BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

TESTOSTERONE REPLACEMENT THERAPY:
ANDROGEL® pump transdermal gel and transdermal gel
AZMIRO™ (testosterone cypionate) injection
FORTESTA® transdermal gel
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 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.

Criteria:

ANDROGEL® pump transdermal gel and transdermal gel
FORTESTA® transdermal gel
NATESTO™ nasal gel
TESTIM® transdermal gel
TESTOPEL® (testosterone) pellet
Testosterone pump transdermal gel and transdermal gel
VOGELXO® pump transdermal gel and transdermal gel

- **Criteria for initial therapy for MALE individual:** Androgel, Fortesta, Natesto, Testim, Testopel, testosterone gel, Vogelxo, and/or generic equivalent (if available) replacement therapy is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Endocrinologist, Urologist, HIV/AIDS Specialist, Pediatrician, or Infectious Disease depending upon indication or use

2. Individual has a confirmed diagnosis of **ONE** of the following:
    a. Male individual 18 years of age or older with an established diagnosis of **primary hypogonadism** (i.e., testicular origin; associated with structural or genetic etiologies) who has at least **three** specific clinical signs and symptoms consistent with hypogonadism **and** has unequivocally and persistently low fasting morning (8-10 AM) testosterone levels (see Definitions section)

    b. Male individual 18 years of age or older with an established diagnosis of **hypogonadotropic hypogonadism** (i.e., pituitary gland or hypothalamus origin; associated with structural or genetic etiologies) who has at least **three** specific clinical signs and symptoms consistent with hypogonadism **and** has unequivocally and persistently low fasting morning (8-10 AM) testosterone levels (see Definitions section)

    c. HIV-infected male individual 18 years of age or older with documented unexplained involuntary weight loss of greater than 10% baseline body weight **and** has unequivocally and persistently low fasting morning (8-10 AM) testosterone levels

    d. Male individual 18 years of age or older on chronic corticosteroid treatment (daily dose of at least 5-7.5 mg of prednisone or equivalent for at least 6 weeks) **and** has unequivocally and persistently low fasting morning (8-10 AM) testosterone levels

    e. Individual 14 years or older with delayed male puberty and pre-pubertal testis

3. Unequivocally and persistently low fasting morning (8-10 AM) baseline testosterone levels is defined as **ONE** of the following:

a. 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)
b. 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)

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

5. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **ONE** of the following (documentation from the prescriber must be submitted):
   a. Testosterone transdermal gel pump 20.25 mg/act (1.62%) (generic for Androgel pump)
   b. Testosterone transdermal gel packet 50 mg/5gm (1%) (generic for Androgel 1%, Testim 1%, or Vogelxo 1%)

6. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **generic intramuscular testosterone injection** (documentation from the prescriber must be submitted)

7. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

8. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
   a. 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:
      i. Digital prostate examination done within the last 12 months with continued monitoring as clinically appropriate for age, race, and risk factors for prostate cancer
      ii. 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
   b. Hematocrit is within the normal range

9. Individual does not have **ANY** of the following:
   a. Palpable prostate nodule or prostate-specific antigen (PSA) greater than 4 ng/mL or PSA more than 3 ng/mL in a man at high risk of prostate cancer (such as such as African-Americans or those with first-degree relative with prostate cancer or an unevaluated prostate nodule or induration), unless cleared by Urological evaluation
   b. Other hypogonadal conditions which are not associated with structural or genetic etiologies such as age-related hypogonadism
   c. Low testosterone levels in the absence of symptoms and conditions of androgen deficiency or symptoms without unequivocally and persistently low testosterone levels
   d. Hematocrit greater than laboratory normal limits
   e. Untreated severe obstructive sleep apnea
   f. Severe lower urinary tract symptoms ([AUA]/ IPSS greater than 19)
   g. Uncontrolled or poorly controlled heart failure
   h. **Additionally for Natesto**: Individual does not have nasal disorder, nasal or sinus surgery, nasal fracture within the last 6 months, mucosal inflammatory disorder (e.g., Sjogren's syndrome), and sinus disease

10. There are **NO** FDA-label contraindications such as:
    a. Known carcinoma of the breast
    b. Suspected carcinoma of the prostate
    c. Known carcinoma of the prostate unless there is documentation of **ONE** of the following:
        i. Individual has undergone radical prostatectomy or radiation therapy for prostate cancer
        ii. Prostate cancer was organ confined
        iii. Individual has been disease free for two (2) years and has an undetectable prostate specific antigen (PSA) level (such as <0.1 ng/dL)

