BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

TESTOSTERONE REPLACEMENT THERAPY:
ANDROGEL® pump transdermal gel
AZMIRO™ (testosterone cypionate) injection
JATENZO® (testosterone undecanoate) oral capsule
KYZATREX™ (testosterone undecanoate) oral capsule
METHITEST™ (methyltestosterone) oral tablet
Methyltestosterone oral capsule
NATESTO™ nasal gel
TESTIM® transdermal gel
TESTOPEL (testosterone) pellet
Testosterone pump transdermal gel and transdermal gel
TLANDO™ (testosterone undecanoate) oral capsule
UNDECATREX™ (testosterone undecanoate) oral capsule
VOGELXO® pump transdermal gel and transdermal gel
XYOSTED™ (testosterone enanthate) solution auto-injector
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and/or Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management

at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Medical Necessity Requirements for ANDROGEL, TESTIM, Testosterone generic, VOGELXO (pump transdermal gel and transdermal gel), NATESTO (nasal gel), and TESTOPEL (testosterone pellet)

Criteria for Initial Therapy:

Prescriber Qualifications

- Prescribed by an Endocrinologist, Urologist, HIV/AIDS Specialist, Pediatrician, or Infectious Disease specialist, or in consultation with one

Indication

- Male with primary hypogonadism (testicular origin; associated with structural or genetic etiologies) with at least **THREE** clinical signs and symptoms
- Male with hypogonadotropic hypogonadism (pituitary/hypothalamus origin; associated with structural or genetic etiologies) with at least **THREE** clinical signs and symptoms
- HIV infected male with unexplained involuntary weight loss greater than 10 percent of baseline body weight
- Male with chronic corticosteroid use (daily dose of at least 5 to 7.5 mg of prednisone or equivalent for at least 6 weeks)
- Delayed male puberty with pre pubertal testis

Age Requirement

- 18 years or older
- 14 years or older for delayed puberty

Baseline Clinical Evaluation

- Persistently low fasting morning (8 to 10 AM) baseline testosterone levels is defined as **ONE** of the following:
  - Total testosterone level less than the reference lab normal value on two separate occasions, must be obtained from the same laboratory or from a laboratory using the same assay (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)
- Diagnosis not made during acute or subacute illness
- Hematocrit is within normal range
- Male individual over age 50 years (or over age 40 years who has a first degree relative with prostate cancer or an unevaluated prostate nodule or induration or is African American) is screened for prostate cancer with **BOTH** of the following:

- Digital prostate examination done within the last 12 months with continued monitoring as clinically appropriate for age, race, and risk factors for prostate cancer
- Prostate specific antigen (PSA) measurement done within the last 12 months with continued monitoring as clinically appropriate for age, race, and risk factors for prostate cancer

Alternative Therapies

- Failure, contraindication, or intolerance to a **generic intramuscular testosterone injection**
- Failure, contraindication, or intolerance to **ONE** of the following:
  - Testosterone transdermal gel pump 20.25 mg/act (1.62 percent) (generic for Androgel pump)
  - Testosterone transdermal gel packet 50 mg/5gm (1 percent) (generic for Androgel 1 percent, Testim 1 percent, or Vogelxo 1 percent)

Brand Specific Criteria

- Have failure, contraindication, or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No concomitant use with other testosterone products
- **NONE** of the following:
  - Palpable prostate nodule
  - PSA greater than 4 ng/mL
  - PSA greater than 3 ng/mL in men with high risk for prostate cancer (e.g., African American, first degree relative with prostate cancer, unevaluated nodule, etc.) unless cleared by Urologist
  - Age related hypogonadism
  - Low testosterone without symptoms or symptoms without persistently low testosterone levels
  - Hematocrit greater than lab normal limits
  - Untreated severe obstructive sleep apnea
  - Severe lower urinary tract symptoms (AUA/IPSS greater than 19)
  - Uncontrolled or poorly controlled heart failure
  - **For Natesto only:** Nasal disorder, nasal/sinus surgery, nasal fracture within last 6 months, mucosal inflammatory disorder, or sinus disease
  - Carcinoma of the breast
  - Suspected carcinoma of the prostate
  - Carcinoma of the prostate unless there is documentation of **ONE** of the following:
    1. Individual has undergone radical prostatectomy or radiation therapy for prostate cancer
    2. Prostate cancer was organ confined
    3. Individual has been disease free for two years and has an undetectable PSA (such as less than 0.1 ng/dL)

Documentation Requirements

- A completed request form must be submitted including:
  - Chart notes

- Lab results (testosterone levels, PSA, hematocrit)
- Supporting clinical documentation

