

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
022219Orig1s009

Trade Name: AVEED

***Generic or
Proper Name:*** testosterone undecanoate

Sponsor: Endo Pharmaceuticals, Inc.

Approval Date: 10/25/2016

Indication: 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)
- Hypogonadotropic hypogonadism (congenital or acquired).

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:
NDA 022219/S-009**

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APPLICATION NUMBER:
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APPROVAL LETTER



NDA 022219/S-009

SUPPLEMENT APPROVAL

Endo Pharmaceuticals, Inc.
Attention: Paula Clark
Senior Director, Regulatory Affairs
1400 Atwater Drive
Malvern, PA 19355

Dear Ms. Clark:

Please refer to your Supplemental New Drug Application (sNDA) dated and received September 1, 2016, and your amendment, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Avedo® (testosterone undecanoate) injection.

We also refer to our letter dated August 10, 2016, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for all approved testosterone replacement therapies (TRT). This information pertains to the risk of serious adverse events associated with testosterone abuse and dependence, typically reported at testosterone doses higher than recommended for the approved indication and when used in combination with other anabolic androgenic steroids (AAS).

This supplemental new drug application provides for revisions to the labeling for Avedo, consistent with our August 10, 2016, letter, which include the addition of a warning to the WARNINGS AND PRECAUTIONS section (5), and updates to the DRUG ABUSE AND DEPENDENCE section (9) of the Physician Insert (PI) that describe the risks of serious adverse events associated with testosterone abuse and dependence.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling text for the package insert, with the

addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available

at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/UCM443702.pdf>).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/UCM443702.pdf>).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Meredith Alpert, MS, Safety Regulatory Project Manager, at (301) 796-1218.

Sincerely,

{See appended electronic signature page}

Christine P. Nguyen, MD
Deputy Director for Safety
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINE P NGUYEN
10/25/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 022219/S-009

LABELING

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 (5.7)

10/2016

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).
- 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, 5.3).
- Pregnant or breastfeeding women. Testosterone may cause fetal harm (4, 8.1, 8.3).
- Known hypersensitivity to Aveed or its ingredients (testosterone undecanoate, refined castor oil, benzyl benzoate) (4).

WARNINGS AND PRECAUTIONS

- Monitor patients with benign prostatic hyperplasia (BPH) for worsening of signs and symptoms of BPH (5.3).
- Venous thromboembolism (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. (5.5)
- Some postmarketing studies have shown an increased risk of myocardial infarction and stroke associated with use of testosterone replacement therapy. (5.6)
- Exogenous administration of androgens may lead to azoospermia (5.9).
- Edema with or without congestive heart failure may be a complication in patients with preexisting cardiac, renal, or hepatic disease (5.11).
- Sleep apnea may occur in those with risk factors (5.13).
- Monitor prostatic specific antigen (PSA), hemoglobin, hematocrit, and lipid concentrations periodically (5.3, 5.4, 5.14).

ADVERSE REACTIONS

The most commonly reported adverse reactions ($\geq 2\%$) 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 Pharmaceuticals 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: 10/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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*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 pulmonary oil microembolism 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 two 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 pulmonary oil microembolism [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.

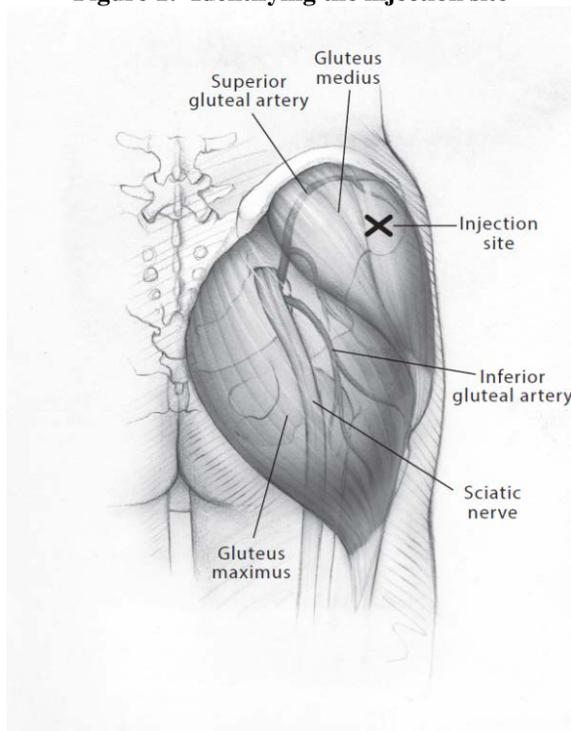
Carefully remove the gray plastic cap from the top of the vial by lifting it up from the edges with your fingers or by pushing the bottom edge of the cap upward using the top of your thumb. Remove only the gray plastic cap while leaving the aluminum metal ring and crimp seal around the gray rubber stopper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

