



PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 1/01/15
LAST REVIEW DATE: 6/27/19
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TESTOSTERONE REPLACEMENT THERAPY:
ANDRODERM® transdermal patch
ANDROGEL® pump transdermal gel and transdermal gel
ANDROID (methyltestosterone) oral capsule
ANDROXY™ (fluoxymesterone) oral tablet
AXIRON® transdermal solution
FORTESTA® transdermal gel
METHITEST™ (methyltestosterone) oral tablet
METHYLTESTOSTERONE oral capsule
NATESTO™ nasal gel
STRIANT® buccal mucoadhesive system
TESTIM® transdermal gel (preferred agent)
TESTOSTERONE pump transdermal gel and transdermal gel
TESTRED (methyltestosterone) oral capsule
VOGELXO® pump transdermal gel and transdermal gel
XYOSTED™ (testosterone enanthate) solution auto-injector

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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TESTOSTERONE REPLACEMENT THERAPY (cont.)

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

Criteria:

- **Criteria for initial therapy: For male individuals** Testosterone Replacement Therapy is considered **medically necessary** and will be approved when **ALL** of the following criteria are met:
1. A confirmed diagnosis of **ONE** of the following:
 - Male individual 18 years of age or older with an established diagnosis of hypogonadism with multiple clinical signs and symptoms consistent with hypogonadism
 - HIV-infected male individual 18 years of age or older with documented weight loss
 - Male individual 18 years of age or older on chronic corticosteroid treatment (use greater than 6 weeks) with persistently low testosterone levels
 - Individual 14 years or older with delayed male puberty and pre-pubertal testis
 2. Has persistently low baseline testosterone levels defined as **ONE** of the following:
 - Total testosterone level less than the reference lab normal value on two separate occasions (copy of laboratory data must be submitted with the request)
 - Serum free testosterone level **and** total testosterone less than reference lab normal on the same day (copy of laboratory data must be submitted with the request)
 3. Androgen/testosterone deficiency diagnosis is not made during an acute or sub-acute illness
 4. Individual has failure, intolerance or contraindication to **Testim, brand or generic** (documentation from the prescriber must be submitted)
 5. Complete physical examination, including a digital prostate examination done within the last 12 months with continued monitoring as clinically appropriate

TESTOSTERONE REPLACEMENT THERAPY (cont.)

6. There is no uncontrolled or poorly controlled heart failure
7. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
 - Liver function tests
 - Hematocrit is < 50%
 - Prostate specific antigen (PSA) measurement done within the last 12 months with continued monitoring as clinically appropriate
 - Baseline HbA1C
8. There are **NO** contraindications.
 - Contraindications include:
 - Men with known carcinoma of the breast or known or suspected carcinoma of the prostate
 - Known hypersensitivity to drug product

Initial approval duration: 12 months

- **Criteria for initial therapy:** For female individuals Testosterone Replacement Therapy is considered **medically necessary** and will be approved when **ALL** of the following criteria are met:

1. Women with a diagnosis of metastatic / inoperable breast cancer
2. There are **NO** contraindications.
 - Contraindications include:
 - Woman of child bearing potential who is pregnant or not currently using effective contraception
 - Woman who is breast feeding an infant or child

Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request):** Testosterone product is considered **medically necessary** and will be approved when **ALL** of the following criteria are met:

1. The individual has met all of the initial criteria for Testosterone Replacement Therapy
2. The individual's condition responded while on therapy
 - Response is defined as:
 - For hypogonadism with clinical signs and symptoms consistent with hypogonadism
 - Testosterone levels are within the normal range with therapy
 - Clinical symptoms have improved
 - Hematocrit is < 54%
 - For HIV-infected male individual 18 years of age or older with documented weight loss

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- Increase in weight over baseline of 1.1-1.54 kg body weight **OR** increase 1.4 kg fat-free mass **OR** increase 1.22-1.3 kg lean body mass
 - Hematocrit is < 54%
 - For male individual 18 years of age or older on chronic corticosteroid treatment
 - Continues to require chronic corticosteroid therapy
 - Hematocrit is < 54%
 - For individual 14 years or older with delayed male puberty and pre-pubertal testis
 - Secondary male sex characteristics have developed but have not reached full development (*once fully developed, testosterone replacement therapy is no longer needed*)
 - Cryptorchidism is still present or there is evidence of small testes
 - Hematocrit is < 54%
 - Determine bone age obtained every six months to assess the effect of treatment on the epiphyseal centers
 - For women with a diagnosis of metastatic / inoperable breast cancer
 - There is no disease progression
3. Individual has been adherent with the medication
4. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
- Contraindications as listed in the criteria for initial therapy section
 - Significant adverse effect such as:
 - Developed DVT or PE
 - Severe hepatotoxicity such as peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, jaundice
 - Hematocrit is persistently > 54%

