VENTURA COUNTY
HEALTH CARE PLAN

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Testosterone Injectable Products Utilization Management Medical Policy

- Depo®-Testosterone (testosterone cypionate intramuscular injection – Pfizer, generic)
- Delatestryl® (testosterone enanthate intramuscular injection – Hikma, generic only)
- Aveed™ (testosterone undecanoate intramuscular injection – Endo)
- Testopel® (testosterone subcutaneous pellet – Endo)
- Xyosted™ (testosterone enanthate subcutaneous injection – Antares)

REVIEW DATE: 10/19/2022

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.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of injectable testosterone. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. In the clinical criteria, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: males are defined as individuals with the biological traits of a male, regardless of the individual's gender identity or gender expression; females are defined as individuals with the biological traits of a female, regardless of the individual's gender identity or gender expression. Because of the specialized skills required for evaluation and diagnosis of patients treated with injectable testosterone as well as the monitoring required for adverse events and long-term efficacy, some approvals require injectable testosterone to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of injectable testosterone as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory reports, prescription claims records, prescription receipts, and/or other information. For patient cases in which documentation is required, if this documentation has been previously received upon a prior coverage review, the documentation requirement is considered to be met.

Automation: None.

*Indications and/or approval conditions noted with **[eviCore]** are managed by eviCore healthcare for those clients who use eviCore for oncology and/or oncology-related reviews. For these conditions, a prior authorization review should be directed to eviCore at www.eviCore.com.*

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of injectable testosterone are recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. **Hypogonadism (Primary or Secondary) in Males* [Testicular Hypofunction/Low Testosterone with Symptoms].** Approve for 1 year if the patient meets the following criteria (A or B):
   Note: The pre-treatment timeframe refers to signs and symptoms of androgen deficiency and serum testosterone levels prior to the administration of any testosterone therapy.
   - **A)** Initial Therapy. Approve in a patient with hypogonadism as confirmed by the following criteria (i, ii, and iii):
     - **i.** Patient has had persistent signs and symptoms of androgen deficiency (pre-treatment); AND
       Note: Signs and symptoms of androgen deficiency include depressed mood, decreased energy, progressive decrease in muscle mass, osteoporosis, and loss of libido.
     - **ii.** Patient has had two pre-treatment serum testosterone (total or bioavailable) measurements **[documentation required]**, each taken in the morning, on two separate days; AND
     - **iii.** The two serum testosterone levels are both low, as defined by the normal laboratory reference values **[documentation required]**.
   - **B)** Patients Currently Receiving Testosterone Therapy. Approve if the patient meets the following criteria (i and ii):
     - **i.** Patient has had persistent signs and symptoms of androgen deficiency (pre-treatment); AND
       Note: Signs and symptoms of androgen deficiency include depressed mood, decreased energy, progressive decrease in muscle mass, osteoporosis, and loss of libido.
     - **ii.** Patient has had at least one pre-treatment serum testosterone (total or bioavailable) level **[documentation required]**, which was low, as defined by the normal laboratory reference values **[documentation required]**.

   *Refer to the Policy Statement

   Dosing. Approve the following dosing regimens (A, B, C, D, or E):
   - **A)** Depo-Testosterone (testosterone cypionate intramuscular injection, generic): Up to 400 mg administered subcutaneously or intramuscularly every 1 to 4 weeks, not to exceed 400 mg every 2 weeks; OR
   - **B)** Delatestryl (testosterone enanthate intramuscular injection, generic): Up to 400 mg administered subcutaneously or intramuscularly every 1 to 4 weeks, not to exceed 400 mg every 2 weeks; OR
   - **C)** Aveed: 750 mg administered intramuscularly, followed by 750 mg injected after 4 weeks, then 750 mg injected every 10 weeks thereafter; OR
   - **D)** Testopel: Up to 150 mg to 450 mg subcutaneously up to every 3 to 6 months; OR
   - **E)** Xyosted: Up to 100 mg subcutaneously once weekly.

2. **Delayed Puberty or Induction of Puberty in Males* 14 years of Age or Older.** Approve Depo-Testosterone (testosterone cypionate), Delatestryl (testosterone enanthate), or Testopel for 6 months

   *Refer to the Policy Statement

   Dosing. Approve the following dosing regimens (A, B, or C):
   A) Depo-Testosterone (testosterone cypionate intramuscular injection, generic): Up to 400 mg administered subcutaneously or intramuscularly every 1 to 4 weeks, not to exceed 400 mg every 2 weeks; OR
   B) Delatestryl (testosterone enanthate intramuscular injection, generic): Up to 400 mg administered subcutaneously or intramuscularly every 1 to 4 weeks, not to exceed 400 mg every 2 weeks; OR
   C) Testopel: Up to 150 mg to 450 mg subcutaneously up to every 3 to 6 months; OR

3. **Breast Cancer in Females* *[eviCore]*.** Approve Delatestryl (testosterone enanthate) for 6 months if prescribed by for in consultation with an oncologist.

   *Refer to the Policy Statement

   Dosing. Approve up to 400 mg administered subcutaneous or intramuscularly every 2 to 4 weeks.

Other Uses with Supportive Evidence

4. **Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Female-to-Male (FTM) Gender Reassignment (i.e., Endocrinologic Masculinization).** Approve for 1 year if prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of transgender patients.
   Note: For a patient who has undergone gender reassignment, use this FTM criterion for hypogonadism indication.

   Dosing. Approve the following dosing regimens (A, B, C, D, or E):
   A) Depo-Testosterone (testosterone cypionate intramuscular injection, generic): Up to 400 mg administered subcutaneously or intramuscularly every 1 to 4 weeks, not to exceed 400 mg every 2 weeks; OR
   B) Delatestryl (testosterone enanthate intramuscular injection, generic): Up to 400 mg administered subcutaneously or intramuscularly every 1 to 4 weeks, not to exceed 400 mg every 2 weeks; OR
   C) Aveed: 750 mg administered intramuscularly, followed by 750 mg injected after 4 weeks, then 750 mg injected every 10 weeks thereafter; OR
   D) Testopel: Up to 150 mg to 450 mg subcutaneously up to every 3 to 6 months; OR
   E) Xyosted: Up to 100 mg subcutaneously once weekly.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of injectable testosterone is not recommended in the following situations:

1. **To Enhance Athletic Performance.** Injectable testosterone products are not recommended for approval because this indication is excluded from coverage in a typical pharmacy benefit.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	12/01/2021
Early Annual Revision	**Hypogonadism:** "Patient continuing therapy" was updated to "Patient currently receiving testosterone therapy". **Documentation:** The following statement was added to the Policy Statement: "For patient cases in which documentation is required, if this documentation has been previously received upon a prior coverage review, the documentation requirement is considered to be met".	10/19/2022