

Brand Name: Aveed

Generic Name: testosterone undecanoate

Manufacturer: Endo Pharmaceuticals Solutions Inc²

Drug Class: Androgens and anabolic steroids²

Uses:

Labeled Uses:

Aveed is indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.²

- Primary hypogonadism (congenital or acquired): testicular failure due to 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): 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 range²

Unlabeled Uses⁶:

- Antineoplastic adverse reaction - Leydig cell failure in adult
- Congenital hypoplasia of penis
- Coronary arteriosclerosis
- Deficiency of testosterone biosynthesis, Female
- Depression
- Osteoporosis, Male
- Postmenopausal osteoporosis; Prophylaxis
- Sexual disorder
- Weight gain

Mechanism of Action⁶: Metabolites of testosterone undecanoate, testosterone and dihydrotestosterone (DHT), modulate the normal growth and development of male sex organs (eg, prostate, seminal vesicles, penis and scrotum) and maintain male secondary sex characteristics such as facial, pubic, chest, and axillary hair, laryngeal enlargement, vocal cord thickening, and body musculature and fat distribution alterations

Pharmacokinetics^{2,6}:

Absorption^{2,6}:

T_{max} : IM: 4 days

V_d: 1.0 L/kg

t_{1/2} : 10-100 minutes

Clearance: Not reported

Protein binding: 40% of testosterone is plasma bound to SHBG, 2% is unbound, and 58% is loosely protein bound

Bioavailability: 100%

Metabolism^{2,6}: Testosterone undecanoate is metabolized to testosterone by ester cleavage. Testosterone is metabolized to various 17-keto steroids through 2 different pathways to estradiol and dihydrotestosterone

Excretion^{2,6}:

Renal: 90%

Feces: 6%

Efficacy:

Citation: Wang C, Harnett M, Dobs AS, Swerdloff RS. Pharmacokinetics and safety of long-acting testosterone undecanoate injections in hypogonadal men: an 84-week phase III clinical trial. *J Androl.* 2010;31(5):457-465

Study design: single-arm, open-label, multicenter trial³

Description of study: 84-week, single-arm, open-label, multicenter trial of 130 hypogonadal men. All men weighed 65 kg or more and were 18 years of age or older (mean age 54.2 years). Inclusion criteria were Male with primary or secondary hypogonadism at least 18 years of age with morning screening serum testosterone concentration <300 ng/dL. If receiving endocrine replacement hormones (eg, thyroid), antihypertensives, lipid lowering agents, antidepressants, or anxiolytic medications, the dose must be stable for at least 28 days prior to the first administration of the study drug.

Patients who had received prior testosterone treatment completed a washout period and were screened for serum total testosterone concentrations <300 ng/dL.³

In all patients, 750 mg of testosterone undecanoate was administered via intramuscular injection at baseline, Week 4, then every 10 weeks thereafter. Blood samples for hormone concentrations were obtained immediately before each injection through the eighth injection (ie, 64-week time point). More frequent samples were drawn for hormones at Days 4, 7, 11, 14, 21, 28, 42, 56, and 70 after the third injection.

The primary outcome for the study was to evaluate the pharmacokinetics of testosterone from Testosterone Undecanoate (TU) 750mg given intramuscularly at baseline, at 4 weeks, and then every 10 weeks thereafter, over the 10-week interval following the 3rd injection, via multiple measurements of serum total testosterone, in up to approximately 130 hypogonadal men. The secondary outcomes for the study were To evaluate the pharmacokinetics of testosterone from TU 750 mg given intramuscularly at baseline, at 4weeks, and then every 10 weeks thereafter, over the 10-week interval following the 4th injection, via multiple measurements of serum total testosterone, to compare serum levels of dihydrotestosterone (DHT), estradiol, and sex hormone binding globulin (SHBG) to simultaneous levels of serum total testosterone over the 3rd injection interval, and to evaluate safety in patients treated with TU 750 mg given intramuscularly at baseline, at 4 weeks, and then every 10 weeks thereafter, through up to 9 injections in hypogonadal men.

