Testosterone Therapy (Oral, Nasal, and Topical)

Overview

This coverage policy addresses the uses of oral, nasal, and topical testosterone therapy. The use of injectable testosterone therapy, including implantable pellets, is addressed in a separate coverage policy. Please refer to the related coverage policy link above (Testosterone Therapy – Injectables and Implantable Pellets).

The use of testosterone therapy for the treatment of gender dysphoria is addressed in a separate coverage policy. Please refer to the related coverage policy link above (Treatment of Gender Dysphoria).

Testosterone Therapy products addressed within this policy include the following:

- Oral Testosterone Products
  - Jatenzo® (testosterone undecanoate capsules)
  - Striant™ (testosterone buccal system)
- Nasal Testosterone Product
  - Natesto™ (testosterone nasal gel)
- Transdermal Gel Testosterone Products
  - AndroGel® (testosterone gel)*
• Fortesta™ (testosterone gel)*
• Testim® (testosterone gel)*
• Vogelxo™ (testosterone gel)*

Transdermal Patch Testosterone Product
• Androderm® (testosterone transdermal system)

Transdermal Solution
• Axiron™ (testosterone topical solution – generics only available)*

*Includes generic formulations, as available, of the above listed medications

Coverage Policy

Testosterone therapy is considered medically necessary when ALL of the following criteria are met:
• Individual is 18 years of age or older
• Diagnosis of hypogonadism or hypogonadotropic hypogonadism (congenital or acquired)
• Documentation of signs and symptoms of androgen deficiency
• Two early morning, low serum testosterone levels drawn on different days. Low serum testosterone level is defined as ANY of the following:
  ▪ Total testosterone level less than 264 ng/dL (9.2 nmol/L)
  ▪ Total testosterone level below the laboratory’s normal reference range
  ▪ Free testosterone level below the laboratory’s normal reference range (by equilibrium dialysis assay)
• No concurrent use of other testosterone products

Coverage for testosterone products varies across plans. Refer to the customer’s benefit plan document for coverage details.

Where coverage requires the use of preferred products, the following will apply in addition to the criteria listed above:

For Employer Group Plans:

<table>
<thead>
<tr>
<th>Non-covered Testosterone Products</th>
<th>Standard Drug List Plan (Not Covered [NC])</th>
<th>Value Drug List Plan (Not Covered [NC])</th>
<th>Legacy Drug List Plan (Prior Auth [PA] Required)</th>
</tr>
</thead>
</table>
| Fortesta™ (testosterone gel)     | • Documented failure/ inadequate response, intolerance, or not a candidate for THREE of the following:  
  ▪ Androgel® 1% or its generic (2.5gm, 5gm gel packets)  
  ▪ Androgel® 1.62% or its generic (1.25gm, 2.5gm gel packet or pump)  
  ▪ Testosterone 30mg/1.5ml (2%) solution (generic for Axiron™)  
  ▪ Testosterone 10mg/0.5gm (2%) gel pump (generic for Fortesta™)  
  ▪ Testosterone 50mg/5gm tube (1%) gel (generic for Testim®) | | |
| Natesto™ (testosterone nasal gel) | | | |
| Testim® (testosterone gel)       | | | |
| Vogelxo™ (testosterone gel)      | | | |
| Jatenzo® (testosterone undecanoate capsules) | • Documented failure / inadequate response, intolerance, or not a candidate for THREE of the following:  
  ▪ Androgel® 1% or its generic (2.5gm, 5gm gel packets)  
  ▪ Androgel® 1.62% or its generic (1.25gm, 2.5gm gel packet or pump)  
  ▪ Testosterone 30mg/1.5ml (2%) solution (generic for Axiron™)  
  ▪ Testosterone 10mg/0.5gm (2%) gel pump (generic for Fortesta™)  
  ▪ Testosterone 50mg/5gm tube (1%) gel (generic for Testim®)  
  ▪ Striant™ 30mg buccal system | | |

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Drug and Biologic Coverage Policy: 2013
Initial authorization is up to 12 months unless otherwise stated.

