

Clinical Criteria

Subject:	Testosterone, Injectable		
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Overview

This document addresses indications for the intramuscular (IM) and subcutaneous (SC) administration of testosterone injectables for the treatment of hormone deficient conditions. The following testosterone injection agents are included:

- Testosterone cypionate intramuscular: Depo-Testosterone, generic testosterone cypionate
- Testosterone enanthate:
 - Intramuscular: generic testosterone enanthate
 - Subcutaneous: Xyosted (auto-injector)
- Testosterone undecanoate intramuscular: Aveed

Testosterone is an androgen hormone responsible for normal growth and development of male sex characteristics. In certain medical conditions such as hypogonadism, the endogenous level of testosterone falls below normal levels. Primary hypogonadism includes conditions such as testicular failure due to cryptorchidism, bilateral torsion, orchitis, or vanishing testis syndrome; bilateral orchidectomy; and inborn errors in the biosynthesis of testosterone. Secondary hypogonadism, also called hypogonadotropic hypogonadism includes conditions such as gonadotropin-releasing hormone (GnRH) deficiency or pituitary-hypothalamic injury resulting from tumors, trauma, surgery, or radiation.

In 2015, the Endocrine Society added the following amended recommendations:

- Men with metabolic syndrome, who were previously unexamined by the 2010 Endocrine Society Clinical Practice Guidelines, may benefit from testosterone replacement therapy (TRT) based on improvements in biometrics and insulin sensitivity. Effects of TRT on similar endpoints in men with type 2 diabetes mellitus remain unclear;
- Effects of TRT on erectile function, even in men refractory to phosphodiesterase type 5 inhibitors, and on quality of life in men with erectile dysfunction remain inconclusive (Seftel, 2015).

The Endocrine Society published clinical practice guidelines on Testosterone Therapy in Men with Androgen Deficiency in 2006, with an update published in 2018 (Bhasin). The 2018 guidelines included the following statements for the diagnosis of androgen deficiency and therapy with testosterone replacement:

- We recommend making the diagnosis of hypogonadism in men with consistent symptoms and signs and unequivocally and consistently low serum testosterone levels. (Strong recommendation; moderate quality of evidence);
- We recommend testosterone therapy in hypogonadal men to induce and maintain secondary sex characteristics and correct symptoms of testosterone deficiency (Strong recommendation; moderate quality of evidence);
- We recommend against testosterone therapy in men planning fertility in the near term or men with breast or prostate cancer, a palpable prostate nodule or induration
- We recommend against testosterone therapy in men planning fertility in the near term or in men with breast or prostate cancer, a palpable prostate nodule or induration, a prostate-specific antigen level > 4 ng/mL, a prostate-specific antigen level > 3 ng/mL combined with a high risk of prostate cancer (without further urological evaluation), elevated hematocrit, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms, uncontrolled heart failure, myocardial infarction or stroke within the last 6 months, or thrombophilia (Strong recommendation; low quality of evidence).
- We suggest that clinicians assess prostate cancer risk in men being considered for testosterone therapy. (Conditional recommendation; very low quality of evidence);
- We suggest against routinely prescribing testosterone therapy to all men 65 years or older with low testosterone concentrations (Strong recommendation; low quality of evidence).

- In men > 65 years who have symptoms or conditions suggestive of testosterone deficiency (such as low libido or unexplained anemia) and consistently and unequivocally low morning testosterone concentrations, we suggest that clinicians offer testosterone therapy on an individualized basis after explicit discussion of the potential risks and benefits. (Conditional recommendation, very low quality of evidence);
- We suggest initiating testosterone therapy with any of the following regimens (75 to 100 mg of testosterone enanthate or cypionate administered IM weekly, or 150 to 200 mg administered every 2 weeks, injectable testosterone undecanoate; also patches, gel, buccal tablets, implanted pellets) chosen on the basis of the patient's preference, consideration of pharmacokinetics, treatment burden, and cost. (Weak recommendation; strength of evidence low).

An established diagnosis of hypogonadism with androgen deficiency includes appropriate evaluation and diagnostic workup of a man who presents with symptoms of hypogonadism. Clinical Practice Guidelines recommend measuring serum testosterone only in men with consistent clinical manifestations of hypogonadism. Screening in asymptomatic populations is not recommended. Measurement of serum total testosterone is initially used; serum-free testosterone levels can be measured when total testosterone is in the low normal range and alterations of serum hormone-binding globulin are suspected. Once a persistently low testosterone level has been established, diagnostic testing of the hypothalamic-pituitary axis should be performed to distinguish primary hypogonadism from secondary hypogonadism. When secondary hypogonadism is identified, the underlying etiology should be identified, and any reversible causes treated appropriately prior to consideration of testosterone replacement.

