Transgender Hormonal Treatment for Pediatrics
Pharmacy Policy

Line of Business: Medi-Cal
P&T Approval Date: February 21, 2018       Effective Date: April 1, 2018

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 Therapeutic Subcommittee.

Policy:

1. Members under the age of 18 are considered eligible for Gonadotropin-releasing hormone (GnRH) analog treatment if they meet all of the following criteria:
   a. The individual must have a diagnosis of gender dysphoria.
   b. It is strongly recommended that the individual be in therapy with a mental health professional.
   c. Demonstration of long-lasting and intense pattern of gender non-conformity or gender dysphoria.
   d. Gender dysphoria emerged or worsened with onset of puberty.
   e. Coexisting psychological, medical or social problems that could interfere with treatment have been addressed.
   f. Informed consent has been obtained by the parent or other caretaker or guardians.
   g. Puberty-suppression hormone therapy typically is provided at Tanner level 2 development.
   h. The medical provider prescribing the gender-affirming hormones may be a Pediatrician or other PCP, an Endocrinologist, or another medical professional with a license to prescribe hormones.

2. Members under the age of 18 are considered eligible for cross-sex hormone treatment if they meet all of the following criteria:
   a. The individual must have a diagnosis of gender dysphoria.
   b. It is strongly recommended that the individual be in therapy with a mental health professional.
   c. Demonstration of long-lasting and intense pattern of gender non-conformity or gender dysphoria.
   d. Gender dysphoria emerged or worsened with onset of puberty.
   e. Coexisting psychological, medical or social problems that could interfere with treatment have been addressed.
   f. Informed consent has been obtained by the parent or other caretaker or guardians.
g. 16 years or older with documented persistence of gender dysphoria and sufficient mental capacity to give informed consent.
   i. Sex hormone treatment prior to the age of 16 years may be granted on a case-by-case review with medical justification that benefits outweigh the risks.

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 7th Version

Fully Reversible Interventions
• Adolescents may be eligible for puberty suppressing hormones as soon as pubertal changes have begun. In order for adolescents and their parents to make an informed decision about pubertal delay, it is recommended that adolescents experience the onset of puberty to at least Tanner Stage 2.

• Two goals justify intervention with puberty suppression hormones: (i) their use gives adolescents more time to explore their gender nonconformity and other developmental issues; and (ii) their use may facilitate transition by preventing the development of sex characteristics that are difficult or impossible to reverse if adolescents continue on to pursue sex reassignment.

• Criteria for puberty suppressing hormones:
  o In order for adolescents to receive puberty suppressive hormones, the following minimum criteria must be met:
    ▪ The adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed).
    ▪ Gender dysphoria emerged or worsened with the onset of puberty.
    ▪ Any co-existing psychological, medical, or social problems that could interfere with treatment have been addressed, such that the adolescent’s situation and functioning are stable enough to start treatment.
    ▪ The adolescent has given informed consent, and particularly when the adolescent has not reached the age of medical consent, the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process.

• Regimens, monitoring and risks for puberty suppression:
  o For puberty suppression, adolescents with male genitalia should be treated with GnRH analogues. Alternatively they may be treated with progestins or with other medications that block testosterone secretion and/or neutralize testosterone action.
  o Adolescents with female genitalia should be treated with GnRH analogues. Alternatively, they may be treated with progestins. Continuous oral contraceptives (or depot medroxyprogesterone) may be used to suppress menses.
  o During pubertal suppression, an adolescent’s physical development should be carefully monitored- preferably by a pediatric endocrinologist- so that any necessary interventions can occur (e.g. to establish an adequate gender appropriate height, to improve iatrogenic low bone marrow density).
  o Early use of puberty suppressing hormones may avert negative social and emotional consequence of gender dysphoria more effectively than their later use would. Intervention in early adolescence should be managed with pediatric endocrinological advice, when available. Adolescents with male genitalia who start GnRH analogues early in puberty should be informed that this could result in insufficient penile tissue for penile inversion vaginoplasty techniques.

Partially Reversible Interventions
• Adolescents may be eligible to begin feminizing/masculinizing hormone therapy, preferably with parental consent. In many countries, 16-year-olds are legal adults for medical decision-making and do not require parental consent. Ideally, treatment decisions should be made among the adolescent, the family, and the treatment team.

