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 (1).

Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone concentrations. Symptoms associated with male hypogonadism include the following: impotence and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics, and osteoporosis (1).

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. Androgens have been shown to stimulate the red blood cell production by the increased production of erythropoietic stimulating factor (2).

Regulatory Status
FDA-approved indications: (2-8)

1. 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.

2. Hypogonadotrophic 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.
3. Delayed puberty in males: to induce pubertal changes in hypogonadal males.

4. In women as secondary treatment with advancing inoperable metastatic (skeletal) mammary cancer who are 1 to 5 years postmenopausal (2). 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:**
Testosterone can be used in the treatment of Gender Dysphoria (GD) and should only be started once a diagnosis of GID or transsexualism has been made per the DSM V or ICD-10 criteria (11).

Chronic high dose therapy of androgens has shown development of peliosis hepatitis and hepatic neoplasms including hepatocellular carcinoma. Peliosis hepatitis can be a life-threatening or fatal complication. Low doses of 17-alpha-alkylandrogens have been associated with cholestatic hepatitis and jaundice. The medication should be discontinued and the cause should be determined if these conditions occur. Drug-induced jaundice is reversible upon withdrawal of medication therapy (2-5).

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 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 age 50 years, or in those over age 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 (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 (10).
Hematocrit levels must be less than 54% prior to initiation of testosterone therapy and reevaluated annually thereafter (7-9).

Androgen use for delayed puberty in males should be prescribed only by specialists who are aware of the adverse effects on bone maturation. An X-ray of the hand and wrist every 6 months will be required to determine bone age and to assess the effect of treatment on the epiphyseal centers (2-4,7).

Androgen therapy in the treatment in 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 (2-4,7).

Patients with severe obstructive sleep apnea and severe lower urinary tract symptoms are recommended not to use androgen therapy due to possible worsening of symptoms and/or even death (2).

Extreme caution should be used in patients with a history of cardiovascular disease (9).

Due to lack of clinical data on the safety or efficacy, Natesto is not recommended for use in the following patients: (6)

- 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

Women and children should not use Natesto (6). Striant is not indicated for use in women (7).

**Summary**

Testosterone is approved for replacement therapy in men for conditions associated with a deficiency of testosterone such as: hypogonadotropic hypogonadism (congenital or acquired),
primary hypogonadism (congenital or acquired), and delayed puberty. In women, testosterone therapy is approved to treat metastatic breast carcinoma. Liver function and hematocrit should be monitored in all patients. In adult men, the following should be monitored: prostate-specific antigen (PSA) levels, serum testosterone concentrations, presence of prostate cancer, and worsening effects of benign prostatic hypertrophy (BPH), if present and has been evaluated for their cardiovascular risk. Calcium levels in women should be monitored. For pubescent males radiographic evidence to determine bone maturation needs to be obtained (1-8).

Prior approval is required to ensure the safe, clinically appropriate and cost effective use of the testosterone products Android, Androxy, Methitest, Natesto, Striant, and Testred while maintaining optimal therapeutic outcomes.

References