Select Injectable Testosterone Products

Policy # 00667
Original Effective Date: 04/24/2019
Current Effective Date: 05/01/2025

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider select injectable testosterone products, including, but not limited to Xyosted™‡ (testosterone enanthate auto-injection) and Azmiro™‡ (testosterone cypionate injection) for the treatment of hypogonadism to be **eligible for coverage**** when the patient selection criteria are met.

Patient Selection Criteria

Coverage eligibility for select injectable testosterone products, including, but not limited to Xyosted (testosterone enanthate auto-injection) and Azmiro (testosterone cypionate injection) will be considered when the following criteria are met:

- Patient has a diagnosis of hypogonadism (primary or secondary); AND
- Diagnosis of hypogonadism has been confirmed by serum testosterone measurements taken in the MORNING on TWO separate days BOTH showing levels BELOW the normal range; AND
- For Xyosted requests: Patient is 18 years of age or older; AND
- For Azmiro requests: Patient is 12 years of age or older; AND
- Patient is a male; AND
- Patient has tried and failed (e.g., intolerance or inadequate response) BOTH prescription GENERIC testosterone enanthate vials for injection and prescription GENERIC testosterone cypionate vials for injection unless there is clinical evidence or patient history that suggests the use of the required products will be ineffective or cause an adverse reaction to the patient. *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*

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When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of select injectable testosterone products, including, but not limited to Xyosted (testosterone enanthate auto-injection) and Azmiro (testosterone cypionate injection) when the patient has not tried and failed (e.g., intolerance or inadequate response) BOTH prescription GENERIC testosterone enanthate vials for injection and prescription GENERIC testosterone cypionate vials for injection to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of select injectable testosterone products, including, but not limited to Xyosted (testosterone enanthate auto-injection) and Azmiro (testosterone cypionate injection) when patient selection criteria are not met (except the criterion denoted above as **not medically necessary****) to be **investigational.***

Based on review of available data, the Company considers the use of select injectable testosterone products, including, but not limited to Xyosted (testosterone enanthate auto-injection) and Azmiro (testosterone cypionate injection) for the treatment of age-related hypogonadism (also referred to as "late-onset hypogonadism") to be **investigational.***

Policy Guidelines

Diagnosis of Androgen Deficiency

An established diagnosis of hypogonadism with androgen deficiency includes appropriate evaluation and diagnostic workup of a man who presents with symptoms of hypogonadism. Clinical practice guidelines recommend measuring serum testosterone only in men with consistent clinical manifestations of hypogonadism. Screening in asymptomatic populations is not recommended. Measurement of serum total testosterone is initially used; serum-free testosterone levels can be measured when total testosterone is in the low to normal range, and alterations of serum hormone binding globulin are suspected. Once a persistently low testosterone level has been established, diagnostic testing of the hypothalamic-pituitary axis should be performed to distinguish primary hypogonadism from secondary hypogonadism. When secondary hypogonadism is determined, the underlying etiology should be identified and any reversible causes treated appropriately before consideration of testosterone replacement.

Persistently low testosterone levels refer to serum levels below the lower limit of normal on at least 2 occasions when measured in the early morning (> 8:00 a.m.). The threshold lower limit for serum testosterone levels is not standardized. The Endocrine Society has recommended a lower limit for

normal levels of 300 ng/dL for total testosterone and 9.0 ng/dL for free testosterone. Joint guidelines from several European and American specialty societies have recommended that replacement therapy be considered at serum total testosterone levels less than 350 ng/dL.

Specific and suggestive symptoms of hypogonadism, as classified by the Endocrine Society, include the following:

- Incomplete or delayed sexual development
- Loss of axillar and/or pubic body hair
- Very small (< 6 mL) or shrinking testes
- Decreased libido
- Decreased spontaneous erections
- Breast discomfort, gynecomastia
- Eunuchoidal body proportions
- Infertility due to low sperm count
- Height loss due to vertebral fractures, low trauma fractures, low bone density
- Hot flushes, sweats.