Testosterone therapy is considered medically necessary for continued use when the following criteria are met:

- Individual met all the criteria for initial therapy

Reauthorization is up to 12 months.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Testosterone therapy is considered experimental, investigational or unproven for ANY other use including the following:

- To enhance athletic performance or to increase muscle mass

Note: Receipt of sample product does not satisfy any criteria requirements for coverage

### FDA Approved Indications

**FDA Approved Indications**

The oral, nasal, and topical testosterone products are all indicated 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. These men usually have low serum testosterone concentrations and gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range.
- Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations but have gonadotropins in the normal or low range.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Limitations of Use</th>
</tr>
</thead>
</table>
| Androderm® (testosterone transdermal system) | Limitations of use:  
  - Safety and efficacy of in men with “age-related hypogonadism” (also referred to as “late-onset hypogonadism”) have not been established.  
  - Safety and efficacy in males less than 18 years old have not been established.  
  - Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure |
| AndroGel® (testosterone gel) |  |
| Axiron™ (testosterone topical solution – generics only available) |  |
| Fortesta™ (testosterone gel) |  |
| Natesto® (testosterone nasal gel) |  |
| Striant™ (testosterone buccal system) |  |
| Testim® (testosterone gel) |  |
| Vogelxo™ (testosterone gel) |  |
| Jatenzo® (testosterone undecanoate capsules) | Limitations of use:  
  - Safety and efficacy in males less than 18 years old have not been established. |
<table>
<thead>
<tr>
<th>Drug</th>
<th>Limitations of Use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Note: Jatenzo labeling specifically states that it is <em>contraindicated</em> in men with hypogonadal conditions, such as “age-related hypogonadism”, that are not associated with structural or genetic etiologies.</td>
</tr>
</tbody>
</table>

### Recommended Dosing

**FDA Recommended Dosing**

**Oral, Nasal, and Topical Testosterone Products**

<table>
<thead>
<tr>
<th>Brand Name (generic name)</th>
<th>Availability</th>
<th>Dose</th>
<th>Dose Delivered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jatenzo® (testosterone undecanoate) capsules</td>
<td>• 158 mg capsules  • 198 mg capsules  • 237 mg capsules</td>
<td>• Starting dose is 237 mg orally once in the morning and once in the evening.  • Adjust the dose to a minimum of 158 mg twice daily and a maximum of 396 mg twice daily based on serum testosterone.</td>
<td>• N/A</td>
</tr>
<tr>
<td>Striant™ (testosterone mucoadhesive buccal system)</td>
<td>• 30 mg buccal systems. There are 10 buccal systems per blister pack and each box contains 6 blister packs (each box contains 60 buccal systems).</td>
<td>• The recommended dose is one buccal system (30 mg) applied to the gum region BID (morning and evening; 12 hours apart).</td>
<td>• N/A</td>
</tr>
<tr>
<td>Natesto™ (testosterone nasal gel)</td>
<td>• Metered dose pump containing 11 g of gel dispensed as 60 metered-pump actuations.</td>
<td>• Recommended dose is 11 mg of testosterone (two pump actuations, one per nostril), applied intranasally, TID.  • If serum total testosterone concentrations consistently exceed 1,050 ng/dL, Natesto therapy should be discontinued.  If the concentrations are consistently &lt; 300 ng/dL, an alternative treatment should be considered.</td>
<td>• One pump actuation delivers 5.5 mg of testosterone in 0.122 g of gel.</td>
</tr>
<tr>
<td>Androderm® (testosterone transdermal system)</td>
<td>• 2 mg/day transdermal system (32 cm² total contact surface area).  • 4 mg/day transdermal system (39 cm² total contact surface area).</td>
<td>2 and 4 mg/day systems:  • Recommended starting dose is 4 mg/day system (not two 2 mg/day systems) applied nightly every 24 hours.  • May increase to 6 mg/day or decrease to 2 mg/day, if needed.</td>
<td>• 2 mg/day patch contains 9.7 mg testosterone and delivers 2 mg/day of testosterone.  • 4 mg/day patch contains 19.5 mg testosterone and delivers 4 mg/day of testosterone.</td>
</tr>
</tbody>
</table>
AndroGel®
(testosterone 1% and 1.62% gel, generics)