Persistently low testosterone levels refers to serum levels that are below the lower limit of normal on at least two occasions when measured in the early morning. The threshold lower limit for serum testosterone levels is not standardized. The Endocrine Society recommends that a lower limit for normal levels is 264 ng/dL* for total testosterone and 9.0 ng/dL for free testosterone... We suggest monitoring testosterone levels 3 to 6 months after initiation of testosterone therapy and then annually to assess whether symptoms have responded to treatment and whether the individual is suffering from any adverse effects. Therapy should aim to raise the serum testosterone level into the mid-normal range. For injectable testosterone enanthate or cypionate: measure serum testosterone level midway between injections. If testosterone is > 700 ng/dl (24.5 nmol/liter) or < 400 ng/dl (14.1 nmol/liter), adjust dose or frequency. Testosterone pellets, measure testosterone levels at the end of dosing intervals. Adjust the number of pellets and/or the dosing interval to achieve serum testosterone levels in the normal range. (Bhasin, 2010)

**Lower limit of normal for total testosterone (TT) harmonized to the CDC standard in healthy nonobese young men; this limit could be used for TT assays that are CDC certified. For laboratories that are not CDC certified, reference range may vary considerably depending on assay and reference population used.*

The Endocrine Society also provided the following list of specific symptoms of hypogonadism:

- Incomplete or delayed sexual development;
- Decreased libido;
- Decreased spontaneous erections;
- Breast discomfort, gynecomastia;
- Loss of axillary and/or pubic body hair;
- Very small (<5 mL) or shrinking testes;
- Infertility due to low sperm count;
- Height loss due to vertebral fractures, low trauma fractures, low bone density;
- Hot flushes, sweats (Bhasin, 2010).

Regarding hypogonadism associated with male aging, in 2009 the International Society for the Study of Aging Male, the International Society of Andrology, the European Association of Urology, the European Academy of Andrology, and the American Society of Andrology issued joint guidelines on the treatment and monitoring of late-onset hypogonadism which provided the following:

The diagnosis of treatable hypogonadism requires the presence of symptoms and signs suggestive of testosterone deficiency (Grade A recommendation; level of evidence 3). The symptom most associated with hypogonadism is low libido (Grade A recommendation; level of evidence 3). Other manifestations of hypogonadism include erectile dysfunction, decreased muscle mass and strength, increased body fat, decreased bone mineral density and osteoporosis, decreased vitality, and depressed mood. None of these symptoms are specific to the low androgen state but may raise suspicion of testosterone deficiency. One or more of these symptoms must be corroborated with a low serum testosterone level (Grade A recommendation; level of evidence 3).

Presentations of natural testosterone should be used for substitution therapy. Currently available intramuscular, subdermal, transdermal, oral, and buccal preparations of testosterone are safe and effective (Grade A recommendations; level of evidence 1b). The selection of the preparation should be a joint decision of an informed patient and physician (Wang, 2009).

Aveed (testosterone undecanoate) is an intramuscular injection approved in May 2015. Because Aveed is an oil based injection, it has a black box warning regarding the risks for serious pulmonary oil microembolism (POME) reactions and anaphylaxis. Individuals should be observed in the healthcare setting for 30 minutes post-injection in order to monitor and, if needed, provide for medical treatment in the event of POME or anaphylaxis. Because of this, Aveed is available only through a restricted REMS program (www.aveedrems.com).

Xyosted (testosterone enanthate) is a subcutaneous testosterone injection approved in September 2018. Xyosted has a black box warning regarding possible blood pressure increases that can lead to major adverse cardiovascular events (MACE). Prior to initiation, baseline cardiovascular risk should be assessed and blood pressure should be adequately controlled. New onset hypertension or

exacerbation of existing hypertension should be cause for re-evaluation of risk versus benefit for continuation of therapy. Due to this risk, Xyosted should only be used for the treatment of men with hypogonadal conditions associated with structural or genetic etiologies.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Testosterone injections for Symptomatic Hypogonadism (Primary or Secondary) in Adults

Requests for testosterone injections **for initiation of replacement therapy** in the treatment of hypogonadism may be approved if the following criteria are met:

- I. Individual is a male; **AND**
 - II. Individual is 18 years or older; **AND**
 - III. Prior to starting testosterone therapy, an initial and a repeat (at least 24 hours apart) morning total testosterone level is provided to confirm a low testosterone serum level indicating one of the following (A or B);
 - A. Individual is 70 years of age or younger with a serum testosterone level of less than 300 ng/dL; **OR**
 - B. Individual is over 70 years of age with a serum testosterone level of less than 200 ng/dL;
- AND**
- IV. Individual has a diagnosis of **one** of the following (A or B):
 - A. Primary hypogonadism (congenital or acquired) (for example, bilateral torsion, cryptorchidism, chemotherapy, Klinefelter Syndrome, orchitis, orchiectomy, toxic damage from alcohol or heavy metals, Vanishing Testis Syndrome, idiopathic primary hypogonadism, age-related hypogonadism [also referred to as late-onset hypogonadism]); **OR**
 - B. Hypogonadotropic hypogonadism (also called secondary hypogonadism) (congenital or acquired) (for example, idiopathic gonadotropic or luteinizing hormone-releasing hormone (LHRH) deficiency, pituitary-hypothalamic injury); **AND**
 - V. Individual presents with symptoms associated with hypogonadism, such as, but not limited, to at least **one** of the following (A through I):
 - A. Reduced sexual desire (libido) and activity; **OR**
 - B. Decreased spontaneous erections; **OR**
 - C. Breast discomfort/gynecomastia; **OR**
 - D. Loss of body (axillary and pubic) hair, reduced need for shaving; **OR**
 - E. Very small (especially less than 5 mL) or shrinking testes; **OR**
 - F. Inability to father children or low/zero sperm count; **OR**
 - G. Height loss, low trauma fracture, low bone mineral density; **OR**
 - H. Hot flashes, sweats; **OR**
 - I. Other less specific signs and symptoms including decreased energy, depressed mood/dysthymia, irritability, sleep disturbance, poor concentration/memory, diminished physical or work performance.

