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Section:	Prescription Drugs	**Effective Date:**	October 1, 2024
Subsection:	Endocrine and Metabolic Drugs	**Original Policy Date:**	May 30, 2014
Subject:	Testosterone Injection Implant	**Page:**	1 of 11

Last Review Date: September 6, 2024

Testosterone Injection and Implant

Description

Aveed (testosterone undecanoate injection), Delatestryl (testosterone enanthate injection), Depo-Testosterone (testosterone cypionate injection), Testopel (testosterone propionate implant), Xyosted (testosterone enanthate injection)

Background
Endogenous androgens, including testosterone and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics (1).

Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone concentrations. Symptoms associated with male hypogonadism include the following: impotence and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics, and osteoporosis (1).

Androgens stimulate growth in adolescence and cause the eventual closure of the femoral epiphysis. In children, exogenous androgens accelerate linear growth rates but may cause a disproportionate advancement in bone maturation. Chronic use may result in fusion of the epiphyseal growth centers and termination of growth process. Androgens have been shown to stimulate the red blood cell production by the increased production of erythropoietic stimulating factor (2).

Regulatory Status
FDA-approved indications: (3-7)

1. Primary hypogonadism (congenital or acquired): testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range.

2. Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations but have gonadotropins in the normal or low range.

3. Delayed puberty in males***:*** to induce pubertal changes in hypogonadal males.

4. In women as secondary treatment with advancing inoperable metastatic (skeletal) mammary cancer who are 1 to 5 years postmenopausal. This treatment has also been used in premenopausal women with breast cancer who have benefitted from oophorectomy and are considered to have a hormone-responsive tumor (4).

Off-Label Use:
Testosterone can be used in the treatment of Gender Dysphoria (GD) and should only be started once a diagnosis of GD or transsexualism has been made per the DSM V or ICD-10 criteria (9).

Aveed carries a boxed warning which states that serious pulmonary oil microembolism (POME) reactions, involving urge to cough, dyspnea, throat tightening, chest pain, dizziness, and syncope; and episodes of anaphylaxis, including life-threatening reactions, have been reported to occur during or immediately after the administration of testosterone undecanoate injection. Because of the risk of this reaction and anaphylaxis, testosterone undecanoate is available only through a restricted program under a risk evaluation and mitigation strategy (REMS) called the Aveed REMS Program. These reactions can occur after any injection of testosterone undecanoate during the course of therapy, including after the first dose. The REMS program ensures the prescriber observes the patient in the health care setting for 30 minutes following each injection in order to provide appropriate medical treatment in the event of serious POME reactions or anaphylaxis (3).

Xyosted has a boxed warning that it can increase blood pressure (BP) which can increase the risk of major adverse cardiovascular events, including non-fatal myocardial infarction, non-fatal

stroke, and cardiovascular death. Before initiating Xyosted, patients' baseline cardiovascular risk should be considered and blood pressure should be controlled. Patients should be monitored periodically for new-onset hypertension and they should be re-evaluated whether the benefits of Xyosted outweigh its risks in patients who develop cardiovascular risk factors or cardiovascular disease on treatment (7).

Chronic high dose therapy of androgens has shown development of peliosis hepatitis and hepatic neoplasms including hepatocellular carcinoma. Peliosis hepatitis can be a life-threatening or fatal complication. Low doses of 17-alpha-alkylandrogens have been associated with cholestatic hepatitis and jaundice. The medication should be discontinued and the cause should be determined if these conditions occur. Drug-induced jaundice is reversible upon withdrawal of medication therapy (3-7).

Male patients, with benign prostatic hyperplasia (BPH), must be monitored for worsening of signs and symptoms of BPH. Physicians should evaluate male patients for the presence of prostate cancer prior to the initiation of therapy. A normal prostate cancer risk is a PSA level that is less than 4 ng/ml. High prostate cancer risk patients, such as African American men and men whose father or brother had prostate cancer, should have a PSA less than 3 ng/ml. Check prostate-specific antigen (PSA) levels in men over age 40 to ensure proper dosing. Patients should be re-evaluated 12 months after initiation of treatment, and then in accordance with prostate cancer screening practices (3-7).

Two total testosterone levels are required to determine medical necessity of testosterone replacement. Two morning samples, drawn between 8:00 a.m. and 10:00 a.m., obtained on different days are required. Total testosterone levels need to be below 300 ng/dL on both days in order to be considered for therapy (8).

Hematocrit levels must be less than 54% prior to initiation of testosterone therapy and reevaluated annually thereafter (3-7).

