Androgens and Anabolic Steroids
Prior Authorization with Quantity Limit Program Summary

This program applies to FlexRx Open, FlexRx Closed, GenRx Open, GenRx Closed, Health Insurance Marketplace, FocusRx and KeyRx formularies.

The program only targets topical androgen agents.

This is a FlexRx standard and GenRx standard prior authorization program.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

Program specific denial language for prerequisite step therapy component does not apply. Instead, supplemental program denial language will apply.

### FDA APPROVED INDICATIONS AND DOSAGE

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

<table>
<thead>
<tr>
<th>Agent</th>
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</tr>
</thead>
</table>
| **AndroGel® / Testosterone**  | (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or | 1% gel:  
- Initial dose is 50 mg of testosterone (4 pump actuations, two 25 mg packets, or one 50 mg packet) once daily in the morning.  
- Dose may be increased to 75 mg and 100 mg daily based on measured serum testosterone levels.  
- If serum testosterone level exceeds normal range at 50 mg dose, therapy should be discontinued.  
1.62% gel:  
- 40.5 mg of testosterone (2 pump actuations or 1 40.5 mg packet) applied topically once daily in the morning.  
- 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. |
| (testosterone gel)            | (testosterone gel)                                                        |                                                                                           |
| 1% gel:                       |                                                                           |                                                                                           |
| 25 mg/2.5 g packet<sup>b</sup> |                                                                           |                                                                                           |
| 50 mg/5 g packet<sup>b</sup>  |                                                                           |                                                                                           |
| 75 g pump                     |                                                                           |                                                                                           |
| (12.5 mg testosterone/actuation; 60 actuations/pump)<sup>b</sup> |                                                                           |                                                                                           |
| 1.62% gel:                    |                                                                           |                                                                                           |
| 75 g pump (20.25 mg testosterone/actuation; 60 actuations/pump)<sup>b</sup> |                                                                           |                                                                                           |
| 20.25 mg/1.25 g packet<sup>b</sup> |                                                                           |                                                                                           |
| 40.5 mg/2.5 g packet<sup>b</sup> |                                                                           |                                                                                           |
| **Axiron®**                   |                                                                           |                                                                                           |
| (testosterone soln)<sup>b</sup> |                                                                           |                                                                                           |
| 30 mg/1.5 mL, 90 mL pump      |                                                                           |                                                                                           |
| **Fortesta™ / Testosterone**  |                                                                           |                                                                                           |
| (testosterone gel)<sup>b</sup> |                                                                           |                                                                                           |
| 2% gel                        |                                                                           |                                                                                           |
| 20 mg/1.25 g packet<sup>b</sup> |                                                                           |                                                                                           |
| 40 mg/2.5 g packet<sup>b</sup> |                                                                           |                                                                                           |

<sup>b</sup> Denotes concentration or actuation information.
<table>
<thead>
<tr>
<th><strong>Topical Androgen Agents</strong></th>
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<th><strong>Dosage and Administration</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Natesto™</strong> (testosterone nasal gel)</td>
<td><strong>Recommended dose of 11 mg (2 pump actuations, one per nostril), applied intranasally 3 times daily.</strong>&lt;br&gt;&lt;br&gt;<strong>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.</strong>&lt;br&gt;&lt;br&gt;<strong>Not recommended for use with nasally administered drugs other than sympathomimetic decongestants (e.g., oxymetazoline)</strong></td>
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<tr>
<td><strong>Striant®</strong> (testosterone buccal system)</td>
<td><strong>Usual dose is one buccal system (30 mg) to the gum region twice daily, morning and evening (about 12 hours apart).</strong></td>
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<tr>
<td><strong>Testim®/Testosterone (testosterone gel)b</strong>&lt;br&gt;1% gel</td>
<td><strong>For testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:</strong>&lt;br&gt;-Primary hypogonadism&lt;br&gt;-Hypogonadotropic hypogonadism (congenital or acquired)</td>
<td><strong>1% gel:</strong>&lt;br&gt;-Initial dose is 50 mg testosterone (5 g gel) once daily at the same time each day.&lt;br&gt;-Dose may be increased to 100 mg daily based on measured serum testosterone levels.&lt;br&gt;-The maximum recommended dose is 100 mg once daily.</td>
</tr>
<tr>
<td><strong>Vogelxo™/Testosterone (testosterone gel)</strong>&lt;br&gt;1% gel</td>
<td></td>
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</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.*
# Oral Androgen and Anabolic Agents

