Testosterone Replacement Therapy

Summary

Testosterone is a type of hormone that the body naturally makes. Both men and women have testosterone with men normally having a much higher level. Testosterone helps the body with many things including supporting bone and muscle health. When the body's level of testosterone is lower than normal, it may lead to symptoms such as:

- Feeling depressed or tired.
- Having little to no interest in sex, also known as having a low libido.
- Low energy.
- Weak muscles or bones.

There are tests available to help health care providers decide whether testosterone replacement therapy is needed for people with low testosterone levels. After examination and learning about symptoms that a person may have, prescribers can order a blood test to check testosterone level. It is recommended to be done in the morning (before 10 am) for the most accurate results. If the test shows that a person has low testosterone, the test will be repeated a second time for confirmation. Depending on the individual, other tests may be needed.

If testing confirms that a person has low testosterone, there are treatment options available. This includes non-drug treatment options such as losing weight (if overweight) or managing other medical

conditions that may cause testosterone to be low (such as diabetes, high blood pressure, sleep apnea, or liver disease). Low testosterone can also be treated by testosterone replacement therapy, available in multiple different forms. As with all medications, there are benefits, but also risks or side effects with their use. Table 1: Testosterone Products for Testosterone Replacement Therapy, lists names of commonly prescribed testosterone products that are used to treat people with low testosterone. These products are sometimes used for other reasons such as treating breast cancer in certain people.

Oral testosterone undecanoate products (e.g., Jatenzo, Tlando, Kyzatrex) have a boxed warning for increased blood pressure which would potentially increase the risk of cardiovascular events. Blood pressure and cardiovascular risk should be assessed prior to initiation.

Injected testosterone undecanoate (Aveed) has a boxed warning for the risk of pulmonary oil microembolism (POME) reactions. Due to this, the Aveed is only available through the AVEED Risk Evaluation and Mitigation Strategy (REMS) program. Individuals who are administered Aveed (testosterone undecanoate) should be monitored for at least 30 minutes after administration for every injection.

Topical testosterone (e.g., Androgel, Testim, Vogelxo, Axiron) have a boxed warning for the risk of virilization in children who are secondary exposed to testosterone gel through contact with an adult who has applied testosterone gel. Children should avoid contact with unwashed or unclothed application sites in those using testosterone gel.

Table 1: Testosterone Products for Testosterone Replacement Therapy

Route of Administration	Dosage Forms	Brand Names	Generic Name	FDA-approved age range
Nasal	Gel	Natesto	Testosterone	ages ≥18 years and adults
Oral	Capsule/tablet	Jatenzo	Testosterone Undecanoate	
		Tlando		
		Kyzatrex		
		Undecatrex		
		Methitest	Methyltestosterone	adolescents and adults
Parenteral	Implant, pellets for sub-Q injection	Testopel	Testosterone	adolescents and adults
	Solution, for sub-Q injection	Xyosted	Testosterone Enanthate	ages ≥18 years and adults

	Injection (in oil), for intramuscular injection	Delatestryl		adolescents and adults
		Depo-Testosterone	Testosterone Cypionate	ages ≥12 years and adults
		Azmiro	Testosterone cypionate	
		Aveed	Testosterone Undecanoate	ages ≥18 years and adults
Topical	Gel	Androgel 1%	Testosterone	
		Androgel 1.62%		
		Testim 1%		
		Vogelxo		
	Solution	Testosterone (Axiron)		
	Transdermal System	Androderm		

NOTE: The Plan requires that members be unable to use, or have tried and failed preferred product(s) first. Requests for non-formulary medications are subject to Non-Formulary Products Criteria (PG069). The above table includes both formulary and non-formulary products. Refer to your member benefits and your state-specific formulary for a complete list of formulary testosterone products.

Definitions

"Acquired" means developed or acquired after birth.

"AIDS or acquired immunodeficiency syndrome" is the medical term that is used to describe a stage of HIV infection when the immune system is at its weakest, causing a person to get infections (opportunistic diseases) that they normally would not get if their immune system was stronger.

"Carcinoma" is another word for cancer.

