HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AVEED® safely and effectively. See full prescribing information for AVEED®.

AVEED® (testosterone undecanoate) injection, for intramuscular use
CIII
Initial U.S. Approval: 1953

WARNING: SERIOUS PULMONARY OIL MICROEMBOLISM (POME) REACTIONS AND ANAPHYLAXIS
See full prescribing information for complete boxed warning

- **Serious 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. These reactions can occur after any injection of testosterone undecanoate during the course of therapy, including after the first dose (5.1).**
- **Following each injection of Aveed, observe patients in the healthcare setting for 30 minutes in order to provide appropriate medical treatment in the event of serious POME reactions or anaphylaxis (5.1).**
- **Aveed is available only through a restricted program called the Aveed REMS Program (5.2).**

----------RECENT MAJOR CHANGES----------

Warnings and Precautions, Venous Thromboembolism (5.4)	07/2025
Warnings and Precautions, Blood Pressure Increases (5.6)	07/2025
Warnings and Precautions, Cardiovascular Risk (5.6)	Removed 07/2025

INDICATIONS AND USAGE

Aveed (testosterone undecanoate) injection is an androgen indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary hypogonadism (congenital or acquired) (1)
- Hypogonadotropic hypogonadism (congenital or acquired) (1)

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 (1).

Limitations of Use

- Safety and efficacy of Aveed in men with "age-related hypogonadism" have not been established (1).
- Safety and efficacy of Aveed in males less than 18 years old have not been established (1, 8.4).

DOSAGE AND ADMINISTRATION

- Prior to initiating Aveed, confirm the diagnosis of hypogonadism by ensuring that serum testosterone has been measured in the morning on at least two separate days and that these concentrations are below the normal range (2).
- For intramuscular use only (2.1).
- Three (3) mL (750 mg) is to be injected intramuscularly at initiation, at 4 weeks, and every 10 weeks thereafter (2.1).
- Following each injection of Aveed, observe patients in the healthcare setting for 30 minutes in order to provide appropriate medical treatment in the event of serious POME reactions or anaphylaxis (2.3).
- Inject Aveed deeply into the gluteal muscle following the usual precautions for intramuscular administration of oily solutions (2.3).

DOSAGE FORMS AND STRENGTHS

- 750 mg/3 mL (250 mg/mL) testosterone undecanoate sterile injectable solution is provided in an amber glass, single use vial with silver-colored crimp seal and gray plastic cap (3).

CONTRAINDICATIONS

- Men with carcinoma of the breast or known or suspected carcinoma of the prostate (4, 5.5).
- Women who are pregnant. Testosterone may cause fetal harm (4, 5.8, 8.1, 8.2).
- Known hypersensitivity to Aveed or its ingredients (testosterone undecanoate, refined castor oil, benzyl benzoate) (4).

WARNINGS AND PRECAUTIONS

- Venous thromboembolism (VTE): VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE), have been reported in patients using testosterone products. Evaluate patients with signs or symptoms consistent with DVT or PE (5.4).
- Worsening of Benign Prostatic Hyperplasia (BPH) and Potential Risk of Prostate Cancer: Monitor patients with BPH for worsening of signs and symptoms of BPH (5.5).
- Blood Pressure Increases: Testosterone can increase blood pressure, which can increase cardiovascular risk over time. Measure blood pressure periodically. Not recommended for use in men with uncontrolled hypertension (5.6)
- Abuse of Testosterone: Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication and in combination with other anabolic androgenic steroids (5.7).

Potential for Adverse Effects on Spermatogenesis:

- Exogenous administration of androgens may lead to azoospermia (5.9).
- Edema: Edema with or without congestive heart failure may be a complication in patients with preexisting cardiac, renal, or hepatic disease (5.11).
- Sleep apnea: Sleep apnea may occur in those with risk factors (5.13).
- Monitor prostatic specific antigen (PSA), hemoglobin, hematocrit, and lipid concentrations periodically (5.3, 5.5, 5.14).

ADVERSE REACTIONS

The most commonly reported adverse reactions (≥2%) are acne, injection site pain, prostatic specific antigen (PSA) increased, estradiol increased, hypogonadism, fatigue, irritability, hemoglobin increased, insomnia, and mood swings (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Endo at 1-800-462-3636 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Androgens may decrease blood glucose, and therefore may decrease insulin requirements in diabetic patients (7.1).
- Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of international normalized ratio (INR) and prothrombin time is recommended in patients taking warfarin (7.2).
- Use of testosterone with corticosteroids may result in increased fluid retention. Use with caution, particularly in patients with cardiac, renal, or hepatic disease (7.3).

USE IN SPECIFIC POPULATIONS

Geriatric Patients: There are insufficient long-term safety data to assess the potential risks of cardiovascular disease and prostate cancer (8.5).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 07/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: SERIOUS PULMONARY OIL MICROEMBOLISM (POME) REACTIONS AND ANAPHYLAXIS
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Dosage
2.2 Preparation Instructions
2.3 Administration Instructions
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Serious Pulmonary Oil Microembolism (POME) Reactions and Anaphylaxis
5.2 AVEED Risk Evaluation and Mitigation Strategy (REMS) Program
5.3 Polycythemia
5.4 Venous Thromboembolism (VTE)
5.5 Worsening of Benign Prostatic Hyperplasia (BPH) and Potential Risk of Prostate Cancer

5.6 Blood Pressure Increases
5.7 Abuse of Testosterone and Monitoring of Serum Testosterone Concentrations
5.8 Not for Use in Women
5.9 Potential for Adverse Effects on Spermatogenesis
5.10 Hepatic Adverse Effects
5.11 Edema
5.12 Gynecomastia
5.13 Sleep Apnea
5.14 Lipid Changes
5.15 Hypercalcemia
5.16 Decreased Thyroxine-binding Globulin
6 ADVERSE REACTIONS
6.1 Clinical Trial Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Insulin
7.2 Oral Anticoagulants
7.3 Corticosteroids
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Testosterone Replacement Therapy
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
17.1 Risks of Serious Pulmonary Oil Microembolism (POME) and Anaphylaxis
17.2 Men with Known or Suspected Carcinoma of the Prostate or Breast
17.3 Potential Adverse Reactions to Androgens
17.4 Patients Should Be Advised of the Following Instructions for Use