11. Will not be used in combination with other testosterone products

Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request) for MALE individual:** Androgel, Fortesta, Natesto, Testim, Testopel, testosterone gel, Vogelxo, and/or generic equivalent (if available) replacement therapy is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Endocrinologist, Urologist, HIV/AIDS Specialist, Pediatrician, Infectious Disease depending upon indication or use

2. Individual has met all of the initial criteria for Testosterone Replacement Therapy

3. Individual's condition has responded while on therapy with response defined as the following:
    a. For hypogonadism with clinical signs and symptoms consistent with hypogonadism
        i. Fasting morning (8-10 AM) testosterone levels are within the normal range with therapy
        ii. Clinical symptoms have improved
        iii. Hematocrit is within laboratory normal limits
    b. For HIV-infected male individual 18 years of age or older with documented weight loss
        i. 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
        ii. Hematocrit is within laboratory normal limits
    c. For male individual 18 years of age or older on chronic corticosteroid treatment
        i. Continues to require chronic corticosteroid therapy
        ii. Hematocrit is within laboratory normal limits
    d. For individual 14 years or older with delayed male puberty and pre-pubertal testis
        i. Secondary male sex characteristics have developed but have not reached full development (once fully developed, testosterone replacement therapy is no longer needed)
        ii. Cryptorchidism is still present or there is evidence of small testes
        iii. Hematocrit is within laboratory normal limits
        iv. Determine bone age obtained every six months to assess the effect of treatment on the epiphyseal centers

4. There is ongoing evaluation for the development of prostate cancer such as a digital rectal exam (DRE) or a 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

5. Individual has been adherent with the medication

6. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

7. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use as follows:
    a. Contraindications as listed in the criteria for initial therapy section
    b. Significant adverse effect such as:
        i. Developed a deep vein thrombosis (DVT) or pulmonary embolism (PE)
        ii. Severe hepatotoxicity such as peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, jaundice
        iii. Hematocrit is persistently greater than laboratory normal limits

8. Will not be used in combination with other testosterone products

Renewal duration: 12 months

- 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**

AZMIRO (testosterone cypionate)
JATENZO (testosterone undecanoate)
KYZATREX (testosterone undecanoate)
TLANDO (testosterone undecanoate)
UNDECATREX (testosterone undecanoate)
XYOSTED™ (testosterone enanthate) solution auto-injector

- **Criteria for initial therapy for MALE individual:** Azmiro (testosterone cypionate), Jatenzo (testosterone undecanoate), Kyzatrex (testosterone undecanoate), Tlando (testosterone undecanoate), Undecatrex (testosterone undecanoate), Xyosted (testosterone enanthate), and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

    1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Endocrinologist or Urologist

    2. Individual is 18 years of age or older male

    3. Individual has a confirmed diagnosis of **ONE** of the following:
        a. **Primary hypogonadism** (i.e., testicular origin; associated with structural or genetic etiologies) who has at least **three** specific clinical signs and symptoms consistent with hypogonadism **and**

has unequivocally and persistently low fasting morning (8-10 AM) testosterone levels (see Definitions section)

b. **Hypogonadotropic hypogonadism** (i.e., pituitary gland or hypothalamus origin; associated with structural or genetic etiologies) who has at least **three** specific clinical signs and symptoms consistent with hypogonadism **and** has unequivocally and persistently low fasting morning (8-10 AM) testosterone levels (see Definitions section)

4. Unequivocally and persistently low fasting morning (8-10 AM) baseline testosterone levels defined as **ONE** of the following:
   a. Total testosterone level less than the reference lab normal value on two separate occasions (copy of laboratory data must be submitted with the request), must be obtained from the same laboratory or from a laboratory using the same assay
   b. 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)

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

6. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **ONE** of the following (documentation from the prescriber must be submitted):
   a. Testosterone transdermal gel pump 20.25 mg/act (1.62%) (generic for Androgel pump)
   b. Testosterone transdermal gel packet 50 mg/5gm (1%) (generic for Androgel 1%, Testim 1%, or Vogelxo 1%)

7. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **generic intramuscular testosterone injection** (documentation from the prescriber must be submitted)

8. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

9. **Additional for Undecatrex:** Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for Kyzatrex (testosterone undecanoate)

10. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
    a. Male individual over age 50 years (or over age 40 years with 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:
       i. Digital prostate examination done within the last 12 months with continued monitoring as clinically appropriate for age, race, and risk factors for prostate cancer
       ii. 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
    b. Hematocrit is within the normal range
    c. Blood pressure is adequately controlled
    d. **Additionally for Tlando**: serum prolactin level

11. Individual does not have **ANY** of the following:

a. Palpable prostate nodule or prostate-specific antigen (PSA) greater than 4 ng/mL or PSA more than 3 ng/mL in a man at high risk of prostate cancer (such as such as African Americans, or those with first-degree relative with prostate cancer or an unevaluated prostate nodule or induration), unless cleared by Urological evaluation
b. Other hypogonadal conditions which are not associated with structural or genetic etiologies such as age-related hypogonadism
c. Low testosterone levels in the absence of symptoms and conditions of androgen deficiency or symptoms without unequivocally and persistently low testosterone levels
d. Hematocrit greater than laboratory normal limits
e. Untreated severe obstructive sleep apnea
f. Severe lower urinary tract symptoms ([AUA]/ IPSS greater than 19)
g. Uncontrolled or poorly controlled heart failure

12. There are **NO** FDA-label contraindications such as:
    a. Other hypogonadal conditions such as age-related hypogonadism, which are not associated with structural or genetic etiologies
    b. Male with carcinoma of the breast
    c. Individual who is pregnant
    d. Suspected carcinoma of the prostate
    e. Known carcinoma of the prostate unless there is documentation of **ONE** of the following:
        i. Individual has undergone radical prostatectomy or radiation therapy for prostate cancer
        ii. Prostate cancer was organ confined
        iii. Individual has been disease free for two (2) years and has an undetectable prostate specific antigen (PSA) level (such as <0.1 ng/dL)

13. Individual does not use other anabolic androgenic steroids

14. Azmiro, Jatenzo, Kyzatrex, Tlando, Undecatrex, and Xyosted will not be used interchangeably or concurrently or with other testosterone products

Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request) for MALE individual:** Azmiro (testosterone cypionate), Jatenzo (testosterone undecanoate), Kyzatrex (testosterone undecanoate), Tlando (testosterone undecanoate), Undecatrex (testosterone undecanoate), Xyosted (testosterone enanthate), and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Endocrinologist or Urologist

2. Individual has met all of the initial criteria for Jatenzo (testosterone undecanoate), Kyzatrex (testosterone undecanoate), Tlando (testosterone undecanoate), or Xyosted (testosterone enanthate)

3. Individual's condition has responded while on therapy with response defined as **ALL** of the following:
    a. Fasting morning (8-10 AM) testosterone levels are within the normal range with therapy
    b. Clinical symptoms have improved
    c. Hematocrit is within the normal range

d. Blood pressure is controlled

4. There is ongoing evaluation for the development of prostate cancer such as a digital rectal exam (DRE) or a 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

5. Individual has been adherent with the medication

6. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

7. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use as follows:
   a. Contraindications as listed in the criteria for initial therapy section
   b. Significant adverse effect such as:
      i. Myocardial infarction
      ii. Stroke
      iii. Developed deep vein thrombosis (DVT) or pulmonary embolism (PE)
      iv. Severe hepatotoxicity such as peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, or jaundice
      v. Hematocrit is persistently elevated above the normal range
      vi. New onset or worsening depression, suicidal ideation, anxiety, or other mood changes
      vii. **Additionally for Tlando**: serum prolactin level remains elevated

8. Azmiro, Jatenzo, Kyzatrex, Tlando, Undecatrex, and Xyosted will not be used interchangeably or concurrently or with other testosterone products

Renewal duration: 12 months

- 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**

METHITEST™ (methyltestosterone) oral tablet
Methyltestosterone oral capsule

- **Criteria for initial therapy for MALE individual:** Methitest (methyltestosterone) or methyltestosterone therapy is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Endocrinologist or Urologist

2. Individual has a confirmed diagnosis of **ONE** of the following:
    a. Male individual 18 years of age or older with an established diagnosis of **primary hypogonadism** (i.e., testicular origin; associated with structural or genetic etiologies) who has at least **three** specific clinical signs and symptoms consistent with hypogonadism **and** has unequivocally and persistently low fasting morning (8-10 AM) testosterone levels (see Definitions section)

    b. Male individual 18 years of age or older with an established diagnosis of **hypogonadotropic hypogonadism** (i.e., pituitary gland or hypothalamus origin; associated with structural or genetic etiologies) who has at least **three** specific clinical signs and symptoms consistent with hypogonadism **and** has unequivocally and persistently low fasting morning (8-10 AM) testosterone levels (see Definitions section)

    c. Individual 14 years or older with delayed male puberty and pre-pubertal testis