Treatment of Hypogonadism with Testosterone

The Endocrine Society published clinical practice guidelines in 2018 on testosterone therapy in men with androgen deficiency. The summary of recommendations for testosterone therapy follows:

- We recommend testosterone therapy in hypogonadal men to induce and maintain secondary sex characteristics and correct symptoms of testosterone deficiency.
- We recommend against testosterone therapy in men planning fertility in the near term or in men with breast or prostate cancer, a palpable prostate nodule or induration, a prostate-specific antigen level > 4 ng/mL, a prostate-specific antigen level > 3 ng/mL combined with a high risk of prostate cancer (without further urological evaluation), elevated hematocrit, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms, uncontrolled heart failure, myocardial infarction or stroke within the last 6 months, or thrombophilia.
- In hypogonadal men 55 to 69 years old, who are being considered for testosterone therapy and have a life expectancy > 10 years, we suggest discussing the potential benefits and risks of evaluating prostate cancer risk and prostate monitoring and engaging the patient in shared decision making regarding prostate cancer monitoring. For patients who choose monitoring, clinicians should assess prostate cancer risk before starting testosterone treatment and 3 to 12 months after starting testosterone. In hypogonadal men being considered for testosterone therapy who are 40 to 69 years old and at increased risk of prostate cancer (e.g., African Americans and men with a first-degree relative with diagnosed prostate cancer), we suggest discussing prostate cancer risk with the patient and offering monitoring options.

- We suggest against routinely prescribing testosterone therapy to all men 65 years or older with low testosterone concentrations. In men > 65 years who have symptoms or conditions suggestive of testosterone deficiency (such as low libido or unexplained anemia) and consistently and unequivocally low morning testosterone concentrations, we suggest that clinicians offer testosterone therapy on an individualized basis after explicit discussion of the potential risks and benefits.
- We suggest that clinicians consider short-term testosterone therapy in HIV-infected men with low testosterone concentrations and weight loss (when other causes of weight loss have been excluded) to induce and maintain body weight and lean mass gain.
- In men with type 2 diabetes mellitus who have low testosterone concentrations, we recommend against testosterone therapy as a means of improving glycemic control.

Testosterone Dosage Guidelines

Dosing of testosterone varies, depending on age, baseline testosterone levels, comorbid disease, response to initial replacement levels, and adverse reactions. General dosing guidelines are provided by the Endocrine Society. Specific dosing guidelines for the agents targeted by this medical policy, taken from the product prescribing information, follow:

- Xyosted: The starting dose of Xyosted is 75 mg, administered subcutaneously in the abdominal region once a week. The total testosterone trough concentrations should be measured 7 days after the most recent dose following 6 weeks of dosing, following 6 weeks after dose adjustment, and periodically while on treatment with Xyosted. The dose should be decreased by 25 mg if the total testosterone trough concentration (C_{trough}) is $\geq$ 650 ng/dL. The dose should be increased by 25 mg if the total testosterone C_{trough} is < 350 ng/dL. The dose should be maintained if the total testosterone C_{trough} is $\geq$ 350 ng/dL and < 650 ng/dL.
- Azmiro: The recommended dosage of Azmiro is 50 mg to 400 mg administered every two to four weeks as a deep intramuscular injection in the gluteal muscle. The dose and schedule of Azmiro should be individualized based on the patient's age, diagnosis, response to treatment, and the appearance of adverse reactions.

Monitoring Strategies for Individuals on Testosterone Therapy

Monitoring of testosterone replacement should be performed beginning 3 to 6 months after replacement is initiated to ascertain whether serum levels are restored to the normal range, to determine whether clinical symptoms have improved, and to monitor for adverse events. The goal of testosterone replacement is to raise levels into the mid-normal range (800 ng/dL or less). Higher replacement levels are unlikely to improve symptoms further and may increase the incidence and/or severity of adverse events.