Androgen use for delayed puberty in males should be prescribed only by specialists who are aware of the adverse effects on bone maturation. An X-ray of the hand and wrist every 6 months will be required to determine bone age and to assess the effect of treatment on the epiphyseal centers (4).

Androgen therapy in the treatment for women with breast cancer should be made by an oncologist with expertise in this field. Hypercalcemia may occur in immobilized patients and in

patients with breast cancer. If hypercalcemia occurs, the testosterone therapy should be discontinued (4).

Extreme caution should be used in patients with a history of cardiovascular disease (2).

Patients with severe obstructive sleep apnea and severe lower urinary tract symptoms are recommended not to use androgen therapy due to possible worsening of symptoms and/or even death (2).

Related policies
Testosterone oral / buccal / nasal, Testosterone powder, Testosterone topical

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Testosterone implant/injectable medications may be considered **medically necessary** if the conditions indicated below are met.

Testosterone implant/injectable medications may be considered **investigational** for all other indications.

Prior-Approval Requirements

Age 12 years of age or older
Gender Male
Diagnosis
Delatestryl, Depo-Testosterone, and Testopel only

Patient must have the following:
Delay in sexual development and/or puberty
a. **NO** dual therapy with another testosterone product

AND confirmation that the following will be monitored every 6 months:
1. Assess bone age of the hand and wrist (as determined by radiographic evidence)
2. Liver function tests

3. Hematocrit levels

Age 18 years of age or older
Gender Male
Diagnosis

Patient must have the following:
Deficiency of testosterone (hypogonadism)

AND ALL of the following:
1. Two morning total testosterone levels less than 300 ng/dL on different days
2. Patients over 40 years of age must have baseline PSA less than 4 ng/ml
    a. Prostatectomy patients excluded from the requirement
3. Absence of current prostate cancer / palpable prostate nodules
4. Hematocrit less than 54%
5. If concurrent diagnosis of benign prostatic hypertrophy (BPH), then patient will be monitored for worsening symptoms
6. Evaluation of cardiovascular risk for MI, angina, stroke
7. Absence of un-treated sleep apnea
8. **NO** dual therapy with another testosterone product
9. **Aveed only:** Physician has been certified by the Aveed REMS program
10. **Xyosted only:** Patient has been counseled that Xyosted can increase blood pressure and the risk of major adverse cardiovascular events

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Age 18 years of age or older
Gender Female only
Diagnosis
Delatestryl only

Patient must have the following:
1. Inoperable metastatic breast or mammary cancer
2. The patient has received at least one prior therapy
3. **NO** dual therapy with another testosterone product

AND confirmation that the following will be monitored every 6 months:
a. Hypercalcemia and agreement to discontinue the drug if present

b. Liver function tests
c. Hematocrit level

Diagnosis
Aveed, Delatestryl/Xyosted, Depo-Testosterone, Testopel only

The patient must have the following:

Gender Dysphoria (GD)

1. Female to male transition
2. **NO** dual therapy with another testosterone product
3. **Aveed only:** Physician has been certified by the Aveed REMS program
4. **Xyosted only:** Patient has been counseled that Xyosted can increase blood pressure and the risk of major adverse cardiovascular events

Prior – Approval *Renewal* Requirements

Age 12 years of age or older
Gender Male only

Same as above

Age 18 years of age or older
Gender Male
Diagnosis

Patient must have the following:
Deficiency of testosterone (hypogonadism)

AND the following:

1. Total testosterone levels of 800 ng/dL or less
2. Absence of worsening effects of benign prostatic hypertrophy (BPH), if present
3. Re-evaluation of cardiovascular risk for MI, angina, stroke
4. **NO** dual therapy with another testosterone product

AND confirmation that the following will be monitored every 12 months:

1. Serum testosterone concentrations
2. Prostate specific antigen (PSA) for patients over 40 years of age
   a. Prostatectomy patients excluded from the requirement
3. Hematocrit levels

Age 18 years of age or older
Gender Female only

Same as above

Diagnosis
Aveed, Delatestryl/Xyosted, Depo-Testosterone, Testopel only

The patient must have the following:

Gender Dysphoria (GD)

1. Female to male transition
2. **NO** dual therapy with another testosterone product

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Quantity

Injectable Testosterone		Gender	Quantity	Days Supply
Aveed (18 years of age or older)		Male	6ml	90
Delatestryl (testosterone enanthate)		Male	15ml	90
		Female	15ml	90
Depo-Testosterone (testosterone cypionate)	100mg/ml	Male	30ml	90
	200mg/ml	Male	30ml	90
Xyosted autoinjector		Male	12	84