"Chemotherapy" refers to treatment involving the use of drugs to kill or slow the growth of cancer cells.

"Congenital" means present from birth.

"Cryptorchidism" is a condition in which one or both testicles fail to descend into the scrotum.

"HIV or human immunodeficiency virus" is the name of a virus that can infect a person, and weaken their immune system, leading to long-term problems, including decreasing their ability to fight off infections.

"Free Testosterone Levels" is the amount of unbound or biologically active testosterone in the blood.

"Hypogonadism" is a condition of having a level of testosterone that is lower than normal.

"Hypogonadotropic Hypogonadism" is a form of hypogonadism caused by the inadequate secretion of gonadotropin-releasing hormone (GnRH) or gonadotropins, hormones responsible for stimulating the production of testosterone.

"Idiopathic" means of unknown cause or origin.

"Oophorectomy" is the surgical removal of one or both ovaries.

"Orchiectomy" is the surgical removal of one or both testicles.

"Palliative treatment" is therapy that helps a person suffering from cancer or other life-threatening diseases to feel better or more comfortable, but does not cure the disease.

"Primary Hypogonadism" is a form of hypogonadism caused by testicular failure or abnormalities in the testes.

"Qualified Healthcare Professional" is a licensed and certified individual who is trained and authorized within the scope of their professional practice to diagnose health conditions and prescribe medications. Examples of qualified healthcare professionals include:

1. Primary Care Physicians: General practitioners who serve as the patient's first point of contact and can diagnose a variety of health conditions.
2. Nurse Practitioners: Advanced practice registered nurses who can prescribe medications, including those that are controlled, in all U.S. states.
3. Physician Assistants: Medical professionals who can diagnose illness, develop and manage treatment plans, and prescribe medications.
4. Specialist Physicians: Such as endocrinologists who specialize in hormonal disorders, urologists who treat conditions of the urinary tract and male reproductive system, infectious disease specialists for conditions like HIV, and oncologists for cancer-related conditions.

The involvement of a specific healthcare professional in prescribing testosterone products should align with their expertise, the patient's specific condition, and the complexity of the care needed.

"Sex Hormone Binding Globulins" are proteins that bind to and transport sex hormones, such as testosterone, in the bloodstream.

"Testosterone" is a chemical, or hormone, that is made mainly in the testicles.

"Total Serum Testosterone Concentrations" is the amount of testosterone present in the blood.

"Viritilization"is a condition in which females develop characteristics associated with male hormones (e.g., testosterone), or where newborns have signs of male hormone exposure at birth. In the setting of topical testosterone exposure, symptoms of excessive male hormone exposure can occur in anyone, especially children, regardless of sex.

Medical Necessity Criteria for Authorization

The Plan considers Testosterone Products medically necessary when ALL the following criteria are met for the applicable indication listed below:

For hormone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone: primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired):

Medical Necessity Criteria for Authorization

The Plan considers Testosterone Products medically necessary when ALL of the following criteria are met:

1. The member has a documented diagnosis of hypogonadism (primary or secondary types); *AND*

   Examples of congenital or acquired primary hypogonadism:

   - *orchiectomy, testicular failure caused by cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, Klinefelter's syndrome, chemotherapy, infection (mumps orchitis), or toxic damage from alcohol or heavy metals*

   Examples of congenital or acquired secondary hypogonadism:

   - *idiopathic gonadotropin or gonadotropin-releasing hormone (luteinizing hormone releasing hormone) deficiency, leptin or leptin receptor mutations, hyperprolactinemia, gonadal steroids (e.g., androgens, estrogens and progestins), glucocorticoid treatment, opioid agonists, chronic illness (e.g., acquired immune deficiency syndrome [AIDS], chronic lung disease, chronic kidney disease), anorexia nervosa, diabetes mellitus, pituitary-hypothalamic injury caused by tumors, trauma, or radiation*
2. The medication is prescribed by a qualified healthcare professional (see Definitions). If the situation requires specialized expertise for accurate diagnosis, prescription, assessment of treatment risks and benefits, proficiency in the preparation and administration of the specific testosterone product, monitoring of side effects, or coordination of care, the prescription should be provided by, or in consultation with, a specialist with relevant training, such as an endocrinologist or urologist*; AND*
3. The member has documented signs and/or symptoms of low testosterone levels (e.g., low sex drive, weak muscles or bones, or low energy); *AND*