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<thead>
<tr>
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</thead>
</table>
| **Android®**     | Males: Androgen replacement therapy related to the following:  
                  | - Primary hypogonadism (congenital or acquired) -  
                  | - Testicular failure due to cryptorchidism, bilateral torsions, orchitis, vanishing testis syndrome; or orchidectomy -  
                  | - Hypogonadotropic hypogonadism (congenital or acquired) -  
                  | - Idiopathic gonadotropin or LHRH deficiency, or pituitary hypothalamic injury from tumors, trauma, or radiation -  
                  | - Delayed puberty in males  
                  | Females: Palliative treatment of breast cancer in women  
                  | Males: - Androgen replacement therapy related to hypogonadism: 10 mg to 50 mg/day  
                  | - Androgen replacement therapy related to cryptorchidism: 10 mg 3 times daily  
                  | - Delayed puberty (adolescents only): 5 mg to 25 mg/day for a limited period, usually for 4 to 6 months  
                  | Females: - 50 mg once daily up to four times/day  
                  | - If suitable response within 2-4 weeks, decrease to 25 mg two times daily  
| **Methitest®**   | 10 mg capsulec  
| **Testred®**     | 10 mg tablet  
| **Androxy®**     | 10 mg tablet  
| **Anadrol-50®**  | 50 mg tablet  

- Treatment of anemias caused by deficient red cell production. Acquired aplastic anemia, congenital aplastic anemia, myelofibrosis and the hypoplastic anemias due to the administration of myelotoxic drugs often respond

- Adults and children  
  - 1 to 5 mg/kg body weight per day.  
  - Usual effective dose is 1 to 2 mg/kg/day; higher doses may be required, dose should be individualized.  
  - Response is not often immediate; minimum trial of 3 to 6 months should be given  
  - Following remission, some patients may be maintained without the drugs; others may be maintained on an established lower daily dosage  
  - A continued maintenance dose is usually necessary in patients with congenital aplastic anemia
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<tr>
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</thead>
<tbody>
<tr>
<td>danazol(^a)</td>
<td>- Fibrocystic breast disease</td>
<td>- Fibrocystic breast disease: 100 to 400 mg/day in 2 divided doses. Although symptoms may be</td>
</tr>
<tr>
<td>50 mg, 100 mg, 200</td>
<td>- Angioedema prophylaxis in patients with hereditary angioedema</td>
<td>relieved, and even eliminated in 3 months, up to 6 months of uninterrupted therapy may be</td>
</tr>
<tr>
<td>mg capsule</td>
<td>- Endometriosis amenable to hormone management</td>
<td>required to eliminate nodularity.</td>
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<td>- Angioedema prophylaxis: Initial 200 mg two to three times daily. If a favorable</td>
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<td>response achieved, dose may be reduced by half at intervals of 1-3 months. If an</td>
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<td></td>
<td>unfavorable response (attack of angioedema during treatment), dose may be increased by</td>
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<td>up to 200 mg/day.</td>
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<td>NOTE: If danazol therapy initiated during exacerbation of angioedema caused by trauma,</td>
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<td>stress or other causes, periodic attempts to reduce or discontinue therapy should be</td>
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<td></td>
<td>considered.</td>
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<td>- Endometriosis: In moderate/severe disease or patients infertile due to</td>
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<td></td>
<td>endometriosis: starting dose of 800 mg given in two divided doses. Gradual downward</td>
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<td>titration to dose sufficient to maintain amenorrhea may be considered. In mild disease:</td>
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<td>starting dose of 200 mg to 400 mg given in two divided doses; adjust depending on patient</td>
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<tr>
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<td>response. Continue therapy for 3 to 6 months, may be extended to 9 months if necessary.</td>
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<tr>
<td>Oxandrin(^b)</td>
<td>- Adjunctive therapy to promote weight gain after weight loss following</td>
<td>Adults</td>
</tr>
<tr>
<td>(oxandrolone)(^b)</td>
<td>extensive surgery, chronic infections, severe trauma, and in some patients</td>
<td>- Daily adult dosage is 2.5 mg to 20 mg given in 2 to 4 divided doses.</td>
</tr>
<tr>
<td>2.5 mg, 10 mg tablet</td>
<td>without definite pathophysiologic reasons who fail to gain or to maintain</td>
<td>- Desired response may be achieved with as little as 2.5 mg or as much as 20 mg daily.</td>
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<td>normal weight, to offset the protein catabolism associated with prolonged</td>
<td>- A course of therapy of 2 to 4 weeks is usually adequate. This may be repeated</td>
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<td>administration of corticosteroids, and for the relief of the bone pain</td>
<td>intermittently as indicated.</td>
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<tr>
<td></td>
<td>frequently accompanying osteoporosis</td>
<td>Children: Total daily dosage is (&lt;0.1) mg/kg body weight or (&lt;0.045) mg per</td>
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<td></td>
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<td>pound of body weight. This may be repeated intermittently as indicated.</td>
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<td>Geriatric: 5 mg twice daily</td>
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</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.
# Injectable Androgen Agents