Safety outcomes were followed during an extension of 20 weeks—2 more injection intervals—through a total of 84 weeks. 7 patients (4.6%) discontinued treatment because of adverse reactions. Adverse reactions leading to discontinuation included: hematocrit increased, estradiol increased, prostatic specific antigen increased, prostate cancer, mood swings, prostatic dysplasia, acne, and deep vein thrombosis. During the 84-week clinical trial, the average serum PSA increased from 1.0 ± 0.8 ng/mL at baseline to 1.5 ± 1.3 ng/mL at the end of study. Fourteen patients (10.9%) in whom the baseline PSA was < 4 ng/mL had a post-baseline serum PSA of > 4 ng/mL during the 84-week treatment period. The average C_{max} was 890.6 ng/dL and the average C_{min} was 323.5 ng/dL during the third dosing interval at steady state.³

Limitations: The patients were mostly all Caucasian (74.6%), which may limit the ability to generalize efficacy to other races. The patients all weighed more than 65 kg (with a mean study BMI of 32 kg/m²), which may limit the ability to assess efficacy and side effects in patients who weigh more or less than the study populations weight selection. Patients in the study were all above the age of 18 which limits the ability to know how the drug could be use in pediatric populations and what kind of side effects or dosing would be required.³

Conclusion: Aveded is mostly safe but should be monitored for adverse reactions like Pulmonary Oil Microembolism and other events that may occur. In addition, while effective in the study population, caution should be used when used in patients outside of the study parameters.³

Citation: Testosterone undecanoate improves sexual function in men with type 2 diabetes and severe hypogonadism: results from a 30-week randomized placebo-controlled study. Geoffrey Hackett, Nigel Cole, Atif Saghir, Peter Jones, Richards C. Strange, Sudarshan Ramachandran *BJU Int.* 2016 Nov; 118(5): 804–813. Published online 2016 May 27. doi: 10.1111/bju.13516

Study design: 30-week randomized placebo-controlled study⁴

Description of study: Men with hypogonadism were identified from seven primary care type 2 diabetes registers.

Inclusion criteria were men aged 18–80 years with an initial finding of either TT level 8.1–12 nmol/L or FT level 0.18–0.25 nmol/L (mild HG group) or TT level \leq 8.0 nmol/L or 0.18 nmol/L or FT level \leq 0.18 nmol/L (severe HG group), according to the current European Association of Urology (EAU) guidelines [1], with symptoms of HG defined according to the Aging Male Symptom scale. Exclusion criteria included men considered too frail for TRT, previous TRT, abnormal DRE, PSA $>$ 4 μ g/L, haematocrit $>$ 0.50 L/L, history of prostate, breast or hepatic carcinoma and other serious comorbidities. Anticoagulation therapy was not allowed, and physicians were instructed, where possible, to avoid changes in diabetes, antihypertensive and lipid-lowering therapy throughout the 30 weeks of the study.

A 30-week randomized placebo-controlled study of testosterone undecanoate was carried out in 199 patients (placebo, n = 107, TU, n = 92). Patients (n=189) were stratified, firstly, by baseline total testosterone (TT) or free testosterone (FT) into mild HG and severe HG groups, and secondly, by intervention (placebo or TU), thereby creating four groups: mild HG/placebo; mild HG/TU; severe HG/placebo and severe HG/TU.⁴ The patient-reported outcome measure was the 15-item International Index of Erectile Function score.

The primary efficacy endpoint was change in HbA1c and secondary endpoints included changes in IIEF scores. Changes in sexual function score within group (from baseline) and between groups (TU vs placebo) were evaluated at each assessment (6, 18 and 30 weeks).⁴

Significant improvement in erectile function was evident only in the severe HG group after 30 weeks of TU treatment; this finding persisted when TU was compared with placebo. Intercourse satisfaction and sexual desire scores were also improved at 6, 18 and 30 weeks in the severe HG group after TU treatment; this increase in scores was also evident when compared with placebo. TU did not appear to alter orgasmic function significantly in any of the patient groups⁴

