Clinical Policy: Testosterone

Reference Number: MDN.CP.PMN.354
Effective Date: 04.01.22
Last Review Date: 11.14.23 Revision Log
Line of Business: Illinois Medicaid

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 (Vogelxo®, Testim®), Testosterone Gel (AndroGel®, Vogelxo®), Testosterone Pump (Androgel Pump®, Fortesta®, Vogelxo Pump®), testosterone transdermal system (Androderm®), testosterone nasal gel (Natesto®), testosterone pellet (Testopel®), testosterone cypionate (Depo®-testosterone), Testosterone (Striant®, Axion®, Xyosted®), Methyltestosterone (Methyltest®) and testosterone undecanoate injection (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 (*testosterone enanthate only*)
- Treatment of women with advancing inoperable metastatic (skeletal) mammary cancer who are one to five years postmenopausal (*testosterone enanthate 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 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, Jatenzo, Vogelxo, Androderm, Androgel, Fortesta, Striant, Axion 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
3. Documentation of serum testosterone level < 300 ng/dL on at least 2 separate days within the last 6 months;
4. Failure of either testosterone cypionate or testosterone enanthate, unless clinically significant adverse effects are experienced or all are contraindicated;
5. If request is for a non-preferred agent, failure of ≥ 2 preferred with PA agents, unless contraindicated or clinically significant adverse effects are experienced (see Appendix E);
6. Dose does not exceed the FDA approved maximum (see section V).

Approval duration: 6 months

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

1. Diagnosis of delayed puberty;
2. Request is for testosterone enanthate for intramuscular administration;
3. Prescribed by or in consultation with an endocrinologist;
4. If request is for Testopel, medical justification supports inability to use injectable testosterone;
5. Dose does not exceed the FDA approved maximum (see Section V).

Approval duration: 6 months

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

1. Diagnosis of gender dysphoria or request is for gender transition;
2. Member meets both of the following (a and b):
   a. Capacity to make a well-informed decision;
   b. Documentation that medical and mental health issues are well-controlled;
3. Failure of either testosterone enanthate or testosterone cypionate, unless clinically significant adverse effects are experienced or all are contraindicated;
4. If request is for a non-preferred agent, failure of ≥ 2 preferred with PA agents, unless contraindicated or clinically significant adverse effects are experienced (see Appendix E);
5. 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: 6 months

D. Other diagnoses/indications (must meet 1 or 2):

1. 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 formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: HIM.PA.33 for health insurance marketplace and CP.PMN.255 for Medicaid; or
b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: HIM.PA.103 for health insurance marketplace and CP.PMN.16 for Medicaid; or

2. 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 above does not apply, refer to the off-label use policy for the relevant line of business: HIM.PA.154 for health insurance marketplace and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Gender Dysphoria, Female-to-Male Transition (off-label) (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 (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 (see Section V) 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

B. Delayed Puberty:

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

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. 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. receiving medication via Centene benefit or member has previously met initial approval criteria;
3. Member is responding positively to therapy
4. 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: 12 months

D. Other diagnoses/indications (must meet 1 or 2)**:**

1. 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 formulary (commercial, health insurance marketplace) or 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 formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.PMN.16 for Medicaid; or
1. 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 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.
C. Erectile Dysfunction;
D. Infertility.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
PA: Prior Authorization

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

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.
- WPATH offers their Global Education Institute (GEI) Certified Training Courses: Best Practices in Transgender Medical and Mental Health Care. Additionally, the following link provides a search tool to locate WPATH member providers: https://www.wpath.org/provider/search
- Transgender Care Therapy Certification Training is also offered by the International Transgender Certification Association (ITCA). Professionals with expertise in transgender care can be located using the following search tool: https://transgendercertification.com/locate-a-professional/
- The draft of WPATH Standards of Care Version 8 are available and open for public comment. These standards of care recommend that adolescents are managed by a multidisciplinary care team that involves both medical and mental health professionals. The list of key disciplines includes but is not limited to: adolescent medicine/primary

care, endocrinology, psychology, psychiatry, speech/language pathology, fertility, social work, support staff, and the surgical team. The need to include a healthcare professional with some expertise in mental health does not dictate the inclusion of a psychologist, psychiatrist or social work in every assessment. Instead, a general practitioner, nurse or other qualified clinician could fulfill this requirement as long as they have sufficient expertise to diagnose gender incongruence, recognize mental health concerns, distinguish between these concerns and gender dysphoria, incongruence or diversity, assist a transgender person in care planning and preparing for gender affirmative medical and surgical treatments, and refer to a mental health professional if needed.