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

• We advise that only MHPs who meet the following criteria should diagnose GD/gender incongruence in children and adolescents: (1) training in child and adolescent developmental psychology and psychopathology, (2) competence in using the DSM and/or the ICD for diagnostic purposes, (3) the ability to make a distinction between GD/gender incongruence and conditions that have similar features (e.g., body dysmorphic disorder), (4) training in diagnosing psychiatric conditions, (5) the ability to undertake or refer for appropriate treatment, (6) the ability to psychosocially assess the person’s understanding and social conditions that can impact gender-affirming hormone therapy, (7) a practice of regularly attending relevant professional meetings, and (8) knowledge of the criteria for puberty blocking and gender-affirming hormone treatment in adolescents.

• We advise that decisions regarding the social transition of prepubertal youths with GD/gender incongruence are made with the assistance of an MHP or another experienced professional.

• We recommend against puberty blocking and gender-affirming hormone treatment in prepubertal children with GD/gender incongruence.

• 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 suggest that adolescents who meet diagnostic criteria for GD/gender incongruence, fulfill criteria for treatment, and are requesting treatment should initially undergo treatment to suppress pubertal development.

• We suggest that clinicians begin pubertal hormone suppression after girls and boys first exhibit physical changes of puberty.

• We recommend that, where indicated, GnRH analogues are used to suppress pubertal hormones.

• In adolescents who request sex hormone treatment (given this is a partly irreversible treatment), we recommend initiating treatment using a gradually increasing dose schedule after a multidisciplinary team of medical and MHPs has confirmed the persistence of GD/gender incongruence and sufficient mental capacity to give informed consent, which most adolescents have by age 16 years.

• We recognize that there may be compelling reasons to initiate sex hormone treatment prior to the age of 16 years in some adolescents with GD/gender incongruence, even
though there are minimal published studies of gender-affirming hormone treatments administered before age 13.5 to 14 years. As with the care of adolescents ≥16 years of age, we recommend that an expert multidisciplinary team of medical and MHPs manage this treatment.

- We suggest monitoring clinical pubertal development every 3 to 6 months and laboratory parameters every 6 to 12 months during 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 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.

### 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/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics)
   2. A strong desire to be rid of one’s primary/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/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., phalloplasty in natal males; mastectomy or phallicplasty in natal females).

Reference: American Psychiatric Association (14).
Table 5. Criteria for Gender-Affirming Hormone Therapy for Adolescents

Adolescents are eligible for GnRH agonist treatment if:
1. A qualified MHP has confirmed that:
   • the adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed),
   • gender dysphoria worsened with the onset of puberty,
   • any coexisting psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent’s situation and functioning are stable enough to start treatment,
   • the adolescent has sufficient mental capacity to give informed consent to this (reversible) treatment,
2. And the adolescent:
   • has been informed of the effects and side effects of treatment (including potential loss of fertility if the individual subsequently continues with sex hormone treatment) and options to preserve fertility,
   • has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,
3. And a pediatric endocrinologist or other clinician experienced in pubertal assessment
   • agrees with the indication for GnRH agonist treatment,
   • has confirmed that puberty has started in the adolescent (Tanner stage ≥ B2),
   • has confirmed that there are no medical contraindications to GnRH agonist treatment.

Adolescents are eligible for subsequent sex hormone treatment if:
1. A qualified MHP has confirmed:
   • the persistence of gender dysphoria,
   • any coexisting psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent’s situation and functioning are stable enough to start sex hormone treatment,
   • the adolescent has sufficient mental capacity (which most adolescents have by age 16 years) to estimate the consequences of this (partly) irreversible treatment, weigh the benefits and risks, and give informed consent to this (partly) irreversible treatment,
2. And the adolescent:
   • has been informed of the (irreversible) effects and side effects of treatment (including potential loss of fertility and options to preserve fertility),
   • has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,
3. And a pediatric endocrinologist or other clinician experienced in pubertal induction:
   • agrees with the indication for sex hormone treatment,
   • has confirmed that there are no medical contraindications to sex hormone treatment.

Reproduced from World Professional Association for Transgender Health (16).

