or cypionate | NF | Usual injectable (valerate) 5-20 mg IM q2 wks; up to 40 mg noted<br><br>Usual injectable (cypionate): 2-10 mg IM qwk | |

| | | | |
|---|---|---|---|
| | | | ▪ Avoid supraphysiologic levels<br><br><u>Hormone level goals</u>:<br>▪ Testosterone levels goal <55 ng/dL<br>▪ Estradiol level NTE physiologic range for pre-menopausal females, 200 pg/mL |
| Spironolactone | F | Usual: 100-200 mg/day<br><br>Initiate at 50/day (or 25 mg/day if low BP)<br><br>Use lowest effective dose<br><br>Max 400 mg/day | <u>Hyperkalemia</u>: 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 (e.g. goserelin) | F with PA | Studied: goserelin 3.6 mg SQ monthly<br><br>Duration: up to 2 years has been reported to be well tolerated | None |
| Progestin | F<br><br>NF | Medroxyprogesterone: 5-30 mg/day (divide higher doses)<br><br>Micronized progesterone (Prometrium): 100-400 mg/day | *Not routinely recommended for use due to lack of clear benefit and concerns for harm* |
| Finasteride | F | Usual: 2.5-5 mg/day<br><br>Lower doses, 2.5 mg every other day, have been used for alopecia only | No studies have been published in TG patients; use is extrapolated from alopecia indication in biologic males, hirsute non-TG females<br><br>Teratogenic drug; should not be crushed or handled by women |

Adapted from Department of Veterans Affairs Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives: Transgender Cross-Sex Hormone Therapy Use Recommendations 2012.

†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; BMD=bone mineral density; BP=blood pressure; LFT=liver function tests; MI=myocardial infarction; TG=transgender; VTE=venous thromboembolism; WHI=Women's Health Initiative

***Transsexual Male (FTM) Testosterone Therapy***

| Drug | Formulary Status | Dosing Guidance† | Issues for consideration |
|---|---|---|---|
| Testosterone, injection in oil<br><br>cypionate<br><br>enanthate | <br><br>F<br><br>F | Initiate at 50-80 mg q2 wks (or 50% weekly); gradually increase monthly<br><br>Usual dose: 100-200 mg q2 wks (or 50% weekly)<br><br>Older, higher dose regimens of 250 mg IM q2 wks noted | <u>Contraindications</u>: breast cancer, prostate cancer, pregnancy, breast-feeding<br><br><u>Precautions</u>: lung disease (sleep apnea), heart failure, hypertension, cardiovascular disease<br><br>Consider factors that increase risk for AEs including increased age, smoking, obesity, hypercholesterolemia, hypertension, diabetes, cardiovascular disease, etc.<br><br><u>Drug interactions</u>: warfarin<br><br><u>Choice of product</u>:<br>▪ IM testosterone products may cause cyclical fluctuations in hormone levels and adverse effects; transdermal products produce more consistent hormone levels<br><br>▪ Transdermal patches commonly cause skin irritation<br><br>▪ 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.<br><br>▪ Buccal system may cause mouth and gum irritation; clinical and safety data are limited<br><br><u>Dosing considerations</u>:<br>▪ Initiate at lower end of dosing range if co-morbid conditions are present<br>▪ Use lowest effective dose<br>▪ Monitor serum levels<br>▪ Avoid supraphysiologic levels<br><br><u>Hormone level goals</u>: |
| Testosterone, transdermal patch | NF | Usual dose 2.5-7.5 mg q24 hrs<br><br>Doses up to 10 mg/day noted | |
| Testosterone, transdermal gel, solution | 1% strength: F with PA<br><br>Others: NF | Several products available with varying dosing; check specific product information for dosing instructions | |
| Testosterone, buccal system | NF | Usual dose (non TG): 30 mg (one) q12 hr | |

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|---|---|---|---|
| | | | ▪ Testosterone levels goal: 320 – 1000 ng/dL<br>▪ See specific product information for recommendations on timing of testing |

Adapted from Department of Veterans Affairs Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives: Transgender Cross-Sex Hormone Therapy Use Recommendations 2012.
†Note: FtM testosterone doses are typically within the usual dosing range for hypogonadal conditions in biologic males. Upon chronic use (2 years 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

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**References:**


1. Coleman E, Bockting W, Botzer M, et al. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. International Journal of Transgenderism. 2011;13:165-232.
2. Dahl M, Feldman JL, Goldberg JM, et al. Physical aspects of transgender endocrine therapy. International Journal of Transgenderism. 2006;9:111-34.
3. Department of Veteran Affairs Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives. Transgender Cross-Sex Hormone Therapy Use. February 2012.
4. Department of Health Care Services All Plan Letter 16-013. October 6, 2016. Available at: http://www.dhcs.ca.gov/formsandpubs/Documents/MMCDAPLsandPolicyLetters/APL2016/APL16-013.pdf. Accessed January 11, 2020.
5. Deutsch, Madeline, "Guideline for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People," Center of Excellence for Transgender Health, Dept. of Family & Community Medicine, UCSF, 2nd edition, June 17, 2016.
6. Hembree, WC, Cohen-Kettenis PT, et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*, November 2017, 102(11): 3869-3903.

| Change Control | | |
|---|---|---|
| **Date** | **Change** | **RPH** |
| 02/19/2020 | • Renew with no change | ND |
| 02/20/2019 | • Updated formulary status for testosterone products and Zoladex | ND |
| 08/15/2018 | • The individual must have the capacity to make a full informed decision to consent to treatment. This should include a discussion regarding options for fertility preservation.<br>• IEHP Transgender Hormone Therapy Symposium (4/19/2018):<br>1. Addition of preferred hormone therapeutic agent(s):<br>Transgender females:<br>a. Estrogen therapy (e.g. estradiol) is the preferred hormone therapeutic agent.<br>b. Request for GnRH agonist requires trial of and inadequate response to estrogen therapy. **Zoladex** (goserelin) is the preferred GnRH product.<br>Transgender males:<br>a. Testosterone therapy (e.g. testosterone enanthate or cypionate, testosterone transdermal gel) is the preferred hormone therapeutic agent.<br>b. Request for GnRH agonist requires trial of and inadequate response to testosterone therapy. **Zoladex** (goserelin) is the preferred GnRH product. | HC |
| | • Changed Format | IK |
| 02/21/2018 | • Adjusted verbiage to align with IEHP Utilization Management departments Gender Dysphoria Policy<br>• Updated 2017 Endocrine Society guideline | CT |