Appendix E: Preferred and Non-Preferred Agents

Drug Name	Strength
Preferred Agents: *One of the following agents must be adequately tried and failed before moving on to preferred with PA agents*	
testosterone enanthate	200 mg/mL
Depot-Testosterone (testosterone cypionate)	100 mg/mL, 200 mg/mL
Preferred with PA Agents *Two or more of the following agents must be adequately tried and failed before moving on to nonpreferred agents*	
Testim, Vogelxo	50 mg/5 g (1%)
Androgel Packet (testosterone gel packet)	25 mg/2.5 g (1%), 50 mg/5 g (1%) 20.25 mg/1.25 g (1.62%), 40.5 mg/2.5 g (1.62%)
Androgel Pump (Testosterone Gel)	20.25 mg/actuation
Fortesta (Testosterone Gel)	10 mg/actuation (2%)
Vogelxo Pump	12.5 mg/actuation (1%)
Non-preferred Agents	
Androderm	2mg/24hr, 4mg/24hr
Aveed	750 mg/3 mL
Jatenzo	158 mg, 198 mg, 237 mg
Xyosted Auto-Injector	50 mg/0/5mL, 75 mg/0.5 mL, 100 mg/0.5 mL
Striant	30 mg
Axiron (testosterone solution)	30 mg/actuation
Methyltestosterone (Methitest, Android)	10 mg

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
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
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
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

Drug Name	Availability
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.
2. Depo-testosterone Prescribing Information. New York, NY: Pfizer Inc.; July 2018. Available at: www.fda.gov. Accessed July 8, 2021.
3. AndroGel 1% Prescribing Information. North Chicago, IL: AbbVie Inc.; February 2019. Available at: www.androgel.com. Accessed July 8, 2021.
4. Jatenzo Prescribing Information. Northbrook, IL: Clarus Therapeutics, Inc.; January 2023. Available at: www.jatenzo.com. Accessed July 23, 2023.
5. Testim Prescribing Information. Malvern, PA: Endo Pharmaceuticals, Inc.; November 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021454s030s031lbl.pdf. Accessed July 8, 2021.
6. Testosterone Cypionate Injection Prescribing Information. Parsippany, NJ: Actavis Pharma, Inc.; October 2019. Available at: https://dailymed.nlm.nih.gov/dailymed/. Accessed July 8, 2021.
7. Testosterone Enanthate Injection Prescribing Information. Eatontown, NJ: West-Ward Pharmaceuticals Corp.; December 2018. Available at: https://dailymed.nlm.nih.gov/dailymed/. Accessed July 8, 2021.
8. Testosterone Gel Prescribing Information. Allergan, MI: Perrigo Pharmaceuticals; July 2020. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=54fcdcb9-fb0e-4164-9e51-f2a5feae3217. Accessed July 8, 2021.
9. Vogelxo Prescribing Information. Maple Grove, MN: Upsher-Smith Laboratories, Inc.; April 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/204399s012lbl.pdf. Accessed July 8, 2021.
10. Xyosted Prescribing Information. Ewing, NJ: Antares Pharma, Inc.; November 2019. Available at: www.xyosted.com. Accessed July 8, 2021.
11. Mulhall JP, Trost LW, Brannigan RE, et al. Evaluation and management of testosterone deficiency AUA guideline. American Urological Association. Published 2018. Available at: http://www.auanet.org/guidelines/testosterone-deficiency-(2018). Accessed July 8, 2021.
12. Basin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2018; 103(5): 1715-1744. Available at: https://academic.oup.com/jcem/article/103/5/1715/4939465. Accessed July 8, 2021.
13. 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.
14. WPATH: World Professional Association for Transgender Health Standards of Care Version 8 Draft. Available at: https://www.wpath.org/soc8. Accessed December 6, 2021.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	03.15.22	04.22
4Q 2023 Annual Review: Template changes applied to other diagnoses/indications and continued therapy section. Added section for Delayed Puberty; references reviewed and updated	11.14.23	

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.

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