Renewal duration: 12 months

Description:

Testosterone is an androgen hormone that is responsible for normal growth and maintenance of male secondary sex characteristics, stimulation and maintenance of sexual function in males, growth spurt seen in adolescents, lean body mass and weight, and other physiologic functions. Testosterone is produced in males by the testes in response to stimuli from the hypothalamic and pituitary glands. Low serum testosterone is caused by deficient production of the hormone, and is also known as androgen deficiency. Other terms used to describe the clinical syndrome of low serum testosterone include testosterone deficiency syndrome, hypogonadism, late-onset hypogonadism, androgen insufficiency syndrome, andropause, low-T, and male menopause.

TESTOSTERONE REPLACEMENT THERAPY (cont.)

As men age there is a decrease in testosterone level and function. Cross-sectional and longitudinal studies confirm a decline of 1-2% per year. Symptoms of low testosterone may include one or more of the following: decrease in sexual activity, loss of libido or sexual interest, sexual thoughts or fantasies, erectile dysfunction, impotence, decrease in volume of ejaculate, decreased orgasmic intensity, irritability, depression and other mood disorders, nervousness, generalized weakness, loss of muscle mass and strength, osteoporosis with a potential for fractures, decrease in height, decrease in body hair, abdominal obesity, gynecomastia or breast tenderness, lack of energy, fatigue, sleep disturbances, poor ability to concentrate, and other symptoms. Expression of the clinical symptoms may vary depending upon the severity and cause of the disorder. It should be noted that androgen deficiency and erectile dysfunction are two independently distributed clinical disorders with distinct pathophysiology.

The clinical significance of age related decline in testosterone levels remains controversial. The same sign and symptoms may also be seen with aging but without a decrease in testosterone level. Androgen supplementation is increasingly being used as a lifestyle therapy for men who are older, frail, or want to look better or feel younger and stronger. There is continued debate on whether older men, with or without androgen deficiency and symptoms of hypogonadism, will benefit from long-term testosterone replacement therapy. There are no published long-term trials using meaningful outcomes in hypogonadal men or older men with low testosterone levels. Long-term risks of replacement therapy are also unclear. Some reported risks include potential worsening of cardiovascular disease, polycythemia, increased risk for benign prostatic hypertrophy and prostate cancer, lipid disturbances such as increased LDL and reduced HDL levels, worsening of obstructive sleep apnea, and sodium and water retention. Recent published studies have suggested an increased risk of cardiovascular events among groups of men prescribed testosterone therapy.

Symptoms along with measured low testosterone level may be indicative of testosterone deficiency syndrome in men. Normal total testosterone levels range from 280-300 to 1000 ng/dL and levels below 300 ng/dL typically result in symptoms. Serum free testosterone levels range is often given as 5-9 pg/mL. Testosterone levels vary from laboratory to laboratory dependent upon the type of assay used. Testing should be done in the morning, before 10 AM, due to diurnal cycle of testosterone. As men age there is a progressive decrease in both total testosterone and free testosterone levels.

Testosterone replacement therapy is primarily indicated for the treatment of male congenital or acquired hypogonadism when symptoms of hypogonadism are present along with low testosterone levels. Testosterone products are FDA-approved only for use in men who lack or have low testosterone levels in conjunction with an associated medical condition. Examples of these conditions include failure of the testicles to produce testosterone because of reasons such as genetic problems or chemotherapy. Other examples include problems with the hypothalamus and pituitary that control the production of testosterone by the testicles. None of the FDA-approved testosterone products are approved for use in men with low testosterone levels who lack an associated medical condition. Some products have FDA approval for the treatment of delayed puberty and androgen-responsive recurrent breast cancer in women who are 1-5 years post-menopausal.

The latest 2010 clinical practice guideline from the Endocrine Society recommend that only men who have unequivocally low serum testosterone levels AND signs and symptoms consistent with low testosterone be diagnosed and treated with testosterone replacement therapy. They recommend against routine screening for testosterone deficiency in the general population and they recommend against testosterone replacement therapy in ALL older men with low testosterone levels. They also do not recommend starting testosterone replacement therapy in male patients with breast or prostate cancer or in individuals with a palpable prostate nodule or

TESTOSTERONE REPLACEMENT THERAPY (cont.)

induration or prostate-specific antigen greater than 4 ng/mL or greater than 3 ng/mL in men at high risk for prostate cancer without further urological evaluation.