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS PULMONARY OIL MICROEMBOLISM (POME) REACTIONS AND ANAPHYLAXIS

- **Serious 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. These reactions can occur after any injection of testosterone undecanoate during the course of therapy, including after the first dose *[see Warnings and Precautions (5.1)]*.**
- **Following each injection of AVEED, observe patients in the healthcare setting for 30 minutes in order to provide appropriate medical treatment in the event of serious POME reactions or anaphylaxis *[see Warnings and Precautions (5.1)]*.**
- **Because of the risks of serious POME reactions and anaphylaxis, AVEED is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the AVEED REMS Program *[see Warnings and Precautions (5.2)]*.**

1 INDICATIONS AND USAGE

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

- 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.
- 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 range.

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 POME and anaphylaxis.

Limitations of Use

- Safety and efficacy of AVEED in men with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established.
- Safety and efficacy of AVEED in males less than 18 years old have not been established *[see Use in Specific Populations (8.4)]*.

2 DOSAGE AND ADMINISTRATION

Prior to initiating AVEED, confirm the diagnosis of hypogonadism by ensuring that serum testosterone concentrations have been measured in the morning on at least 2 separate days and that these serum testosterone concentrations are below the normal range.

2.1 Dosage

AVEED is for intramuscular use only. Dosage titration is not necessary.

Inject AVEED deeply into the gluteal muscle following the usual precautions for intramuscular administration; care must be taken to avoid intravascular injection *[see Dosage and Administration (2.3)]*. Intravascular injection of AVEED may lead to POME *[see Warnings and Precautions (5.1)]*.

The recommended dose of AVEED 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.

2.2 Preparation Instructions

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

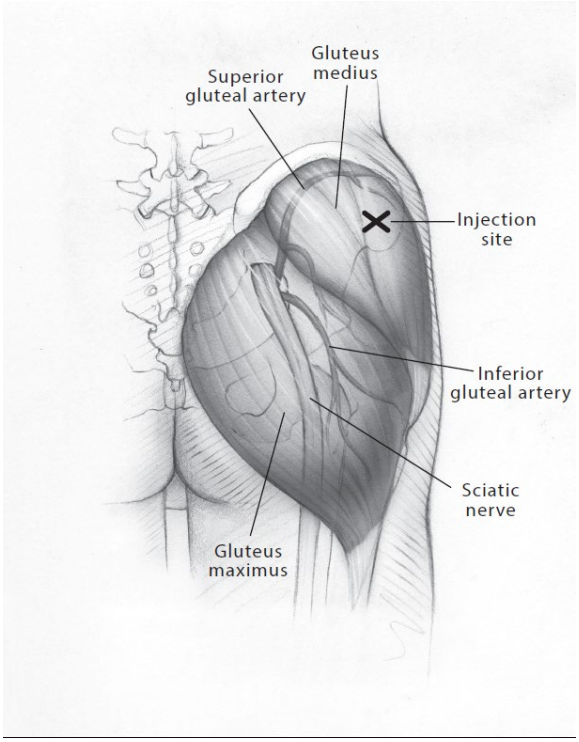
Carefully remove the gray plastic cap from the top of the vial by lifting it up from the edges with your fingers or by pushing the bottom edge of the cap upward using the top of your thumb. Remove only the gray plastic cap while leaving the aluminum metal ring and crimp seal around the gray rubber stopper in place. To facilitate the removal of medication from the vial, attach an 18-gauge needle and draw 3 mL of air into the syringe. Hold the needle at a 45° angle to the stopper with the bevel in the up orientation. Inject 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.

2.3 Administration Instructions

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.

Figure 1: Identifying the Injection Site



Following antiseptic skin preparation, enter the muscle and maintain the syringe at a 90° angle with the needle in its deeply imbedded position. Grasp the barrel of the syringe firmly with one hand. With the other hand, pull back on the plunger and aspirate for several seconds to ensure that no blood appears. If any blood is drawn into the syringe, immediately withdraw and discard the syringe and prepare another dose.

If no blood is aspirated, reinforce the current needle position to avoid any movement of the needle and slowly (over 60 to 90 seconds) depress the plunger carefully and at a constant rate, until all the medication has been delivered. Be sure to depress the plunger completely with sufficient controlled force. Withdraw the needle.

Immediately upon removal of the needle from the muscle, apply gentle pressure with a sterile pad to the injection site. If there is bleeding at the site of injection, apply a bandage.

Following each injection of AVEED, observe patients in the healthcare setting for 30 minutes in order to provide appropriate medical treatment in the event of serious POME reactions or anaphylaxis *[see Warnings and Precautions (5.1)]*.

3 DOSAGE FORMS AND STRENGTHS

750 mg/3 mL (250 mg/mL) testosterone undecanoate sterile injectable solution is provided in an amber glass, single use vial with silver-colored crimp seal and gray plastic cap.

4 CONTRAINDICATIONS

AVEED should not be used in any of the following patients:

- Men with carcinoma of the breast or known or suspected carcinoma of the prostate *[see Warnings and Precautions (5.5)]*.
- Women who are pregnant. Testosterone can cause virilization of the female fetus when administered to a pregnant woman *[see Use in Specific Populations (8.1, 8.2)]*.
- Men with known hypersensitivity to AVEED or any of its ingredients (testosterone undecanoate, refined castor oil, benzyl benzoate).

5 WARNINGS AND PRECAUTIONS

5.1 Serious Pulmonary Oil Microembolism (POME) Reactions and Anaphylaxis

Serious POME reactions, involving cough, urge to cough, dyspnea, hyperhidrosis, throat tightening, chest pain, dizziness, and syncope, have been reported to occur during or immediately after the injection of intramuscular testosterone undecanoate 1000 mg (4 mL). The majority of these events lasted a few minutes and resolved with supportive measures; however, some lasted up to several hours and some required emergency care and/or hospitalization. To minimize the risk of intravascular injection of AVEED, care should be taken to inject the preparation deeply into the gluteal muscle, being sure to follow the recommended procedure for intramuscular administration *[see Dosage and Administration (2.2, 2.3) and Adverse Reactions (6.2)]*.

