

Aveed (testosterone undecanoate)

STRENGTH	DOSAGE FORM	ROUTE	GPID
750mg	injectable	intramuscularly	36193

MANUFACTURER

Endo Pharmaceuticals, Inc.

INDICATION(S)

For testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

- Primary hypogonadism (congenital or acquired)
- Hypogonadotropic hypogonadism (congenital or acquired)

Aveed should only be used in patients who require testosterone replacement therapy and in whom the benefits of the product outweigh the serious risks of pulmonary oil microembolism and anaphylaxis.

Limitations of use:

- Safety and efficacy of Aveed in males less than 18 years old have not been established

DRUG CLASS

HORMONAL DEFICIENCY; ANDROGENIC AGENTS

PLACE IN THERAPY

Aveed is a new, long-acting injectable testosterone formulation. Testosterone is an endogenous androgen responsible for the development of male sex organs and for the maintenance of secondary sex characteristics. Potential advantages of Aveed over other long-acting injectable include reduced testosterone serum level fluctuations during therapy and less frequent injections (maintenance therapy is dosed once every 10 weeks after 2 initial doses). Other long-acting injectable testosterone products are Delatestryl (testosterone enanthate) and Depo-testosterone (testosterone cypionate), both available as generics. Other formulations of testosterone (available as brands) include transdermal gel packets and pumps such as Androgel, Axiron and Testim; a buccal mucoadhesive (Striant) and subcutaneous pellet (Testopel) are also available as branded products.

Prescribing and demand for prescription testosterone products have increased significantly over several years due to direct-to-consumer advertising and marketing of new products such as testosterone transdermal gels. Testosterone gels generate over \$2 billion in U.S. sales each year. Additionally, demand for testosterone is expected to increase as the aging population in the US increases. Hypogonadism, also referred to as testosterone deficiency, affects approximately 30% of men ages 40 to 79 years old. The prevalence increases with age. While prescriptions for injectable testosterone products represent just under one third of all prescription claims for testosterone products indicated to treat

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hypogonadism, they may be preferred by some patients due to reduced frequency of administration and because of the risk of secondary exposure to testosterone to children or pets that may occur with transdermal formulations.

Recently concern has increased regarding the safety of testosterone therapy. Although no large, randomized, controlled trials are available to verify rates of cardiovascular adverse events, an association was found between testosterone therapy and cardiovascular events in older men with low testosterone levels. A 2013 retrospective review of over 8700 males (Veterans Affairs cohort) with low testosterone levels demonstrated a 30% increased risk of death, myocardial infarction, or ischemic stroke among those that received prescription testosterone therapy. Another study, the Testosterone in Older Men with Mobility Limitations (TOM) trial, was stopped early in December 2009 due to a four-fold increase in cardiovascular events observed in the treatment group receiving testosterone 100mg daily as a transdermal gel. TOM study limitations included a small sample size, and an elderly study population with multiple comorbidities. However, a 2010 meta-analysis comparing the risk of adverse events in adult men on testosterone therapy found contradictory results; there was no additional cardiovascular risk for men using testosterone therapy.

EFFICACY

The efficacy of Aveed was evaluated in one 84-week, single arm, open-label study of 130 males (mean age 54.2) with hypogonadism. All patients were at least 18 years of age, weighed at least 65kg, and had a morning serum testosterone level less than 300ng/dL and a mean screening testosterone level of 215ng/dL. The primary efficacy endpoint was percentage of patients with average serum total testosterone concentration within the normal range (300-1000ng/dL) after the third injection. The secondary endpoint was percentage of patients with maximum total testosterone concentration (Cmax) within the following categories: above 2500ng/dL, between 1800 and 2499ng/dL, and above 1500ng/dL. For the primary efficacy endpoint, 94% of patients maintained an average serum testosterone level within the normal range (300-1000ng/dL). Approximately 5% of patients had average concentrations below the normal range (less than 300ng/dL) and 1% had average concentrations above the normal range.

SAFETY

The most common adverse events of Aveed observed in clinical trials ($\geq 2\%$) were acne, injection site pain, increased prostatic specific antigen (PSA), increased estradiol level, hypogonadism, fatigue, irritability, increased hemoglobin, insomnia and mood swings.