<table>
<thead>
<tr>
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| testosterone enanthate<sup>b</sup> | 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.  
  - Terminal growth phase: 100 mg/m² IM monthly until growth ceases  
  - 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 |
| 200 mg/mL                          |                                                                           |                            |
| Depo-Testosterone®<sup>b</sup> (testosterone cypionate)<sup>b</sup> | For replacement therapy in the male in conditions associated with symptoms of 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 LHRH deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation. | - Hypogonadism: 50-400 mg every 4 weeks |
| 100 mg/mL, 200 mg/mL               |                                                                           |                            |
## Injectable Androgen Agents

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<tr>
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</thead>
<tbody>
<tr>
<td><strong>Testopel®</strong>&lt;br&gt;(testosterone pellets)&lt;br&gt;75 mg</td>
<td>Males&lt;br&gt;-Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome; or orchiectomy&lt;br&gt;-Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation.&lt;br&gt;-Delayed puberty</td>
<td><strong>-Hypogonadism</strong> (adult males and children): 150 mg to 450 mg (2-6 pellets) inserted subcutaneously by a healthcare professional every 3 to 6 months&lt;br&gt;• Dosage is based on the minimal daily requirements of testosterone propionate determined by a gradual reduction of the amount administered parenterally&lt;br&gt;  ○ For every 75 mg/week of testosterone propionate, 150 mg (2 pellets) should be implanted every 3—6 months&lt;br&gt;-Delayed puberty (adolescents only): 150 mg to 450 mg (2-6 pellets) inserted subcutaneously by a healthcare professional every 3 to 6 months, although the lower end of the dosing range is typically sufficient&lt;br&gt;• Treatment is usually only required for 4—6 months&lt;br&gt;• Dosage is based on the minimal daily requirements of testosterone propionate determined by a gradual reduction of the amount administered parenterally&lt;br&gt;For every 75 mg/week of testosterone propionate, 150 mg (2 pellets) should be implanted every 3—6 months</td>
</tr>
<tr>
<td><strong>Aveed™</strong>&lt;br&gt;(testosterone undecanoate)&lt;br&gt;250 mg/mL</td>
<td>-Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome; or orchiectomy&lt;br&gt;-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>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.</td>
</tr>
</tbody>
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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 <6ml)

- 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 \( \geq \) 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. 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.

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. 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 sclerosus. 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.

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.