In addition to serious POME reactions, episodes of anaphylaxis, including life-threatening reactions, have also been reported to occur following the injection of intramuscular testosterone undecanoate.

Both serious POME reactions and anaphylaxis can occur after any injection of testosterone undecanoate during the course of therapy, including after the first dose. Patients with suspected hypersensitivity reactions to AVEED should not be re-treated with AVEED.

Following each injection of AVEED, observe patients in the healthcare setting for 30 minutes in order to provide appropriate medical treatment in the event of serious POME reactions and anaphylaxis.

5.2 AVEED Risk Evaluation and Mitigation Strategy (REMS) Program

AVEED is available only through a restricted program called the AVEED REMS Program because of the risk of serious POME and anaphylaxis.

Notable requirements of the AVEED REMS Program include the following:

- Healthcare providers who prescribe AVEED must be certified with the REMS Program before ordering or dispensing AVEED.

- Healthcare settings must be certified with the REMS Program and have healthcare providers who are certified before ordering or dispensing AVEED. Healthcare settings must have on-site access to equipment and personnel trained to manage serious POME and anaphylaxis.

Further information is available at www.aveedrems.com or call 1-855-755-0494.

5.3 Polycythemia

Increases in hematocrit, reflective of increases in red blood cell mass, may require discontinuation of testosterone.

Check hematocrit prior to initiating testosterone treatment. It would be appropriate to re-evaluate the hematocrit 3 to 6 months after starting testosterone treatment, and then annually. If hematocrit becomes elevated, stop therapy until hematocrit decreases to an acceptable level. An increase in red blood cell mass may increase the risk of thromboembolic events.

5.4 Venous Thromboembolism (VTE)

There have been postmarketing reports of venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients using testosterone products, such as AVEED.

In the Testosterone Replacement therapy for Assessment of long-term Vascular Events and efficacy ResponSE in hypogonadal men (TRAVERSE) Study, a randomized, double-blind, placebo-controlled, cardiovascular (CV) outcomes study, compared to placebo, topical testosterone gel was associated with a numerically higher incidence of VTE (1.7% vs 1.2%) which included DVT (0.6% vs 0.5%) and PE events (0.9% vs 0.5%) *[see Adverse Reactions (6.1)]*.

Evaluate patients who report symptoms of pain, edema, warmth and erythema in the lower extremity for DVT and those who present with acute shortness of breath for PE. If a venous thromboembolic event is suspected, discontinue treatment with AVEED and initiate appropriate workup and management.

5.5 Worsening of Benign Prostatic Hyperplasia (BPH) and Potential Risk of Prostate Cancer

Patients with BPH treated with androgens are at an increased risk of worsening of signs and symptoms of BPH. Monitor patients with BPH for worsening signs and symptoms.

Patients treated with androgens may be at an increased risk for prostate cancer. Evaluate patients for prostate cancer prior to initiating and during treatment with androgens *[see Contraindications (4)]*.

5.6 Blood Pressure Increases

AVEED can increase blood pressure. In an ambulatory blood pressure monitoring (ABPM) study, AVEED increased the mean systolic/diastolic blood pressure by 3.1/2.0 mm Hg from baseline after 16 weeks of treatment. In patients with hypertension on antihypertensive therapy, AVEED increased the mean systolic/diastolic BP by 2.1/1.5 mm Hg from baseline. Blood pressure increases can increase cardiovascular (CV) risk over time.

The CV risk associated with topical testosterone gel was evaluated in TRAVERSE, a randomized, double-blind, placebo-controlled, CV outcomes study in men with a history of CV disease or multiple CV risk factors. In TRAVERSE, topical testosterone gel increased mean systolic blood pressure by 1.0 mm Hg from baseline to 36 months, whereas a mean decrease from baseline of 0.5 mm Hg was observed in the placebo group at this timepoint, for a mean between-group difference of 1.5 mm Hg. However, the incidences of major adverse cardiovascular events (MACE), including cardiovascular death, non-fatal myocardial infarction [MI] and non-fatal stroke, were similar between treatment groups (7% for topical testosterone gel vs 7.3% for placebo) *[See Adverse Reactions (6.1)]*.

Monitor blood pressure periodically in men using AVEED, especially men with hypertension. AVEED is not recommended for use in patients with uncontrolled hypertension.

5.7 Abuse of Testosterone and Monitoring of Serum Testosterone Concentrations

Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication and in combination with other anabolic androgenic steroids. Anabolic androgenic steroid abuse can lead to serious cardiovascular and psychiatric adverse reactions *[see Drug Abuse and Dependence (9)]*.

If testosterone abuse is suspected, check serum testosterone concentrations to ensure they are within therapeutic range. However, testosterone levels may be in the normal or subnormal range in men abusing synthetic testosterone derivatives. Counsel patients concerning the serious adverse reactions associated with abuse of testosterone and anabolic androgenic steroids. Conversely, consider the possibility of testosterone and anabolic androgenic steroid abuse in suspected patients who present with serious cardiovascular or psychiatric adverse events.

5.8 Not for Use in Women

Due to lack of controlled evaluations in women and potential virilizing effects, AVEED is not indicated for use in women *[see Contraindications (4) and Use in Specific Populations (8.1, 8.2)]*.

5.9 Potential for Adverse Effects on Spermatogenesis

With large doses of exogenous androgens, including AVEED, spermatogenesis may be suppressed through feedback inhibition of pituitary FSH which could possibly lead to adverse effects on semen parameters including sperm count.

5.10 Hepatic Adverse Effects

Prolonged use of high doses of orally active 17-alpha-alkyl androgens (eg, 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 (eg, jaundice). If these occur, promptly discontinue AVEED while the cause is evaluated.

