

## **TESTOSTERONE**

(Injectable and Implant Agents)

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Aveed (testosterone undecanoate injection), Delatestryl (testosterone enanthate injection), Depo-Testosterone and Testone CIK (testosterone cypionate injection), Testopel (testosterone propionate implant)

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### **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:

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. Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury

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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. 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 (4).

Aveed carries a boxed warning which states that serious pulmonary oil microembolism (POME) reactions, involving urge to cough, dyspnea, throat tightening, chest pain, dizziness, and syncope; and episodes of anaphylaxis, including life-threatening reactions, have been reported to occur during or immediately after the administration of testosterone undecanoate injection. Because of the risk of this reaction and anaphylaxis, testosterone undecanoate is available only through a restricted program under a risk evaluation and mitigation strategy (REMS) called the Aveed REMS Program. These reactions can occur after any injection of testosterone undecanoate during the course of therapy, including after the first dose. The REMS program ensures the prescriber observes the patient in the health care setting for 30 minutes following each injection in order to provide appropriate medical treatment in the event of serious POME reactions or anaphylaxis (3).

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 (3-6).

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-

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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 (3-6).

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 300 ng/dL on both days in order to be considered for therapy (7).

Hematocrit levels must be less than 54% prior to initiation of testosterone therapy and reevaluated annually thereafter (3-6).

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 (4).

Androgen therapy in the treatment for 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 hypercalcemia occurs, the testosterone therapy should be discontinued (4).

Extreme caution should be used in patients with a history of cardiovascular disease (2).

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).

### **Summary**

Testosterone is approved for testosterone 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.

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Prior approval is required to ensure the safe, clinically appropriate and cost effective use of the testosterone products Aveed (testosterone undecanoate injection), Delatesteryl (testosterone enanthate injection), Depo-Testosterone (testosterone cypionate injection), and Testopel (testosterone propionate implant) while maintaining optimal therapeutic outcomes.

### References

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