Clinical Policy: Testosterone

Reference Number: ERX.NPA.52
Effective Date: 01.11.17
Last Review Date: 11.21
Line of Business: Commercial, Medicaid

Revision Log

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

Description
Testosterone is an androgen. All testosterone agents require prior authorization.

FDA Approved Indication(s)
Testosterone is indicated for:

- Replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:
  - Primary hypogonadism (congenital or acquired): testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle-stimulating hormone, luteinizing hormone) above the normal range
  - Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations but have gonadotropins in the normal or low range
- Treatment of delayed puberty in carefully selected males (*pellets 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") have 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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that testosterone is **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. If request is for Testopel, medical justification supports inability to use transdermal (e.g., patch, gels) and injectable testosterone;
5. If request is for a non-formulary agent other than Testopel, failure of 2 formulary agents, unless contraindicated or clinically significant adverse effects are experienced;
6. Dose does not exceed the FDA approved maximum (see section V).

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

B. Delayed Puberty (must meet all)**:**
1. Request is for testosterone cypionate, testosterone enanthate, or Testopel;
2. Diagnosis of delayed puberty;
3. Prescribed by or in consultation with an endocrinologist;
4. If request is for Testopel, documentation supports inability to use injectable testosterone;
5. Dose does not exceed the FDA approved maximum (see section V).

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: 12 months

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: 6 months

E. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 a health plan affiliated with Envolve Pharmacy Solutions 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: 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 a health plan affiliated with Envolve Pharmacy Solutions 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: 12 months

D. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 policy – ERX.PA.01 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 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
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 500-1,250 ng/dL.	70 mg/day

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
  - Depo-testosterone, testosterone cypionate: patients with serious cardiac, hepatic or renal disease
  - Jatenzo, Xyosted: men with hypogonadal conditions not associated with structural or genetic etiologies
- Boxed warning(s):
  - Aveed: serious pulmonary oil microembolism reactions and anaphylaxis
  - Axiron, Fortesta, Testim, Voxelgo: secondary exposure to testosterone
  - Jatenzo, 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, luteinizing hormone) above the normal range. Patients with hypogonadotropic hypogonadism have low testosterone serum 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

Refer to the individual prescribing information for each agent.

VI. Product Availability

Refer to the individual prescribing information for each agent.

VII. References

1. Aveed Prescribing Information. Malvern, PA: Endo Pharmaceutical Inc.; June 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022219s014lbl.pdf. Accessed July 8, 2021.
2. Axiron Prescribing Information. Indianapolis, IN: Lilly USA, LLC; July 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022504s016lbl.pdf. Accessed July 8, 2021.

3. Depo-Testosterone Prescribing Information. New York, NY: Pharmacia and Upjohn Co.; August 2018. Available at: https://dailymed.nlm.nih.gov/dailymed/. Accessed July 8, 2021.
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5. Jatenzo Prescribing Information. Northbrook, IL: Clarus Therapeutics, Inc.; March 2019. Available at: www.jatenzo.com. Accessed July 8, 2021.
6. 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.
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13. 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 August 6, 2020.
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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.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created.	12.16	01.17
4Q17 Annual Review Converted to new template. Specified concentration of testosterone that is below the normal range per PI within the last 6 months. Added age restriction as safety and efficacy in pediatric patients < 18 years have not been established. Increased initial approval duration from 3 to 12 months. Added max dose requirement on re-auth. Added age-related hypogonadism or late-onset hypogonadism as indications for which coverage is not authorized as safety and efficacy have not been established per PI.	09.12.17	11.17
4Q 2018 annual review: policy combined with ERX.NPA.53 Testosterone for Injection and generalized to include all testosterone agents, including Testopel implantable pellets; added re-direction to formulary agents for non-formulary agent requests; added COC for breast cancer; references reviewed and updated.	08.07.18	11.18

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Delayed puberty: corrected Testopel re-direction to require only injectable formulations of testosterone since topical formulations are not indicated for delayed puberty.	03.14.19	
4Q 2019 annual review: no significant changes; added therapeutic alternatives to *Appendix B*; references reviewed and updated.	08.08.19	11.19
4Q 2020 annual review: no significant changes; delayed puberty dosing added to appendix B; contraindications added to appendix C; references reviewed and updated.	08.11.20	11.20
4Q 2021 annual review: added criteria for gender dysphoria/transition; removed coverage of testosterone cypionate for breast cancer; references reviewed and updated.	07.07.21	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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.