TESTOSTERONE REPLACEMENT THERAPY:
ANDRODERM® transdermal patch
ANDROGEL® pump transdermal gel and transdermal gel
AXIRON® transdermal solution
FORTESTA® transdermal gel
NATESTO™ nasal gel
STRIANT® buccal mucoadhesive system
TESTIM® transdermal gel (preferred agent)
TESTOSTERONE pump transdermal gel and transdermal gel
VOGELXO® pump transdermal gel and transdermal gel

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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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, andropause, low-T, and male menopause.

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 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.

Drug related events:
- **Ineffective / failure**
  Use of a drug employing optimal doses (FDA-recommended doses) for optimal duration; where the condition being treated has not improved or worsened

  A request for branded agent due to generic drug failure or ineffectiveness will be assessed for potential approval with documentation of use of optimal dose / duration of the generic product and meeting other criteria within the coverage guideline. When the drug in question is a combination product, there must be documentation of failure / ineffectiveness of concurrent use (each ingredient used at the same time) of individual generic components. When the drug in question is a low dose formulation, there must be documentation of failure / ineffectiveness of low dose generic formulation.

**Adverse Drug Event: Allergic reaction / Hypersensitivity / Intolerance**
Use of a drug produced a significant reaction where continued use of the drug places the individual at risk for either lack of improvement or worsening of the condition being treated or at risk for harm and the concern is documented in medical record. A significant adverse drug event is when an individual’s outcome is death, life-threatening, hospitalization (initial or prolonged), disability resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the individuals’ body function/structure, physical activities or quality of life, or requires intervention to prevent permanent impairment or damage.

*Allergic reaction / hypersensitivity* – may or may not involve the active ingredient. When the active ingredient is involved, use of same or a chemically similar agent places the individual at risk for harm when the same or chemically similar agent is used. The subsequent reaction may be the same as the original reaction or a more exaggerated response may be seen, potentially placing the individual at even greater risk for harm.

If the reaction occurred from the active/main generic ingredient; request for branded agent with same active ingredient will not be considered unless it is proven (documented) that active ingredient did not cause reaction and the request meets other criteria within the coverage guideline

*Intolerance* – these events represent circumstance(s) where use of a drug produced a significant reaction and continued use may result in non-adherence to proposed therapy and this concern is documented in medical record

**Contraindication**
Use of a drug that is not recommended by the manufacturer or FDA labelling

  Use of any drug in the face of a contraindication is outside of the FDA and manufacturer’s labelled recommendation and is considered investigational or experimental

**Non-adherence**
Individual does not follow prescribed regimen that places the individual at risk for lack of improvement or worsening of the condition being treated and this concern is documented in medical record
TESTOSTERONE REPLACEMENT THERAPY (cont.)

Testosterone Products:
- Androderm® Transdermal Patch*
- Androgel® Pump Transdermal Gel*
- Androgel® Transdermal Gel*
- Axiron® Transdermal Solution*
- Fortesta® Transdermal Gel*
- Natesto™ Nasal Gel*
- Striant® Buccal Mucoadhesive System*
- **Testim® Transdermal Gel (preferred agent)***
- Testosterone Cypionate Intramuscular Solution
- Testosterone Enanthate Intramuscular Solution
- Testosterone Pump Transdermal Gel*
- Testosterone Transdermal Gel*
- Vogelxo® Pump Transdermal Gel*
- Vogelxo® Transdermal Gel*

* requires precertification

Precertification:

Precertification (Prior Authorization) is required for members with a Blue Cross Blue Shield of Arizona (BCBSAZ) pharmacy benefit for medication(s) or product(s) indicated in this guideline.

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](http://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.

Criteria:

See “Resources” section for FDA-approved dosage.

- Precertification for Testosterone Replacement Therapy (with the exception of Testosterone Cypionate and Testosterone Enanthate) requires completion of the specific request form in its entirety. 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 will be returned.
FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Testosterone Replacement Therapy is considered *medically necessary* with medical record documentation of ALL of the following:

1. Individual has medical record documentation of a confirmed diagnosis of ONE of the following:
   - Male with an established diagnosis of hypogonadism with persistently low testosterone levels defined as ANY of the following:
     - Total testosterone level less than the reference lab normal value on two separate occasions
     - Serum free testosterone level and total testosterone less than reference lab normal on the same day
   - HIV-infected male with ALL of the following:
     - Low testosterone level less than the reference lab normal value on two separate occasions
     - Weight loss
   - Male on chronic (use greater than 6 weeks) corticosteroid treatment with low testosterone levels
   - Delayed male puberty with ALL of the following:
     - Age 14 years or older
     - Pre-pubertal testis
     - Total testosterone level less than the reference lab normal value on two separate occasions

2. Androgen/testosterone deficiency diagnosis is not made during an acute or sub-acute illness

3. Individual is unable to use preferred testosterone product – Brand Testim – due to ONE of the following (documentation from the prescriber must be submitted):
   - The condition did not improve or worsened when Testim was used
   - Experienced a significant hypersensitivity adverse drug event when Testim was used
   - Experienced a significant intolerant reaction when Testim was used

4. ALL of the following baseline tests have been completed before initiation of treatment:
   - Complete physical examination, including a digital prostate examination. A digital prostate examination should be done periodically during therapy
   - Prostate specific antigen (PSA) measurement

5. Absence of ALL of the following contraindications:
   - Men with known carcinoma of the breast or known or suspected carcinoma of the prostate

FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Testosterone Replacement Therapy is considered *medically necessary* with medical record documentation of ANY of the following:

1. Women with metastatic / inoperable breast cancer

2. Absence of ALL of the following contraindications:
   - Woman of child bearing potential who is pregnant or not currently using effective contraception
   - Woman who is breast feeding an infant or child
TESTOSTERONE REPLACEMENT THERAPY (cont.)

- **Continuation of coverage (renewal request):** Testosterone product is considered *medically necessary* with documentation of **ALL** of the following:
  1. The individual has benefited from therapy but remains at high risk
  2. The condition has not progressed or worsened while on therapy
  3. Individual has not developed any contraindications or other exclusions to its continued use

- Testosterone Replacement Therapy for all other indications not previously listed is considered *experimental or investigational* based upon:
  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

This includes but is not limited to the following:
  - Older men with low testosterone level in the absence of clinical signs and symptoms of hypogonadism

**Resources:**


