This program applies to Medicaid.

The program only targets topical androgen agents.

**Medicaid** targets the formulary agents, generic testosterone 1% gel and generic testosterone solution, and the non-formulary agents. Additional FE review needed for non-formulary medications.

Diagnoses related to gender reassignment (e.g. gender dysphoria, gender identity disorder, transgender, gender reassignment surgery, other gender reassignment medical procedures including drug therapy) are covered for MN Medicaid.

### FDA APPROVED INDICATIONS AND DOSAGE

<table>
<thead>
<tr>
<th>Topical Androgen Agents</th>
<th>Indication</th>
<th>Dosage and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Androderm</strong>® (testosterone transdermal system)</td>
<td>For testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone: -Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. -Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone</td>
<td>Hypogonadism 2 mg/day and 4 mg/day system -Recommended starting dose is one 4 mg/day system (not two 2 mg/day systems) applied nightly for 24 hours. -Dose may be decreased to 2 mg (i.e., one 2 mg/day system) or increased to 6 mg (i.e., one 4 mg/day and one 2 mg/day system) Switching from 2.5 mg/day, 5 mg/day, and 7.5 mg/day to 2 mg/day, 4 mg/day and 6 mg/day dosage -Patients using 2.5 mg daily may be switched to 2 mg/day systems at the next scheduled dose -Patients using 5 mg daily may be switched to 4 mg/day systems at the next scheduled dose -Patients using 7.5 mg daily may be switched to 6 mg (2 mg/day and 4 mg/day systems) at the next scheduled dose</td>
</tr>
</tbody>
</table>
### Topical Androgen Agents

<table>
<thead>
<tr>
<th>Agent</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>AndroGel® / Testosterone</strong> (testosterone gel)</td>
<td>(LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation.</td>
<td>1% gel:</td>
</tr>
<tr>
<td>1% gel:</td>
<td></td>
<td>- Initial dose is 50 mg of testosterone (4 pump actuations, two 25 mg packets, or one 50 mg packet) once daily in the morning.</td>
</tr>
<tr>
<td>25 mg/2.5 g packet&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>- Dose may be increased to 75 mg and 100 mg daily based on measured serum testosterone levels.</td>
</tr>
<tr>
<td>50 mg/5.0 g packet&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>- If serum testosterone level exceeds normal range at 50 mg dose, therapy should be discontinued.</td>
</tr>
<tr>
<td>75 g pump (12.5 mg testosterone/actuation; 60 actuations/pump)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.62% gel:</td>
<td></td>
<td>1.62% gel:</td>
</tr>
<tr>
<td>75 g pump (20.25 mg testosterone/actuation; 60 actuations/pump)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>- 40.5 mg of testosterone (2 pump actuations or 1 40.5 mg packet) applied topically once daily in the morning.</td>
</tr>
<tr>
<td>20.25 mg/1.25 g packet&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>- Dose may be adjusted between a minimum of 20.25 mg testosterone (1 pump actuation or 1 packet) or maximum 81 mg testosterone (4 pump actuations or 2 40.5 mg packets) based on measured serum testosterone levels.</td>
</tr>
<tr>
<td>40.5 mg/2.5 g packet&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Axiron®</strong> (testosterone soln)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>- Initial dose is 60 mg testosterone (2 pump actuations) applied once daily.</td>
</tr>
<tr>
<td>30 mg/1.5 mL, 90 mL pump</td>
<td></td>
<td>- Dose of testosterone may be decreased to 30 mg (1 pump actuation) or increased to 90 mg (3 pump actuations) or 120 mg (4 pump actuations) based on the measured serum testosterone.</td>
</tr>
<tr>
<td><strong>Fortesta™ / Testosterone</strong> (testosterone gel)</td>
<td></td>
<td>- If serum testosterone concentration exceeds 1050 ng/dL at 30 mg, therapy should be discontinued.</td>
</tr>
<tr>
<td>2% gel&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>- Initial dose is 40 mg of testosterone (4 pump actuations) once daily in the morning.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Dose may be adjusted between a minimum of 10 mg of testosterone and a maximum of 70 mg of testosterone based on measured serum testosterone levels.</td>
</tr>
</tbody>
</table>
## Topical Androgen Agents