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:
- 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

- Recommend clinicians evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones before beginning treatment
- 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
- 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

- 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. 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.”2

Normal Calcium Values
Normal calcium blood values range: 8.5 to 10.2 mg/dL; may vary slightly among laboratories.3

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

OBJECTIVE
The intent of the Androgens and Anabolic Steroids Prior Authorization with Quantity Limit (PA) 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). In addition, the program will encourage use of a generic topical androgen agents prior to a brand topical androgen agent. Use of a brand topical androgen agent will be evaluated if the prescriber indicates a history of a trial of or documented intolerance, FDA labeled contraindication, or hypersensitivity to a brand topical androgen agents. 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, and will apply to brand and generic topical agents.

TARGET AGENTS
Topical Androgen Agents:
- AndroGel® 1% (testosterone gel 1%)<sup>b</sup>
- AndroGel® 1.62% (testosterone gel 1.62%)<sup>b</sup>
- Androderm® (testosterone transdermal system)
- Axiron® (testosterone solution)<sup>b</sup>
- Fortesta™ (testosterone gel)<sup>b</sup>
- Nasteto™ (testosterone nasal gel)
- Striant® (testosterone buccal system)
- Testim® (testosterone gel)<sup>b</sup>
- Testosterone (testosterone gel)
- Vogelxo™ (testosterone gel)

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.

c – Generic available and included in prior authorization program only.

d – Generic anticipated and will be included in prior authorization and quantity limit

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><strong>Topical Androgen Agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Androderm® (testosterone transdermal system)</td>
<td>2 mg/day transdermal system</td>
<td>23100030008503 1 patch</td>
<td>M, N, O, or Y</td>
</tr>
<tr>
<td></td>
<td>4 mg/day transdermal system</td>
<td>23100030008510 1 patch</td>
<td>M, N, O, or Y</td>
</tr>
<tr>
<td><strong>AndroGel® / Testosterone (testosterone gel)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1% gel, 2.5 g packet&lt;sup&gt;b&lt;/sup&gt;</td>
<td>23100030004025 2 packets (5 g)</td>
<td>M, N, O, or Y</td>
<td></td>
</tr>
<tr>
<td>1% gel, 5 g packet&lt;sup&gt;b&lt;/sup&gt;</td>
<td>23100030004030 2 packets (10 g)</td>
<td>M, N, O, or Y</td>
<td></td>
</tr>
<tr>
<td>1% gel, 75 g pump bottle (1.25 g/actuation; 60 actuations/pump bottle)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>23100030004040 8 actuations/day, 4 pump bottles/30 days (10 g/day)</td>
<td>M, N, O, or Y</td>
<td></td>
</tr>
<tr>
<td>1% gel, 2 x 75 g pump bottle (1.25 g/actuation; 60 actuations/pump bottle)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>23100030004040 8 actuations/day, 4 pump bottles/30 days (10 g/day)</td>
<td>M, N, O, or Y</td>
<td></td>
</tr>
<tr>
<td>Brand (generic)</td>
<td>GPI</td>
<td>Quantity Per Day Limit Or As Noted</td>
<td>Multisource Code</td>
</tr>
<tr>
<td>----------------</td>
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<td>-----------------</td>
</tr>
<tr>
<td>1.62% gel, 1.25 g packet&lt;sup&gt;b&lt;/sup&gt;</td>
<td>23100030004044</td>
<td>1 packet (1.25 g/day)</td>
<td>M, N, O, or Y</td>
</tr>
<tr>
<td>1.62% gel, 2.5 g packet&lt;sup&gt;b&lt;/sup&gt;</td>
<td>23100030004047</td>
<td>2 packets (5 g/day)</td>
<td>M, N, O, or Y</td>
</tr>
<tr>
<td>1.62% gel, 75 g pump-bottle (1.25 g/actuation; 60 actuations/pump bottle)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>23100030004050</td>
<td>4 actuations/day, 2 pump-bottles/30 days (5 g/day)</td>
<td>M, N, O, or Y</td>
</tr>
</tbody>
</table>

