Clinical Policy: Testosterone

Reference Number: OR.CP.PHAR.354
Effective Date: 04.01.22
Last Review Date: 10.22
Line of Business: Medicaid – Trillium Oregon Health Plan

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

The following are testosterone agents requiring prior authorization: testosterone undecanoate capsule (Jatenzo, Kyzatrex, Tlando), testosterone transdermal gel (Androgel, Vogelxo, Testim), testosterone nasal gel (Natesto), testosterone pellet (Testopel), and testosterone undecanoate (Aveed). Testosterone enanthate injection (Xyosted) and testosterone cypionate (Depo®-testosterone) require prior authorization for member less than 18 years of age.

**Please refer to OR.CP.PHAR.1002 Gender Dysphoria for testosterone requests for gender-affirming hormone therapy.*

Preferred Agents:

- Testosterone cypionate: 100mg/ml; 200mg/ml Intramuscular Oil
- Testosterone enanthate: 200mg/ml Intramuscular Oil
- Testosterone TD gel: 1% and 1.62% gel

FDA Approved Indication(s)

Testosterone is indicated for:

- Replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone:
  - Primary hypogonadism (congenital or acquired) - testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testes syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals
  - Hypogonadotropic hypogonadism (congenital or acquired) - gonadotropic lutenizing hormone-releasing hormone (LHRH) deficiency, or pituitary - hypothalamic injury from tumors, trauma, or radiation

Treatment of delayed puberty in carefully selected males (*Testopel and enanthate salt only*)

- Treatment of women with advancing inoperable metastatic (skeletal) mammary cancer who are one to five years postmenopausal (*enanthate salt only*)

Limitation(s) of use:

- Safety and efficacy in men with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") has not been established.
- Safety and efficacy in males < 18 years old have not been established for agents other than Testopel, testosterone cypionate, and testosterone enanthate.
- Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of Trillium Community Health Plan that Aveed, Depo-testosterone, Jatenzo, Testim, Vogelxo, Natesto, testosterone, Testopel, Tlando and Xyosted are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Hypogonadism (must meet all)**:**
1. Diagnosis of primary hypogonadism or hypogonadotropic hypogonadism;
2. Age ≥ 18 years, unless request is for testosterone cypionate, testosterone enanthate, or Testopel®;
3. Documentation of serum testosterone level < 300 ng/dL on at least 2 separate days within the last 6 months;
4. Member has no contraindicated diagnoses for testosterone therapy (see appendix C);
5. Request is for a preferred agent listed above, unless clinically significant adverse effects are experienced or all are contraindicated;
6. Dose does not exceed the FDA approved maximum (see section V).

Approval duration:
Testopel – 6 months
All other agents – 12 months

B. Breast Cancer (must meet all)**:**
1. Request is for testosterone enanthate;
2. Diagnosis of breast cancer;
3. Prescribed by or in consultation with an oncologist;
4. Disease is metastatic;
5. Dose does not exceed the FDA approved maximum (see section V).

Approval duration: 12 months

C. Delayed Puberty (must meet all)**:**
1. Diagnosis of delayed puberty;
2. Request is for Testopel;
3. Prescribed by or in consultation with an endocrinologist;
4. Member must use injectable testosterone, unless clinically significant adverse effects are experienced or all are contraindicated;
5. Dose does not exceed 450 mg (6 pellets) every 3 months.

Approval duration: 6 months

D. Other diagnoses/indications (must meet 1, 2 or 3)**:**
1. Refer to OR.CP.PHAR.1002 for requests related to Gender Dysphoria, Female-to-Male Transition.

2. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the PDL (Medicaid), the non-formulary policy for the relevant line of business: OR.CP.PMN.1001 for Medicaid; or
3. For all other requests refer to off-label use policy for the relevant line of business if diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 or 2 above does not apply, refer to the off-label use policy for the relevant line of business: CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration:
Testopel – 6 months
All other agents – 12 months

B. Other diagnoses/indications (must meet 1, 2, or 3)**:**

1. Refer to OR.CP.PHAR.1002 for requests related to Gender Dysphoria, Female-to-Male Transition.
2. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the PDL (Medicaid), the non-formulary policy for the relevant line of business: OR.CP.PMN.1001 for Medicaid; or
3. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 or 2 above does not apply, refer to the off-label use policy for the relevant line of business: CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.PMN.53 for Medicaid, or evidence of coverage documents;
B. Age-related hypogonadism or late-onset hypogonadism.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
LHRH: luteinizing hormone-releasing hormone