5.11 Edema

Androgens, including AVEED, may promote retention of sodium and water. Edema with or without congestive heart failure may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease. In addition to discontinuation of the drug, diuretic therapy may be required.

5.12 Gynecomastia

Gynecomastia occasionally develops and occasionally persists in patients being treated for hypogonadism *[see Adverse Reactions (6.1)]*.

5.13 Sleep Apnea

The treatment of hypogonadal men with testosterone products may potentiate sleep apnea in some patients, especially those with risk factors such as obesity or chronic lung diseases.

5.14 Lipid Changes

Changes in serum lipid profile may require dose adjustment of lipid lowering drugs or discontinuation of testosterone therapy, such as AVEED. Monitor the lipid profile periodically, particularly after starting testosterone therapy.

5.15 Hypercalcemia

Androgens, including AVEED, should be used with caution in cancer patients at risk of hypercalcemia (and associated hypercalciuria). Regular monitoring of serum calcium concentrations is recommended in these patients.

5.16 Decreased Thyroxine-binding Globulin

Androgens, including AVEED, may decrease concentrations of thyroxine-binding globulin, resulting in decreased total T4 serum concentrations and increased resin uptake of T3 and T4. Free thyroid hormone concentrations remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

AVEED was evaluated in an 84-week clinical study using a dose regimen of 750 mg (3 mL) at initiation, at 4 weeks, and every 10 weeks thereafter in 153 hypogonadal men. The most commonly reported adverse reactions (>2%) were: acne (5.2%), injection site pain (4.6%), prostate specific antigen increased (4.6%), hypogonadism (2.6%) and estradiol increased (2.6%).

Table 1 presents adverse reactions reported by ≥1% of patients in the 84-week clinical study.

Table 1: Adverse Reactions Reported in at Least 1% of Patients in the 84-Week Clinical Study of AVEED

MedDRA Preferred Term	Number of Patients (%)
	AVEED 750 mg (N=153)
Acne	8 (5.2%)
Injection site pain	7 (4.6%)
Prostatic specific antigen increased*	7 (4.6%)
Estradiol increased	4 (2.6%)
Hypogonadism	4 (2.6%)
Fatigue	3 (2%)
Irritability	3 (2%)
Hemoglobin increased	3 (2%)
Insomnia	3 (2%)
Mood swings	3 (2%)
Aggression	2 (1.3%)
Ejaculation disorder	2 (1.3%)
Injection site erythema	2 (1.3%)
Hematocrit increased	2 (1.3%)
Hyperhidrosis	2 (1.3%)
Prostate Cancer	2 (1.3%)
Prostate induration	2 (1.3%)
Weight increased	2 (1.3%)

*Prostate-specific antigen increased defined as a serum PSA concentration >4 ng/mL.

In the 84-week clinical trial, 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 (14) 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.

A total of 725 hypogonadal men received intramuscular testosterone undecanoate in a total of 7 controlled clinical trials. In these clinical trials, the dose and dose frequency of intramuscular testosterone undecanoate varied from 750 mg to 1000 mg, and from every 9 weeks to every 14 weeks. Several of these clinical trials incorporated additional doses upon initiation of therapy (eg, loading doses). In addition to those adverse reactions noted in Table 1, the following adverse events were reported by at least 3% of patients in these trials, irrespective of the investigator's assessment of relationship to study medication: sinusitis, prostatitis, arthralgia, nasopharyngitis, upper respiratory tract infection, bronchitis, back pain, hypertension, diarrhea and headache.

Pulmonary Oil Microembolism (POME) and Anaphylaxis in Controlled Clinical Studies

Adverse events attributable to POME and anaphylaxis were reported in a small number of patients in controlled clinical trials. In the 84-week clinical trial of AVEED, 1 patient experienced a mild coughing fit lasting 10 minutes after his third injection, which was retrospectively attributed to POME. In another clinical trial of intramuscular testosterone undecanoate (1000 mg), a hypogonadal male patient experienced the urge to cough and respiratory distress at 1 minute after his tenth injection, which was also retrospectively attributed to POME.

During a review that involved adjudication of all cases meeting specific criteria, 9 POME events in 8 patients and 2 events of anaphylaxis among 3,556 patients treated with intramuscular testosterone undecanoate in 18 clinical trials were judged to have occurred.

Blood Pressure Increases

In a 4-month clinical study, 24-hour ambulatory blood pressure monitoring (ABPM) was conducted on 222 patients. ABPM was conducted at baseline and at Week 16 of AVEED therapy. A total of 139 patients had acceptable ABPM recordings at both baseline and Week 16 and were at least 85% compliant with study drug. In that group, the mean change in 24-hour systolic blood pressure (BP) and diastolic BP from baseline to end-of-treatment at Week 16 (n=139) was 3.1 mm Hg (95% CI 1.2, 4.9) and 2.0 mm Hg (95% CI 0.9, 3.1), respectively. In patients with a history of hypertension who were receiving antihypertensive therapy, the mean ABPM systolic and diastolic BP increased by 2.1 mm Hg [95% CI -0.7, 5.0] and 1.5 mm Hg [95% CI -0.1, 3.2], respectively [n=73]). In patients with no history of hypertension, the mean systolic and diastolic blood pressure increased by 3.3 mm Hg [95% CI 0.8, 5.8] and 2.5 mm Hg [95% CI 1.0, 4.0], respectively [n=65].

2 patients (1.4%) on AVEED, both of whom were receiving antihypertensive medications at baseline, either started new antihypertensive medications (n=2) or had their antihypertensive medication regimen adjusted (n=0) during the ABPM study.

Of the 222 patients in the ABPM study who used AVEED, 8 patients (3.6%) were reported to have either an adverse reaction of hypertension (7 patients, 3.2%) or increased blood pressure (1 patient, 0.4%).