3. Unequivocally and persistently low fasting morning (8-10 AM) baseline testosterone levels defined as **ONE** of the following:
    a. Total testosterone level less than the reference lab normal value on two separate occasions (copy of laboratory data must be submitted with the request), must be obtained from the same laboratory or from a laboratory using the same assay
    b. 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)

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

5. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **ONE** of the following (documentation from the prescriber must be submitted):
    a. Testosterone transdermal gel pump 20.25 mg/act (1.62%) (generic for Androgel pump)
    b. Testosterone transdermal gel packet 50 mg/5gm (1%) (generic for Androgel 1%, Testim 1%, or Vogelxo 1%)

6. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **generic intramuscular testosterone injection** (documentation from the prescriber must be submitted)

7. **For brand Methitest:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for **generic methyltestosterone** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

8. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring as clinically appropriate:
    a. Liver function tests
    b. Male individual over age 50 years (or over age 40 years with 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:
        i. Digital prostate examination done within the last 12 months with continued monitoring as clinically appropriate for age, race, and risk factors for prostate cancer
        ii. 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
    c. Hematocrit is within the normal range

9. Individual does not have **ANY** of the following:
    a. Palpable prostate nodule or prostate-specific antigen (PSA) greater than 4 ng/mL or PSA more than 3 ng/mL in a man at high risk of prostate cancer (such as such as African-Americans, or those with first-degree relative with prostate cancer or an unevaluated prostate nodule or induration), unless cleared by Urological evaluation
    b. Male with other hypogonadal conditions, such as age-related hypogonadism, which are not associated with structural or genetic etiologies
    c. Hematocrit greater than laboratory normal limits
    d. Untreated severe obstructive sleep apnea
    e. Severe lower urinary tract symptoms ([AUA]/ IPSS greater than 19)
    f. Uncontrolled or poorly controlled heart failure

10. There are **NO** FDA-label contraindications such as:
    a. Known carcinoma of the breast
    b. Known or suspected carcinoma of the prostate

Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request) for MALE individual:** Methitest (methyltestosterone) or methyltestosterone therapy is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Endocrinologist or Urologist

2. Individual has met all the initial criteria

3. Individual's condition has responded while on therapy with response defined as **ALL** of the following:
    a. Fasting morning (8-10 AM) testosterone levels are within the normal range with therapy
    b. Clinical symptoms have improved
    c. Hematocrit is within the normal range
    d. Blood pressure is controlled
    e. For individual 14 years or older with delayed male puberty and pre-pubertal testis
        i. Secondary male sex characteristics have developed but have not reached full development (once fully developed, testosterone replacement therapy is no longer needed)
        ii. Cryptorchidism is still present or there is evidence of small testes
        iii. Determine bone age obtained every six months to assess the effect of treatment on the epiphyseal centers

4. There is ongoing evaluation for the development of prostate cancer such as a digital rectal exam (DRE) or a 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

5. Individual has been adherent with the medication

6. **For brand Methitest:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for **generic methyltestosterone** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

7. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use as follows:
    a. Contraindications as listed in the criteria for initial therapy section
    b. Significant adverse effect such as:
        i. Myocardial infarction
        ii. Stroke
        iii. Developed deep vein thrombosis (DVT) or pulmonary embolism (PE)
        iv. Severe hepatotoxicity such as peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, or jaundice
        v. Hematocrit is persistently elevated above the normal range
        vi. New onset or worsening depression, suicidal ideation, anxiety, or other mood changes

8. Will not be used with other testosterone products

Renewal duration: 12 months

- **Criteria for initial therapy for FEMALE individual:** Methitest (methyltestosterone) or methyltestosterone therapy is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

2. Women with a diagnosis of **ONE** of the following:
    a. Metastatic / inoperable breast cancer in an individual who is 1-5 years post-menopausal
    b. Premenopausal female who has benefited from oophorectomy and is considered to have hormone responsive tumor

3. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
    a. Liver function tests
    b. Hematocrit is within the normal range
    c. Blood pressure is adequately controlled

4. **For brand Methitest:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for **generic methyltestosterone** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. There are **NO** FDA-label contraindications such as:
    a. Individual of childbearing potential who is pregnant or not currently using effective contraception
    b. Individual who is breast feeding an infant or child