4. Clinical chart documentation has been provided confirming ONE of the following:
    a. Prior to treatment, total serum testosterone concentrations have been measured in the morning on at least two separate days and these total serum testosterone concentrations are below 300 ng/dL; *or*
    b. The member has elevated sex hormone binding globulins and has two low free testosterone levels that are at the lower limit of normal for the reference laboratory*; or*
    c. When already on treatment, a total serum testosterone concentration has been measured and is less than or within the normal reference range; *or*
    d. Documentation that serum testosterone level monitoring would not be required for appropriate testosterone replacement therapy based on the diagnosis (i.e., bilateral orchiectomy, Klinefelter's syndrome, Panhypopituitarism, congenital anorchia).

If the above prior authorization criteria are met, the requested medication will be approved for 36 months.

For hormone therapy for transgender and gender diverse individuals

Medical Necessity Criteria for Authorization

The Plan considers Testosterone Products medically necessary when the following criteria is met:

1. The requested medication is being used for endocrine treatment of gender dysphoric/gender incongruent persons.

If the above prior authorization criteria are met, the requested medication will be approved for the member's lifetime.

For hypogonadism associated with HIV infection

Medical Necessity Criteria for Authorization

The Plan considers Testosterone Products medically necessary when BOTH of the following criteria are met:

1. The member has documented human immunodeficiency virus (HIV) infection; *AND*
2. The requested medication is being requested for the treatment of ONE of the following:
    a. androgen deficiency (e.g., hypogonadism); *or*
    b. HIV/AIDS-related symptoms.

If the above prior authorization criteria are met, the requested medication will be approved for 36 months.

For palliative treatment of breast cancer that is inoperable in women:

Medical Necessity Criteria for Authorization

The Plan considers testosterone cypionate, testosterone enanthate, or methyltestosterone medically necessary when ALL of the following criteria is met:

1. The requested medication is prescribed by or in consultation with a qualified clinician (e.g., oncologist) experienced in the treatment of breast cancer; *AND*
2. The requested medication is being used for palliative treatment of inoperable carcinoma of the breast (androgen-responsive, advanced, inoperable, metastatic breast carcinoma); *AND*
3. The member is considered to have a hormone-responsive tumor; *AND*
4. The member is a female member and meets ONE (1) of the following:
    a. is pre-menopausal AND has benefited from oophorectomy; *or*
    b. is one (1) to five (5) years post-menopausal AND is unable to use or has tried and failed other hormonal agents (e.g., tamoxifen, anastrozole, letrozole, exemestane).

If the above prior authorization criteria are met, the requested medication will be approved for the member's lifetime.

For the treatment of delayed puberty in males

Medical Necessity Criteria for Authorization

The Plan considers Testosterone Products medically necessary when ALL of the following criteria are met:

1. The medication is prescribed by a qualified specialist (e.g., pediatric endocrinologist) experienced in treating carefully selected males with delayed puberty; *AND*
2. Diagnosis of delayed puberty; *AND*
3. Safety and efficacy of the requested medication has been established for the member's age as evidenced by FDA-approved labeling (Use in Specific Populations); *AND*
4. Documentation of BOTH of the following:
    a. prior to initiation of therapy, fully discussing the potential risk of therapy with the member and his parents; *and*
    b. The prescriber has assessed the bone maturation (i.e., with radiographic evidence using the left hand and wrist) AND determined the member would benefit from testosterone therapy.

If the above prior authorization criteria are met, the requested medication will be approved for 12 months.