<table>
<thead>
<tr>
<th>1% gel:</th>
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<th>1% gel:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Unit-dose foil packet containing 2.5 g of gel and 5 g of gel packaged in separate boxes of 30 packets each.</td>
<td>• Recommended starting dose is 5 g of gel/day applied QD, preferably in the morning.</td>
<td>• 1.25 g of gel delivers 12.5 mg of testosterone systemically.</td>
</tr>
<tr>
<td>• A non-aerosol, metered-dose pump which dispenses 75 g or 60 metered doses of 1.25 g of gel. Packaged as two pumps per carton.</td>
<td>• May increase the dose to 7.5 and 10 g of gel/day.</td>
<td>• 2.5 g of gel delivers 25 mg of testosterone systemically.</td>
</tr>
<tr>
<td><strong>1.62% gel:</strong></td>
<td>• If using the metered-dose pump then a 5 g dose is obtained with four pump actuations</td>
<td>• 5 g of gel delivers 50 mg of testosterone systemically.</td>
</tr>
<tr>
<td>• A metered-dose pump which dispenses 60 metered doses of 1.25 g of gel.</td>
<td><strong>1.62% Gel:</strong></td>
<td><strong>1.62% Gel:</strong></td>
</tr>
<tr>
<td></td>
<td>• Recommended starting dose is 40.5 mg of testosterone (two pumps) applied QD.</td>
<td>• One pump actuation delivers 1.25 g of gel (20.25 mg of testosterone).</td>
</tr>
<tr>
<td></td>
<td>• May increase the dose to 81 mg (four pumps) per day or decrease to 20.25 mg (one pump) per day.</td>
<td><strong>1% gel:</strong></td>
</tr>
<tr>
<td></td>
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</tr>
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<td></td>
<td>• 5 g of gel delivers 50 mg of testosterone systemically.</td>
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</table>

Axiron™
(testosterone 2% solution, generics only)

- A metered-dose pump containing 110 mL of solution capable of dispensing 90 mL of solution in 60 metered sprays.
- Recommended starting dose is 60 mg (two pumps) applied to the axilla QD in the morning.
- May increase dose to 90 mg or 120 mg or decrease dose to 30 mg if needed.
- Each pump delivers 30 mg of testosterone in 1.5 mL of solution.
- One pump delivers 10 mg testosterone in 0.5 g of gel.

Fortesta™
(testosterone 2% gel, generic)

- A metered-dose pump that delivers 10 mg of testosterone per pump.
- Each 60 g canister is capable of dispensing 120 pumps.
- Recommended starting dose is 40 mg (four pumps) applied QD to the inner thighs in the morning.
- May increase dose to a maximum of 70 mg (seven pumps) or decrease dose to a minimum of 10 mg (one pump)
- One pump delivers 10 mg testosterone in 0.5 g of gel.

Testim®
(testosterone 1% gel, generics)

- Unit-dose tubes containing 5 g of gel and packaged in a box of 30 tubes.
- Each 5 g tube contains 50 mg of testosterone.
- Recommended starting dose is 5 g of gel/day (one tube) applied QD, preferably in the morning.
- May increase to 10 g of gel/day.
- Approximately 10% of applied dose is absorbed.
- The 5 g unit-dose gel delivers 50 mg of testosterone.

Vogelxo™
(testosterone 1% gel, generic)

- Unit-dose tubes and packets containing 5 g of gel and packaged in a carton of 30 tubes or packets.
- Metered-dose pumps dispensing 75 g of gel or 60-metered pump actuations in cartons of two pumps.
- Recommended starting dose is 50 mg of testosterone applied QD at approximately the same time each day.
- A unit-dose tube or packet delivers 50 mg of testosterone.
- Each actuation of the metered-dose pump delivers 12.5 mg of testosterone (four pump actuations = 50 mg).