Initial Therapy Criteria Approval Duration

- 12 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy):

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Prescriber Qualification

- Continues to be seen by or in consultation with Endocrinologist, Urologist, HIV/AIDS Specialist, Pediatrician, or Infectious Disease specialist

Clinical Response

- Has met initial criteria for Testosterone Replacement Therapy
- Hypogonadism:
  - Fasting morning testosterone levels within normal range
  - Improved clinical symptoms
  - Hematocrit within normal limits
- HIV related weight loss:
  - Weight gain of 1.1 to 1.54 kg, increase of 1.4 kg in fat free mass, or increase of 1.22 to 1.3 kg in lean body mass
  - Hematocrit within normal limits
- Chronic corticosteroid use:
  - Ongoing corticosteroid therapy
  - Hematocrit within normal limits
- Delayed male puberty with pre pubertal testis
  - Secondary male sex characteristics developing but not fully developed (once fully developed, testosterone replacement therapy is no longer needed)
  - Cryptorchidism or small testes present
  - Bone age monitored every six months to assess the effect of treatment on the epiphyseal centers
  - Hematocrit within normal limits

Adherence

- Adherence to prescribed therapy regimen has been documented

Brand Specific Criteria

- Have failure, contraindication, or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

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Safety

- No concomitant use with other testosterone products
  - Carcinoma of the breast
  - Suspected carcinoma of the prostate
  - Carcinoma of the prostate unless there is documentation of **ONE** of the following:
    1. Individual has undergone radical prostatectomy or radiation therapy for prostate cancer
    2. Prostate cancer was organ confined
    3. Individual has been disease free for two years and has an undetectable PSA (such as less than 0.1 ng/dL)
- No new contraindications or significant adverse effects such as:
  - Deep vein thrombosis or pulmonary embolism
  - Severe hepatotoxicity (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, jaundice)
  - Hematocrit persistently above normal limits
- Digital rectal exam (DRE) or PSA within the last 12 months to monitor for prostate cancer

Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement
- Lab values confirming safe use

Continuation Therapy Criteria Approval Duration

- 12 months OR end of plan year

Medical Necessity Requirements for AZMIRO (testosterone cypionate) injection, JATENZO, KYZATREX, TLANDO, UNDECATREX (testosterone undecanoate) oral capsule, and XYOSTED (testosterone enanthate) solution auto-injector

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Criteria for Initial Therapy:

Prescriber Qualifications

- Prescribed by an Endocrinologist or Urologist, or in consultation with one

Indication

- Male with primary hypogonadism (testicular origin; associated with structural or genetic etiologies) with at least **THREE** clinical signs and symptoms
- Male with hypogonadotropic hypogonadism (pituitary/hypothalamus origin; associated with structural or genetic etiologies) with at least **THREE** clinical signs and symptoms

Age Requirement

- 18 years or older

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TESTOSTERONE REPLACEMENT THERAPY

Baseline Clinical Evaluation

- Persistently low fasting morning (8 to 10 AM) baseline testosterone levels is defined as **ONE** of the following:
  - Total testosterone level less than the reference lab normal value on two separate occasions, must be obtained from the same laboratory or from a laboratory using the same assay (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)
- Diagnosis not made during acute or subacute illness
- Hematocrit is within normal range
- Blood pressure is adequately controlled
- Male individual over age 50 years (or over age 40 years who has a first degree relative with prostate cancer or an unevaluated prostate nodule or induration or is African American) is screened for prostate cancer with **BOTH** of the following:
  - Digital prostate examination done within the last 12 months with continued monitoring as clinically appropriate for age, race, and risk factors for prostate cancer
  - Prostate specific antigen (PSA) measurement done within the last 12 months with continued monitoring as clinically appropriate for age, race, and risk factors for prostate cancer
- **For Tlando:** serum prolactin level

Alternative Therapies

- Failure, contraindication, or intolerance to a **generic intramuscular testosterone injection**
- Failure, contraindication, or intolerance to **ONE** of the following:
  - Testosterone transdermal gel pump 20.25 mg/act (1.62 percent) (generic for Androgel pump)
  - Testosterone transdermal gel packet 50 mg/5gm (1 percent) (generic for Androgel 1 percent, Testim 1 percent, or Vogelxo 1 percent)
- **For Undecatrex:** Failure, contraindication, or intolerance to Kyzatrex (testosterone undecanoate)