Cardiovascular Outcomes

TRAVERSE was a randomized, double-blind, cardiovascular outcomes study to assess the cardiovascular (CV) safety of topical testosterone gel compared to placebo in 5198 hypogonadal men aged 45 to 80 years with a history of CV disease or with multiple CV risk factors. The primary outcome was the incidence of the composite endpoint of major adverse cardiovascular events (MACE), consisting of CV death, non-fatal myocardial infarction (MI), and non-fatal stroke.

The mean duration of therapy was approximately 22 months. The mean duration of follow-up was 33 months. Approximately 61% of all patients discontinued topical testosterone gel or placebo therapy.

The mean patient age (±SD) was 63.3 (7.9) years, with 2452 patients aged 65 years or more (47%); 2847 (about 55%) patients had pre-existing cardiovascular disease, whereas 2357 patients (about 45%) had an elevated cardiovascular risk at baseline, and mean BMI was 35 kg/m^2. Approximately 80% of patients were White, 17% were Black, and 3% were of other races or ethnic groups. Approximately 69%, 84%, and 93% had diabetes mellitus, hyperlipidemia, and hypertension, respectively.

The mean serum testosterone concentration at baseline in patients receiving topical testosterone gel was 220.4 ng/dL (n=2596). The mean serum testosterone concentrations at 12 months, 24 months, 36 months, and 48 months in patients receiving topical testosterone gel were 440.5 ng/dL (n=1683), 420.9 ng/dl (n=1125), 428.7 ng/dL (n=731), and 365.2 ng/dL (n=220), respectively.

For patients treated with topical testosterone gel, the incidence of MACE was 7.0% (n=182 events) and for those receiving placebo, the incidence of MACE was 7.3% (n=190 events). The study demonstrated non-inferiority of topical testosterone gel versus placebo because the upper bound of 95% CI was less than the pre-specified risk margin, of 1.5 for MACE (Hazard Ratio 0.96 [95% CI: 0.78, 1.17]).

Additional Adverse Reactions Reported in TRAVERSE

Additional adverse reactions reported in TRAVERSE at an incidence rate >2% in either treatment group and greater in topical testosterone gel versus placebo included: nonfatal arrythmias warranting intervention (5.2% vs 3.3%), atrial fibrillation (3.5% vs 2.4%), acute kidney injury (2.3% vs 1.5%) and bone fracture (3.5% vs 2.5%). For the adverse reaction of bone fracture, each event was adjudicated by clinical review.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of AVEED. Because the reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Pulmonary Oil Microembolism (POME) and Anaphylaxis

Serious POME reactions, involving cough, urge to cough, dyspnea, hyperhidrosis, throat tightening, chest pain, dizziness, and syncope, have been reported to occur during or immediately after the injection of intramuscular testosterone undecanoate 1000 mg (4 mL) in post-approval use outside the United States. The majority of these events lasted a few minutes and resolved with supportive measures; however, some lasted up to several hours and some required emergency care and/or hospitalization.

In addition to serious POME reactions, episodes of anaphylaxis, including life-threatening reactions, have also been reported to occur following the injection of intramuscular testosterone undecanoate in post-approval use outside of the United States.

Both serious POME reactions and anaphylaxis have been reported to occur after any injection of testosterone undecanoate during the course of therapy, including after the first dose.

Other Events

The following treatment emergent adverse events or adverse reactions have been identified during post-marketing clinical trials and during post-approval use of intramuscular testosterone undecanoate. In most cases, the dose being used was 1000 mg.

Blood and Lymphatic System Disorders: polycythemia, thrombocytopenia

Cardiac Disorders: angina pectoris, cardiac arrest, cardiac failure, coronary artery disease, coronary artery occlusion, myocardial infarction, tachycardia

Ear and Labyrinth Disorders: sudden hearing loss, tinnitus

Endocrine Disorders: hyperparathyroidism, hypoglycemia

Gastrointestinal Disorders: abdominal pain upper, diarrhea, vomiting

General Disorders and Administrative Site Conditions: chest pain, edema peripheral, injection site discomfort, injection site hematoma, injection site irritation, injection site pain, injection site reaction, malaise, paresthesia, procedural pain

Immune System Disorders: anaphylactic reaction, anaphylactic shock, asthma, dermatitis allergic, hypersensitivity, leukocytoclastic vasculitis

Infections and Infestations: injection site abscess, prostate infection

Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, blood glucose increased, blood pressure increased, blood prolactin increased, blood testosterone decreased, blood testosterone increased, blood triglycerides increased, gamma-glutamyltransferase increased, hematocrit increased, intraocular pressure increased, liver

function test abnormal, prostate examination abnormal, prostatic specific antigen increased, transaminases increased

Metabolism and Nutrition Disorders: diabetes mellitus, fluid retention, hyperlipidemia, hypertriglyceridemia

Musculoskeletal and Connective Tissue Disorders: musculoskeletal chest pain, musculoskeletal pain, myalgia, osteopenia, osteoporosis, systemic lupus erythematosus

Neoplasms Benign, Malignant and Unspecified (including cysts and polyps): prostate cancer, prostatic intraepithelial neoplasia

Nervous System Disorders: stroke, cerebrovascular insufficiency, reversible ischemic neurological deficiency, transient ischemic attack

Psychiatric Disorders: aggression, anxiety, depression, insomnia, irritability, Korsakoff's psychosis non-alcoholic, male orgasmic disorder, nervousness, restlessness, sleep disorder

Renal and Urinary Disorders: calculus urinary, dysuria, hematuria, nephrolithiasis, pollakiuria, renal colic, renal pain, urinary tract disorder

Reproductive System and Breast Disorders: azoospermia, benign prostatic hyperplasia, breast induration, breast pain, erectile dysfunction, gynecomastia, libido decreased, libido increased, prostate induration, prostatitis, spermatocele, testicular pain

Respiratory, Thoracic and Mediastinal Disorders: asthma, chronic obstructive pulmonary disease, cough, dysphonia, dyspnea, hyperventilation, obstructive airway disorder, pharyngeal edema, pharyngolaryngeal pain, pulmonary microemboli, pulmonary embolism, respiratory distress, rhinitis, sleep apnea syndrome, snoring

Skin and Subcutaneous Tissue Disorders: acne, alopecia, angioedema, angioneurotic edema, dermatitis allergic, erythema, hyperhidrosis, pruritus, rash

Vascular Disorders: cerebral infarction, cerebrovascular accident, circulatory collapse, deep venous thrombosis, hot flush, hypertension, syncope, thromboembolism, thrombosis, venous insufficiency

7 DRUG INTERACTIONS

7.1 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.