Limitations: The study was conducted at healthcare facilities which may increase compliance and increase the level of monitoring the patients receive which may be inconsistent with real world levels. The participants of the study were all living in England which may limit the generalizability to the United States. There was also extensive inclusion and exclusion criteria which may limit its generalizability to the general population. The study used self-report assessments to analyze sexual function which may be an unreliable way to gather data. In addition, sexual function could have been effected by any number of things, which could confound the results.⁴

Conclusion: The present study suggests that benefit in sexual symptoms after TU treatment is evident principally in patients with HG with TT levels \leq 8 nmol/L and FT levels \leq 0.18 nmol/L. The study also suggests that 30 weeks of treatment is necessary before evaluating improvement in erectile function⁴

Citation: The efficacy of combination treatment with injectable testosterone undecanoate and daily tadalafil for erectile dysfunction with testosterone deficiency syndrome. Min Gu Park, Jeong Kyun Yeo, Dae-Yeon Cho, Jin Wook Kim, Jong Wook Kim, Mi Mi Oh, Je Jong Kim, Du Geon Moon J Sex Med. 2015 Apr; 12(4): 966–974. Published online 2015 Feb 4. doi: 10.1111/jsm.12842

Study design: Randomized, controlled clinical trial⁵

Description of study: Sixty patients were consecutively enrolled and followed for 36 weeks. Thirty patients were randomly assigned to group I and received 1,000 mg of parenteral TU on day 1, followed by additional injections at weeks 6 and 18 with on-demand tadalafil 10-20 mg during the 30 weeks of treatment. The remaining 30 patients received the same dose and schedule of TU as group I, and were prescribed once-daily tadalafil 5 mg during 30 weeks. Primary outcome measures were the scores on the International Index of Erectile Function (IIEF), Aging Males' Symptoms (AMS) questionnaires, and Global Assessment Question (GAQ). Total IIEF and AMS scores were significantly improved during the 30 weeks of treatment in both groups. When IIEF scores were compared between the two groups, group II showed better symptom scores than group I at weeks 6 and 30. A similar pattern was observed when comparing AMS scores between the groups. At week 36, changes in IIEF and AMS scores that indicated worsened symptoms compared with week 30 were observed in both groups; group II showed better symptom scores than group I. On the GAQ, the ratio of patients reporting improvement in erectile function was significantly higher in group II than group I. ⁵ Adverse effects were not reported.

Limitations: The methods used to assess the patients were questionnaires which may be an unreliable way to gather data. Both groups received both the testosterone and the tadalafil which makes the actual treatment difference in both groups questionable and bias may have been present in the study results as the patients were not blinded during this study. Other factors may also be contributing to the change in sexual function that the study did not or could not control for.⁵

Conclusion: The combination of long-acting injectable TU and once-daily tadalafil 5 mg produced a significant improvement in erectile function. Moreover, the improvement in erectile function was well maintained, even after the cessation of treatment.⁵

Contraindications⁶:

- Men with carcinoma of the breast or known or suspected carcinoma of the prostate
- Women who are or may become pregnant, or who are breastfeeding. Testosterone can cause fetal harm when administered to a pregnant woman. Testosterone undecanoate may cause serious adverse reactions in nursing infants. Exposure of a female fetus or nursing infant to androgens may result in varying degrees of virilization
- Men with known hypersensitivity to Avedo or any of its ingredients (testosterone undecanoate, refined castor oil, benzyl benzoate).

Precautions⁶:

- Black box warning: Serious pulmonary oil microembolism (POME) reactions (eg, urge to cough, dyspnea, hyperhidrosis, throat tightening, chest pain, dizziness, and syncope) have been reported; monitoring recommended
- Black box warning: Anaphylaxis, sometimes life-threatening, has been reported; monitoring recommended
- Beers Criteria: In older adults, avoid use unless indicated for moderate to severe hypogonadism due to potential for cardiac toxicities. Contraindicated in men with prostate cancer
- Abuse: Abuse, usually at higher than prescribed doses and usually in conjunction with other anabolic androgenic steroids, has been reported and may result in serious safety risks (eg, heart attack, heart failure, stroke, depression, hostility, aggression, liver toxicity, infertility); if suspected, measure serum testosterone
- Cardiovascular:
 - A possible increased risk of heart attack, stroke, or death has been reported; testosterone therapy should only be used in male patients with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests
 - Edema with or without congestive heart failure may occur in patients with cardiac, hepatic, or renal disease; discontinuation may be necessary
- Endocrine and metabolic:
 - Lipid abnormalities may occur; discontinuation may be necessary
 - Cancer patients at risk for hypercalcemia or hypercalciuria; monitoring recommended
- Hematologic:
 - Hematocrit and red blood cell mass increases may occur and increase risk for thromboembolism; monitoring recommended and interrupt or discontinue if necessary
 - Venous thromboembolic events, including DVT and pulmonary embolism, have been reported; monitoring recommended; discontinue use if suspected
- Hepatic: Serious hepatic adverse effects (eg, peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, jaundice) have been reported with prolonged use of high doses of other androgens (eg, oral methyltestosterone); discontinue use if suspected
- Neurologic: A possible increased risk of heart attack, stroke, or death has been reported; testosterone therapy should only be used in male patients with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests
- Reproductive:
 - Prostate cancer may occur; monitoring recommended
 - Worsening of signs and symptoms of benign prostatic hyperplasia (BPH) may occur in patients with BPH; monitoring recommended
 - Virilizing effects may occur in women (unapproved use)
 - Spermatogenesis suppression, resulting in adverse effects on sperm count, may occur with large doses of androgens
 - Gynecomastia may occur in patients treated for hypogonadism
- Respiratory: Sleep apnea may occur; increased risk with obesity or chronic lung disease

Adverse Effects⁶:

- **Dermatologic:** Acne (5.2%), Injection site pain (4.6%)
- **Endocrine metabolic:** Increased estradiol level (2.6%)
- **Hematologic:** Increased hemoglobin (2%)
- **Neurologic:** Insomnia (2%)
- **Psychiatric:** Irritability (2%), Mood swings (2%)
- **Reproductive:** Hypogonadism (2.6%), Raised prostate specific antigen (4.6%)
- **Other:** Fatigue (2%)
- **Hematologic:** Deep venous thrombosis, Erythrocytosis, Hematocrit - PCV - high (1.3%)
- **Immunologic:** Anaphylaxis
- **Reproductive:** Prostate cancer (1.3%)
- **Respiratory:** Pulmonary embolism, Oil microembolism

Drug Interactions²:

- **Insulin** - Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, may necessitate a decrease in the dose of anti-diabetic medication.
- **Oral Anticoagulants** - Changes in anticoagulant activity may be seen with androgens, therefore, more frequent monitoring of international normalized ratio (INR) and prothrombin time are recommended in patients taking warfarin, especially at the initiation and termination of androgen therapy.
- **Corticosteroids** - The concurrent use of testosterone with corticosteroids may result in increased fluid retention and requires careful monitoring, particularly in patients with cardiac, renal or hepatic disease.

Dosing/Administration^{2,6}:

Adult Dosing: The recommended dose of Avedd is 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.

Preparation:

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Carefully remove the gray plastic cap from the top of the vial by lifting it up from the edges with your fingers or by pushing the bottom edge of the cap upward using the top of your thumb. Remove only the gray plastic cap while leaving the aluminum metal ring and crimp seal around the gray rubber stopper in place. To facilitate the removal of medication from the vial, you can draw 3 mL of air into the

syringe and inject it through the gray rubber stopper into the vial to create positive pressure within the vial chamber.

Withdraw 3 mL (750 mg) of Aveed solution from the vial. Expel excess air bubbles from the syringe. Replace the syringe needle used to draw up the solution from the vial with a new intramuscular needle and inject. Discard any unused portion in the vial.

Administration:

The site for injection for Aveed is the gluteus medius muscle site located in the upper outer quadrant of the buttock. Care must be taken to avoid the needle hitting the superior gluteal arteries and sciatic nerve. Between consecutive injections, alternate the injection site between left and right buttock.

