MEDICAL MUTUAL®

Drug Policy

Policy:	**201602**	**Initial Effective Date: 03/03/2016** **Annual Review Date: 11/21/2023** **Last Revised Date: 01/18/2023**
Code(s):	**HCPCS J1071, J3121, J3145, J3490 and S0189**	
SUBJECT:	**Testosterone Injection and Pellet:** • **Aveed (testosterone undecanoate)** • **Testosterone enanthate IM** • **Depo-Testosterone (testosterone cypionate)** • **Testone CIK** • **Testopel (testosterone) pellet (for SQ implantation)** • **Testosterone propionate** • **Xyosted (testosterone enanthate injection SQ)**	

☐Subject to Site of Care

OVERVIEW

Endogenous androgens are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. Some of these effects include alterations in body musculature and maturation of prostate, seminal vesicles, penis and scrotum. Androgens are also responsible for the growth spurt of adolescence and for the eventual termination of linear growth. Exogenous androgens in children can accelerate linear growth rates but may also cause a disproportionate advancement in bone maturation.

Testosterone replacement regimens supply exogenous testosterone and restore serum testosterone levels in the normal range (300 to 1,000 ng/dL). The International Society of Andrology (ISA), International Society for the Study of the Aging Male (ISSAM), European Association of Urology (EAU), European Academy of Andrology (EAA), and the American Society of Andrology (ASA) propose 230 ng/dL as the lower limit of serum testosterone at which patients will benefit from testosterone replacement therapy. The Endocrine Society recommends 300 ng/dL, and the American Association of Clinical Endocrinologists (AACE) suggests 200 ng/dL as the lower limit for initiating testosterone replacement. 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. Given this inherent variability in testosterone levels in men based on age, it is also prudent to consider other variables that could affect a laboratory drawn testosterone level (e.g., time of day when the level is drawn, laboratory specific normal values for testosterone, total vs. free testosterone levels) before initiating replacement therapy.

Male hypogonadism is characterized by low serum levels of testosterone and is classified according to the level of the hypothalamus-pituitary-testis axis involvement. 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 a clinical suspicion 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.

Testosterone regimens can be administered orally, parenterally, or transdermally. Injectable testosterone replacement products include testosterone cypionate, testosterone propionate, testosterone enanthate, and Aveed injections, and Testopel, which is implanted subcutaneously. These agents are all indicated for congenital or acquired primary hypogonadism and hypogonadotropic hypogonadism (secondary hypogonadism). Testopel and Testosterone enanthate are also indicated for delayed puberty. Testosterone enanthate may also be used secondarily in women with advanced inoperable metastatic mammary cancer that are 1 to 5 years postmenopausal. The primary goal of this therapy is to ablate the ovaries. It can also be used in premenopausal women with breast cancer who have benefited from oophorectomy and are considered to have a hormone-responsive tumor. The prescribing information notes that the judgment regarding the use of androgen therapy in females should be made by an oncologist with expertise in the area. Compared with the other two intramuscular injections, Aveed has a longer duration between dosing after it reaches steady state levels. After the first injection, a second injection is administered after 4 weeks. After this second dosing, subsequent administration is once every 10 weeks. Dose titration is not necessary. The safety and efficacy of Aveed in males < 18 years of age have not been established.

POLICY STATEMENT

This policy involves the use of testosterone injection and pellet formulations. Prior authorization is recommended for pharmacy benefit coverage of testosterone injection and pellet formulations. Approval is recommended for those who meet the conditions of coverage in the **Criteria and Initial/Extended Approval** for the diagnosis provided. **Conditions Not Recommended for Approval** are listed following the recommended authorization criteria. Requests for uses not listed in this policy will be reviewed for evidence of efficacy and for medical necessity on a case-by-case basis.