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 (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 (5.3)*].
- Women who are or may become pregnant, or who are breastfeeding. Testosterone can cause fetal harm when administered to a pregnant woman. Aveed may cause serious adverse reactions in nursing infants. Exposure of a fetus or nursing infant to androgens may result in varying degrees of virilization [*see Use in Specific Populations (8.1, 8.3)*].
- 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 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)*].

5.4 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.

5.5 Venous Thromboembolism

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. 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.

5.6 Cardiovascular Risk

Long term clinical safety trials have not been conducted to assess the cardiovascular outcomes of testosterone replacement therapy in men. To date, epidemiologic studies and randomized controlled trials have been inconclusive for determining the risk of major adverse cardiovascular events (MACE), such as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, with the use of testosterone compared to non-use. Some studies, but not all, have reported an increased risk of MACE in association with use of testosterone replacement therapy in men. Patients should be informed of this possible risk when deciding whether to use or to continue to use Aveed.

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 Use in Women

Due to lack of controlled evaluations in women and potential virilizing effects, Aveed is not indicated for use in women.

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 follicle-stimulating hormone (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 (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.

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 Lipids

Changes in serum lipid profile may require dose adjustment of lipid lowering drugs or discontinuation of 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 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 (e.g., 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 pulmonary oil microembolism 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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Aved. 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 pulmonary oil microembolism (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 outside the United States 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: 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

Pregnancy Category X: Aved is contraindicated in pregnant women or in women who may become pregnant. Testosterone is teratogenic and may cause fetal harm. Exposure of a fetus to androgens, such as testosterone, may result in varying degrees of virilization. If this drug is used in pregnancy or if the patient becomes pregnant while taking this drug, the patient should be made aware of the potential hazard to the fetus.

8.3 Nursing Mothers

Although it is not known how much testosterone transfers into human milk, Aved is contraindicated in nursing women because of the potential for serious adverse reactions in nursing infants.

8.4 Pediatric Use

Safety and effectiveness of Aved 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 Aved 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 Aved, 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 (5.3)*].

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 one 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.

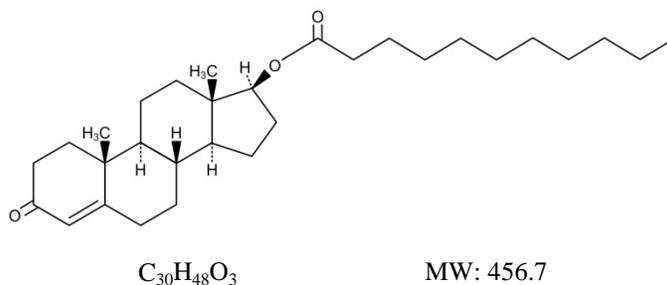
Treatment of overdosage would consist of discontinuation of Aveed together with appropriate symptomatic and supportive care.

