



PRIOR AUTHORIZATION POLICY

POLICY: Testosterone (Injectable) Products

- Depo® – Testosterone (testosterone cypionate injection – Pfizer, generics)
- Delatestryl® (testosterone enanthate injection – Actavis Pharma, Inc., generics only)
- Aveed™ (testosterone undecanoate injection – Endo Pharmaceuticals, Inc.)
- Testopel® (testosterone pellet – Endo Pharmaceuticals, Inc.)
- Xyosted™ (testosterone enanthate injection – Antares Pharma, Inc.)

TAC APPROVAL DATE: 8/15/2018; selected revision 11/7/2018

OVERVIEW

Testosterone replacement regimens supply exogenous testosterone and restore serum testosterone levels in the normal range (300 to 1,000 ng/dL).⁴ 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.

Male hypogonadism is characterized by low serum levels of testosterone and is classified according to the level of the hypothalamus-pituitary-testis axis involvement.⁶ It is classified as primary hypogonadism when the main problem involves the testes (elevated luteinizing 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.⁴

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.^{4,7} These agents are all indicated in adult men for use in congenital or acquired primary hypogonadism and hypogonadotropic hypogonadism (secondary hypogonadism).^{1-3,7,12} Testopel and Delatestryl (testosterone enanthate) are also indicated for delayed puberty.²⁻³ Delatestryl (testosterone enanthate) may also be used secondarily in women with advanced inoperable metastatic mammary cancer that are 1 to 5 years postmenopausal.²

Guidelines

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.⁸ 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.

Endocrine Society

The Endocrine Society recommends 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).⁹

The World Professional Association for Transgender Health (WPATH)

The WPATH Standards of Care document (2011) states that exogenous administration of hormone therapy to induce feminizing or masculinizing changes is a medically necessary intervention for many transsexual, transgender, and gender nonconforming individuals with gender dysphoria.¹⁰

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of injectable testosterone (e.g., testosterone cypionate, testosterone enanthate, Aveed, Testopel, Xyosted). All approvals are provided for the duration noted below. 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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of injectable testosterone (e.g., testosterone cypionate, testosterone enanthate, Aveed, Testopel, Xyosted) is recommended in those who meet the following criteria:

FDA-Approved Indications

1. Hypogonadism (Primary or Secondary) in Males* [Testicular Hypofunction/Low Testosterone with Symptoms].

A) Initial Therapy. Approve for 1 year in patients with hypogonadism as confirmed by the following criteria (i, ii, and iii):

- i.** Patient has had persistent signs and symptoms (e.g., depressed mood, decreased energy, progressive decrease in muscle mass, osteoporosis, loss of libido) of androgen deficiency (pre-treatment); AND
- ii.** Patient has had two pre-treatment serum testosterone (total or bioavailable) measurements, 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.

B) Patients Continuing Therapy. Approve for 1 year if the patient meets the following criteria (i and ii):

- i.** Patient has had persistent signs and symptoms (e.g., depressed mood, decreased energy, progressive decrease in muscle mass, osteoporosis, loss of libido) of androgen deficiency (pre-treatment); AND
- ii.** Patient has had at least one pre-treatment serum testosterone (total or bioavailable) level, which was low, as defined by the normal laboratory reference values.

* Refer to the Policy Statement.

Note: The pre-treatment timeframe refers to signs and symptoms of androgen deficiency and serum testosterone levels prior to the initiation of any testosterone therapy.

The injectable testosterone products are indicated for primary and secondary hypogonadism (congenital or acquired). The limitation of use for these products states that safety and efficacy in men with “age-related hypogonadism” (also referred to as “late-onset hypogonadism”) have not been established. The diagnosis of androgen deficiency or hypogonadism is made only in men with consistent signs and symptoms, along with unequivocally low serum testosterone levels.⁹ The guidelines and prescribing information recommend confirming the diagnosis of hypogonadism by ensuring that serum testosterone concentrations have been measured in the morning on at least two separate days and that the measured testosterone concentrations are below the normal range.

- 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.

Evidence supports the use of injectable testosterone agents for delayed puberty.¹¹ The safety and efficacy of Aveed and Xyosted in males < 18 years of age have not been established.^{7,12}

- 3. Palliative Treatment of Inoperable Metastatic Breast Cancer in Females*** Approve Delatestryl (testosterone enanthate) injection in women for 6 months if it is prescribed by or in consultation with an oncologist.