Because of the specialized skills required for evaluation and diagnosis of patients treated with testosterone injection and pellet products, as well as the monitoring required for adverse events and long-term efficacy, initial approval requires testosterone injection and pellet formulations be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is allowed, a response to therapy is required for continuation of therapy unless otherwise noted below. Topical Testosterone (including nasal) and oral testosterone products should be evaluated based on the criteria found in the "Testosterone Topical and Oral" policy.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of testosterone injection or pellet formulations are recommended in those who meet the following criteria:

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

Criteria. *Patient must meet the following criteria (A or B):*

A. Initial Therapy (a and b):
   a. The patient has had persistent signs and symptoms (for example, depressed mood, decreased energy, progressive decrease in muscle mass, osteoporosis, loss of libido) of androgen deficiency (pre-treatment); AND
   b. The patient has had two pre-treatment serum testosterone measurements, each taken in the morning on two separate days, and both levels were low, as defined by the normal laboratory reference values.

B. Continuation of therapy (a AND b):
   a. Prior to treatment, the patient has had persistent signs and symptoms (for example, depressed mood, decreased energy, progressive decrease in muscle mass, osteoporosis, loss of libido) of androgen deficiency; AND
   b. The patient has had at least one total serum testosterone level within the last 6 months within or below the normal limits of the reporting lab OR one total serum testosterone level beyond the normal limits despite a dose adjustment.

Injectable dosing in hypogonadism:

I. Depo-testosterone:
   i. 50-400 mg IM every 2 to 4 weeks; OR
   ii. 75 to 100 mg IM every week; OR
   iii. 150 to 200 mg IM every 2 weeks

   Note: Administration of 800 mg once every 4 weeks is not FDA approved dosing for the above indication with testosterone cypionate.

II. Testosterone enanthate:
   i. 50 to 400 mg IM every 2 to 4 weeks.

   Note: Administration of 800 mg once every 4 weeks is not FDA approved dosing for the above indications with testosterone enanthate.

III. Aveed:
   i. 3 mL (750 mg) IM, followed by 3 mL (750 mg) IM after 4 weeks, then 3 mL (750 mg) IM every 10 weeks thereafter.

IV. Xyosted:
   i. Follows FDA approved dosing.

V. Testopel:
   i. 150 mg – 450 mg SC every 3 to 6 months
   ii. For Initial Therapy:
      1. Approve up to 6 pellets; OR
      2. If patient has BMI of ≥ 25, approve up to 12 pellets
   iii. For Continuation Therapy:
      1. If request is for up to 6 pellets, approve.

2. If request is for 7 to 12 pellets, approve if:
    a. Patient has BMI of ≥25; OR
    b. Patient has not responded to lower dose confirmed by a morning serum testosterone level that is not within the mid-normal range of 250-500ng/dl 1 month after initiation of testosterone therapy.

2. Delayed Puberty or Induction of Puberty in Males 14 to 25 Years of Age (Testosterone cypionate, testosterone enanthate and Testopel)

Criteria. *Approve if the medication is being prescribed for the treatment of hypogonadism (primary or secondary) in a male patient, delayed puberty or induction of puberty in a male patient 14 to 18 years of age for testosterone cypionate or 14 to 25 years of age for testosterone enanthate.*

Injectable dosing in males with delayed puberty:

a. Depo-testosterone:
    i. 50-100mg every 2 to 4 weeks for a limited duration, for example, 4-6 months.
b. Testosterone enanthate:
    i. 50-200 mg IM every 2 to 4 weeks for a limited duration, for example, 4 to 6 months.
c. Testopel:
    i. 150 mg – 450 mg SC every 3 to 6 months
    ii. For Initial Therapy:
        i. Approve up to 6 pellets; OR
        ii. If patient has BMI of ≥ 25, approve up to 12 pellets
    iii. For Continuation Therapy:
        i. If request is for up to 6 pellets, approve.
        ii. If request is for 7 to 12 pellets, approve if:
            1. Patient has BMI of ≥25; OR
            2. Patient has not responded to lower dose confirmed by a morning serum testosterone level that is not within the mid-normal range of 250-500ng/dl 1 month after initiation of testosterone therapy.