7.2 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.

7.3 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

AVEED is contraindicated in pregnant women. Testosterone is teratogenic and may cause fetal harm based on data from animal studies and its mechanism of action *[see Contraindications (4) and Clinical Pharmacology (12.1)]*. Exposure of a female fetus to androgens may result in varying degrees of virilization. In animal development studies, exposure to testosterone in utero resulted in hormonal and behavioral changes in offspring and structural impairments of reproductive tissues in female and male offspring. These studies did not meet current standards for nonclinical development toxicity studies.

Data

Animal Data

In developmental studies conducted in rats, rabbits, pigs, sheep and rhesus monkeys, pregnant animals received intramuscular injection of testosterone during the period of organogenesis. Testosterone treatment at doses that were comparable to those used for testosterone replacement therapy resulted in structural impairments in both female and male offspring. Structural impairments observed in females included increased anogenital distance, phallus development, empty scrotum, no external vagina, intrauterine growth retardation, reduced ovarian reserve, and increased ovarian follicular recruitment. Structural impairments seen in male offspring included increased testicular weight, larger seminal tubular lumen diameter, and higher frequency of occluded tubule lumen. Increased pituitary weight was seen in both sexes.

Testosterone exposure in utero also resulted in hormonal and behavioral changes in offspring. Hypertension was observed in pregnant female rats and their offspring exposed to doses approximately twice those used for testosterone replacement therapy.

8.2 Lactation

Risk Summary

AVEED is not indicated for use in females.

8.3 Females and Males of Reproductive Potential

Infertility

During treatment with large doses of exogenous androgens, including AVEED, spermatogenesis may be suppressed through feedback inhibition of the hypothalamic-pituitary-testicular axis *[see*

Warnings and Precautions (5.9)], possibly leading to adverse effects on semen parameters including sperm count. Reduced fertility is observed in some men taking testosterone replacement therapy. Testicular atrophy, subfertility, and infertility have also been reported in men who abuse anabolic androgenic steroids *[see Drug Abuse and Dependence (9.2)]*. With either type of use, the impact on fertility may be irreversible.

8.4 Pediatric Use

Safety and effectiveness of AVEED in pediatric patients less than 18 years old have not been established. Improper use may result in acceleration of bone age and premature closure of epiphyses.

8.5 Geriatric Use

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. Of the 153 patients enrolled in the pivotal clinical study utilizing AVEED, 26 (17.0%) were over 65 years of age. Additionally, there are insufficient long-term safety data in geriatric patients to assess the potentially increased risk of cardiovascular disease and prostate cancer.

Geriatric patients treated with androgens may also be at risk for worsening of signs and symptoms of BPH *[see Warnings and Precautions (5.5)]*.

8.6 Renal Impairment

No studies were conducted in patients with renal impairment.

8.7 Hepatic Impairment

No studies were conducted in patients with hepatic impairment.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

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

9.2 Abuse

Drug abuse is intentional non-therapeutic use of a drug, even once, for its rewarding psychological and physiological effects. Abuse and misuse of testosterone are seen in male and female adults and adolescents. Testosterone, often in combination with other anabolic androgenic steroids (AAS), and not obtained by prescription through a pharmacy, may be abused by athletes and bodybuilders. There have been reports of misuse of men taking higher doses of legally obtained testosterone than prescribed and continuing testosterone despite adverse events or against medical advice.

Abuse-Related Adverse Reactions

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 also been reported in men: transient ischemic attacks, convulsions, hypomania, irritability, dyslipidemias, testicular atrophy, subfertility, and infertility.

The following additional 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.

Because these reactions are reported voluntarily from a population of uncertain size and may include abuse of other agents, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

9.3 Dependence

Behaviors Associated with Addiction

Continued abuse of testosterone and other anabolic steroids, leading to addiction is characterized by the following behaviors:

- Taking greater dosages than prescribed
- Continued drug use despite medical and social problems due to drug use
- Spending significant time to obtain the drug when supplies of the drug are interrupted
- Giving a higher priority to drug use than other obligations
- Having difficulty in discontinuing the drug despite desires and attempts to do so
- Experiencing withdrawal symptoms upon abrupt discontinuation of use

Physical dependence is characterized by withdrawal symptoms after abrupt drug discontinuation or a significant dose reduction of a drug. Individuals taking supratherapeutic doses of testosterone may experience withdrawal symptoms lasting for weeks or months which include depressed mood, major depression, fatigue, craving, restlessness, irritability, anorexia, insomnia, decreased libido, and hypogonadotropic hypogonadism.

Drug dependence in individuals using approved doses of testosterone for approved indications has not been documented.

10 OVERDOSAGE

There have been no reports of overdosage in the AVEED clinical trials. There is 1 report of acute overdosage with use of an approved injectable testosterone product: this subject had serum testosterone levels of up to 11,400 ng/dL with a cerebrovascular accident.

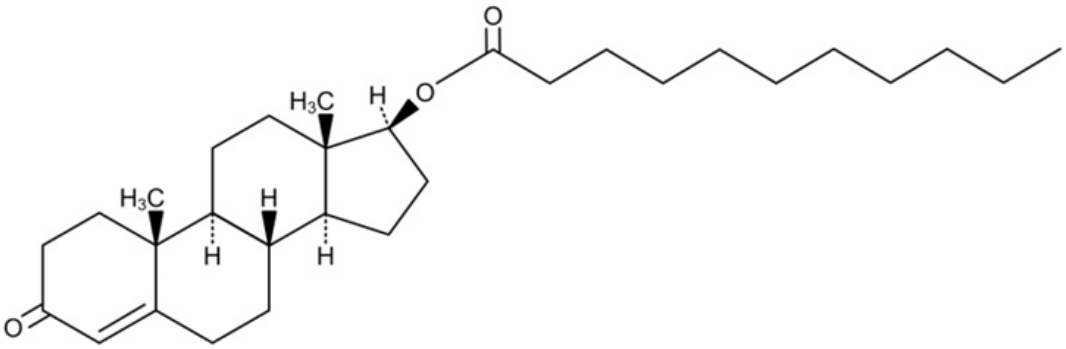
Treatment of overdosage would consist of discontinuation of AVEED together with appropriate symptomatic and supportive care.