**Axiron**<sup>®</sup> (**testosterone solution**)<sup>b</sup>

| 30 mg/1.5 mL, 90 mL pump bottle (1.5 mL/actuation; 60 actuations/pump bottle) | 23100030002020 | 4 actuations/day, 2 pump bottles/30 days (6 mL/day) | M, N, O, or Y |

**Fortesta™ / Testosterone (testosterone gel)**<sup>b,c</sup>

| 2% gel, 60 g pump bottle (0.5 g/actuation; 120 actuations/pump bottle) | 23100030004070 | 8 actuations/day, 2 pump bottles/30 days (4 g/day) | M, N, O, or Y |

**Natesto™ (testosterone nasal gel)**

| 5.5 mg/0.122g, 11 g pump bottle (0.122 g/actuation; 60 actuations/pump bottle) | 23100030004080 | 6 actuations/day, 3 pump bottles/30 days (0.732 g/day) | M, N, O, or Y |

**Striant**<sup>®</sup> (**testosterone buccal system**)

| 30 mg buccal system | 23100030006320 | 2 systems | M, N, O, or Y |

**Testim**<sup>®</sup> / **Testosterone (testosterone gel)**<sup>b</sup>

| 1% gel, 5 g tube | 23100030004030 | 2 tubes (10 g) | M, N, O, or Y |

**Vogelxo™ / Testosterone (testosterone gel)**

| 1% gel, 50 mg/5 g tube | 23100030004030 | 2 tubes (10 g) | M, N, O, or Y |
| 1% gel, 50 mg/5 g packet | 23100030004030 | 2 packets (10 g) | M, N, O, or Y |
| 1% gel, 75 g pump bottle (12.5 mg/actuation; 60 actuations/pump bottle) | 23100030004040 | 8 actuations/day, 4 pump bottles/30 days (10 g/day) | M, N, O, or Y |

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*<sup>a</sup> – Brand drug has been discontinued by the manufacturer but may still be available.  
<sup>b</sup> – Generic available and included in prior authorization and quantity limit programs  
<sup>c</sup> – Quantity limit adjusted to accommodate packaging of agent

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. 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. The patient has ONE of the following levels (documentation requirement to be determined by client):
1. The patient is not currently receiving testosterone replacement therapy AND 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

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

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

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

AND
3. ONE of the following:
   a. The requested agent is a generic topical androgen agent
   OR
   b. ONE of the following:
      i. The patient’s medication history indicates use of a generic topical androgen agent
      OR
      ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to a generic topical androgen agent

AND
4. ONE of the following:
   a. The patient is not currently being treated with another androgen or anabolic steroid agent (in the past 90 days)
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

AND

5. 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
Step Therapy Supplement

This program applies to FlexRx Closed, FlexRx Open, GenRx Closed, GenRx Open, Health Insurance Marketplace, FocusRx and KeyRx formularies.

Please note, this does not include or apply to quantity limit questions.

STEP THERAPY SUPPLEMENT

OBJECTIVE
The intent of the Step Therapy Supplement is to provide additional questions, to ensure compliance to MN Statute 62Q.184. These questions will apply if the step therapy component within a Prior Authorization or Step Therapy program is not able to be approved.

CONDITIONS FOR APPROVAL
The requested agent will be approved when ONE of the following are met:

1. The patient is currently being treated with the requested agent as indicated by ALL of the following:
   a. A statement by the prescriber that the patient is currently taking the requested agent 
      \[\text{AND}\]
   b. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent 
      \[\text{AND}\]
   c. The prescriber states that a change in therapy is expected to be ineffective or cause harm

OR

2. The patient’s medication history include the required prerequisite/preferred agent(s) as indicated by:
   a. Evidence of a paid claim(s) within the past 999 days
   \[\text{OR}\]
   b. The prescriber has stated that the patient has tried the required prerequisite/preferred agent(s) in the past 999 days AND the required prerequisite/preferred agent(s) was discontinued due to lack of effectiveness or an adverse event

OR

3. The prescriber has provided documentation that the required prerequisite/preferred agent(s) cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

Length of Approval: As per program specific criteria