3. Palliative Treatment of Inoperable Metastatic Breast Cancer in Females (Testosterone enanthate)

Criteria. *Approve if the medication is being prescribed by, or in consultation with, an oncologist.*

Injectable dosing in palliation of inoperable mammary cancer in woman:

a. Testosterone enanthate:
    i. 200 to 400 mg IM every 2 to 4 weeks.

Initial Approval/ Extended Approval.

A) *Initial Approval:* 6 months for delayed puberty/induction of puberty and inoperable metastatic breast cancer
1 year for hypogonadism in males and female-to-male gender reassignment

B) *Extended Approval:* 6 months for delayed puberty/induction of puberty and inoperable metastatic breast cancer

1 year for hypogonadism in males and female-to-male gender reassignment

OTHER USES WITH SUPPORTIVE EVIDENCE

4. <u>Female-to-Male (FTM) Gender Reassignment (i.e., Endocrinologic Masculinization, Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Female-To-Male (FTM) Gender Reassignment)</u> Criteria. *Approve for 365 days if the requested medication is being prescribed by, or in consultation with, an endocrinologist or a physician who specializes in the treatment of transgender patients.*

Initial Approval/ Extended Approval.

A) *Initial Approval:* 6 months for delayed puberty/induction of puberty and inoperable metastatic breast cancer
1 year for hypogonadism in males and female-to-male gender reassignment

B) *Extended Approval:* 6 months for delayed puberty/induction of puberty and inoperable metastatic breast cancer
1 year for hypogonadism in males and female-to-male gender reassignment

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. (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.

Documentation Requirements:

The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the drug provided or services performed were not medically necessary, investigational or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

REFERENCES

1. Depo®-Testosterone [prescribing information]. New York, NY: Pfizer; August 2018.

2. Delatestryl® [prescribing information]. Lexington, MA: Indevus Pharmaceuticals, Inc.; August 2014.
3. Testopel® [prescribing information]. Morrisville, NC: Slate Pharma; August 2018.
4. 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.
5. 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.
6. Aveed™ [prescribing information]. Malvern, PA: Endo Pharmaceuticals Solutions Inc.; June 2020.
7. Xyosted [prescribing information]. Ewing, NJ: Antares Pharma, Inc.; November 2019

8. Paduch DA, Brannigan RE, Fuchs EF, et al. The laboratory diagnosis of testosterone deficiency. White paper. American Urological Association, Inc. Available at: http://www.auanet.org/common/pdf/education/clinical-guidance/Testosterone-Deficiency-WhitePaper.pdf. Accessed on October 2, 2015.
9. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2010;95(6):2536-2559.
10. Alenazi MS, Alqahtani AM, Ahmad MM, Almalki EM, AlMutair A, Almalki M. Puberty Induction in Adolescent Males: Current Practice. Cureus. 2022 Apr 5;14(4):e23864. doi: 10.7759/cureus.23864. PMID: 35530907; PMCID: PMC9073269.
11. 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.
12. Palmert MR, Dunkel L. Clinical Practice. Delayed Puberty. *N Engl J Med.* 2012;366:443-453.
13. Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, et al. Endocrine treatment of the transsexual persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2009; 94:3132-3154.
14. Wierman ME, Basson R, Davis SR, et al. Androgen therapy in women: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2006;91(10):3697-3710.
15. American College of Obstetricians and Gynecologists Committee on Practice Bulletins-Gynecology. ACOG Practice Bulletin No. 119: Female sexual dysfunction. *Obstet Gynecol*. 2011;117(4):996-1007 (reaffirmed 2013).
16. Sipe CS, Thomas MR, Stegmann BJ, van Voorhis BJ. Effects of exogenous testosterone supplementation in gonadotrophin stimulated cycles. *Hum Reprod*. 2010;25(3):690-696.
17. 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.