* Refer to the Policy Statement.

Testosterone enanthate may be used secondarily in women with advanced inoperable metastatic breast cancer that are 1 to 5 years postmenopausal.² 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.

Other Uses with Supportive Evidence

- 4. 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 patients who have undergone gender reassignment, use this FTM criterion for hypogonadism indication.

Clinical studies have demonstrated the efficacy of several different androgen preparations (i.e., oral, parenteral, or transdermal testosterone) to induce masculinization in FTM transsexual persons. Regimens to change secondary sex characteristics follow the general principle of hormone replacement treatment of male hypogonadism. A clinical practice guideline published by the Endocrine Society, 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.⁵ 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.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Injectable testosterone (e.g., testosterone cypionate, testosterone enanthate, Aveed, Testopel) has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

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; October 2017.
2. Testosterone enanthate injection [prescribing information]. Parsippany, NJ: Actavis Pharma, Inc.; December 2017.
3. Testopel[®] [prescribing information]. Malvern, PA: Endo Pharmaceuticals, Inc.; October 2016.
4. Lee M. Erectile Dysfunction. Urologic Disorders. In: Dipro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A pathophysiologic approach. 8th ed. New York: McGraw Hill Medical; 2008: 1437-1454.
5. 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.
6. Giagulli VA, Triggiani V, Corona G, et al. Evidence-based medicine update on testosterone replacement therapy (TRT) in male hypogonadism: Focus on new formulations. *Curr Pharm Des.* 2011;17:1500-1511.
7. Aveed[™] [prescribing information]. Malvern, PA: Endo Pharmaceuticals Solutions Inc.; January 2018.
8. Mulhall JP, Trost LW, Brannigan RE, et al. Evaluation and Management of Testosterone Deficiency. American Urological Association. 2018. Available at: [http://www.auanet.org/guidelines/testosterone-deficiency-\(2018\)](http://www.auanet.org/guidelines/testosterone-deficiency-(2018)). Accessed on August 1, 2018.
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10. Coleman E, Bockting W, Botzer M, et al. Standards of care for the health of transsexual, transgender, and gender nonconforming people. The World Professional Association for Transgender Health. 7th Version. *International Journal of Transgenderism.* 2011;13:165-232.
11. Palmert MR, Dunkel L. Clinical Practice. Delayed Puberty. *N Engl J Med.* 2012;366:443-453.
12. Xyosted [prescribing information]. Ewing, NJ: Antares Pharma, Inc.; September 2018.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Early annual revision	Added criteria for hypogonadism requiring two separate pretreatment serum testosterone measurements which are low to confirm diagnosis, along with persistent signs and symptoms of androgen deficiency. Delatestryl brand is now archived in IDF (since 2011), only generics available.	09/09/2015
Selected revision	Added criteria for patients Continuation Therapy. The Continuation Therapy only asks for one pre-treatment serum testosterone level. Also defined Hypogonadism as “testicular hypofunction/low testosterone with symptoms” to clarify for prescribers. Also clarified in Initial therapy that the two pre-treatment serum testosterone measurements had to be taken “on two separate days”.	11/18/2015
Early annual revision	Under Conditions Not Recommended for Approval deleted the following: “Use in females for indications other than female-to-male gender reassignment and palliative treatment of metastatic breast cancer,” “Use in males with carcinoma of the breast” and “Use in males with known or suspected carcinoma of the prostate.”	08/17/2016
Selected revision	In the Policy Statement, added legal language to define males and females specified in approval indications. This is noted with “*” next to “males” or “females” in the indication. A note was added below the approval criteria to refer to the Policy Statement.	10/05/2016
Annual revision	Added “Note” to use gender reassignment criterion for patients who have undergone reassignment and have hypogonadism.	08/09/2017
Annual revision	No criteria changes	08/15/2018
Selected revision	Added Xyosted subcutaneous (testosterone enanthate) to the policy. This product is added as an approved product for hypogonadism (primary or secondary) in males and for female-to-male gender reassignment with the same approval criteria as already in the policy.	11/7/2018

* For a further summary of criteria changes, refer to respective TAC minutes available at: <http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx>; TAC – Therapeutic Assessment Committee.