Brand Specific Criteria

- Have failure, contraindication, or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No concomitant use with other testosterone products or other anabolic androgenic steroids
- **NONE** of the following:
  - Palpable prostate nodule
  - PSA greater than 4 ng/mL
  - PSA greater than 3 ng/mL in men with high risk for prostate cancer (e.g., African American, first degree relative with prostate cancer, unevaluated nodule, etc.) unless cleared by Urologist
  - Age related hypogonadism
  - Low testosterone without symptoms or symptoms without persistently low testosterone levels

- Hematocrit greater than lab normal limits
- Untreated severe obstructive sleep apnea
- Severe lower urinary tract symptoms (AUA/IPSS greater than 19)
- Uncontrolled or poorly controlled heart failure
- Carcinoma of the breast
- Suspected carcinoma of the prostate
- Carcinoma of the prostate unless there is documentation of **ONE** of the following:
  1. Individual has undergone radical prostatectomy or radiation therapy for prostate cancer
  2. Prostate cancer was organ confined
  3. Individual has been disease free for two years and has an undetectable PSA (such as less than 0.1 ng/dL)

Documentation Requirements

- A completed request form must be submitted including:
  - Chart notes
  - Lab results (testosterone levels, hematocrit, PSA, blood pressure, prolactin if applicable)
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration

- 12 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy):

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Prescriber Qualification

- Continues to be seen by or in consultation with an Endocrinologist or Urologist

Clinical Response

- Has met initial criteria for Testosterone Replacement Therapy
- Fasting morning testosterone levels within normal range
- Clinical symptoms improved
- Hematocrit within normal range
- Blood pressure controlled

Adherence

- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria

- Have failure, contraindication, or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

PHARMACY COVERAGE GUIDELINE

TESTOSTERONE REPLACEMENT THERAPY

Safety

- No concomitant use with other testosterone products or other anabolic androgenic steroids
- **NONE** of the following:
  - Palpable prostate nodule
  - PSA greater than 4 ng/mL
  - PSA greater than 3 ng/mL in men with high risk for prostate cancer (e.g., African American, first degree relative with prostate cancer, unevaluated nodule, etc.) unless cleared by Urologist
  - Age related hypogonadism
  - Low testosterone without symptoms or symptoms without persistently low testosterone levels
  - Hematocrit greater than lab normal limits
  - Untreated severe obstructive sleep apnea
  - Severe lower urinary tract symptoms (AUA/IPSS greater than 19)
  - Uncontrolled or poorly controlled heart failure
- No new contraindications or significant adverse effects including:
  - Myocardial infarction
  - Stroke
  - Deep vein thrombosis or pulmonary embolism
  - Severe hepatotoxicity
  - Hematocrit persistently elevated
  - New or worsening depression, suicidal ideation, anxiety
  - Carcinoma of the breast
  - Suspected carcinoma of the prostate
  - Carcinoma of the prostate unless there is documentation of **ONE** of the following:
    1. Individual has undergone radical prostatectomy or radiation therapy for prostate cancer
    2. Prostate cancer was organ confined
    3. Individual has been disease free for two years and has an undetectable PSA (such as less than 0.1 ng/dL)
  - **For Tlando:** serum prolactin level remains elevated

Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement
- Lab values confirming safe use

Continuation Therapy Criteria Approval Duration

- 12 months OR end of plan year

Medical Necessity Requirements for METHITEST (methyltestosterone oral tablet) and Methyltestosterone oral capsule generic

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TESTOSTERONE REPLACEMENT THERAPY

Criteria for Initial Therapy:

Prescriber Qualifications

- Prescribed by an Endocrinologist or Urologist or in consultation with an Endocrinologist or Urologist

Indication

- Male with primary hypogonadism (testicular origin; associated with structural or genetic etiologies) with at least **THREE** clinical signs and symptoms
- Male with hypogonadotropic hypogonadism (pituitary/hypothalamus origin; associated with structural or genetic etiologies) with at least **THREE** clinical signs and symptoms
- Delayed male puberty with pre pubertal testis
- Female with metastatic / inoperable breast cancer in an individual who is 1 to 5 years post menopausal
- Premenopausal female who has benefited from oophorectomy and is considered to have hormone responsive tumor

