Testosterone Therapy (Injectables and Implantable Pellets)

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Related Coverage Resources

- Infertility Services
- Male Sexual Dysfunction Treatment: Non-pharmacologic
- Treatment of Gender Dysphoria
- Testosterone Therapy (Oral, Nasal, and Topical)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer’s particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer’s benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer’s benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

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

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:

- **Injectable Testosterone**
  - Avedr® (testosterone undecanoate injection)
  - Xyosted™ (testosterone enanthate injection)
- **Implantable Pellet Testosterone**
  - Testopel® (testosterone pellet)
Testosterone therapy (Aveed®, Xyosted™, or Testopel®) is considered medically necessary when ALL of the following criteria are met:

- Individual is 18 years of age or older
- Male
- 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

Testopel® (testosterone pellet) is considered medically necessary for the treatment of delayed puberty* when ALL of the following criteria are met:

- Individual is 14 years of age or older
- Male
- Documentation of limited or no signs of puberty
- Testosterone is being used short term (4 to 6 months) to stimulate puberty

*Note: Aveed® and Xyosted™ are not indicated for the treatment of delayed puberty

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

Where coverage requires the use of preferred products, the following criteria apply.

For Employer Group Plans the following will apply for Xyosted™ in addition to the applicable criteria listed above.

ALL of the following:
- 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 2% (30mg/1.5ml) solution (generic for Axiron™)
  - Testosterone 10mg/0.5gm (2%) gel pump (generic for Fortesta™)
  - Testosterone 50mg/5gm tube (1%) gel (generic for Testim®)
  - Testosterone cypionate injection (Depo-testosterone®) or testosterone enanthate injection (Delatrestyl®)
  - Androderm® transdermal system (2mg/24hr, 4mg/24hr patches)

Initial authorization is up to 12 months unless otherwise stated.

For Testopel
Initial authorization is 6 pellets per 90 days.
Quantities greater than 6 pellets per 90 days require:
- Documentation of continued signs and symptoms of androgen deficiency
- Documentation of a persistent early morning, low testosterone level. 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)

Testosterone therapy (Aveed®, Xyosted™, or Testopel®) is considered medically necessary for continued use when the following criteria are met:
- Individual met all 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 and Recommended Dosing**

<table>
<thead>
<tr>
<th>Brand (generic/dosage form)</th>
<th>Indications</th>
<th>Dosing</th>
<th>Availability</th>
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</table>
| Aveed® (testosterone undecanoate injection) | • Primary hypogonadism  
• Hypogonadotropic hypogonadism  
Limitation of use:  
• Safety and efficacy in males < 18 years of age have not been established.  
• Safety and efficacy in men with “age-related hypogonadism” have not been established.  
Aveed should only be used in patients who require testosterone replacement therapy and in whom the benefits of the product outweigh the serious risks of pulmonary oil microembolism and anaphylaxis. | • Inject 3 mL (750 mg) by IM administration, followed by another 3 mL injected after 4 weeks.  
• Subsequent dosing of 3 mL is injected every 10 weeks thereafter.  
Because of the risks of serious pulmonary oil microembolism (POME) reactions and anaphylaxis, Aveed is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Aveed REMS Program [see Warnings and Precautions (5.2)]. | • 750 mg/3 mL sterile injection solution in single-use vials.  
• Other components of Aveed are a mixture of benzyl benzoate and refined castor oil. |
<table>
<thead>
<tr>
<th>Brand (generic/dosage form)</th>
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<th>Dosing</th>
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</tr>
</thead>
</table>
| **Testopel**® (testosterone pellet) | • Primary hypogonadism  
• Hypogonadotropic hypogonadism  
• Stimulate puberty in carefully selected males with clearly delayed puberty. | • Hypogonadism: 150 mg to 450 mg for SC implantation every 3 to 6 months.  
• Delayed puberty: doses are in the lower range and for a limited duration (~ 4 to 6 months). | • One 75 mg pellet per vial.  
• Other inactive ingredients include stearic acid and polyvinylpyrrolidone |

