Testosterone Agents – Topical/Buccal/Nasal/Oral/Injection

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the Testosterone Agents drug policy is to provide coverage consistent with product labeling, FDA guidance, standards of medical practice, evidence-based drug information, and/or published guidelines.

FDA Approved Indications

Topical, buccal, nasal, implant, oral, and injectable testosterone products are indicated for replacement therapy in adult 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, orchidectomy, Klinefelter Syndrome, chemotherapy, or toxic damage from alcohol or heavy metals These men usually have low serum testosterone concentrations and gonadotropins (FSH, LH) above the normal range.
Hypogonadotropic hypogonadism (also called secondary hypogonadism) (congenital or acquired) - gonadotropin or luteinizing hormone-releasing hormone (LHRH) 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.

Limitations of Use

Safety and efficacy of topical, buccal, nasal, implant, oral, and injectable testosterone products in men with “age-related hypogonadism” (also referred to as “late-onset hypogonadism”) have not been established.

Safety and efficacy of topical, buccal, nasal, implant, oral and injectable testosterone products in males less than 18 years old have not been established.

Topical testosterone products may have different doses, strengths or application instructions that may result in different systemic exposure.

Compendial Uses
Gender Dysphoria

POLICY

Criteria for Initial Approval

A. Oral methyltestosterone tablets and capsules will be considered **medically necessary** when the following criteria are met for the requested indication:

1. **Primary or hypogonadotropic hypogonadism** [Note: Safety and efficacy of testosterone products in members with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established.]
   - The member has had an inadequate treatment response, intolerance, or contraindication to one non-oral form of testosterone supplementation
   - Before the start of testosterone therapy, the member has at least two confirmed low morning testosterone levels according to current practice guidelines or your standard lab reference values

Approval will be for **36 months**.

2. **Breast cancer**
   - The member has had an inadequate treatment response, intolerance, or contraindication to one non-oral form of testosterone supplementation; AND the requested drug is being prescribed for one of the following:
     - Inoperable metastatic breast cancer in a member who is 1 to 5 years postmenopausal AND the patient had an incomplete response to other therapy for metastatic breast cancer; **OR**
     - Premenopausal member with breast cancer who has benefited from oophorectomy and is considered to have a hormone-responsive tumor

Approval will be for **36 months**.

3. **Delayed puberty**
   - The drug is being prescribed for delayed puberty AND the member has had an inadequate treatment response, intolerance, or contraindication to one non-oral form of testosterone supplementation

Approval will be for **36 months**.

B. All other testosterone products will be considered **medically necessary** when the following criteria are met for the requested indication:

1. **Primary hypogonadism**
   - Member has signs and symptoms of testosterone deficiency (see Appendix A)
   - Prior to initiating therapy, member has two confirmed low **total** testosterone levels drawn on separate days, during the morning, and in a fasted state UNLESS the member has anorchia or has undergone bilateral orchidectomy

- Member does not have risk factors that are a contraindication to therapy (see Appendix B)
- Members requesting Xyosted, Jatenzo, Natesto, or Striant must have a trial and failure of, or clinical contraindication/intolerance to two generic testosterone products

2. **Hypogonadotropic hypogonadism (Secondary hypogonadism)**
   - Member has one of the following: congenital hypogonadotropic hypogonadism (also referred to as idiopathic hypogonadotropic hypogonadism), LHRH deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation
   - Functional causes that may be managed without testosterone treatment have been assessed (see Appendix C for examples)
   - Member has signs and symptoms of testosterone deficiency (see Appendix A)
   - Prior to initiating therapy, member has two confirmed low total testosterone levels drawn on separate days, during the morning, and in a fasted state
   - Member does not have risk factors that are a contraindication to therapy (see Appendix B)
   - Members requesting Xyosted, Jatenzo, Natesto, or Striant must have a trial and failure of, or clinical contraindication/intolerance to two generic testosterone products

   [Note: Safety and efficacy of testosterone products in members with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established.]

3. **Gender dysphoria**
   - The requested drug is being prescribed for gender-affirming hormonal therapy for a transgender individual
   - The member is able to make an informed decision to engage in therapy
   - Members requesting Xyosted, Jatenzo, Natesto, or Striant must have a trial and failure of, or clinical contraindication/intolerance to two generic testosterone products

Approval will be for **12 months**.