Age Requirement

- 18 years or older
- 14 years or older for delayed puberty

Baseline Clinical Evaluation

- Hematocrit is within normal range
- Liver function tests
- Blood pressure is adequately controlled
- **Males:**
  - Persistently low fasting morning (8 to 10 AM) baseline testosterone levels is defined as **ONE** of the following:
  - Total testosterone level less than the reference lab normal value on two separate occasions, must be obtained from the same laboratory or from a laboratory using the same assay (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)
  - Diagnosis not made during acute or subacute illness
  - Male individual over age 50 years (or over age 40 years who has a first degree relative with prostate cancer or an unevaluated prostate nodule or induration or is African American) is screened for prostate cancer with **BOTH** of the following:
    1. Digital prostate examination done within the last 12 months with continued monitoring as clinically appropriate for age, race, and risk factors for prostate cancer
    2. Prostate specific antigen (PSA) measurement done within the last 12 months with continued monitoring as clinically appropriate for age, race, and risk factors for prostate cancer

Alternative Therapies

- **Males:** Failure, contraindication, or intolerance to a **generic intramuscular testosterone injection**

- **Males**: Failure, contraindication, or intolerance to **ONE** of the following:
  - Testosterone transdermal gel pump 20.25 mg/act (1.62 percent) (generic for Androgel pump)
  - Testosterone transdermal gel packet 50 mg/5gm (1 percent) (generic for Androgel 1 percent, Testim 1 percent, or Vogelxo 1 percent)

Brand Specific Criteria

- **For brand Methitest:** Individual has failure after adequate trial, contraindication, or intolerance to **generic methyltestosterone** [**Note:** Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

Safety

- No concomitant use with other testosterone products
- **Males, NONE** of the following:
  - Palpable prostate nodule
  - PSA greater than 4 ng/mL
  - PSA greater than 3 ng/mL in men with high risk for prostate cancer (e.g., African American, first degree relative with prostate cancer, unevaluated nodule, etc.) unless cleared by Urologist
  - Age related hypogonadism
  - Low testosterone without symptoms or symptoms without persistently low testosterone levels
  - Hematocrit greater than lab normal limits
  - Untreated severe obstructive sleep apnea
  - Severe lower urinary tract symptoms (AUA/IPSS greater than 19)
  - Uncontrolled or poorly controlled heart failure
  - Carcinoma of the breast
  - Suspected carcinoma of the prostate
- **Females, NONE** of the following:
  - Childbearing potential who is pregnant or not currently using effective contraception
  - Individual who is breast feeding an infant or child

Documentation Requirements

- A completed request form must be submitted including:
  - Chart notes
  - Lab results (testosterone levels, PSA, hematocrit, liver function tests)
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration

- 12 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy):

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

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TESTOSTERONE REPLACEMENT THERAPY

Prescriber Qualifications

- Continues to be seen by or in consultation with an Endocrinologist, Oncologist, or Urologist

Clinical Response

- Has met initial criteria for Testosterone Replacement Therapy
- **Hypogonadism:**
  - Fasting morning testosterone levels within normal range
  - Improved clinical symptoms
  - Hematocrit within normal limits
- **Delayed male puberty with pre pubertal testis:**
  - Secondary male sex characteristics developing but not fully developed (once fully developed, testosterone replacement therapy is no longer needed)
  - Cryptorchidism or small testes present
  - Bone age monitored every six months to assess the effect of treatment on the epiphyseal centers
  - Hematocrit within normal limits
- **Females:** No disease progression

Adherence

- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria

- **For brand Methitest:** Individual has failure after adequate trial, contraindication, or intolerance to **generic methyltestosterone** [**Note:** Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

Safety

- No concomitant use with other testosterone products
- **NONE** of the following:
  - Myocardial infarction
  - Stroke
  - Developed deep vein thrombosis (DVT) or pulmonary embolism (PE)
  - Severe hepatotoxicity such as peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, or jaundice
  - Hematocrit is persistently elevated above the normal range
  - New onset or worsening depression, suicidal ideation, anxiety, or other mood changes
  - Hypercalcemia
  - **Males**: Carcinoma of the breast
  - **Males**: Suspected carcinoma of the prostate
  - **Females**: Childbearing potential who is pregnant or not currently using effective contraception
  - **Females**: Individual who is breast feeding an infant or child

Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement

- Lab values confirming safe use

Continuation Therapy Criteria Approval Duration

- 12 months OR end of plan year

Criteria for Off-Label Use Requests:

Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. Off-Label Use of Non-Cancer Medications
2. Off-Label Use of Cancer Medications

Benefit Type:

Pharmacy Benefit:

ANDROGEL® pump transdermal gel and transdermal gel
AZMIRO® (testosterone cypionate) injection
JATENZO® (testosterone undecanoate) oral capsule
KYZATREX™ (testosterone undecanoate) oral capsule
METHITEST™ (methyltestosterone) oral tablet
Methyltestosterone oral capsule
NATESTO™ nasal gel
TESTIM® transdermal gel
Testosterone pump transdermal gel and transdermal gel
TLANDO™ (testosterone undecanoate) oral capsule
UNDECATREX™ (testosterone undecanoate) oral capsule
VOGELXO® pump transdermal gel and transdermal gel
XYOSTED™ (testosterone enanthate) solution auto-injector

Medical Benefit:

AZMIRO® (testosterone cypionate) injection
TESTOPEL® (testosterone) pellet

Coding:

HCPCS: S0189 and J3490

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.