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Natesto™ (testosterone nasal gel)</td>
<td>Recommended dose of 11 mg (2 pump actuations, one per nostril), applied intranasally 3 times daily.</td>
<td>- If total testosterone concentrations consistently exceed 1040 ng/dL, therapy should be discontinued. If total testosterone concentrations are consistently below 300 ng/dL, an alternative treatment should be considered.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not recommended for use with nasally administered drugs other than sympathomimetic decongestants (e.g., oxymetazoline)</td>
</tr>
<tr>
<td>Striant® (testosterone buccal system)</td>
<td>Usual dose is one buccal system (30 mg) to the gum region twice daily, morning and evening (about 12 hours apart).</td>
<td></td>
</tr>
<tr>
<td>Testim®/Testosterone (testosterone gel)b</td>
<td>- Initial dose is 50 mg of testosterone (one tube) once daily in the morning.</td>
<td>- Dose may be increased to 100 mg testosterone (two tubes) once daily based on measured serum testosterone.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vogelxo™/Testosterone (testosterone gel)</td>
<td>For testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:</td>
<td>1% gel:</td>
</tr>
<tr>
<td></td>
<td>- Primary hypogonadism</td>
<td>- Initial dose is 50 mg testosterone (5 g gel) once daily at the same time each day.</td>
</tr>
<tr>
<td></td>
<td>- Hypogonadotropic hypogonadism (congenital or acquired)</td>
<td>- Dose may be increased to 100 mg daily based on measured serum testosterone levels.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- The maximum recommended dose is 100 mg once daily.</td>
</tr>
</tbody>
</table>

a – Brand drug no longer available; available as generic only.
b – Generic available.
c – Brand drug has been discontinued by the manufacturer but may still be available.
<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>Android®</td>
<td>Males: Androgen replacement therapy related to the following:</td>
<td>Males: Androgen replacement therapy related to hypogonadism: 10 mg to 50 mg/day</td>
</tr>
<tr>
<td>(methyltestosterone)</td>
<td>- Primary hypogonadism (congenital or acquired) - testicular failure due to</td>
<td>- Androgen replacement therapy related to cryptorchidism: 10 mg 3 times daily</td>
</tr>
<tr>
<td>10 mg capsule</td>
<td>cryptorchidism, bilateral torsions, orchitis, vanishing testis syndrome;</td>
<td>- Delayed puberty (adolescents only): 5 mg to 25 mg/day for a limited period,</td>
</tr>
<tr>
<td></td>
<td>or orchidectomy - Hypogonadotropic hypogonadism (congenital or acquired)</td>
<td>usually for 4 to 6 months</td>
</tr>
<tr>
<td></td>
<td>- idiopathic gonadotropin or LHRH deficiency, or pituitary hypothalamic</td>
<td>Females:</td>
</tr>
<tr>
<td></td>
<td>injury from tumors, trauma, or radiation - Delayed puberty in males</td>
<td>- 50 mg once daily up to four times/day</td>
</tr>
<tr>
<td>Methitesc®</td>
<td>Females: Palliative treatment of breast cancer in women</td>
<td>- If suitable response within 2-4 weeks, decrease to 25 mg two times daily</td>
</tr>
<tr>
<td>(methyltestosterone)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testred®</td>
<td>Males: Androgen replacement in male hypogonadism</td>
<td>Males:</td>
</tr>
<tr>
<td>(methyltestosterone)</td>
<td>- Treatment of delayed puberty in males</td>
<td>- Androgen replacement: 5 mg given 1 to 4 times daily, although higher initial doses</td>
</tr>
<tr>
<td>10 mg capsule</td>
<td>Females: Inoperable breast cancer</td>
<td>(i.e. 10 mg/day) with subsequent dose adjustment are usually preferable</td>
</tr>
<tr>
<td>Androxy®</td>
<td></td>
<td>- Delayed puberty (adults/adolescents): 2.5 mg - 10 mg daily for up to 4 to 6</td>
</tr>
<tr>
<td>(fluoxymesterone)</td>
<td></td>
<td>months. Doses up to 20 mg daily have been used.</td>
</tr>
<tr>
<td>10 mg tablet</td>
<td></td>
<td>Females:</td>
</tr>
<tr>
<td>Anadrol-50®</td>
<td>Treatment of anemias caused by deficient red cell production.</td>
<td>10 mg - 40 mg per day in divided doses. Treatment should continue at least 2-3 months.</td>
</tr>
<tr>
<td>(oxymetholone)</td>
<td>Acquired aplastic anemia, congenital aplastic anemia, myelofibrosis and</td>
<td></td>
</tr>
<tr>
<td>50 mg tablet</td>
<td>the hypoplastic anemias due to the administration of myelotoxic drugs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>often respond</td>
<td></td>
</tr>
</tbody>
</table>
### Oral Androgen and Anabolic Agents