Limitation of use:  
• Safety and efficacy in men with "age-related hypogonadism" have not been established.

| Xyosted™ (testosterone enanthate injection) | • Primary hypogonadism  
• Hypogonadotropic hypogonadism | • Starting dose is 75 mg administered SC once a week.  
• Continuing dose is determined based on a testosterone trough concentration. Decrease the dose by 25 mg if > 650 ng/dL; Increase the dose by 25 mg if < 350 ng/dL; Maintain if > 350 ng/dL and < 650 ng/dL. | • Available in a single-dose autoinjector  
50 mg/0.5 mL  
75 mg/0.5 mL  
100 mg/0.5 mL |

Limitation of use:  
• Safety and efficacy in males < 18 years of age have not been established.  
• Safety and efficacy in men with "age-related hypogonadism" have not been established.

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**General Background**

**Overview**

Testosterone replacement regimens supply exogenous testosterone and restore serum testosterone levels in the normal range (300 to 1,000 ng/dL). Testosterone level increases in males until 17 years of age and stabilizes to a serum level in the range of 300 to 1,000 ng/dL, until about 40 years of age. After this, the levels begin to decline at 1.2% to 2% per year. About 20% of men > 60 years of age and 50% of men > 80 years of age are estimated to have serum testosterone levels that are subnormal compared with younger men. (Lee, 2008)

Male hypogonadism is characterized by low serum levels of testosterone and is classified according to the level of the hypothalamus-pituitary-testis axis involvement. (Giagulli, 2011) It is classified as primary hypogonadism when the main problem involves the testes (elevated lutenizing hormone [LH] and follicle stimulating hormone [FSH]). It is secondary hypogonadism (hypogonadotropic hypogonadism) if the hypothalamus/pituitary axis are involved; low testosterone levels in this case are associated with low or inadequately normal levels of LH and FSH. The diagnosis of male hypogonadism is based on both signs/symptoms and low testosterone levels. By restoring normal levels of testosterone, the replacement regimens correct symptoms of hypogonadism, which can include malaise, loss of muscle strength, depressed mood, and decreased libido. (Lee, 2008)

Testosterone regimens can be administered orally, parenterally, or transdermally. Injectable testosterone replacement products include Depo-Testosterone (testosterone cypionate) for intramuscular [IM] use, Delatestryl (testosterone enanthate) for IM use, Xyosted (testosterone enanthate) for subcutaneous [SC] use, Aveed injections for IM use, and Testopel, which is implanted subcutaneously. These agents are all indicated in adult men for use in congenital or acquired primary hypogonadism and hypogonadotropic hypogonadism (secondary hypogonadism). Testopel and Delatestryl (testosterone enanthate) are also indicated for delayed puberty. The safety and efficacy of Aveed and Xyosted in males < 18 years of age have not been established. Delatestryl (testosterone enanthate) may also be used secondarily in women with advanced inoperable metastatic...
mammary cancer that are 1 to 5 years postmenopausal. The goal of therapy is ablation of ovaries. It can also be used in premenopausal women with breast cancer that have benefited from oophorectomy and are considered to have hormone-responsive tumor. 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 non-obese 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 Aveed®, Xyosted™, or Testopel®

Experimental, Investigational, Unproven Uses
Compendia and other published clinical studies 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: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Covered when medically necessary when criteria in the applicable policy statements listed above are met:
**CPT® Codes**

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>11980†</td>
<td>Subcutaneous hormone pellet implantation (implantation of estradiol and/or testosterone pellets beneath the skin)</td>
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</table>

**HCPCS Codes**

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>S0189†</td>
<td>Testosterone pellet, 75 mg</td>
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**HCPCS Codes**

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<tbody>
<tr>
<td>J3145</td>
<td>Injection, testosterone undecanoate, 1 mg</td>
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</table>

*Note: Considered Experimental/Investigational/Unproven when used to report subcutaneous implantation of compounded testosterone for any indication.*


**References**