Multiple formulations of exogenous testosterone are available. Testosterone replacement therapy may be delivered by mouth (including buccal and nasal formulations), intramuscular injection, topically (as a gel, patch, solution, or cream formulations), or subcutaneously (using pellets).

Definitions:

Hypogonadism:

The clinical syndrome associated with androgen deficiency. The clinical syndrome results from failure of the testis to produce physiological levels of testosterone and normal number of spermatozoa due to disruption of one or more levels of the hypothalamic-pituitary-testicular axis. Symptoms are dependent upon age, severity of androgen deficiency, duration of androgen deficiency, individual sensitivity to androgen, and comorbid illness.

The Endocrine Society 2010 Clinical Practice Guidelines on Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes classifies signs and symptoms of hypogonadism as follows:

More specific signs and symptoms of hypogonadism:

- Breast discomfort, gynecomastia
- Decreased spontaneous erections
- Height loss, low trauma fracture, low bone mineral density
- Hot flashes, sweats
- Inability to father children, low or zero sperm count
- Incomplete or delayed sexual development, eunuchoidism
- Loss of body (axillary and pubic) hair, reduced shaving
- Reduced sexual desire (libido) and activity
- Very small (especially <5 ml) or shrinking testes

Less specific symptoms and signs of hypogonadism:

- Decreased energy, motivation, initiative, and self-confidence
- Diminished physical or work performance
- Feeling sad or blue, depressed mood, dysthymia
- Increased body fat, body mass index
- Mild anemia (normochromic, normocytic, in the female range)
- Poor concentration and memory
- Reduced muscle bulk and strength
- Sleep disturbance, increased sleepiness

Chronic Corticosteroid Treatment:

Corticosteroid used in men for the treatment of manifestations of a chronic condition, as opposed to episodic treatment for an acute condition or acute flare of a chronic condition. The length of acute episodic corticosteroid treatment may vary from several days to several months, but in most cases will be less than 4-6 weeks.

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Testosterone Products:

- Androderm® Transdermal Patch*
- Androgel® Pump Transdermal Gel*
- Androgel® Transdermal Gel*
- Android (methyltestosterone) oral capsule*
- Androxy™ (fluoxymesterone) oral tablet*
- Axiron® Transdermal Solution*
- Fortesta® Transdermal Gel*
- Methitest™ (methyltestosterone) oral tablet*
- Methyltestosterone oral capsule*
- Natesto™ Nasal Gel*
- Striant® Buccal Mucoadhesive System*
- **Testim® Transdermal Gel (brand or generic, preferred agent)***
- Testosterone Cypionate Intramuscular Solution
- Testosterone Enanthate Intramuscular Solution
- Testosterone Pump Transdermal Gel*
- Testosterone Transdermal Gel*
- Testred (methyltestosterone) oral capsule*
- Vogelxo® Pump Transdermal Gel*
- Vogelxo® Transdermal Gel*
- Xyosted™ (testosterone enanthate) injection*

* requires precertification

Resources:

5.01.23BCBS Association Medical Policy Reference Manual. Issue date 12/12/2013 Testosterone Replacement Therapies.

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 June, 95(6):2536-2599.

Vigen R, O'Donnell CI, Baron AE, et al. Association of Testosterone Therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA 2013; 310 (17):1829-1836.

Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with Testosterone administration. NEJM 2010; 363 (2):109-122.

Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following Testosterone Therapy prescription in men. PLOS ONE 2014 Jan; 9 (1)e85805:1-7.

UpToDate: Testosterone treatment of hypogonadism. Current through Jan 2018. https://www.uptodate.com.mwu.idm.oclc.org/contents/testosterone-treatment-of-male-hypogonadism?search=testosterone%20replacement&source=search_result&selectedTitle=1~68&usage_type=default&display_rank=1



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UpToDate: Diagnosis and treatment of delayed puberty. Current through Jan 2018. https://www.uptodate-com.mwu.idm.oclc.org/contents/diagnosis-and-treatment-of-delayed-puberty?sectionName=Testosterone%20therapy&anchor=H9&source=see_link#H9

UpToDate: Overview of testosterone deficiency in older men. Current through Jan 2018. https://www.uptodate-com.mwu.idm.oclc.org/contents/overview-of-testosterone-deficiency-in-older-men?source=see_link

Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: _____ Date: _____

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.