<table>
<thead>
<tr>
<th>Agent</th>
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</tr>
</thead>
</table>
| danazol<sup>a</sup>    | - Fibrocystic breast disease  
- Angioedema prophylaxis in patients with hereditary angioedema  
- Endometriosis amenable to hormone management | - Fibrocystic breast disease: 100 to 400 mg/day in 2 divided doses. Although symptoms may be relieved, and even eliminated in 3 months, up to 6 months of uninterrupted therapy may be required to eliminate nodularity.  
- Angioedema prophylaxis: Initial 200 mg two to three times daily. If a favorable response achieved, dose may be reduced by half at intervals of 1-3 months. If unfavorable response (attack of angioedema during treatment), dose may be increased by up to 200 mg/day. NOTE: If danazol therapy initiated during exacerbation of angioedema caused by trauma, stress or other causes, periodic attempts to reduce or discontinue therapy should be considered  
- Endometriosis: In moderate/severe disease or patients infertile due to endometriosis: starting dose of 800 mg given in two divided doses. Gradual downward titration to dose sufficient to maintain amenorrhea may be considered. In mild disease: starting dose of 200 mg to 400 mg given in two divided doses; adjust depending on patient response. Continue therapy for 3 to 6 months, may be extended to 9 months if necessary. |
| 50 mg, 100 mg, 200 mg capsule |                                                                 |                                                                                                                                                          |
| Oxandrin<sup>b</sup>   | - Adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, severe trauma, and in some patients without definite pathophysiologic reasons who fail to gain or to maintain normal weight, to offset the protein catabolism associated with prolonged administration of corticosteroids, and for the relief of the bone pain frequently accompanying osteoporosis | Adults  
- Daily adult dosage is 2.5 mg to 20 mg given in 2 to 4 divided doses.  
- Desired response may be achieved with as little as 2.5 mg or as much as 20 mg daily.  
- A course of therapy of 2 to 4 weeks is usually adequate. This may be repeated intermittently as indicated.  
Children: Total daily dosage is <0.1 mg/kg body weight or <0.045 mg per pound of body weight. This may be repeated intermittently as indicated.  
Geriatric: 5 mg twice daily |
| (oxandrolone)          |                                                                 |                                                                                                                                                          |
| 2.5 mg, 10 mg tablet   |                                                                 |                                                                                                                                                          |

<sup>a</sup> – Brand drug no longer available; available as generic only.  
<sup>b</sup> – Generic available.  
<sup>c</sup> – Brand drug has been discontinued by the manufacturer but may still be available.
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</thead>
</table>
| testosterone enanthate<sup>b</sup> 200 mg/mL | Males: For replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone:  
- Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, or orchidectomy  
- Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation. Prior to puberty, androgen replacement therapy needed during adolescent years for development of secondary sexual characteristics. Prolonged androgen treatment required to maintain sexual characteristics in these and other males who develop testosterone deficiency after puberty  
- Delayed puberty  
Females: Palliative treatment of breast cancer that is inoperable in women | Males:  
- Hypogonadism  
  - Adult males: 50 mg to 400 mg IM every 2 to 4 weeks  
  - Children (initiation of pubertal growth): 40 mg to 50 mg/m² IM monthly until growth rate falls to prepubertal levels.  
    o Terminal growth phase: 100 mg/m² IM monthly until growth ceases  
    o Maintenance of virilization: 100 mg/m² IM twice monthly  
- Delayed puberty: 50 mg to 200 mg IM every 2 to 4 weeks for a limited duration, for example, 4 to 6 months or 40 mg to 50 mg/m²/dose IM monthly for 6 months  
Females:  
- Palliation of inoperable breast cancer: 200 mg to 400 mg IM every 2 to 4 weeks |
| Xyosted™ (testosterone enanthate) 50 mg/0.5 mL 75 mg/0.5 mL 100 mg/0.5 mL | Testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone | 75 mg subcutaneously in the abdominal region once weekly.  
Dose Adjustment: Based upon total testosterone trough concentrations (measured 7 days after most recent dose) obtained following 6 weeks of dosing and periodically thereafter. |
# Injectable Androgen Agents

<table>
<thead>
<tr>
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<th>Dosage and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depo-Testosterone</strong></td>
<td>For replacement therapy in the male in conditions associated with symptoms of deficiency or absence of endogenous testosterone:</td>
<td>- Hypogonadism: 50-400 mg every 4 weeks</td>
</tr>
<tr>
<td>(testosterone cypionate)**</td>
<td>- Primary hypogonadism (congenital or acquired) - testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome; or orchidectomy.</td>
<td></td>
</tr>
<tr>
<td>100 mg/mL, 200 mg/mL</td>
<td>- Hypogonadotropic hypogonadism (congenital or acquired) - idiopathic gonadotropin or LHRH deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation.</td>
<td></td>
</tr>
<tr>
<td>Testopel®</td>
<td>Males</td>
<td>- Hypogonadism (adult males and children): 150 mg to 450 mg (2-6 pellets) inserted subcutaneously by a healthcare professional every 3 to 6 months</td>
</tr>
<tr>
<td>(testosterone pellets)</td>
<td>- Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome; or orchidectomy</td>
<td>- Dosage is based on the minimal daily requirements of testosterone propionate determined by a gradual reduction of the amount administered parenterally</td>
</tr>
<tr>
<td>75 mg</td>
<td>- Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation.</td>
<td>- For every 75 mg/week of testosterone propionate, 150 mg (2 pellets) should be implanted every 3—6 months</td>
</tr>
<tr>
<td></td>
<td>- Delayed puberty</td>
<td>- Delayed puberty (adolescents only): 150 mg to 450 mg (2-6 pellets) inserted subcutaneously by a healthcare professional every 3 to 6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Treatment is usually only required for 4—6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Dosage is based on the minimal daily requirements of testosterone propionate determined by a gradual reduction of the amount administered parenterally</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For every 75 mg/week of testosterone propionate, 150 mg (2 pellets) should be implanted every 3—6 months</td>
</tr>
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### Injectable Androgen Agents

