Endogenous androgens are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. Some of these effects include alterations in body musculature and maturation of prostate, seminal vesicles, penis and scrotum. Androgens are also responsible for the growth spurt of adolescence and for the eventual termination of linear growth.
Exogenous androgens in children can accelerate linear growth rates but may also cause a disproportionate advancement in bone maturation.

Testosterone replacement regimens supply exogenous testosterone and restore serum testosterone levels in the normal range (300 to 1,000 ng/dL). The International Society of Andrology (ISA), International Society for the Study of the Aging Male (ISSAM), European Association of Urology (EAU), European Academy of Andrology (EAA), and the American Society of Andrology (ASA) propose 230 ng/dL as the lower limit of serum testosterone at which patients will benefit from testosterone replacement therapy. The Endocrine Society recommends 300 ng/dL, and the American Association of Clinical Endocrinologists (AACE) suggests 200 ng/dL as the lower limit for initiating testosterone replacement. Testosterone level increases in males until 17 years of age and stabilizes to a serum level in the range of 300 to 1,000 ng/dL, until about 40 years of age. After this, the levels begin to decline at 1.2% to 2% per year. About 20% of men > 60 years of age and 50% of men > 80 years of age are estimated to have serum testosterone levels that are subnormal compared with younger men. Given this inherent variability in testosterone levels in men based on age, it is also prudent to consider other variables that could affect a laboratory drawn testosterone level (e.g., time of day when the level is drawn, laboratory specific normal values for testosterone, total vs. free testosterone levels) before initiating replacement therapy.

Male hypogonadism is characterized by low serum levels of testosterone and is classified according to the level of the hypothalamus-pituitary-testis axis involvement. It is classified as primary hypogonadism when the main problem involves the testes (elevated lutenizing hormone [LH] and follicle stimulating hormone [FSH]). It is secondary hypogonadism (hypogonadotrophic hypogonadism) if the hypothalamus/pituitary axis are involved; low testosterone levels in this case are associated with low or inadequately normal levels of LH and FSH. The diagnosis of male hypogonadism is based on both a clinical suspicion and low testosterone levels. By restoring normal levels of testosterone, the replacement regimens correct symptoms of hypogonadism, which can include malaise, loss of muscle strength, depressed mood, and decreased libido.

Testosterone regimens can be administered orally, parenterally, or transdermally. Injectable testosterone replacement products include testosterone cypionate, testosterone enanthate, and Aveed injections, and Testopel, which is implanted subcutaneously. These agents are all indicated for congenital or acquired primary hypogonadism and hypogonadotropic hypogonadism (secondary hypogonadism). Testopel and testosterone enanthate are also indicated for delayed puberty. Testosterone enanthate may also be used secondarily in women with advanced inoperable metastatic mammary cancer that are 1 to 5 years postmenopausal. The primary goal of this therapy is to ablate the ovaries. It can also be used in premenopausal women with breast cancer who have benefited from oophorectomy and are considered to have a hormone-responsive tumor. The prescribing information notes that the judgment regarding the use of androgen therapy in females should be made by an oncologist with expertise in the area. Compared with the other two intramuscular injections, Aveed has a longer duration between dosing after it reaches steady state levels. After the first injection, a second injection is administered after 4 weeks. After this second dosing subsequent administration is once every 10 weeks. Dose titration is not necessary. The safety and efficacy of Aveed in males < 18 years of age have not been established.

POLICY STATEMENT
Prior approval is recommended for prescription benefit coverage of testosterone injections or pellet formulations. Because of the specialized skills required for evaluation and diagnosis of patients treated with testosterone injections or pellet formulations for the indications given below, as well as the monitoring required for adverse events and long-term efficacy, initial and continuing approval requires to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 6 months in duration unless otherwise noted below. Topical Testosterone products may also follow the Topical Testosterone Step Therapy.