Contraindications for Aveed include men with carcinoma of the breast or known or suspected carcinoma of the prostate, pregnant or breastfeeding women, or known sensitivity to castor oil, benzyl benzoate, or the active ingredient.

Drug interactions include insulin and other medications to treat diabetes (may decrease blood glucose and therefore lower anti-diabetes medication requirements), anticoagulants (monitor international normalized ratio (INR) and prothrombin time (PT) for patients using warfarin), and corticosteroids (may increase fluid retention).

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Use caution in geriatric patients; there is not sufficient long-term data to assess potential risks of testosterone such as cardiovascular disease and prostate cancer. Use caution in patients with preexisting cardiac, renal, or hepatic disease; edema with or without congestive heart failure may occur.

Aveed contains a boxed warning regarding the risk of life-threatening anaphylaxis and pulmonary oil microembolism (POME). After receiving Aveed patients should be monitored for 30 minutes in a healthcare setting for signs of anaphylaxis or pulmonary oil microembolism (POME symptoms may include urge to cough, dyspnea, throat tightening, chest pain, dizziness and syncope). Due to the risk of anaphylaxis and pulmonary oil microembolism, Aveed is restricted and available only through a Risk Evaluation and Mitigation Strategy (REMS) program. Prescribers must be certified through the REMS program prior to ordering or dispensing Aveed.

Aveed is pregnancy category X.

DOSAGE

The recommended dose of Aveed is 750mg (3mL) injected intramuscularly at the start of therapy, at 4 weeks, and every 10 weeks thereafter. Aveed should be administered via a deep gluteal injection using the usual precautions for intramuscular administration of oily solutions. Patients should be observed by a healthcare provider for 30 minutes in order to monitor for or treat potential pulmonary oil microembolism events or anaphylaxis.

COST

Drug	Cost/unit	Cost per 10 weeks
Aveed (testosterone undecanoate) 750mg/3mL injection, 3 mL vial, maintenance therapy (use after first 4 weeks)*	AWP=\$990/3 ml vial	\$990*
testosterone cypionate injection 200mg/mL (200-400mg IM every 2-4 weeks) [#] , 1 or 10 mL vial	AWP=\$23.18/ mL	\$23 - \$232 [#]
testosterone enanthate 200mg/mL injection (50-400mg every 2-4 weeks), 5mL vial	MAC=\$68.25/5 mL vial	\$136 – 341 ^{&}
Androderm(testosterone) transdermal patch	AWP=\$14.96/ patch	\$1047
Androgel (testosterone) gel (metered dose pump with 60 actuations) (2 actuations daily; dose may be adjusted 1-4 pumps daily)	AWP=\$453/bottle	\$1057
Axiron (testosterone) gel (metered dose pump with applicator, 60 actuations) (2 actuations daily; dose may be adjusted 1-4 pumps daily)	AWP=\$471.60/bottle	\$1100

* = New starts will require an initial dose and one dose 4 weeks later (\$1980 additional cost)

= Cost per mL (200mg/mL concentration) varies by manufacturer and package size (from \$10.14 to \$28.63 per mL, vials cannot be split); no MAC pricing available. Average cost per prescription (Medimpact utilization data) is \$93.20 per 10 weeks.

& = 5mL vials cannot be split

FORMULARY PLACEMENT RECOMMENDATIONS

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Based on this initial assessment of available clinical and financial information, consider NOT ADDING Aveed to the formulary pending complete review by the appropriate oversight committee for the plan.

REFERENCES

- Aveed [Prescribing Information]. Malvern, PA: Endo Pharmaceuticals, Inc.; March 2014.
- Basaria S, Coviello A, Travison T, Storer T, and Farwell W. Adverse events associated with testosterone administration. *NEJM* 2010; 363 (2): 109-122.
- **Dandona P and Rosenberg M.** A practical guide to male hypogonadism in the primary care setting. *The International Journal of Clinical Practice* 2010; 64:682-696.
- Fernandez-Balsells M, Murad M, et al. Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. *Journal of Clinical Endocrinology and Metabolism* 2010; 95: 2560-2575.
- Vigen R, O'Donnell, Baron AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA* 2013; 310:1829-1835.