Experimental or Investigational / Not Medically Necessary

Testosterone Products for any other indication are considered not medically necessary by the Plan, as they are deemed to be experimental, investigational, or unproven. These include but are not limited to:

- for men with late-onset hypogonadism (i.e., low testosterone concentrations related to aging), without a clinical diagnosis of hypogonadism.
- for nonmedical use such as for cosmetic purposes to achieve bodies with lean muscle mass, or to enhance athletic performance or physique.
- for the management of vasomotor symptoms associated with menopause.
- for the prevention of postpartum breast pain and engorgement.
- for the treatment of erectile dysfunction in men with normal serum testosterone concentrations.
- for the treatment of hypoactive sexual desire disorder.
- for the treatment of depression, fatigue, cognitive decline, or cardiovascular disease in men without documented hypogonadism.
- any other uses not supported by robust clinical evidence and/or widely accepted clinical practice guidelines.

Appendix

In the interest of promoting safe, effective, and evidence-based use of Testosterone Products, the Plan considers uses outside of established medical indications as not medically necessary. These uses are considered experimental, investigational, or lacking sufficient evidence to demonstrate clear health benefits that outweigh potential risks. The following provides examples of such uses, although this is not an exhaustive list:

It is important to note that such uses may also be considered non-covered benefits by the Plan.

1. For men with late-onset hypogonadism (i.e., low testosterone concentrations related to aging), without a clinical diagnosis of hypogonadism: Clinical evidence and guidelines have not sufficiently established that age-related decline in testosterone is detrimental or that replacement therapy is beneficial in males without a clinical diagnosis of hypogonadism (e.g., subnormal serum testosterone levels and clinical signs and symptoms of androgen deficiency).
2. For nonmedical use such as for cosmetic purposes to achieve bodies with lean muscle mass, or to enhance athletic performance or physique: Testosterone is not approved for use in nonmedical or performance-enhancement purposes due to potential adverse health effects and ethical considerations.
   NOTE: These uses may also be considered a non-covered benefit by the Plan.
3. For the management of vasomotor symptoms associated with menopause: While testosterone may affect vasomotor symptoms, it's not approved for this indication due to lack of robust clinical evidence showing significant benefits outweighing potential risks.
4. For the prevention of postpartum breast pain and engorgement: Current clinical evidence does not support the use of testosterone for this indication, with other treatments showing more efficacy and safety.

5. For the treatment of erectile dysfunction in men with normal serum testosterone concentrations: Testosterone is not typically first-line therapy for erectile dysfunction, particularly in men with normal serum testosterone. Other treatments are typically more effective. Testosterone therapy may be applicable in the use of males with erectile dysfunction who also have a diagnosis of hypogonadism.
   NOTE: This use may also be considered a non-covered benefit by the Plan.
6. For the treatment of hypoactive sexual desire disorder: The clinical evidence supporting testosterone use for this indication is not sufficiently robust, and the potential risks may outweigh benefits. Studies have shown that in older adults males, there is a moderate benefit of testosterone on sexual function. However, these studies were conducted in those with hypogonadism as determined by clinical signs and symptoms of androgen deficiency and subnormal serum testosterone levels (less than 275 ng/dl). Thus use for hypoactive sexual desire disorder without a diagnosis of hypogonadism has not been adequately studied or shown to be safe and effective.
7. For the treatment of depression, fatigue, cognitive decline, or cardiovascular disease in men without documented hypogonadism: Clinical evidence and guidelines does not support the use of testosterone for these indications in the absence of hypogonadism. The Testosterone Trials found a non-significant improvement in fatigue, inconclusive evidence to support cardiovascular safety and statistically significant improvement in depression scores. However, the Testosterone Trials were only conducted in males with clinical signs and symptoms of androgen deficiency and subnormal serum testosterone levels (less than 275 ng/dl). While depression and cognitive deficits can be side effects of low testosterone (hypogonadism), studies have found inconclusive evidence of testosterone on mood and cognition in those without hypogonadism.
   NOTE: This use may also be considered a non-covered benefit by the Plan.
8. Any other uses not supported by robust clinical evidence and/or widely accepted clinical practice guidelines: The Plan aims to ensure treatments are used in a safe and effective manner. Therefore, indications lacking robust clinical evidence or guideline support are deemed not medically necessary.

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