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
testosterone cypionate injection	Male hypogonadism: 50 to 400 mg IM once every 2 to 4 weeks	400 mg every 2 to 4 weeks
testosterone enanthate injection	Male hypogonadism: 50 to 400 mg IM once every 2 to 4 weeks Males with delayed puberty: 50 to 200 mg every 2 to 4 weeks for a limited duration, for example, 4 to 6 months.	400 mg every 2 to 4 weeks
testosterone 1% gel (AndroGel®)	Male hypogonadism: Starting dose: 50 mg applied topically QD. Dose may be titrated to a maximum of 100 mg QD based on serum testosterone level.	100 mg/day
testosterone 1.62% gel (AndroGel®)	Male hypogonadism: Starting dose: 40.5 mg applied topically QD. Dose may be titrated to a maximum of 81 mg QD based on serum testosterone level.	81 mg/day
testosterone 2% gel (Fortesta®)	Male hypogonadism: 40 mg (4 pump actuations) applied topically QD to the thighs. Dose may be titrated to a maximum of 70 mg (4 pump actuations on one thigh and 3 pump actuations on the other thigh) QD based on serum testosterone level. Dose should be titrated to maintain serum testosterone in the range of 500-1250 ng/dL.	70 mg/day
testosterone transdermal patch (Androderm®)	Male hypogonadism: 1 patch topically nightly for 24 hours	1 patch/day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Men with known carcinoma of the breast or known or suspected carcinoma of the prostate
  - Pregnant or breastfeeding women
  - Aveed, depo-testosterone, Jatenzo, Kyzatrex, testosterone cypionate, testosterone enanthate, Xyosted: hypersensitivity to product or ingredients
  - Jatenzo, Xyosted: men with hypogonadal conditions not associated with structural or genetic etiologies
  - Testosterone cypionate: patients with serious cardiac, hepatic or renal disease
- Boxed warning(s):
  - Aveed: serious pulmonary oil microembolism reactions and anaphylaxis
  - Fortesta, Testim, Vogelxo: secondary exposure to testosterone
  - Jatenzo, Kyzatrex Xyosted: increases in blood pressure

Appendix D: General Information

- Per the Endocrine Society (2018), the diagnosis of hypogonadism requires unequivocally and consistently low testosterone levels on at least 2 separate mornings. Although the lower limit of normal for testosterone can vary depending on the laboratory used, clinical trials for a number of testosterone agents defined it as < 300 ng/dL. Additionally, the American Urological Association suggests < 300 ng/dL as a reasonable cut-off in support of low testosterone diagnosis (2018).
- Patients with primary hypogonadism usually have low serum testosterone concentrations and gonadotropins (follicle stimulating hormone and luteinizing hormone) above the normal range. Patients with hypogonadotropic hypogonadism have low serum testosterone concentrations but have gonadotropins in the normal or low range.
- Androgens may be used cautiously to stimulate puberty in carefully selected patients with clearly delayed puberty. Brief treatment with conservative doses may occasionally be justified in these patients if they do not respond to psychological support.
- Testopel implantation has much less flexibility for dosage adjustment than oral administration or intramuscular injections of oil solutions or aqueous suspensions, requires surgical removal if testosterone should be discontinued, and carries a risk of sloughing out of the skin.

V. Dosage and Administration

Drug Name	Dosing Regimen	Maximum Dose
Aveed	Initially, 750 mg IM. After 4 weeks, give a repeat dose of 750 mg IM, then 750 mg IM every 10 weeks thereafter	750 mg/10 weeks
Depo-testosterone	50 to 400 mg intramuscularly once every 2 to 4 weeks	400 mg/2 weeks