11 DESCRIPTION

AVEED (testosterone undecanoate) injection contains testosterone undecanoate (17β-undecanoyloxy-4-androsten-3-one) which is an ester of the androgen, testosterone. Testosterone is formed by cleavage of the ester side chain of testosterone undecanoate.

Testosterone undecanoate is a white to off-white crystalline substance. The empirical formula of testosterone undecanoate is $C_{30}H_{48}O_3$ and a molecular weight of 456.7. The structural formula is:

Figure 2: Testosterone Undecanoate



$C_{30}H_{48}O_3$ MW: 456.7

AVEED is a clear, yellowish, sterile oily solution containing testosterone undecanoate, a testosterone ester, for intramuscular injection. Each single use vial contains 3 mL of 250 mg/mL testosterone undecanoate solution in a mixture of 1500 mg of benzyl benzoate and 885 mg of refined castor oil.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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. These effects include the growth and maturation of prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement; vocal cord thickening; and alterations in body musculature and fat distribution.

Male hypogonadism, a clinical syndrome resulting from insufficient secretion of testosterone, has 2 main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter's syndrome or Leydig cell aplasia, whereas secondary hypogonadism is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (FSH, LH).

12.3 Pharmacokinetics

Absorption

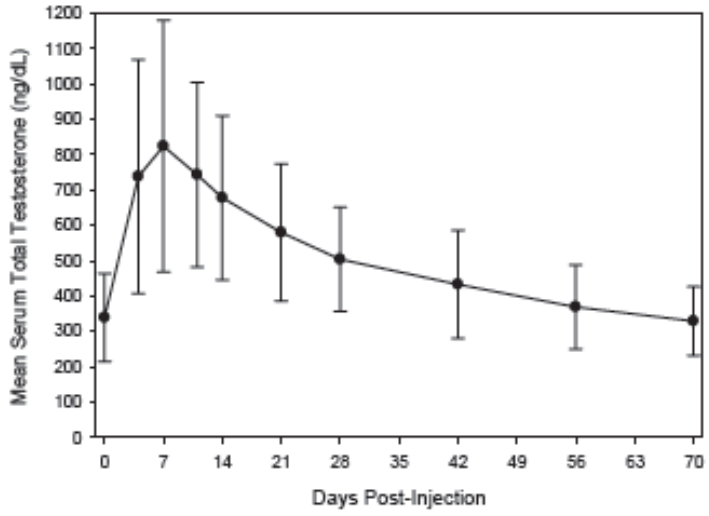
AVEED 750 mg delivers physiologic amounts of testosterone, producing circulation testosterone concentrations that approximate normal concentrations (300-1000 ng/dL) seen in healthy men.

Testosterone esters in oil injected intramuscularly are absorbed from the lipid phase. Cleavage of the undecanoic acid side chain of AVEED by tissue esterases releases testosterone.

Following intramuscular injection of 750 mg of AVEED, serum testosterone concentrations reach a maximum after a median of 7 days (range 4 to 42 days) then slowly decline (Figure 3). Steady-state serum testosterone concentration was achieved with the third injection of AVEED at 14 weeks.

Figure 3 shows the mean serum total testosterone concentration-time profile during the third injection interval (at steady state, 14 to 24 weeks) for hypogonadal men (less than 300 ng/dL) given 750 mg AVEED at initiation, at 4 weeks, and every 10 weeks thereafter. Intramuscular injection of 750 mg of AVEED generates mean steady-state serum total testosterone concentrations in the normal range for 10 weeks.

Figure 3: Mean (SD) Serum Total Testosterone Concentrations (ng/dL) at 14 to 24 Weeks



Distribution

Circulating testosterone is chiefly bound in the serum to sex hormone-binding globulin (SHBG) and albumin.

Approximately 40% of testosterone in plasma is bound to SHBG, 2% remains unbound (free), and the rest is loosely bound to albumin and other proteins.

Metabolism

Testosterone undecanoate is metabolized to testosterone via ester cleavage of the undecanoate group. The mean (SD) maximum concentration of testosterone undecanoate was 90.9 (68.8) ng/dL on Day 4 following injection of AVEED. Testosterone undecanoate was nearly undetectable 42 days following injection of AVEED.

Testosterone is metabolized to various 17-keto steroids through 2 different pathways. The major active metabolites of testosterone are estradiol and DHT.

DHT concentrations increased in parallel with testosterone concentrations during AVEED treatment. Average DHT concentrations during a dosing interval ranged from 244 to 451 ng/dL. The mean DHT to testosterone ratios ranged from 0.05 to 0.07.

Excretion

There is considerable variation in the half-life of testosterone as reported in the literature, ranging from 10 to 100 minutes. About 90% of a testosterone dose given intramuscularly is excreted in the urine as glucuronic and sulfuric acid-conjugates of testosterone or as metabolites. About 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver.

Effect of Body Weight and Body Mass Index (BMI)

Analysis of serum testosterone concentrations from 117 hypogonadal men in the 84-week clinical study of AVEED indicated that serum testosterone concentrations achieved were inversely correlated with the patient's body weight. In 60 patients with pretreatment body weight of ≥100 kg, the mean (±SD) serum testosterone average concentration was 426 ± 104 ng/dL. A higher serum testosterone average concentration (568 ± 139 ng/dL) was observed in 57 patients weighing 65 to 100 kg. A similar trend was also observed for maximum serum testosterone concentrations.