Requests for testosterone injections **for continuation of replacement therapy** may be approved if the following criteria are met:

- I. Individual met all diagnostic criteria for initial therapy; **AND**
- II. Individual has had serum testosterone level measured in the previous 180 days; **AND**
- III. Individual has obtained clinical benefits as noted by symptom improvement.

Testosterone injections **for replacement therapy** may not be approved for the following:

- I. Untreated obstructive sleep apnea (OSA); **OR**
- II. Polycythemia as defined by hematocrit greater than 48% and 50% for men living at higher altitudes (Bhasin et al, 2018); **OR**
- III. Severe congestive heart failure (CHF); **OR**
- IV. Known, suspected, or history of prostate cancer unless individual has undergone radical prostatectomy, prostate cancer was organ-confined, has been disease free for two (2) years and has an undetectable prostate-specific antigen (PSA) level (such as <0.1 ng/dL); **OR**
- IV-V. Individual is requesting Xyosted (testosterone enanthate) subcutaneous autoinjector for hypogonadal conditions, such as "age-related hypogonadism," that are not associated with structural or genetic etiologies.

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Testosterone injections for delayed puberty

Requests for **testosterone enanthate injections** (Delatestryl) for treatment of delayed puberty may be approved if the following criteria are met:

- I. Individual is a male 14 years of age or older; **AND**
- II. Individual is using to stimulate puberty; **AND**
- III. Documentation is provided indicating few to no signs of puberty.

Testosterone enanthate injections for treatment of delayed puberty may not be approved for the following:

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- I. Individual is requesting Xyosted (testosterone enanthate) subcutaneous autoinjector.

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Testosterone injections for breast cancer

Requests for **testosterone enanthate injections (Delatestryl)** for treatment of **breast cancer** may be approved if the following criteria are met:

- I. Female 1-5 years post-menopause; **AND**
 - II. Individual is using secondarily for advanced inoperable metastatic (skeletal) breast cancer;
- OR**
- III. Premenopausal female who has benefited from oophorectomy and is considered to have a hormone responsive tumor.

Testosterone enanthate injections for treatment of breast cancer may not be approved for the following:

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- I. Individual is requesting Xyosted (testosterone enanthate) subcutaneous autoinjector.

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Testosterone injections for HIV-associated weight loss and wasting

Requests for **testosterone enanthate (Delatestryl)** **OR** **testosterone cypionate injections** for treatment of **HIV-associated weight loss and wasting** may be approved if the following criteria are met (AHFS):

- I. Individual has been diagnosed with low testosterone; **AND**
- II. Individual has HIV-associated weight loss and wasting.

Testosterone injections for treatment of HIV-associated weight loss and wasting may not be approved for the following:

- I. Individual is requesting Xyosted (testosterone enanthate) subcutaneous autoinjector.

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Testosterone injections for transgender individuals

Requests for **testosterone injections for transgender individuals** may be approved if the following criteria are met:

- I. Individual is 16 years of age or older; **AND**
- II. Individual has a diagnosis of gender dysphoria/incongruence or gender identity disorder (DrugDex B, IIa); **AND**
- III. The goal of treatment is female-to-male gender reassignment.

Testosterone injections for transgender individuals may not be approved for the following:

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- I. Individual is requesting Xyosted (testosterone enanthate) subcutaneous autoinjector.

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Requests for testosterone injections may not be approved when the above criteria are not met and for all other indications.

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Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J1071	Injection, testosterone cypionate, 1 mg [Depo®-Testosterone]
J3121	Injection, testosterone enanthate, 1 mg [Delatestryl®]
J3145	Injection, testosterone undecanoate, 1 mg [Aveed®]
J3490	Unclassified drugs when specified as Xyosted

C9399 Unclassified drugs or biologicals when specified as Xyosted

ICD-10 Diagnosis

All diagnoses

Document history

Revised: 08/16/2019

Document History:

- 08/16/2019 – Annual Review: Update criteria to restrict use of Xyosted due to black box warning and contraindications. Coding Reviewed: No changes.
- 05/21/2019 – Coding Reviewed: Added HCPCS J3490, C9399 for Xyosted
- 03/18/2019 – Select Review (Xyosted): Wording and formatting changes. Coding Reviewed: No changes
- 11/09/2018 – Coding Review: No changes needed
- 08/07/2018 – Annual Review: Annual review. First review of Testosterone injections; Updated definition of polycythemia based on 2018 guidelines.

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