Pediatrics^{2,6}: Safety and efficacy of Aveed in males less than 18 years old have not been established.

Geriatric dose^{2,6}: There have not been sufficient numbers of geriatric patients in controlled clinical studies with AVEED[®] to determine whether efficacy or safety in those over 65 years of age differs from younger subjects. There are insufficient long-term safety data in geriatric patients to assess the potential risks of cardiovascular disease and prostate cancer.

Renal impairment^{2,6}: No dose adjustments necessary

Hepatic impairment^{2,6}: Prolonged use of high doses of orally active 17-alpha-alkyl androgens (e.g., methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, and jaundice). Peliosis hepatis can be a life-threatening or fatal complication. Long-term therapy with intramuscular testosterone enanthate, which elevates blood levels for prolonged periods, has produced multiple hepatic adenomas. AVEED[®] is not known to produce these adverse effects. Nonetheless, patients should be instructed to report any signs or symptoms of hepatic dysfunction (e.g., jaundice). If these occur, promptly discontinue AVEED[®] while the cause is evaluated.

Use in special circumstances:

Pregnancy^{2,6}: Testosterone is rated as US FDA Category X. Studies, adequate well-controlled or observational, in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant

Lactation^{2,6}: Infant risk has been demonstrated: Evidence and/or expert consensus has demonstrated harmful infant effects when Testosterone is used during breast-feeding. An alternative to Testosterone should be prescribed or patients should be advised to discontinue breast-feeding.

Drug Abuse and Dependence^{2,6}:

AVEED® contains testosterone undecanoate, a Schedule III controlled substance in the Controlled Substances Act.

- Abuse and misuse of testosterone are seen in male and female adults and adolescents. Testosterone, often in combination with other anabolic androgenic steroids, may be abused by athletes and bodybuilders.
- Serious adverse reactions have been reported in individuals who abuse anabolic androgenic steroids, and include cardiac arrest, myocardial infarction, hypertrophic cardiomyopathy, congestive heart failure, cerebrovascular accident, hepatotoxicity, and serious psychiatric manifestations, including major depression, mania, paranoia, psychosis, delusions, hallucinations, hostility, and aggression.
- The following adverse reactions have been reported in men: transient ischemic attacks, convulsions, hypomania, irritability, dyslipidemia, testicular atrophy, subfertility, and infertility.
- The following adverse reactions have been reported in women: hirsutism, virilization, deepening of voice, clitoral enlargement, breast atrophy, male pattern baldness, and menstrual irregularities.
- The following adverse reactions have been reported in male and female adolescents: premature closure of bony epiphyses with termination of growth, and precocious puberty.
- Withdrawal symptoms can be experienced upon abrupt discontinuation in patients with addiction. Withdrawal symptoms include depressed mood, major depression, fatigue, craving, restlessness, irritability, anorexia, insomnia, decreased libido, and hypogonadotropic hypogonadism. Drug dependence in individuals using approved doses for approved indications have not been documented.

Conclusion:

Aveed is given less often and only has one recommended dose compared to other similarly effective testosterone products. This will increase compliance and decrease any errors that may occur with multiple strengths and more complex dosing schedules that other testosterone products have. In addition, although there are a few serious side effects, they are very uncommon and can be managed appropriately with proper monitoring. Aveed should be tested in more diverse populations to extend the FDA indications and in order to have a better idea of its side effect complications long term.

Recommended References:

1. Edelstein D, Basaria S. Testosterone undecanoate in the treatment of male hypogonadism. *Expert Opin Pharmacother*. 2010;11(12):2095-2106.
2. AVEED® (Prescribing Information). Malvern, PA: Endo Pharmaceuticals Inc
3. Wang C, Harnett M, Dobs AS, Swerdloff RS. Pharmacokinetics and safety of long-acting testosterone undecanoate injections in hypogonadal men: an 84-week phase III clinical trial. *J Androl*. 2010;31(5):457-465.

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Prepared by: Alyssa Ruberto, MBA, Doctor of Pharmacy Candidate