(testosterone enanthate)		autoinjectors	
Implant Testosterone	**Gender**	**Quantity**	**Days Supply**
Testopel Pellet	Male	6 pellets	90

Duration 6 months for all diagnoses except GD
2 years for GD

Prior – Approval *Renewal* Limits

Quantity

Injectable Testosterone		**Gender**	**Quantity**	**Days Supply**
Aveed (18 years of age or older)		Male	6ml	90
Delatestryl (testosterone enanthate)		Male	15ml	90
		Female	15ml	90
Depo-Testosterone (testosterone cypionate)	100mg/ml	Male	30ml	90
	200mg/ml	Male	30ml	90
Xyosted autoinjector (testosterone enanthate)		Male	12 autoinjectors	84
Implant Testosterone		**Gender**	**Quantity**	**Days Supply**
Testopel Pellet		Male (18 years of age or older)	6 pellets	90
		Male (12-17 years of age)	6 pellets	90 *One renewal only

Duration 12 months for all diagnoses except GD
2 years for GD

Rationale

Summary

Testosterone is approved for testosterone replacement therapy in men for conditions associated with a deficiency of testosterone such as: hypogonadotropic hypogonadism (congenital or

acquired), primary hypogonadism (congenital or acquired), and delayed puberty. In women, testosterone therapy is approved to treat metastatic breast carcinoma (3-7).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use of the testosterone products Aveed (testosterone undecanoate injection), Delatestryl/Xyosted (testosterone enanthate injection), Depo-Testosterone (testosterone cypionate injection), and Testopel (testosterone propionate implant) while maintaining optimal therapeutic outcomes.

References

1. Male Hypogonadism. Mayo Foundation for Medical Education and Research: 1998-2014.
2. Bhasin S, Cunningham GR, Hayes FJ et al. Testosterone therapy in men with androgen deficiency syndromes: an endocrine society clinical practice guideline*. J Clin Endocrinol Metab.* 2010;95(6):2536-59.
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4. Delatestryl [package insert]. Malvern, PA: Endo Pharmaceuticals Inc.; October 2016.
5. Depo-Testosterone [package insert]. New York, NY: Pharmacia and Upjohn Co.; August 2020.
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8. Carnegie C. Diagnosis of Hypogonadism: Clinical Assessments and Laboratory Tests. Rev Urol. 2004; 6(Suppl 6): S3-S8. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1472884.
9. Hembree, WC, Cohen-Kettenis, P, et al. Endocrine Treatment of Transsexual Persons: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab..* 2009; 94(9):3132-3154.

Policy History

Date	Action
June 2014	Addition to PA
June 2014	Removal of absence of severe sleep apnea, severe lower urinary tract symptoms and addition of hematocrit level of 54% Revision of testosterone levels for continuation
August 2014	Revision of diagnosis for male patients 18 years or older to deficiency of testosterone/hypogonadism. Revision of renewal duration to 12 months.
October 2014	Revision on the Delatestryl and Depo-Testosterone injectable quantities to accommodate vial sizes. Change of age from 9 to 12 years of age for delayed puberty.

December 2014	Annual review and reference update. Change for patients over 40 years of age must have baseline PSA less than 4 ng/ml and prostatectomy patients excluded from the requirement
March 2015	Annual review and reference update.
April 2015	Addition of assessment of cardiovascular risk to criteria
June 2015	Addition of Testone CIK Addition of the evaluation of cardiovascular risk for MI, angina, stroke and absence of un-treated sleep apnea and no dual therapy with another testosterone product
September 2015	Annual review
December 2015	Annual review Addition of Gender Dysphoria (GD) use and duration
May 2016	Addition of transgender specialist to GD prescriber requirement Policy number change from 5.08.33 to 5.30.33
June 2016	Annual review
September 2016	Annual review and reference update
January 2017	Removal of GD age requirement
March 2017	Annual Review
December 2017	Annual editorial review and reference update Removal of Testone CIK
October 2018	Addition of Xyosted
November 2018	Annual editorial review and reference update
March 2019	Annual review
July 2019	Added gender dysphoria diagnosis for Xyosted. Changed approval duration for gender dysphoria from lifetime to 2 years
September 2019	Annual review
December 2020	Annual review and reference update
December 2021	Annual review and reference update
September 2022	Annual review
December 2022	Annual review. Removed GD requirements of meeting DSM criteria and being prescribed by an endocrinologist or transgender specialist
September 2023	Annual review
September 2024	Annual review

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on September 6, 2024 and is effective on October 1, 2024.