Table 7. Baseline and Follow-Up Protocol During Suppression of Puberty

Every 3–6 mo
Anthropometry: height, weight, sitting height, blood pressure, Tanner stages
Every 6–12 mo
Laboratory: LH, FSH, E2/T, 25OHD vitamin D
Every 1–2 y
Bone density using DXA
Bone age on X-ray of the left hand (if clinically indicated)

Adapted from Hembree et al. (118).
Abbreviations: DXA, dual-energy X-ray absorptiometry; E2, estradiol; FSH, follicle stimulating hormone; LH, luteinizing hormone; T, testosterone;
Table 8. Protocol Induction of Puberty

Induction of female puberty with oral 17β-estradiol, increasing the dose every 6 mo:
- 5 μg/kg/d
- 10 μg/kg/d
- 15 μg/kg/d
- 20 μg/kg/d
Adult dose = 2–6 mg/d
*In postpubertal transgender female adolescents, the dose of 17β-estradiol can be increased more rapidly:
  - 1 mg/d for 6 mo
  - 2 mg/d

Induction of female puberty with transdermal 17β-estradiol, increasing the dose every 6 mo (new patch is placed every 3.5 d): 6.25–12.5 μg/24 h (cut 25-μg patch into quarters, then halves)
- 25 μg/24 h
- 37.5 μg/24 h
Adult dose = 50–200 μg/24 h
*For alternatives once at adult dose, see Table 11.
*Adjust maintenance dose to mimic physiological estradiol levels (see Table 15).

Induction of male puberty with testosterone esters increasing the dose every 6 mo (IM or SC):
- 25 mg/m²/2 wk (or alternatively, half this dose weekly, or double the dose every 4 wk)
- 50 mg/m²/2 wk
- 75 mg/m²/2 wk
- 100 mg/m²/2 wk
Adult dose = 100–200 mg every 2 wk
*In postpubertal transgender male adolescents the dose of testosterone esters can be increased more rapidly:
  - 75 mg/2 wk for 6 mo
  - 125 mg/2 wk
*For alternatives once at adult dose, see Table 11.
*Adjust maintenance dose to mimic physiological testosterone levels (see Table 14).

Adapted from Hembree et al. (118).

Abbreviations: IM, intramuscularly; SC, subcutaneously.

Table 9. Baseline and Follow-up Protocol During Induction of Puberty

Every 3–6 mo
- Anthropometry: height, weight, sitting height, blood pressure, Tanner stages

Every 6–12 mo
- In transgender males: hemoglobin/hematocrit, lipids, testosterone, 25OHD vitamin D
- In transgender females: prolactin, estradiol, 25OHD vitamin D

Every 1–2 y
- BMD using DXA
- Bone age on X-ray of the left hand (if clinically indicated)

BMD should be monitored into adulthood (until the age of 25–30 y or until peak bone mass has been reached).
For recommendations on monitoring once pubertal induction has been completed, see Tables 14 and 15.

Adapted from Hembree et al. (118).

Abbreviation: DXA, dual-energy X-ray absorptiometry.
### Table 10. Medical Risks Associated With Sex Hormone Therapy

<table>
<thead>
<tr>
<th>Transgender female: estrogen</th>
<th>**Very high risk of adverse outcomes:**</th>
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<tbody>
<tr>
<td>Thromboembolic disease</td>
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<table>
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<tr>
<th>Moderate risk of adverse outcomes:</th>
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<tbody>
<tr>
<td>Macroprolactinoma</td>
</tr>
<tr>
<td>Breast cancer</td>
</tr>
<tr>
<td>Coronary artery disease</td>
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<tr>
<td>Cerebrovascular disease</td>
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<tr>
<td>Cholelithiasis</td>
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<tr>
<td>Hypertriglyceridemia</td>
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<tr>
<th>Transgender male: testosterone</th>
<th>**Very high risk of adverse outcomes:**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocytosis (hematocrit &gt; 50%)</td>
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<tr>
<th>Moderate risk of adverse outcomes:</th>
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<tbody>
<tr>
<td>Severe liver dysfunction (transaminases &gt; threefold upper limit of normal)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>Hypertension</td>
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<td>Breast or uterine cancer</td>
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### Table 11. Hormone Regimens in Transgender Persons

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

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. 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.

*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.

References:

<table>
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<tr>
<th>Date</th>
<th>Change</th>
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| 02/21/2018 | • Updated verbiage to align with IEHP Utilization Management departments Gender Dysphoria policy  
|            | • Updated 2017 Endocrine Society guideline                              
|            | • Adjusted age limit for sex hormone in accordance to 2017 Endocrine guideline |