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. These effects include the growth and maturation of prostate, seminal vesicles, penis and scrotum; the development of male hair distribution such as facial, pubic, chest and axillary hair; laryngeal enlargement, vocal cord thickening, alterations in body musculature and fat distribution.

Male hypogonadism is a clinical syndrome resulting from insufficient secretion of testosterone, that has two main etiologies. Primary hypogonadism caused by defects of the gonads such as Klinefelter syndrome or Leydig cell aplasia, whereas secondary hypogonadism (also known as hypogonadotropic hypogonadism) is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (FSH, LH).

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:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

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.

Primary hypogonadism *defined as* testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter 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 normal range.

Hypogonadotropic hypogonadism *defined as* gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumor, trauma, or radiation having low testosterone serum concentrations, but gonadotropins are in the normal to low range

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 signs and symptoms 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.

Testosterone Products:

1) Androgel® Pump Transdermal Gel
2) Azmiro® (testosterone cypionate) injection*
3) Jatenzo (testosterone undecanoate) oral capsule*
4) Kyzatrex (testosterone undecanoate) oral capsule*
5) Tlando (testosterone undecanoate) oral capsule*
6) Methitest™ (methyltestosterone) oral tablet*
7) Methyltestosterone oral capsule*
8) Natesto™ Nasal Gel*
9) Striant® Buccal Mucoadhesive System*
10) Testopel® (testosterone) implant pellet*
11) Testim® Transdermal Gel (brand & generic) *
12) Testosterone Cypionate Intramuscular Solution
13) Testosterone Enanthate Intramuscular Solution
14) Testosterone Pump Transdermal Gel*
15) Testosterone Transdermal Gel*
16) Undecatrex (testosterone undecanoate)
17) Vogelxo® Pump Transdermal Gel*
18) Vogelxo® Transdermal Gel*
19) Xyosted™ (testosterone enanthate) injection*

* requires prior authorization

Resources:

AndroGel (testosterone gel) 1.62% pump & 20.25 mg, & 40.5 mg packets product information, revised by manufacturer Ascend Therapeutics U.S., LLC. 10-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 1, 2026.

Azmiro (testosterone cypionate) 200mg/ml injection product information, revised by manufacturer Azurity Pharmaceuticals, Inc. 07-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 12, 2026.

Jatenzo (testosterone undecanoate) 158 mg, 198 mg, & 237 mg capsules product information, revised by manufacturer Tolmar, Inc., 09-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 12, 2026.

Kyzatrex (testosterone undecanoate) 100 mg, 150 mg, & 200 mg capsules product information, revised by manufacturer Marius Pharmaceuticals. 10-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 12, 2026.

Methitest (methyltestosterone) 10 mg tablet product information, revised by manufacturer Amneal Pharmaceuticals of New York, LLC. 05-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 12, 2026.

Methyltestosterone 10 mg capsule product information, revised by manufacturer Amneal Pharmaceuticals of New York, LLC. 05-2025, at DailyMed http://dailymed.nlm.nih.gov. Accessed February 12, 2026.

Natesto (testosterone) 5.5 mg per actuation nasal gel product information, revised by manufacturer Acerus Pharmaceuticals Corporation. 07-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 12, 2026.

Testim (testosterone) 1% gel (50 mg tube) product information, revised by manufacturer Endo USA, Inc. 07-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 12, 2026.

Testopel (testosterone pellet) product information, revised by the manufacturer Endo USA, Inc. 07-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 12, 2026.

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Undecatrex (testosterone undecanoate) 200mg capsules product information, revised by manufacturer Trifluent Pharma LLC, 09/2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 18, 2025.

Vogelxo (testosterone) gel 50 mg tube, 50 mg packet, & 12.5 mg pump product information, revised by manufacturer Upsher-Smith Laboratories, LLC. 04-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 12, 2026.

Xyosted (testosterone enanthate) 50 mg/0.5 mL, 75 mg/0.5 mL, & 100 mg/0.5 mL injection product information, revised by manufacturer Antares Pharma, Inc. 07-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 12, 2026.

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