BlueCross BlueShield
Federal Employee Program

TESTOSTERONE ORAL / BUCCAL / NASAL AGENTS
Methitest (methyltestosterone tablet)
methyltestosterone capsule
Natesto (testosterone nasal gel)
Striant (testosterone buccal system)
Jatenzo, Kyzatrex, Tlando* (testosterone undecanoate capsule)

*Non-covered medications must go through prior authorization and the formulary exception

RATIONALE FOR INCLUSION IN PA PROGRAM

Background

Endogenous androgens, including testosterone and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis and scrotum; the development of male hair distribution, such as facial, pubic, chest and axillary hair; laryngeal enlargement, vocal cord thickening, alterations in body musculature and fat distribution (1-7).

Androgens stimulate growth in adolescence and cause the eventual closure of the femoral *epiphysis.* In children, exogenous androgens accelerate linear growth rates but may cause a disproportionate advancement in bone maturation. Chronic use may result in fusion of the epiphyseal growth centers and termination of growth process (1-2).

Regulatory Status

FDA-approved indications: Androgens are indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone. Jatenzo, Kyzatrex, Methitest, methyltestosterone capsule, Natesto, Striant and Tlando are indicated for the treatment of: (1-7)

- 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 [FSH], luteinizing hormone [LH]) above the normal range.
- 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 testosterone serum concentrations but have gonadotropins in the normal or low range.

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Methitest and methyltestosterone capsule are also indicated for the treatment of: (1-2)

0. Delayed puberty in males*:* to induce pubertal changes in hypogonadal males. The potential adverse effect on bone maturation should be discussed with the patient and parents prior to androgen administration. An X-ray of the hand and wrist to determine bone age should be obtained every 6 months to assess the effect of treatment on the epiphyseal centers.
1. In women as secondary treatment with advancing inoperable metastatic (skeletal) mammary cancer who are 1 to 5 years postmenopausal. This treatment has also been used in premenopausal women with breast cancer who have benefitted from oophorectomy and are considered to have a hormone-responsive tumor.

Off-Label Use: (10)
Testosterone can be used in the treatment of Gender Dysphoria (GD) and should only be started once a diagnosis of GD or transsexualism has been made per the DSM V or ICD-10 criteria.

The drugs addressed by this policy have warnings regarding polycythemia, worsening of benign prostatic hyperplasia (BPH) and potential risk of prostate cancer, venous thromboembolism (VTE), abuse of testosterone and monitoring of serum testosterone concentration, potential for adverse effects on spermatogenesis, edema, sleep apnea, lipid changes and increases in prolactin. Prolonged use of high doses of androgens has been associated with the development of peliosis hepatitis and hepatic neoplasms including hepatocellular carcinoma (1-7).

Hematocrit levels and liver function tests must be monitored while on testosterone therapy (1-7).

Male patients, with benign prostatic hyperplasia (BPH), must be monitored for worsening of signs and symptoms of BPH. Physicians should evaluate male patients for the presence of prostate cancer prior to the initiation of therapy. A normal prostate cancer risk is a PSA level

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that is less than 4 ng/ml. High prostate cancer risk patients, such as African American men and men whose father or brother had prostate cancer, should have a PSA less than 3 ng/ml. Check prostate-specific antigen (PSA) levels in men over 50 years of age, or in those over 40 having a family history of prostate cancer or if African-American; to ensure proper dosing. Patients should be re-evaluated 12 months after initiation of treatment, and then in accordance with prostate cancer screening practices (1-9).

Two total testosterone levels are required to determine medical necessity of testosterone replacement. Two morning samples drawn between 8:00 a.m. and 10:00 a.m. obtained on different days are required. Total testosterone levels need to be below 300ng/dL on both days in order to be considered for therapy (9).

Androgen therapy in the treatment of women with breast cancer should be made by an oncologist with expertise in this field. Hypercalcemia may occur in immobilized patients and in patients with breast cancer. If this occurs, the drug should be discontinued (1-2).

Jatenzo and Tlando have a boxed warning regarding blood pressure (BP) increases that can increase the risk of major adverse cardiovascular events (MACE), including non-fatal myocardial infarction, non-fatal stroke and cardiovascular death (5-6). Patients should be assessed for cardiovascular risk prior to initiating treatment with androgens (1-7).

Due to lack of clinical data on the safety or efficacy, Natesto is not recommended for use in patients with the following: (3)

- History of nasal disorders
- History of nasal or sinus surgery
- History of nasal fracture within the previous 6 months or nasal fracture that caused a deviated anterior nasal septum
- Mucosal inflammatory disorders (e.g., Sjogren’s syndrome), and
- Sinus disease

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The safety and effectiveness of Jatenzo, Kyzatrex, Natesto, Striant and Tlando in pediatric patients less than 18 years of age have not been established (3-7).

Methitest and methyltestosterone capsule therapy should be used very cautiously in pediatric patients and only by specialists who are aware of the adverse effects on bone maturation (1-2).

Summary

Testosterone is approved for replacement therapy in men for conditions associated with testosterone deficiency such as: hypogonadotropic hypogonadism, primary hypogonadism, and delayed puberty. In women, methyltestosterone is approved to treat metastatic breast cancer. Liver function and hematocrit levels should be monitored in all patients taking testosterone. In adult men, the following should also be monitored: prostate-specific antigen (PSA) levels, serum testosterone concentrations, presence of prostate cancer, worsening of *benign prostatic hypertrophy* (BPH), and cardiovascular risk. For pubescent males, radiographic evidence to determine bone maturation needs to be obtained. Testosterone can also be used off-label in the treatment of Gender Dysphoria (GD) (1-10).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use of the testosterone products while maintaining optimal therapeutic outcomes.

References

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5. Jatenzo [package insert]. Northbrook, IL: Clarus Therapeutics, Inc.; March 2019.
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