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</table>
| Aveed™ (testosterone undecanoate) 250 mg/mL | - Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome; or orchiectomy  
-Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation | The recommended dose of Aveed is 3 mL (750 mg) injected intramuscularly, followed by 3 mL (750 mg) injected after 4 weeks, then 3 mL (750 mg) injected every 10 weeks thereafter. |

a – Brand drug no longer available; available as generic only.  
b – Generic available.  
c – Brand drug has been discontinued by the manufacturer but may still be available.
CLINICAL RATIONALE

Efficacy

Androgen Deficiency Syndromes

Testosterone replacement therapy should be initiated in symptomatic men with hypogonadism with a subnormal serum testosterone.\textsuperscript{12,47} Signs and symptoms of hypogonadism include:\textsuperscript{12}

- Specific symptoms and signs:
  - Incomplete or delayed sexual development
  - Loss of body (axillary and pubic) hair
  - Very small testes (especially <6 ml)

- Suggestive symptoms and signs:
  - Reduced sexual desire (libido) and activity
  - Decreased spontaneous erections, erectile dysfunction
  - Breast discomfort, gynecomastia
  - Eunuchoidal body proportions
  - Inability to father children, low sperm count
  - Height loss, low trauma fracture, low bone mineral density
  - Hot flushes, sweats

- Nonspecific symptoms and signs:
  - Decreased energy, motivation, initiative, and self-confidence
  - Feeling sad or blue, depressed mood, persistent low-grade depressive disorder
  - Poor concentration and memory
  - Sleep disturbance, increased sleepiness
  - Mild unexplained anemia (normochromic, normocytic)
  - Reduced muscle bulk and strength
  - Increased body fat, body mass index

Low testosterone levels should be assessed to confirmed diagnosis. The principal goal of testosterone therapy is to restore serum testosterone concentration to normal range.\textsuperscript{12,47}

Hereditary Angioedema (HAE)

Danazol is FDA approved for use in angioedema prophylaxis in patients with hereditary angioedema (HAE).\textsuperscript{40} Guidelines also recommend the use of Danazol as one of the initial prophylaxis options for HAE.\textsuperscript{48,49}

Off Label Use – AIDS/HIV

Androgens and anabolic steroids have been studied for use in AIDS/HIV-associated wasting syndrome and Turner syndrome. Clinical studies support the use of the following agents in men for AIDS/HIV-associated wasting syndrome: testosterone transdermal system\textsuperscript{16}, testosterone enanthate\textsuperscript{17,18,21}, oxandrolone\textsuperscript{19,20}, and cypionate\textsuperscript{42}. The use of topical testosterone to treat AIDS wasting in women is supported by several studies.\textsuperscript{28,29} Oxandrolone was studied in both male and female pediatric patients.\textsuperscript{20}

Off Label Use – Turner Syndrome

The Turner Syndrome Consensus Study Group, sponsored by the National Institutes of Health’s National Institute of Child Health and Human Development, recommends oxandrolone for treatment of Turner syndrome, when used in conjunction with growth hormone (GH).\textsuperscript{15} Recommended dose of oxandrolone is 0.05 mg/kg/d or less in conjunction with growth hormone only. Therapy may be continued until a satisfactory height has been attained or until little growth potential remains (bone age > 14 yr and growth velocity <2 cm/yr).

Off Label Use – Chronic Kidney Disease Anemia

The National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney
Disease have a strong recommendation against the use of androgens as adjuvant to erythropoiesis-stimulating agent (ESA) treatment in anemia patients with chronic kidney disease.\textsuperscript{22} The current guideline has serious safety concerns and states evidence for androgens’ efficacy is low quality. Before the availability of epoetin therapy, androgens were used regularly in the treatment of anemia in dialysis patients.