In 70 patients with pretreatment BMIs of >30 kg/m^2, the mean (±SD) serum testosterone average concentration was 445 ± 116 ng/dL. Higher serum testosterone average concentrations (579 ± 101 ng/dL and 567± 155ng/dL) were observed in patients with BMIs <26 kg/m^2 and 26 to 30 kg/m^2, respectively. A similar trend was also observed for maximum serum testosterone concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their

susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats.

Mutagenesis

AVEED was negative in the in vitro Ames assays, the chromosomal aberration assay in human lymphocytes, and in the in vivo mouse micronucleus assay.

Impairment of Fertility

The administration of exogenous testosterone has been reported to suppress spermatogenesis in the rat, dog, and non-human primates, which was reversible on cessation of the treatment.

14 CLINICAL STUDIES

14.1 Testosterone Replacement Therapy

AVEED was evaluated for efficacy in an 84-week, single-arm, open-label, multicenter study of 130 hypogonadal men. Eligible patients weighed at least 65 kg, were 18 years of age and older (mean age 54.2 years), and had a morning serum total testosterone concentration <300 ng/dL (mean screening testosterone concentration 215 ng/dL). Patients were caucasian (74.6%), black (12.3%), Hispanic (10.8%), and of other ethnicities (2.3%). The mean BMI was 32 kg/m^2.

All patients received injections of AVEED 750 mg at baseline, at 4 weeks, and then every 10 weeks thereafter.

The primary endpoint was the percentage of patients with average serum total testosterone concentration (C_{avg}) within the normal range (300-1000 ng/dL) after the third injection, at steady state.

The secondary endpoint was the percentage of patients with maximum total testosterone concentration (C_{max}) above 3 pre-determined limits: greater than 1500 ng/dL, between 1800 and 2499 ng/dL, and greater than 2500 ng/dL.

A total of 117 out of 130 hypogonadal men completed study procedures through Week 24 and were included in the evaluation of testosterone pharmacokinetics after the third AVEED injection. Ninety-four percent (94%) of patients maintained a C_{avg} within the normal range (300 to 1000 ng/dL). The percentages of patients with C_{avg} below the normal range (less than 300 ng/dL) and above the normal range (greater than 1000 ng/dL) were 5.1% and 0.9%, respectively.

Table 2 summarizes the mean (SD) serum total testosterone pharmacokinetic parameters at steady state for these 117 patients.

Table 2: Mean (SD) Serum Total Testosterone Concentrations at Steady State

	AVEED 750 mg (N=117)
$C_{avg\ (0\ to\ 10\ weeks)}$ (ng/dL)	495 (142)
C_{max} (ng/dL)	891 (345)
C_{min} (ng/dL)	324 (99)

C_{avg} = average concentration; C_{max} = maximum concentration; C_{min} = minimum concentration

The percentage of patients with C_{max} >1500 ng/dL was 7.7%. No patient had a C_{max} > 1800 ng/dL.

16 HOW SUPPLIED/STORAGE AND HANDLING

AVEED, NDC 67979-511-43: 750 mg/3 mL (250 mg/mL) testosterone undecanoate sterile injectable solution is provided in an amber glass vial with silver-colored crimp seal and gray plastic cap. Each vial is individually packaged in a carton box.

Store at controlled room temperature 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP controlled room temperature] in its original carton until the date indicated.

Before use, each vial should be visually inspected. Only vials free from particles should be used.

Single Use Vial. Discard unused portion.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the **FDA-approved patient labeling (Medication Guide).**

Advise patients of the following:

17.1 Risks of Serious Pulmonary Oil Microembolism (POME) and Anaphylaxis

- Serious POME reactions, involving cough, urge to cough, shortness of breath, sweating, throat tightening, chest pain, dizziness, and syncope, have been reported to occur during or immediately after the injection of intramuscular testosterone undecanoate. The majority of these events lasted a few minutes and resolved with supportive measures; however, some lasted up to several hours and some required emergency care and/or hospitalization.
- Episodes of anaphylaxis, including life-threatening reactions, have also been reported to occur following the injection of intramuscular testosterone undecanoate.
- Both serious POME reactions and anaphylaxis can occur after any injection of testosterone undecanoate during the course of therapy, including after the first dose.

- Advise the patient to read the AVEED REMS information sheet titled ***"What You Need to Know About AVEED® Treatment: A Patient Guide"***.
- Instruct patients to remain at the healthcare setting for 30 minutes after each AVEED injection.

17.2 Men with Known or Suspected Carcinoma of the Prostate or Breast

Men with known or suspected prostate or breast cancer should not use AVEED *[see Contraindications (4)]*.

17.3 Potential Adverse Reactions to Androgens

Patients should be informed that treatment with androgens may lead to adverse reactions which include:

- Changes in urinary habits, such as increased urination at night, trouble starting the urine stream, passing urine many times during the day, having an urge to go the bathroom right away, having a urine accident, or being unable to pass urine or weak urine flow
- Breathing disturbances, including those associated with sleep or excessive daytime sleepiness
- Too frequent or persistent erections of the penis
- Nausea, vomiting, changes in skin color, or ankle swelling
- Venous thromboembolism, the signs and symptoms of which may include lower limb pain, edema, or erythema; dyspnea; or chest pain.
- Increased blood pressure that can increase cardiovascular risk over time

17.4 Patients Should Be Advised of the Following Instructions for Use

- **Read the Medication Guide before starting AVEED therapy and reread the Guide before each injection.**
- Adhere to all recommended monitoring.
- Report any changes in their state of health, such as signs and symptoms of venous thromboembolism, changes in urinary habits, breathing, sleep, and mood.
- Be aware of the importance of monitoring BP periodically while on AVEED. If BP increases while on AVEED, antihypertensive medications may need to be started, added, or adjusted, or AVEED may need to be discontinued.

Manufactured for:
Endo USA
Malvern, PA 19355

© 2025 Endo, Inc. or one of its affiliates.

Revised: 07/2025