C. All Testosterone products are considered **not medically necessary** for members who do not meet the criteria set forth above.

Continuation Criteria

A. Continuation of therapy of oral methyltestosterone tablets and capsules may be considered **medically necessary** when the following criteria are met:
- Criteria for Initial Approval has been met

Note: If the requested drug is being prescribed for primary or hypogonadotropic hypogonadism, continuation criteria will only require a confirmed low morning testosterone level according to current practice guidelines or your standard lab reference values before the member started testosterone therapy.

Approval will be for **36 months**.

B. Continuation of therapy of other testosterone products may be considered **medically necessary** when the following criteria are met:
- Signs and symptoms have responded to treatment
- Testosterone levels have been drawn within the past 12 months and are in the mid-normal range
- Member has been assessed for adverse effects within the past 12 months and the member has not developed an adverse effect such as an elevated hematocrit or a prostatic abnormality that would require a discontinuation of testosterone therapy

Approval will be for **12 months**.

Dosing and Administration
Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

Quantity Limits
Xyosted – 4 pens/28 days
Jatenzo 158mg and 237mg capsules – 60 capsules/30 days
Jatenzo 198mg capsules – 120 capsules/30 days

APPENDICES

Appendix A

Specific signs and symptoms	Suggestive signs and symptoms	Nonspecific signs and symptoms associated with testosterone deficiency
Incomplete or delayed sexual development	Reduced sexual desire (libido) and activity	Decreased energy, motivations, initiative, and self-confidence
Loss of body (axillary and pubic) hair	Decreased spontaneous erections, erectile dysfunction	Feeling sad or blue, depressed mood, persistent low-grade depressive disorder
Very small testes (<6 mL)	Breast discomfort, gynecomastia	Poor concentration and memory
	Eunuchoidal body proportions	Sleep disturbance, increased sleepiness
	Inability to father children, low sperm count	Mild unexplained anemia (normochromic, normocytic)
	Height loss, low-trauma fracture, low BMD	Reduced muscle bulk and strength
	Hot flashes, sweats	Increased body fat, body mass index

Appendix B

Very high risk of serious adverse outcomes	Moderate to high risk of adverse outcomes
Metastatic prostate cancer	Unevaluated prostate nodule or induration
Breast cancer	Unevaluated PSA>4ng/mL (3ng/mL in individuals at high risk for prostate cancer, such a s African Americans or men with a first-degree relative with prostate cancer
	Hematocrit >48% (>50% for men living at high altitude)
	Severe LUTS associated with BPH as indicated by AUA/IPSS >19
	Poorly or un-controlled congestive heart failure
	Desire for fertility in the near term

Abbreviations: AUA, America Urological Association; IPSS, International Prostate Symptom Score; BPH, Benign Prostatic Hyperplasia; PSA, prostate-specific antigen.

Appendix C

Functional Causes of Secondary Hypogonadism (Hypogonadotropic Hypogonadism)	
Hyperprolactinemia	Use of opioids, anabolic steroids, glucocorticoids
Systemic illness	Alcohol and marijuana abuse
Nutritional deficiency/excessive exercise	Severe obesity, some sleep disorders
Organ failure (liver, heart, lung)	Comorbid illness associated with aging

CLINICAL RATIONALE

The intent of the criteria is to provide coverage consistent with product labeling, FDA guidance, standards of medical practice, evidence-based drug information, and/or published guidelines. Topical, buccal, and nasal testosterone products are indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone: congenital or acquired primary hypogonadism (testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter Syndrome, chemotherapy, or toxic damage from alcohol or heavy metals), congenital or acquired hypogonadotropic hypogonadism (gonadotropin or luteinizing hormone-releasing hormone [LHRH] deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation). Safety and efficacy of topical, buccal, and nasal testosterone products in men with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established.

A testosterone determination, in conjunction with a free testosterone or sex hormone-binding globulin level, is the threshold test in the evaluation of suspected male hypogonadism (serum total testosterone levels less than 300 ng/dL). Testosterone levels should be determined in the morning, and studies should be repeated in patients with subnormal levels. The normative ranges for total and free testosterone levels in healthy young men vary among laboratories and assays. In some laboratories, the lower limit of the normal range for total testosterone level in healthy young men is 280-300 ng/dL and for serum free testosterone level is 5–9 pg/mL. The clinicians should use the lower limit of normal range for healthy young men established in their laboratory. For initial therapy, testosterone will be approved for patients with at least two confirmed low morning testosterone levels according to current practice guidelines or standard lab reference values. If the patient is already on testosterone therapy and did not get a repeat testosterone level before starting therapy, it would be inappropriate for the patient to stop treatment to get a repeat testosterone level. For continuation therapy, one low morning testosterone level is required before the patient started testosterone therapy.