**Off Label Use – Duchenne Muscular Dystrophy**

The DMD (Duchenne muscular dystrophy) Care Considerations Working Group guidelines recommend glucocorticoids as first-line treatment for Duchenne muscular dystrophy. Glucocorticoids are the only medication currently available that slow the decline in muscle strength and function in DMD, which in turn reduces the risk of scoliosis and stabilizes pulmonary function. Oxandrolone is not considered necessary or appropriate, either with or without glucocorticoid therapy.\textsuperscript{23}

**Off Label Use – Vulvar Skin Disorder**

The American Congress of Obstetricians and Gynecologists (ACOG) guidelines for vulvar skin disorders recommend a high potency topical steroid such as clobetasol propionate for treatment of lichen sclerosus. Topical testosterone has shown inconsistent results in trials.\textsuperscript{24} The British Association of Dermatologists’ guidelines state that “there appears to be no evidence base for the use of topical testosterone” for treatment of female anogenital lichen sclerosis.\textsuperscript{27} Testosterone propionate has been used for decreased libido and vulva atrophy/dystrophy; such indications are not FDA approved. The Endocrine Society recommends against the generalized use of testosterone by women because the indications are inadequate and evidence of long-term studies is lacking.\textsuperscript{28}

**Off Label Use – Erectile Dysfunction**

The American Urology Association (AUA) recommends that phosphodiesterase type 5 inhibitors should be first-line therapy for erectile dysfunction. AUA also recommend that testosterone therapy is not indicated for the treatment of erectile dysfunction in patients with a normal serum testosterone level. Also, the role of testosterone therapy in men with sexual dysfunction with low, borderline normal, and normal testosterone levels is not well defined.\textsuperscript{37}

**Off Label Use – Gender Identity Disorder / Gender Dysphoria / Gender Incongruence**

The Endocrine Society states the following for the diagnosis and treatment of gender identity disorder (GID) / gender dysphoria / gender incongruence:\textsuperscript{45}

- Recommend that a diagnosis be made by a mental health professional (MHP). For children and adolescents, the MHP must also be training in child and adolescent developmental psychopathology
- Recommend all transsexual individuals should be informed and counseled regarding option 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
- For the treatment of adolescents
  - Recommend for adolescents initiating treatment with sex hormones that the individual have sufficient mental capacity to give informed consent, which most adolescents have by age 16
  - Recognize that there may be compelling reasons to initiate sex hormone treatment prior to the age of 16 years in some adolescents even though there are limited studies of gender-affirming hormone treatment administered before age 13.5 -14 years of age.
  - Suggest monitoring of clinical pubertal development every 3-6 months and laboratory parameters every 6-12 months during sex hormone treatment
  - Criteria for treatment with gender-affirming sex hormone therapy
    - A qualified mental health professional 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 year) to estimate the consequences of this (partly) irreversible treatment, weight the benefits and risks, and give informed consent to this (partly) irreversible treatment

- 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

- A pediatric endocrinologist or other clinician experience in pubertal induction:
  - Agrees with the indication for sex hormone treatment
  - Has confirmed that there are no medical contraindications to sex hormone treatment

- For the treatment of adults
  o Recommend clinicians evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones before beginning treatment
  o Suggest clinicians measure hormone levels during treatment to ensure that endogenous sex steroids are suppressed and administered sex hormones are maintained in the normal physiologic range for the affirmed gender
  o Suggest regular clinical evaluation for physical changes and potential adverse changes in response to sex steroid hormones and laboratory monitoring of sex hormone levels every 3 months during the first year of hormone therapy for transgender males and females and then once or twice yearly
  o Criteria for treatment with gender-affirming hormone therapy
    ▪ Persistent, well-documented gender dysphoria/gender incongruence
    ▪ The capacity to make a fully informed decision and to consent for treatment
    ▪ The age of majority in a given country
    ▪ Mental health concerns, if present, must be reasonably well controlled

Generally, transdermal testosterone, parenteral testosterone, and oral testosterone undecenoate can be used in (female to male) FTM transition. Other forms of testosterone (e.g. implantable and buccal) are also available.45,46

Safety
Androgens and anabolic steroids are associated with cardiomyopathy, increased low density lipoprotein (LDL), decreased high density lipoprotein (HDL), hepatotoxicity (including hepatic neoplasms), hypertrophy of the prostate and anabolic-androgenic steroids-induced hypogonadism.13 Testosterone treatment in men aged 65 years and older who have
Limitations in mobility was associated with an increased risk for cardiovascular events, including myocardial infarction and hypertension, according to a study published by Basaria, et al. Anabolic steroids are mainly abused by males and athletes to increase muscle mass and improve athletic performance.

On September 17, 2014, the FDA Bone, Reproductive and Urologic Drugs Advisory Committee stated that the available studies informing the cardiovascular safety signal with testosterone therapy are limited in scope, quality, design, and size. Nonetheless, there was agreement amongst committee members that a weak signal of cardiovascular risk had emerged from results of cardiovascular-related adverse events with testosterone use. The committee agreed that additional studies on the risk of therapy are needed to assess cardiovascular and other risks associated with short term and long term use of testosterone for age-related hypogonadism.

