Clinical Policy: Testosterone

Reference Number: CP.CPA.291
Effective Date: 11.16.16
Last Review Date: 11.21
Line of Business: Commercial

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®), testosterone transdermal gel (Vogelxo®, Testim®), testosterone nasal gel (Natesto®), testosterone pellet (Testopel®), testosterone enanthate injection (Xyosted®), testosterone cypionate (Depo®-testosterone), and testosterone undecanoate (Aveed®).

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 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 health plans affiliated with Centene Corporation® that Aveed, Depo-testosterone, Jatenzo, Testim, Vogelxo, Natesto, testosterone, Testopel, 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 meets one of the following (a or b):
5. If request is for Testopel: Medical justification supports inability to use transdermal (e.g., patch, gel) and injectable testosterone;
6. For all other agents: Failure of generic testosterone transdermal gel at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
7. Dose does not exceed the FDA approved maximum (see section V).

Approval duration:
Testopel – 6 months
Injectables – 6 months or to the member's renewal date, whichever is longer
All other agents – 12 months

B. Delayed Puberty (must meet all)**:**

1. Request is for Testopel;
2. Diagnosis of delayed puberty;
3. Prescribed by or in consultation with an endocrinologist;
4. Medical justification supports inability to use injectable testosterone;
5. Dose does not exceed 450 mg (6 pellets) every 3 months.

Approval duration: 6 months

C. 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: 6 months or to the member's renewal date, whichever is longer

D. Gender Dysphoria, Female-to-Male Transition (off-label) (must meet all)**:**

1. Diagnosis of gender dysphoria or request is for gender transition;
2. Prescribed by or in consultation with an endocrinologist and an expert in gender dysphoria and transgender medicine (e.g., mental health professional such as psychologist, psychiatrist);
3. Member meets one of the following (a or b):
   a. For Testopel: Medical justification supports inability to use transdermal (e.g., patch, gel) and injectable testosterone;
   b. For all other agents: Both (i and ii):
      i. Age ≥ 18 years;

ii. Failure of generic testosterone transdermal gel at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;

4. Member demonstrates understanding of expected testosterone treatment outcomes and has given consent for such treatment;
5. If member has a psychiatric comorbidity, member is followed by mental health provider;
6. Psychosocial support will be provided during treatment;
7. 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:
Injectables – 6 months or to the member's renewal date, whichever is longer
All other agents – 6 months

E. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial.

II. Continued Therapy

A. Delayed Puberty

1. Re-authorization is not permitted. Members must meet the initial approval criteria.

Approval duration: Not applicable

B. Gender Dysphoria, Female-to-Male Transition (off-label) (must meet all)**:**

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member is responding positively to therapy (e.g., developing a masculinized body while minimizing feminine characteristics, consistent with member's gender goals);
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:
Injectables – 6 months or to the member's renewal date, whichever is longer
All other agents – 12 months

C. All Other Indications in Section I (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. Documentation supports that member is currently receiving testosterone for breast cancer and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed the FDA-approved maximum (see section V).

Approval duration:
Testopel – 6 months
Injectables – 6 months or to the member's renewal date, whichever is longer
All other agents – 12 months

D. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial.

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.CPA.09 for commercial 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

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 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
Androderm® transdermal system 2.5/2/4/5 mg per 24 hr (testosterone patch)	Male hypogonadism: Initiate with 1 patch of the 4 mg/day system (not two 2 mg/day systems) applied nightly to an area of dry, clean skin on the upper arms, thighs, back or abdomen. The patch should be worn for 24 hours. Approximately 2 weeks following initiation or any dose change, measure the early morning serum testosterone concentration following system application the previous evening. If the serum concentration is outside the target range of 400 to 930 ng/dL, increase the daily dose	6 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	to 6 mg (i.e., one 4 mg/day and one 2 mg/day system) or decrease the daily dose to 2 mg (i.e., one 2 mg/day system), maintaining nightly application.	
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 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

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, 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, Xyosted: increases in blood pressure

Appendix D: General Information

- 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.
- 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).

- 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
Testopel	150-450 mg (2-6 pellets) SC every 3-6 months For every 25 mg/week of testosterone propionate, 150 mg (2 pellets) should be implanted every 3-6 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	33 mg/day

Drug Name	Dosing Regimen	Maximum Dose
	considered if total testosterone concentration is consistently below 300 ng/dL.	
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
Jatenzo	Starting dose: 237 mg PO BID Adjust the dose based on serum testosterone levels	792 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

VII. References

1. Aveed Prescribing Information. Malvern, PA:Endo Pharmaceuticals Inc.; June 2020. Available at: www.fda.gov. Accessed July 8, 2021.
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15. Coleman E, Bockting W, Botzer M, et al. Standards of care for the health of transsexual, transgender, and gender nonconforming people. WPATH: World Professional Association for Transgender Health. 7th version; 2012. Available at https://www.wpath.org/media/cms/Documents/SOC%20v7/SOC%20V7_English2012.pdf?_t=1613669341. Accessed July 7, 2021.

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

HCPCS Codes	Description
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	P&T Approval Date
Converted to new template. Minor changes to verbiage and grammar. References updated.	07.25.17	11.17
4Q 2018 annual review: incorporated Testopel criteria; clarified requirement for "deficiency of testosterone" to "diagnosis of hypogonadism"; hypogonadism: added requirement for documentation of testosterone levels per PI and guidelines, decreased approval duration from length of benefit to 12 months; delayed puberty: added requirement for specialist involvement in care; Testopel: clarified language from failure of other testosterone formulations to inability to use other testosterone formulations; agents other than Testopel: added age; references reviewed and updated.	08.07.18	11.18
No clinically significant changes; removed Axiron and Fortesta from criteria as they no longer require PA; modified redirection from trial of AndroGel to generic topical testosterone per SDC.	02.01.19	
RT4: added Jatenzo and Xyosted to the policy, following previously approved criteria for hypogonadism. References reviewed and updated.	04.09.19	
4Q 2019 annual review: added age-related hypogonadism or late-onset hypogonadism to Section III for excluded diagnoses; references reviewed and updated.	08.08.19	11.19
4Q 2020 annual review: no significant changes; delayed puberty dosing and transdermal patch product added to appendix B; contraindications added to appendix C; references reviewed and updated.	08.11.20	11.20
Added intramuscular testosterone products in accordance with prior clinical guidance.	03.23.21	
Added criteria for gender dysphoria/transition; added criteria for breast cancer per label for testosterone enanthate; clarified age and alternative therapy requirements for hypogonadism indication; updated HCPCS codes; clarified approval durations for 6 months or to the member's renewal date, whichever is longer applies to injectable products generally rather than indicating specific products; references reviewed and updated.	07.07.21	08.21

Reviews, Revisions, and Approvals	Date	P&T Approval Date
4Q 2021 annual review: no significant changes; references reviewed and updated.	09.02.21	11.21

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.