Oral androgens may be used secondarily in women with advancing inoperable metastatic (skeletal) mammary cancer who are one to five years postmenopausal. Primary goals of therapy in these women include ablation of the ovaries. Other methods of counteracting estrogen activity are adrenalectomy, hypophysectomy, and/or anti-estrogen therapy.1-5 Since testosterone is not a first-line drug for breast cancer, the patient must have had an incomplete response to other breast cancer therapy before using testosterone.

This treatment has also been used in premenopausal women with breast cancer who have benefited from oophorectomy and are considered to have a hormone-responsive tumor. Judgment concerning androgen therapy should be made by an oncologist with expertise in this field.1-5

Oral androgens may be used to stimulate puberty in carefully selected males with clearly delayed puberty. Brief treatment with conservative doses may occasionally be justified in these patients if they do not respond to psychological support.1-5

Orally administered testosterone is quickly metabolized by the liver and cannot achieve sufficient blood levels over time to be useful. The orally administered alkylated androgen preparations currently available are generally not recommended as first line therapy because of poor androgen effects, adverse lipid

changes, and hepatic side effects such as hemorrhagic liver cysts, cholestasis, and hepatocellular adenoma.6 Since oral androgens are not recommended as first line therapy, the patient must have an inadequate treatment response, intolerance, or contraindication to one non-oral form of testosterone before oral androgens will be approved.

Topical, buccal, and nasal testosterone products have a compendial use for gender dysphoria in transgender patients who were assigned female sex at birth.

Transgender persons seeking to develop the physical characteristics of the desired gender require a safe, effective hormone regimen that will suppress endogenous hormone secretion and maintain sex hormone levels within the normal range for the person's desired gender. The two major goals of hormonal therapy are to reduce endogenous hormone levels and, thereby, the secondary sex characteristics of the individual's birth-assigned gender and to replace endogenous sex hormone levels with those of the affirmed gender. The Endocrine Society suggests that pubertal development of the affirmed gender be initiated at about the age of 16 years, using a gradually increasing dose schedule of gender-affirming hormones. However, the Endocrine Society Guidelines also state that identifying an age at which pubertal development is initiated can be difficult and may depend on several factors (such as the age when pubertal suppression was begun, medications used to initiate pubertal suppression, relative risks of prolonged pubertal suppression, and the level of severity of the patient's distress due to gender dysphoria),, and the goal is to start the process at a time when the individual will be able to make informed, mature decisions to engage in the treatment. Some patients may advance to Tanner stage 2 of pubertal development at an early age (such as 9 or 10) and using pubertal suppression therapy for 6 or 7 years may be deemed inappropriate. Medical professionals involved in the patient's care should be involved in assessing whether the patient is ready to make the decision to begin hormone therapy and pubertal development. Therefore, individuals who are able to make an informed decision to engage in hormone therapy will be approved.

For transgender male persons, regimens to change secondary sex characteristics follow the general principle of hormone replacement treatment of male hypogonadism. Either parenteral or transdermal preparations can be used to achieve testosterone values in the normal male range (320-1000 ng/dL). The agent primarily used for endocrine treatment of transgender male or transmasculine patients is testosterone. When determining the appropriate method of testosterone delivery, many considerations should be taken into account. The most well-described formulation of testosterone therapy used to treat transgender male patients is injectable testosterone esters (cypionate or enanthate). Because injectable testosterone cypionate or enanthate is often administered every 1-4 weeks, some patients may notice a cyclic variation in effects as well as more time outside the normal physiologic levels. Transdermal testosterone has been shown to provide less variation in serum testosterone levels compared with injectable preparations and more closely mimics physiologic testosterone levels. However, transdermal preparations achieve low-normal ranges of testosterone levels in hypogonadal men, which may translate to a lessened change in physical appearance and virilization in the transgender male patient.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- Code(s), if applicable

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POLICY HISTORY

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