In an FDA safety communication [03-03-2015], FDA cautioned that the benefit and safety of these medications have not been established for the treatment of low testosterone levels due to aging, even if a man’s symptoms seem related to low testosterone. Testosterone product manufacturers must clarify approved uses, and add information to labeling regarding possible increased risk of heart attacks and strokes in patients taking testosterone. Testosterone is FDA-approved as replacement therapy only for men who have low testosterone levels due to disorders of the testicles, pituitary gland, or brain that cause a condition called hypogonadism. Examples of these disorders include failure of the testicles to produce testosterone due to genetic problems, or damage from chemotherapy or infection. FDA has become aware that testosterone is being used extensively in attempts to relieve symptoms in men who have low testosterone for no apparent reason other than aging. The benefits and safety of this use have not been established.

Prescribing information (2015) for testosterone products contains the following warnings: Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients using testosterone products. Some post-marketing studies have shown an increased risk of myocardial infarction and stroke associated with the use of testosterone replacement therapy. Safety and efficacy in men with “age-related hypogonadism” have not been established. Safety and efficacy in males less than 18 years old have not been established.

A retrospective cohort study (2015) compared cardiovascular safety of testosterone injections, patches, and gels. Adult male initiators (N=431,687) of new dosage formulations of testosterone patches, gels, or injections following 180 days free of any testosterone use were followed for up to one year of use. Of the subjects followed, 36% used injection products, 9% used patch products, and 55% used gel products. Testosterone injections were associated with a greater risk of CV events, hospitalizations, and deaths vs. gels. Patches and gels had similar risk profiles. This study did not assess whether patients met criteria for use of testosterone and did not assess the safety of testosterone among users compared to non-users of the drug.

On October 25th, 2016, the FDA approved a class wide labeling changes for all prescription testosterone products, adding a new Warning and updating the Abuse and Dependence section to include new safety information from published literature and case reports regarding the risks associated with abuse and dependence of testosterone and other Androgen, Anabolic Steroids (AAS). The new Warning will alert prescribers to the abuse potential of testosterone and the serious adverse outcomes, especially those related to heart and mental health that have been reported in association with testosterone/AAS abuse. In addition to the new Warning, all testosterone labeling has been revised to include information in the Abuse and Dependence section about adverse outcomes reported in association with abuse and dependence of testosterone/AAS, and information in the Warning and Precautions section...
advising prescribers of the importance of measuring serum testosterone concentration if abuse is suspected.44

For additional clinical information see Prime Therapeutics Formulary Chapter 4.2: Androgens/Anabolic Steroids.

REFERENCES


41. JAMA Intern Med. 2015;175(7): 1187–1196


ADDITIONAL INFORMATION
HIV Wasting Syndrome
HIV/AIDS wasting was historically common, particularly in later stages of the disease. The incidence of wasting has declined since the introduction of anti-retroviral therapy (ART). Tissue wasting responds rapidly to ART, and the primary therapy for HIV wasting is ART. The diagnosis of HIV wasting requires one of the following: 4, 5
- Weight loss of greater than:
  - 10% within 12 months or from baseline visit
  - 7.5% within 6 months
  - 5% within 3 months
- At least 5% total body cell mass (BCM) loss within 6 months
- Body mass index (BMI) < 20 kg/m²
- In men: BCM < 35% of total body weight and BMI < 27 kg/m²
- In women: BCM < 23% of total body weight and BMI < 27 kg/m²

Normal Testosterone Values
The Endocrine Society states “The normative ranges for total and free testosterone levels in healthy young men vary among laboratories and assays. In some laboratories, the lower limit of the normal range for total testosterone level in healthy young men is 280–300 ng/dL (9.8–10.4 nmol/liter). Similarly, in some reference laboratories, the lower limit of the normal range for serum free testosterone level, measured by the equilibrium dialysis method, is 5–9 pg/mL (0.17–0.31 nmol/liter). The clinicians should use the lower limit of normal range for healthy young men established in their laboratory.”

Normal Calcium Values
Normal calcium blood values range: 8.5 to 10.2 mg/dL; may vary slightly among laboratories.

ADDITIONAL INFORMATION REFERENCES
Androgens/Anabolic Steroids Prior Authorization with Quantity Limit

OBJECTIVE
The intent of the Androgens and Anabolic Steroids Prior Authorization (PA) with Quantity Limit program is to appropriately select patients for therapy according to product labeling and/or clinical guidelines and/or clinical studies and according to dosing recommended in product labeling. The PA criteria will approve these agents for the FDA approved indications and off label use that is medically necessary for certain indications (e.g. AIDS/HIV-associated wasting syndrome, Turner Syndrome). The program will approve only one of these agents at a time. The program will approve topical and injectable androgens for doses within the FDA labeled dosage range. Determination of quantity limits takes into account the packaging of the agents. Quantity limits apply only to the topical and injectable androgens.