Recommendations for monitoring for testosterone-related adverse events have been provided by Endocrine Society guidelines on testosterone therapy in men with androgen deficiency. These recommendations include:

- Determine hematocrit levels at baseline, at 3 to 6 months, and then annually. If the hematocrit level is above 54%, stop therapy until the hematocrit level decreases to a safe level, evaluate the individual for hypoxia and sleep apnea, and reinitiate therapy at a reduced dose.
- Repeat bone mineral density of the lumbar spine, femoral neck, and hip after 1 to 2 years of testosterone therapy in hypogonadal men with osteoporosis.
- For men 55 to 69 years of age, and for men 40 to 69 years of age who are at increased risk for prostate cancer, conduct a digital examination of the prostate and prostate-specific antigen (PSA) measurement before initiating treatment, at 2 to 3 months after initiating treatment, and then in accordance with evidence-based guidelines for prostate cancer screening, depending on the age and race of the individual.
- Obtain urologic consultation if there is:
    - An increase in serum or plasma PSA concentration greater than 1.4 ng/mL within 12 months of initiating testosterone treatment.
    - A confirmed PSA of more than 4 ng/mL at any time.
    - Detection of a prostatic abnormality on digital rectal examination.
    - Substantial worsening of lower urinary tract symptoms.

Background/Overview

Xyosted and Azmiro are androgens indicated for testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. Xyosted is approved for use in adult males, while Azmiro is approved for use in males, no age specified. Safety and efficacy of Xyosted and Azmiro in adult males with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established. Safety and efficacy of Xyosted in males less than 18 years old have not been established. Safety and effectiveness in pediatric patients below the age of 12 have not been established for Azmiro. Prior to initiating Xyosted or Azmiro, the diagnosis of hypogonadism should be confirmed by ensuring that serum testosterone has been measured in the morning on at least two separate days and that these concentrations are below the normal range. The starting dose of Xyosted is 75 mg subcutaneously in the abdominal region once weekly. Xyosted should not be given via the intramuscular and intravascular route. Dose adjustments are based upon total testosterone trough concentrations (measured 7 days after most recent dose) obtained following 6 weeks of dosing and periodically thereafter. Xyosted is available in 50 mg, 75 mg, and 100 mg strengths in auto-injector form. The recommended dosage of Azmiro is 50 mg to 400 mg administered every two to four weeks as a deep intramuscular injection in the gluteal muscle. The dose and schedule should be individualized based on patient's age, diagnosis, response to treatment, and the appearance of adverse reactions. Azmiro is available as a prefilled syringe containing a concentration of 200 mg/mL of testosterone cypionate, and it should be administered by a healthcare professional only.

As mentioned, this product is approved for primary or secondary hypogonadism:

- Primary hypogonadism (congenital or acquired) – testicular failure due to 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 accompanied by gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range.
- Secondary hypogonadism (i.e., hypogonadotropic hypogonadism) (congenital or acquired) – idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low serum testosterone concentrations without associated elevations in gonadotropins. Appropriate adrenal cortical and thyroid hormone replacement therapy may be necessary in patients with multiple pituitary or hypothalamic abnormalities.

Other forms of testosterone for injection (available in generic form) are indicated for hypogonadism. None of these versions of testosterone have been studied head to head versus Xyosted or Azmiro, so no superiority claims can be made between these products. Generic products offer a more cost effective, yet efficacious option for treatment.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Xyosted is an androgen indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

Azmiro is an androgen indicated for testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

Xyosted

Xyosted was evaluated in a 52-week, open-label study to evaluate its efficacy and safety when administered subcutaneously once weekly to 150 adult males with hypogonadism. The study included a Screening Phase, a Treatment Titration Phase, and an Extended Treatment Phase. Patients were trained on proper use of Xyosted to self-administer the initial dose of 75 mg once weekly on

the same day of the week and at approximately the same time (7:00 am ± 2 hours). The dose was increased by 25 mg at Week 7 if the Week 6 serum total testosterone concentration at the end of the dosing interval (C_{trough}) was < 350 ng/dL, and was decreased by 25 mg if the C_{trough} was ≥ 650 ng/dL.

