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Coverage Policy Number **IP0351**

Testosterone (Injectables and Implantable Pellets)

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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 policy supports medical necessity review for the following testosterone injectable and implantable pellet products:

Injectable Testosterone

- Aveed® (testosterone undecanoate intramuscular injection)
- Xyosted™ (testosterone enanthate subcutaneous injection)

Implantable Pellet Testosterone

- Testopel® (testosterone subcutaneous pellet)

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

The use of non-FDA approved hormone pellets, including compounded testosterone pellets, is addressed in a separate coverage policy. Please refer to the related coverage policy link above (Compounded Medications). Note: Testopel (testosterone) 75mg pellet is currently the only FDA approved pellet formulation of testosterone.

Coverage for treatment of gender dysphoria varies across plans. Coverage of drugs for hormonal therapy, as well as whether the drug is covered as a medical or a pharmacy benefit, varies across plans. Refer to the customer's benefit plan document for coverage details. In addition, coverage for treatment of gender dysphoria, including gender reassignment surgery and related services may be governed by state and/or federal mandates.[1]

Additional criteria that support the review for medical necessity exceptions of non-covered products are located in the Non-Covered Product Table by the respective plan type and drug list where applicable.

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

Medical Necessity Criteria

Testosterone injectable and implantable pellet products (Aveed, Xyosted, or Testopel) are considered medically necessary when the following are met:

1. **Hypogonadism in Males (Testicular Hypofunction/Low Testosterone with Symptoms).** Individual meets **ALL** of the following criteria:
    - A. Age 18 years or older
    - B. Documentation of **ONE** of the following:
        - i. Initial Therapy. **ALL** of the following are met:
            - a. Has had persistent pre-treatment signs and symptoms of androgen deficiency (for example depressed mood, decreased energy, progressive decrease in muscle mass, osteoporosis, and loss of libido)
            - b. Has had **TWO** pre-treatment serum testosterone (total or free) measurements, each taken in the early morning, on two separate days (free testosterone levels are to be measured by equilibrium dialysis assay)
            - c. The **TWO** serum testosterone levels (total or free) are **BOTH** low, as defined by the normal laboratory reference values.
        - ii. Currently Receiving Testosterone Therapy and Records are Available. **BOTH** of the following are met:
            - a. Has had persistent pre-treatment signs and symptoms of androgen deficiency (for example depressed mood, decreased energy, progressive decrease in muscle mass, osteoporosis, and loss of libido)
            - b. Has had at least **ONE** pre-treatment serum testosterone (total or free) measurement taken in the early morning, which was low, as defined by the normal laboratory reference values (free testosterone levels are to be measured by equilibrium dialysis assay)
        - iii. Currently Receiving Testosterone Therapy and There is a Loss of Records or an Inability to Provide Pre-treatment Clinical Information. The individual has a recent serum testosterone (total or free) measurement which indicates appropriate treatment (testosterone level within the normal laboratory reference values) while receiving testosterone replacement therapy (free testosterone levels are to be measured by equilibrium dialysis assay)
    - C. No concurrent use with other testosterone products
    - D. Preferred product criteria is met for the products listed in the below table(s)

Employer Group Products and Criteria:

Product	Criteria
Xyosted (testosterone enanthate injection)	**Standard/Performance/Value/Advantage/Cigna Total Savings Drug List Plans:** Documentation of failure, contraindication, or intolerance to **ONE** of the following: 1. Testosterone cypionate injection (Depo-testosterone) 2. Testosterone enanthate injection (Delatestryl)

Individual and Family Plan Products and Criteria:

Product	Criteria
Xyosted (testosterone enanthate injection)	Documentation of failure, contraindication, or intolerance to **ONE** of the following: 1. Testosterone cypionate injection (Depo-testosterone) 2. Testosterone enanthate injection (Delatestryl)

Dosing. **ONE** of the following dosing regimens:

1. Aveed: 750 mg administered intramuscularly, followed by 750 mg injected after 4 weeks, then 750 mg injected every 10 weeks thereafter
2. Testopel: Up to 150 mg to 450 mg subcutaneously up to every 3 to 6 months (for doses that exceed 6 pellets every 90 days refer to additional criteria in Reauthorization Criteria section)
3. Xyosted: Up to 100 mg subcutaneously once weekly

2. **Delayed Puberty or Induction of Puberty in Males [Testopel ONLY].** Individual meets **ALL** of the following criteria:
   A. Age 14 years or older
   B. Documentation of limited or no signs of puberty
   C. Testosterone is being used short term (4 to 6 months) to stimulate puberty

   Aveed and Xyosted are not indicated for the treatment of delayed puberty
   Dosing. Testopel: Up to 150 mg to 450 mg subcutaneously up to every 3 to 6 months (for doses that exceed 6 pellets every 90 days refer to additional criteria in Reauthorization Criteria section)

3. **Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Female-To-Male (FTM) Gender Reassignment (i.e., Endocrinologic Masculinization).** The medication is prescribed by, or in consultation with, an endocrinologist or a physician who specializes in the treatment of transgender individuals.

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.

Reauthorization Criteria

Continuation of testosterone injectable and implantable pellet products (Aveed, Xyosted, or Testopel) are considered medically necessary for ALL covered diagnoses when the above medical necessity criteria are met AND there is documentation of beneficial response.