TARGET AGENTS
Topical Androgen Agents:
- Androderm® (testosterone transdermal system)
- AndroGel® (testosterone gel)\(^a\)
- Axiron® (testosterone solution)\(^b\)
- Fortesta™ (testosterone gel)\(^b\)
- Natesto™ (testosterone nasal gel)
- Striant® (testosterone buccal system)
- Testim® (testosterone gel)\(^b\)
- Testosterone (testosterone gel)\(^b\)
- Vogelxo™ (testosterone gel)\(^b\)

\(^a\) - Brand drug has been discontinued by the manufacturer but may still be available.
\(^b\) - Generic available and included in prior authorization and quantity limit programs

PROGRAM QUANTITY LIMITS – TOPICAL AND INJECTABLE ANDROGENS

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>GPI</th>
<th>Quantity Per Day Limit Or As Noted</th>
<th>Multisource Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical Androgen Agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Androderm® (testosterone transdermal system)</td>
<td>2 mg/day transdermal system</td>
<td>23100030008503</td>
<td>1 patch</td>
</tr>
<tr>
<td></td>
<td>4 mg/day transdermal system</td>
<td>23100030008510</td>
<td>1 patch</td>
</tr>
<tr>
<td>AndroGel® / Testosterone (testosterone gel)</td>
<td>1% gel, 2.5 g packet(^b)</td>
<td>23100030004025</td>
<td>2 packets (5 g)</td>
</tr>
<tr>
<td></td>
<td>1% gel, 5 g packet(^b)</td>
<td>23100030004030</td>
<td>2 packets (10 g)</td>
</tr>
<tr>
<td></td>
<td>1% gel, 75 g pump bottle (1.25 g/actuation; 60 actuations/pump bottle)(^b)</td>
<td>23100030004040</td>
<td>8 actuations/day, 4 pump bottles/30 days (10 g/day)</td>
</tr>
<tr>
<td></td>
<td>1% gel, 2 x 75 g pump bottle (1.25 g/actuation; 60 actuations/pump bottle)(^b)</td>
<td>23100030004040</td>
<td>8 actuations/day, 4 pump bottles/30 days (10 g/day)</td>
</tr>
<tr>
<td></td>
<td>1.62% gel, 1.25 g packet(^b)</td>
<td>23100030004044</td>
<td>1 packet (1.25 g/day)</td>
</tr>
<tr>
<td></td>
<td>1.62% gel, 2.5 g packet(^b)</td>
<td>23100030004047</td>
<td>2 packets (5 g/day)</td>
</tr>
<tr>
<td></td>
<td>1.62% gel, 75 g pump bottle (1.25 g/actuation; 60 actuations/pump bottle)(^b)</td>
<td>23100030004050</td>
<td>4 actuations/day, 2 pump bottles/30 days</td>
</tr>
</tbody>
</table>
### Prior Authorization Criteria for Approval

**Androderm, AndroGel, Axiron, Fortesta, Natesto, Striant, Testim, Testosterone, or Vogelxo** will be approved when ALL of the following are met:

1. ONE of the following:
   a. BOTH of the following:
      i. The patient has AIDS/HIV-associated wasting syndrome, confirmed by BOTH of the following:
         1. ONE of the following:
            a. The patient has had weight loss of greater than ONE of the following:
               i. 10% within 12 months or from baseline visit
               **OR**
               ii. 7.5% within 6 months
               **OR**
               iii. 5% within 3 months
               **OR**
b. The patient has a body cell mass (BCM) loss ≥5% within 6 months  
   OR  

c. The patient is male and has BCM <35% of total body weight and body mass index (BMI) <27 kg/m²  
   OR  

d. The patient is female and has BCM <23% of total body weight and BMI <27 kg/m²  
   OR  

e. The prescriber has provided documentation that the patient’s BCM <35% or <23% and BMI <27 kg/m² are medically appropriate for diagnosing AIDS wasting/cachexia for the patient's gender  

AND  

2. All other causes of weight loss have been ruled out  

   AND  

ii. ONE of the following:  

   1. The patient is female  
      OR  

   2. The prescriber has provided documentation that checking for testosterone levels is medically inappropriate for the patient’s gender  
      OR  

   3. The patient has ONE of the following levels (documentation requirement to be determined by client):  
      a. The patient is not currently receiving testosterone replacement therapy AND has ONE of the following pretreatment levels:  
         i. Total serum testosterone level that is below the testing laboratory’s lower limit of the normal range or is less than 300 ng/dL  
         OR  
         ii. Free serum testosterone level that is below the testing laboratory’s lower limit of the normal range  
         OR  

   b. The patient is currently receiving testosterone replacement therapy AND the patient has ONE of the following current levels:  
      i. Total serum testosterone level that is within OR below the testing laboratory’s lower limit of the normal range OR is less than 300 ng/dL  
      OR  
      ii. Free serum testosterone level is within OR below the testing laboratory’s normal range  