The primary endpoint was the percentage of patients with a time-averaged serum total testosterone concentration (C_{avg}) over the 7-day dosing interval (0 to 168 hours) within the normal range (300 to 1100 ng/dL) at Week 12. Secondary endpoints were the percentage of patients with a maximum total testosterone concentration (C_{max}) above three predetermined limits: greater than 1500 ng/dL, between 1800 and 2500 ng/dL, and greater than 2500 ng/dL.

One hundred and thirty five (90%) of the 150 hypogonadal men who received Xyosted had a serum total testosterone concentration C_{avg}(0-168h) within the normal range (300 to 1100 ng/dL) at Week 12. There were no patients (0%) with C_{max} > 1500 ng/dL at Week 12.

Azmiro
Azmiro was approved via the 505 (b) pathway. The safety of Azmiro was evaluated in Study 1, a randomized, single-dose, open-label study conducted in 27 adult males with hypogonadism. Patients were 18 to 65 years of age with a body mass index of 18 to 35 kg/m^2. Patients received a single intramuscular dose Azmiro 200 mg or comparator intramuscular testosterone replacement therapy product and were observed for adverse reactions and injection site reactions over 31 days. The most common adverse reactions in patients who received Azmiro were injection site erythema (26%) and injection site reaction (4%). All cases of injection site erythema and injection site reaction were categorized as mild based on a pre-defined injection site assessment scale that defined injection site reactions as mild if they were slight or barely perceptible.

This policy is intended to ensure that these products are used per their FDA approved usage. Also, it should be noted that other forms of testosterone for injection (available in generic form) are indicated for hypogonadism. None of these versions of testosterone have been studied head to head versus Xyosted or Azmiro, so no superiority claims can be made among these products. Generic products offer a more cost effective, yet efficacious option for treatment.

References

1. Xyosted [package insert]. Antares Pharma, Inc. Ewing, New Jersey. Updated November 2019.
2. Male Hypoganadism. Merck Manual, 18th edition. p1944-1948.
3. Azmiro [package insert]. Azurity Pharmaceuticals. Woburn, Massachusetts. Updated May 2024.
4. Shalender Bhasin, Juan P Brito, Glenn R Cunningham, Frances J Hayes, Howard N Hodis, Alvin M Matsumoto, Peter J Snyder, Ronald S Swerdloff, Frederick C Wu, Maria A Yialamas, Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline, The Journal of Clinical Endocrinology & Metabolism, Volume 103, Issue 5, May 2018, Pages 1715–1744, https://doi.org/10.1210/jc.2018-00229

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Policy History

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04/04/2019	Medical Policy Committee review
04/24/2019	Medical Policy Implementation Committee approval. New policy.
04/02/2020	Medical Policy Committee review
04/08/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/01/2021	Medical Policy Committee review
04/14/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/07/2022	Medical Policy Committee review
04/13/2022	Medical Policy Implementation Committee approval. Added a clarifying statement for age-related hypogonadism (also known as "late-onset hypogonadism") to be considered investigational.
06/10/2022	Coding update
04/06/2023	Medical Policy Committee review
04/12/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/04/2024	Medical Policy Committee review
04/10/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/03/2025	Medical Policy Committee review
04/09/2025	Medical Policy Implementation Committee approval. Changed title of policy from "Xyosted (testosterone enanthate auto injection)" to "Select Injectable Testosterone Products." Added new drug, Azmiro, to policy with criteria. Added Policy Guideline section.

Next Scheduled Review Date: 04/2026

Coding

The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2024 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J1072 Delete codes effective 05/01/2025: J3490, J3590
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;

B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.