**General Background**

**Overview**

Testosterone therapy treats hypogonadism in males by supplementing exogenous testosterone to bring serum testosterone levels to within normal range. Hypogonadism is associated with low serum testosterone levels and is characterized by symptoms such as decreased libido, malaise, loss of muscle strength, and depressed mood.
Improvements in these symptoms can be seen within days to weeks once testosterone replacement is initiated. No advantage has been demonstrated in having the testosterone concentration on the upper end versus the lower end of normal. Testosterone should never be supplemented in individuals that have normal serum testosterone levels. (Lee, 2008)

Testosterone can be supplemented to the body in a variety of dosage forms. An ideal testosterone replacement regimen would mimic the normal circadian pattern of serum testosterone concentrations such that peak and trough concentrations would occur in the early morning and late afternoon, respectively, and would produce serum concentrations in the normal range. (Lee, 2008) All of the oral, nasal, and topical testosterone products have demonstrated efficacy in normalizing testosterone levels in the majority of patients.

Oral testosterone replacement, available as Jatenzo (testosterone capsule), is taken twice daily. Striant is available as buccal administration used twice daily and Natesto is a nasal testosterone gel that is applied intranasally three times daily. Transdermal testosterone replacement products include gels (Fortesta [generic], Testim [generics], Vogelxo [generic], and AndroGel [generics]), solution (generics; Axiron), and a transdermal patch (Androderm). These products are applied once daily, preferably in the morning for the gels and solution and nightly for the patches. An appropriate agent for a patient can be chosen based on the pharmacokinetics, pharmacodynamics, side effects, and cost considerations. (Bhasin, 2018) All of these testosterone replacement products are considered Schedule III (CIII) controlled substances as defined by the Anabolic Steroids Control Act.

Professional Societies/Organizations

American Urological Association (AUA)
Guidelines from the AUA (2018) note that clinicians should use a total testosterone level below 300 ng/dL as a reasonable cut-off in support of the diagnosis of low testosterone. The guidelines additionally note that a diagnosis of low testosterone should be made only after two total testosterone measurements are taken on separate occasions with both conducted in an early morning fashion and that a clinical diagnosis should be made when patients have low testosterone levels combined with signs or symptoms. (Mulhall, 2018)

Endocrine Society
The Endocrine Society guidelines on testosterone therapy in men with hypogonadism (2018) recommend diagnosing hypogonadism in men with symptoms and signs of testosterone deficiency and unequivocally and consistently low serum total testosterone and/or free testosterone concentrations (when indicated). Guidelines state that the lower limit of the normal total testosterone be aligned to the CDC standard in healthy nonobese young men is 264 ng/dL or 9.2 nmol/L and suggest that this value could be used for total testosterone assays that are certified by the CDC. For non-CDC certified laboratories, the reference range may greatly vary. For free testosterone, a harmonized range for reference has not been established, therefore reference ranges vary considerably. Using the lower limit of the range established in local laboratories may not accurately identify men with hypogonadism. Endocrine Society recommends free testosterone (FT) should be measured by an equilibrium dialysis method or estimated from total testosterone, SHBG, and albumin using a formula that accurately reflects FT by equilibrium dialysis. In addition, the Endocrine Society recommends therapy with testosterone in hypogonadal men to induce and maintain secondary sex characteristics and also to correct the symptoms of a deficiency of testosterone. (Bhasin, 2018)

The American Board of Internal Medicine’s (ABIM) Foundation Choosing Wisely® Initiative:
Choosing Wisely Initiative recommendations state that the Endocrine Society recommends the use of a total testosterone level obtained in the morning. In addition, a low level should be confirmed on a different day, with re-measuring the total testosterone. In some situations, a free testosterone level may be of additional value.

Centers for Medicare & Medicaid Services - National Coverage Determinations (NCDs)
There are no CMS National Coverage Determinations for testosterone therapy.

Other Covered Uses
Treatment of Gender Dysphoria
The use of testosterone therapy for the treatment of gender dysphoria is addressed in a separate coverage policy. Please refer to the related coverage policy link Treatment of Gender Dysphoria.

AHFS Drug Information 2020 Edition does not support any off-label uses of testosterone.

**Experimental, Investigational, Unproven Uses**
Compendia and other published clinical studies do not currently support any uses other than the FDA indications. Criteria will be updated as new published data are available.

**Coding/Billing Information**
Note: Oral, nasal, and topical testosterone therapies are typically covered under pharmacy benefit plans. Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed. Medical drug coding and diagnosis codes, however, are generally not required for pharmacy claims submissions, therefore, this section is not in use.

**References**