   OR  

b. ALL of the following:  

   i. The patient has primary or secondary (hypogonadotrophic) hypogonadism  
      AND  

   ii. For patients not currently receiving testosterone replacement therapy, prior to testosterone replacement therapy, the patient had sign/symptom of hypogonadism  
      AND  

   iii. ONE of the following levels (documentation requirement to be determined by client):  
        1. The patient is not currently receiving testosterone replacement therapy AND has ONE of the following pretreatment levels:
a. Total serum testosterone level that is below the testing laboratory’s lower limit of the normal range or is less than 300 ng/dL  
OR
b. Free serum testosterone level that is below the testing laboratory’s lower limit of the normal range  
OR
2. The patient is currently receiving testosterone replacement therapy AND the patient has ONE of the following current levels:
   a. Total serum testosterone level that is within OR below the testing laboratory’s lower limit of the normal range OR is less than 300 ng/dL
   OR
   b. Free serum testosterone level is within OR below the testing laboratory’s normal range
   OR
   c. The patient has a diagnosis of gender identity disorder (GID), gender dysphoria, or gender incongruence AND ONE of the following:
      i. The patient is an adolescent and ONE of the following:
         1. The patient is initiating sex hormone treatment AND ALL of the following:
            a. A persistent diagnosis was confirmed by a mental health professional who is trained in child and adolescent developmental psychopathy
            AND
            b. The patient’s indication for sex hormone treatment has been confirmed by an endocrinologist OR clinician experienced in pubertal sex hormone induction
            AND
            c. The patient does not have any medical contraindications to sex hormone treatment as confirmed by an endocrinologist OR clinician experienced in pubertal sex hormone induction
            AND
            d. The patient has been informed and counseled regarding effects and side effects of sex hormone treatment including those which are irreversible, and regarding loss of fertility and options to preserve fertility
            AND
            e. ONE of the following:
               i. The patient is 16 years of age or greater
               OR
               ii. The prescriber has provided documentation in support of initiating therapy prior to 16 years of age
               AND
            f. The patient has sufficient mental capacity to give consent
            AND
            g. The patient has provided consent AND, as applicable, the parents or other caretakers or guardians have provided consent to therapy
            AND
            h. The patient’s coexisting psychological, medical, or social problems that could interfere with treatment have been addressed and the patient’s functioning is stable enough to start sex hormone therapy
   OR
2. The patient is continuing therapy with sex hormone treatment AND the patient is being monitored at least once per year 

\textbf{OR}

ii. The patient is an adult AND ONE of the following:
1. The patient is initiating sex hormone treatment AND ALL of the following:
   a. A persistent diagnosis has been confirmed by a mental health professional
   AND
   b. The patient has sufficient mental capacity to give consent
   AND
   c. The patient’s coexisting mental health concerns, if present, are reasonably well controlled
   AND
   d. The patient’s medical conditions that can be exacerbated by treatment with sex hormones have been evaluated and addressed

\textbf{OR}

2. The patient is currently on sex hormone treatment and BOTH of the following:
   a. ONE of the following:
      i. The patient’s current testosterone level is ONE of the following:
         1. Total serum testosterone level that is within OR below the testing laboratory’s lower limit of the normal range OR is less than 300 ng/dL
         OR
         2. Free serum testosterone level is within OR below the testing laboratory’s normal range

      OR
      ii. The prescriber has provided documentation in support of continuing therapy with the patient’s current testosterone level
   AND
   b. The patient is being monitored at least once per year

2. The patient does NOT have any FDA labeled contraindication(s) to the requested agent

\textbf{AND}

3. ONE of the following:
   a. The patient is not currently being treated with another androgen or anabolic steroid agent (in the past 90 days)
   OR
   b. The patient will discontinue the current androgen or anabolic steroid agent before starting the requested agent
   OR
   c. The prescriber has submitted documentation in support of therapy with more than one agent which has been reviewed and approved by the Clinical Review pharmacist

\textbf{AND}

4. ONE of the following:
   a. The requested quantity (dose) is less than or equal to the program quantity limit
   OR
   b. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit
      AND
ii. The requested quantity (dose) is less than the maximum FDA labeled dose (for the requested indication)  
   **AND**  
iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit  
   **OR**  
   c. **ALL** of the following:  
      i. The requested quantity (dose) is greater than the program quantity limit  
         **AND**  
      ii. The requested quantity (dose) is greater than the maximum FDA labeled dose (for the requested indication)  
         **AND**  
      iii. The prescriber has submitted documentation in support of therapy with a higher dose for the requested indication  

**Length of Approval:** 12 months