Reauthorization of Testopel for continuing therapy **for dosages that exceed 6 pellets implanted every 90 days** requires **ALL** of the following criteria to be met**:**

1. Documentation of continued signs and symptoms of androgen deficiency
2. Documentation of a persistent low testosterone level (total or free) as defined by the normal laboratory reference values (free testosterone levels are to be measured by equilibrium dialysis assay)
3. Increments of up to 4 additional pellets are allowed

Authorization Duration

Initial approval duration:

1. Hypogonadism in Males (Testicular Hypofunction/Low Testosterone with Symptoms): up to 12 months
2. Delayed Puberty or Induction of Puberty in Males [**Testopel ONLY**]: up to 6 months
3. Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Female-To-Male (FTM) Gender Reassignment (i.e., Endocrinologic Masculinization): up to 12 months

Reauthorization approval duration:

1. Hypogonadism in Males (Testicular Hypofunction/Low Testosterone with Symptoms): up to 12 months
2. Delayed Puberty or Induction of Puberty in Males [**Testopel ONLY**]: Not applicable for continuation beyond initial approval duration
3. Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Female-To-Male (FTM) Gender Reassignment (i.e., Endocrinologic Masculinization): up to 12 months

Aveed and Xyosted are not indicated for the treatment of delayed puberty

Conditions Not Covered

Any other use is considered not medically necessary, including the following (this list may not be all inclusive):

1. **To Enhance Athletic Performance.**

Coding 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.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
11980	Subcutaneous hormone pellet implantation (implantation of estradiol and/or testosterone pellets beneath the skin)

HCPCS Codes	Description
J3145	Injection, testosterone, undecanoate, 1 mg
S0189	Testosterone pellet, 75 mg

Background

OVERVIEW

Testosterone regimens can be administered orally, parenterally, or transdermally. All the injectable agents are indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.[1-5] The prescribing information defines those patients and/or conditions for which testosterone replacement products are indicated:

- **Primary hypogonadism (congenital or acquired),** for testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, or orchiectomy.
- **Hypogonadotropic hypogonadism (congenital or acquired),** for gonadotropin or luteinizing hormone-releasing hormone deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation.

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.[6]

Testopel and Delatestryl (testosterone enanthate) are also indicated for **delayed puberty.**[2,3] Delatestryl (testosterone enanthate) [per the product labeling] may also be used secondarily in **advanced inoperable metastatic mammary cancer** in women who are 1 to 5 years postmenopausal.[2] The goal of therapy is ablation of ovaries. Per labeling, it also can be used in premenopausal women with breast cancer that have benefited from oophorectomy and are considered to have hormone-responsive tumors.

Dosing Information

Testosterone injections are used in clinical practice as intramuscular or subcutaneous injections. For Depo-Testosterone and Delatestryl, as replacement therapy for male hypogonadism, the suggested dose is 50 to 400 mg every 2 to 4 weeks.[1,2] In general, total doses of above 400 mg per month are not required because of prolonged action of the preparation.[2] For delayed puberty, various dosage regimens have been used, but dosage is generally within the range of 50 to 200 mg every 2 to 4 weeks.[2] The suggested dosage for testosterone injection varies depending on the age, sex, and diagnosis of the individual patient; dosage is adjusted according to the patient's response and the appearance of adverse reactions.[1-3] 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.[4] The suggested dose for Testopel (testosterone pellet) is 150 mg to 450 mg subcutaneously every 3 to 6 months; dosages for delayed puberty are generally in the lower range.[3] Xyosted is administered subcutaneously once weekly[5] and dosages above 100 mg per week have not been studied.

Guidelines

- **Hypogonadism:** Guidelines from the American Urological Association (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.[7] 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. Clinical diagnosis should be made when patients have low testosterone levels combined with signs and symptoms. 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).[8]
- **Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Female-To-Male Gender Reassignment (i.e., Endocrinologic Masculinization):** A clinical practice guideline published by the Endocrine Society (2017) recommends that, prior to initiation of hormonal therapy, the treating endocrinologist should confirm the diagnostic criteria of gender dysphoria/gender incongruence and the criteria for the endocrine phase of gender transition.[9] The clinician should also evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment. Guidelines mention that clinicians can use either parenteral or transdermal preparations to achieve appropriate testosterone values. Testosterone regimens for transgender males include testosterone enanthate or cypionate of 100 mg to 200 mg intramuscularly every 2 weeks or subcutaneously 50% per week.

References

1. Depo®-Testosterone [prescribing information]. New York, NY: Pfizer; August 2018.
2. Testosterone enanthate injection [prescribing information]. Berkeley Heights, NJ: Hikma; January 2021.
3. Testopel® [prescribing information]. Malvern, PA: Endo; August 2018.
4. Aveed™ [prescribing information]. Malvern, PA: Endo; August 2021.
5. Xyosted [prescribing information]. Ewing, NJ: Antares; November 2019
6. Lee M. Erectile Dysfunction. Urologic Disorders. In: Dipiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A pathophysiologic approach. 8th ed. New York: McGraw Hill Medical; 2008: 1437-1454.
7. Mulhall JP, Trost LW, Brannigan RE, et al. Evaluation and Management of Testosterone Deficiency. American Urological Association. 2018. Available at: Testosterone Deficiency Guideline - American Urological Association (auanet.org). Accessed on October 12, 2022.
8. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2018;103(5):1715-1744.
9. Hembree WC, Cohen-Kettenis P, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2017; 102(11):3869-3903.