6. Will not be used with other testosterone products

Initial approval duration: 12 months

PHARMACY COVERAGE GUIDELINE

TESTOSTERONE REPLACEMENT THERAPY

- **Criteria for continuation of coverage (renewal request) for FEMALE individual:** Methitest (methyltestosterone) or methyltestosterone therapy is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist
  2. Individual has met all of the initial criteria
  3. Individual's condition has responded while on therapy with response defined as there is no disease progression
  4. Individual has been adherent with the medication
  5. **For brand Methitest:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for **generic methyltestosterone** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)
  6. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use as follows:
     a. Contraindications as listed in the criteria for initial therapy section
     b. Significant adverse effect such as:
        i. Myocardial infarction
        ii. Stroke
        iii. Developed deep vein thrombosis (DVT) or pulmonary embolism (PE)
        iv. Severe hepatotoxicity such as peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, or jaundice
        v. Hematocrit is persistently elevated above the normal range
        vi. New onset or worsening depression, suicidal ideation, anxiety, or other mood changes
        vii. Hypercalcemia
  7. Will not be used with other testosterone products

  Renewal duration: 12 months

- 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
FORTESTA® transdermal gel

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).

PHARMACY COVERAGE GUIDELINE

TESTOSTERONE REPLACEMENT THERAPY

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.

PHARMACY COVERAGE GUIDELINE

TESTOSTERONE REPLACEMENT THERAPY

Testosterone Products:

1) Androgel® Pump Transdermal Gel
2) Androgel® Transdermal Gel*
3) Azmiro® (testosterone cypionate) injection*
4) Fortesta® Transdermal Gel*
5) Jatenzo (testosterone undecanoate) oral capsule*
6) Kyzatrex (testosterone undecanoate) oral capsule*
7) Tlando (testosterone undecanoate) oral capsule*
8) Methitest™ (methyltestosterone) oral tablet*
9) Methyltestosterone oral capsule*
10) Natesto™ Nasal Gel*
11) Striant® Buccal Mucoadhesive System*
12) Testopel® (testosterone) implant pellet*
13) Testim® Transdermal Gel (brand & generic) *
14) Testosterone Cypionate Intramuscular Solution
15) Testosterone Enanthate Intramuscular Solution
16) Testosterone Pump Transdermal Gel*
17) Testosterone Transdermal Gel*
18) Undecatrex (testosterone undecanoate)
19) Vogelxo® Pump Transdermal Gel*
20) Vogelxo® Transdermal Gel*
21) 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. 11-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 17, 2025.

Azmiro (testosterone cypionate) 200mg/ml injection product information, revised by manufacturer Azurity Pharmaceuticals, Inc. 05-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 17, 2025.

Fortesta (testosterone) 2% gel pump (10 mg per actuation) product information, revised by manufacturer Endo Pharmaceutical, Inc. 01-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 06, 2024. **Discontinued 05-31-2024**

Jatenzo (testosterone undecanoate) 158 mg, 198 mg, & 237 mg capsules product information, revised by manufacturer Tolmar, Inc., 08-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 17, 2025.

Kyzatrex (testosterone undecanoate) 100 mg, 150 mg, & 200 mg capsules product information, revised by manufacturer Marius Pharmaceuticals. 09-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 17, 2025.

Methitest (methyltestosterone) 10 mg tablet product information, revised by manufacturer Amneal Pharmaceuticals of New York, LLC. 09-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 17, 2025.

Methyltestosterone 10 mg capsule product information, revised by manufacturer Novitium Pharma, LLC. 06-2021, at DailyMed http://dailymed.nlm.nih.gov. Accessed February 17, 2025.

Natesto (testosterone) 5.5 mg per actuation nasal gel product information, revised by manufacturer Acerus Pharmaceuticals Corporation. 12-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 18, 2025.

Testim (testosterone) 1% gel (50 mg tube) product information, revised by manufacturer Endo USA, Inc. 08-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 18, 2025.

Testopel (testosterone pellet) product information, revised by the manufacturer Endo USA, Inc. 03-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 18, 2025.

Testosterone 1 % gel (12.5 mg per actuation) pump, 25 mg pack, 50 mg pack product information, revised by manufacturer Encube Ethicals Private Limited. 01-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 18, 2025.

Tlando (testosterone undecanoate) 112.5 mg capsules product information, revised by manufacturer Antares Pharma, Inc., 03-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 18, 2025.

Undecatrex (testosterone undecanoate) 100mg, 150mg, 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 18, 2025.

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. 01-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 18, 2025.

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