**RECOMMENDED AUTHORIZATION CRITERIA**

Coverage of testosterone injection, pellet, oral, or topical formulations are recommended in those who meet the following criteria:

**Approved Indications:**

1. **Hypogonadism (Primary or Secondary) in Males [Testicular Hypofunction/Low Testosterone with Symptoms].**
   - Coverage is provided in situations where the patient has had persistent signs and symptoms (for example, depressed mood, decreased energy, progressive decrease in muscle mass, osteoporosis, loss of libido) of androgen deficiency (pre-treatment).
   - For initial therapy, coverage is provided in situations where the patient has had two pre-treatment serum testosterone measurements, each taken in the morning on two separate days, and both levels were low, as defined by the normal laboratory reference values. **Approval is for one year.**
   - For continuation of therapy, coverage is provided in situations where the patient has had at least one pre-treatment serum testosterone (total or bioavailable) level, which was low as defined by the normal laboratory reference value. **Approval is for one year.**

2. **Delayed Puberty or Induction of Puberty in Males 14 years of Age or Older (does not include Aveded or any topical formulation).**
   - Coverage is provided in situations where this medication is being prescribed for the treatment of hypogonadism (primary or secondary) in a male patient, delayed puberty or induction of puberty in a male patient 14 years of age or older. **Approval is for 6 months.**

3. **Palliative Treatment of Inoperable Metastatic Breast Cancer in Females (Delatestryl (testosterone enanthate), oral testosterone products).**
   - Coverage is provided in situations where this medication is being prescribed by, or in consultation with, an oncologist. **Approval is for 6 months.**

**Other Uses with Supportive Evidence**

**Female-to-Male (FTM) Gender Reassignment (i.e., Endocrinologic Masculinization).**
   - Coverage is provided in situations where the requested medication is being prescribed by, or in consultation with, an endocrinologist or a physician who specializes in the treatment of transgender patients. **Approval is for one year.**

**CONDITIONS NOT RECOMMENDED FOR APPROVAL**
Injectable testosterone (e.g., testosterone cypionate, testosterone enanthate, Aveed, Testopel) has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Use in Females for Indications Other than Female-to-Male (FTM) Gender Reassignment and Palliative Treatment of Metastatic Breast Cancer (see above).** All of the injectable testosterone products are contraindicated for use in pregnant women. In the 2006 guidelines on androgen therapy in women from the Endocrine Society, despite some short-term efficacy evidence, it recommends against the generalized use of testosterone by women because the indications are inadequate and the evidence of safety in long-term (> 24 weeks) studies is lacking. The American College of Obstetricians and Gynecologists (ACOG) clinical management guidelines for management of female sexual dysfunction (reaffirmed in 2013) mentions testosterone as an option for the short-term treatment (e.g., 6 months) of hypoactive sexual desire disorder. However, the FDA-approved testosterone formulations provide doses larger than the dosages studied in and typically required by women. More data are needed regarding long-term safety of testosterone use in women and patient selection before it can be recommended in this patient population. Testosterone supplementation has also been evaluated in a small number of women for the effect on follicle stimulation with no significant effect noted.

2. **To Enhance Athletic Performance.** Injectable testosterone products are not recommended for approval because this indication is excluded from coverage in a typical pharmacy benefit.

3. **Use in Males with Carcinoma of the Breast.** All of these testosterone replacement products are contraindicated for use in men with carcinoma of the breast.

4. **Use in Males with Known or Suspected Carcinoma of the Prostate (excluding males with treated and cured prostate cancer).** All of these testosterone replacement products are contraindicated for use in men with known or suspected carcinoma of the prostate.

5. **Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria.** Criteria will be updated as new published data are available.

**Dosing for injectables**

Depo-testosterone for hypogonadal males – 500-400 mg IM every two to four weeks  
Delatestyl  
- Male hypogonadism - 50 to 400 mg IM every 2 to 4 weeks.
- Males with delayed puberty - 50 to 200 mg IM every 2 to 4 weeks for a limited duration, for example, 4 to 6 months
- Palliation of inoperable mammary cancer in woman - 200 to 400 mg IM every 2 to 4 weeks

Aveed - 3 mL (750 mg) injected intramuscularly, followed by 3 mL (750 mg) injected after 4 weeks, then 3 mL (750 mg) injected every 10 weeks thereafter
Approval Duration

Approval for Delayed Puberty or Induction of Puberty in Males 14 years of Age or Older, Palliative Treatment of Inoperable Metastatic Breast Cancer in Females = 6 months

Approval for Hypogonadism (Primary or Secondary) in Males and Female-to-Male (FTM) Gender Reassignment = 1 year

REFERENCES