Drug Name	Dosing Regimen	Maximum Dose
Testopel	150 to 450 mg (2 to 6 pellets) SC every 3 to 6 months For every 25 mg/week of testosterone propionate, 150 mg (2 pellets) should be implanted every 3 to 6 months. If testosterone therapy needs to be discontinued (e.g., for severe adverse reactions), the pellets may need to be removed by a health care professional. Dosages in delayed puberty generally are in the lower range of that listed above and, for a limited duration, for example 4 to 6 months.	450 mg (6 pellets) every 3 months
Testim	50 mg (1 tube) applied topically QD to the shoulders and/or upper arms. Dose may be titrated to a maximum of 100 mg QD based on serum testosterone level. Dose should be titrated to maintain serum testosterone in the range of 300-1,000 ng/dL.	100 mg/day
Vogelxo	50 mg (1 tube or 1 packet or 4 pump actuations) applied topically QD at approximately the same time each day to the shoulders and/or upper arms. Dose may be titrated to a maximum of 100 mg QD based on serum testosterone level. Dose should be titrated to maintain serum testosterone in the range of 300-1,000 ng/dL.	100 mg/day
Natesto	11 mg (2 pump actuations; 1 actuation per nostril) administered intranasally TID. Discontinue therapy when total testosterone concentration consistently exceeds 1,050 ng/dL. Alternative treatment should be considered if total testosterone concentration is consistently below 300 ng/dL.	33 mg/day
Testosterone gel	50 mg (4 pump actuations, two 25 mg packets, or one 50 mg packet) applied topically QD in the morning to the shoulders and upper arms and/or abdomen area (preferably at the same time every day). Dose may be titrated to 100 mg as instructed by the physician. Dose should be titrated to maintain normal range of 298-1,043 ng/dL.	100 mg/day

Drug Name	Dosing Regimen	Maximum Dose
Jatenzo	Starting dose: 237 mg PO BID Adjust the dose based on serum testosterone levels	792 mg/day
Kyzatrex	Starting dosage: 200 mg PO BID Adjust the dosage to a minimum of 100 mg once in the morning and a maximum of 400 mg BID based on serum testosterone drawn 3 to 5 hours after the morning dose at least 7 days after starting treatment or following dose adjustment and periodically thereafter	800 mg/day
Tlando	225 mg (two 112.5 mg capsules) PO BID	450 mg/day
Xyosted	75 mg SC once weekly in the abdominal region. Avoid IM and IV administration.	Varies based on testosterone concentration.

VI. Product Availability

Drug Name	Availability
Aveed	Oil for injection: 750 mg/3 mL
Depo-testosterone	Oil for injection: 100 mg/mL, 200 mg/mL, 1,000 mg/10 mL, 2,000 mg/10 mL
Testopel	Pellet for implantation: 75 mg
Testim	1% gel in tube: 5 gm (50 mg testosterone)
Vogelxo	Gel in unit-dose tube or packet: 50 mg testosterone in 5 gm of gel Gel in metered-dose pump: 12.5 mg testosterone 1.25 gm of gel per actuation; each 75-gm pump is capable of dispensing 60 metered pump actuations
Natesto	Intranasal gel in metered dose pump: 11 gm dispensed as 60 metered pump actuations. One pump actuation delivers 5.5 mg of testosterone
Testosterone gel	Gel in metered-dose pump: 88 gm capable of dispensing 60 metered pump actuations; each pump actuation delivers 12.5 mg testosterone in 1.25 gm of gel Gel in unit-dose packet: 25 mg testosterone in 2.5 gm of gel, 50 mg testosterone in 5 gm of gel
Jatenzo	Oral capsules: 158 mg, 198 mg, 237 mg
Xyosted	Autoinjector: 50 mg/0.5 mL, 75 mg/0.5 mL, 100 mg/0.5 mL
Kyzatrex	Oral capsules: 100 mg, 150 mg, 200 mg
Tlando	Capsules: 112.5 mg

VII. References

1. Aveed Prescribing Information. Malvern, PA:Endo Pharmaceuticals Inc.; June 2020. Available at: www.fda.gov. Accessed September 16, 2022.

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Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
S0189	Testosterone pellet, 75 mg
J3145	Injection, testosterone undecanoate, 1 mg
J1071	Injection, testosterone cypionate, 1 mg
J1070	Injection, testosterone cypionate, up to 100 mg
J1080	Injection, testosterone cypionate, 1 cc, 200 mg
J3120	Injection, testosterone enanthate, up to 100 mg
J3121	Injection, testosterone enanthate, 1 mg
J3130	Injection, testosterone enanthate, up to 200 mg

Reviews, Revisions, and Approvals	Date	Plan Approval Date
Policy created.	01.14.22	02.07.22
4Q 2022 annual review: for continued approval duration for Testim modified from 12 to 6 months; clarified redirection is required unless all alternatives are contraindicated; RT4: added newly approved Kyzatrex to the policy; references reviewed and updated.	09.16.22	10.06.22
4Q 2023 annual review: no significant changes; template changes applied to other diagnoses/indications and continued therapy section; references reviewed and updated.	9.19.23	11.21.23

Important Reminder
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in

developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.