11 DESCRIPTION

Aveed (testosterone undecanoate) injection contains testosterone undecanoate (17 β -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



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 two 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

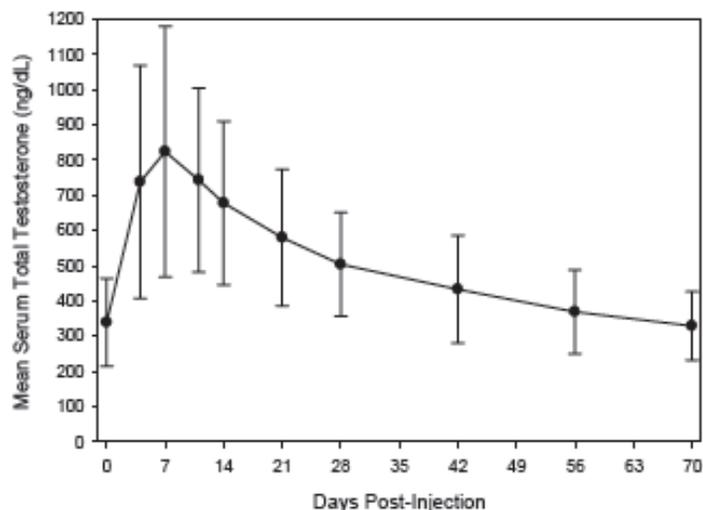
Aveed 750 mg delivers physiologic amounts of testosterone, producing circulation testosterone concentrations that approximate normal concentrations (300-1000 ng/dL) seen in healthy men.

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 – 42 days) then slowly decline (Figure 3). Steady state serum testosterone concentration was achieved with the 3rd injection of Aveed at 14 weeks.

Figure 3 shows the mean serum total testosterone concentration-time profile during the 3rd injection interval (at steady state, 14-24 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 14-24 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 two 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:T 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 (\pm 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 body mass index of >30 kg/m², the mean (\pm SD) serum testosterone average concentration was 445 ± 116 ng/dL. Higher serum testosterone average concentrations (579 ± 101 ng/dL and 567 ± 155 ng/dL) were observed in patients with BMIs <26 kg/m² and 26 to 30 kg/m², respectively. A similar trend was also observed for maximum serum testosterone concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

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.

Mutagenicity

Mutagenic effects of testosterone undecanoate were not detected in a battery of *in vitro* tests including bacterial mutation assays (Ames test) and chromosomal aberration tests in human lymphocytes. Testosterone undecanoate was also negative in an *in vivo* bone marrow micronucleus assay in mice. Testosterone was negative in the *in vitro* Ames and in the *in vivo* mouse micronucleus assays.

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 body mass index was 32 kg/m².

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 three 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 - 30 °C (59 - 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

See FDA-Approved Medication Guide

Advise patients of the following:

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

- Serious pulmonary oil microembolism (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

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 changes in urinary habits, breathing, sleep, and mood.

Distributed by:

Endo Pharmaceuticals Solutions Inc.
Malvern, PA 19355

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MEDICATION GUIDE

AVEED® (Uh-Veed)
(testosterone undecanoate)
injection

Read this Medication Guide before you receive AVEED and before each injection. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about AVEED?

AVEED may cause serious side effects, including:

- **A serious lung problem.** AVEED can cause a serious lung problem called a pulmonary oil microembolism (POME) reaction. POME is caused by tiny droplets of oil that have traveled to the lungs. Symptoms of a POME reaction may include:
 - cough or urge to cough
 - difficulty breathing
 - sweating
 - tightening of your throat
 - chest pain
 - dizziness
 - fainting
- **Serious allergic reactions (anaphylaxis).** AVEED can cause a serious allergic reaction right after receiving the injection. Some of these allergic reactions may be life threatening. These reactions can happen after you receive your first dose of AVEED or may happen after receiving more than 1 dose.

You may need emergency treatment in a hospital, especially if these symptoms get worse over the 24 hours after your AVEED injection.

These side effects may happen during or right after each injection. To be sure that you are not having one of these reactions:

- **You need to stay in the doctor's office, clinic, or hospital for 30 minutes after having your AVEED injection so that your doctor can watch you for symptoms of POME or a serious allergic reaction.**
- **You can only get AVEED at your doctor's office, clinic, or hospital.**

AVEED is only available through a restricted program called the AVEED Risk Evaluation and Mitigation Strategy (REMS) Program. For more information about the AVEED REMS Program go to www.AveedREMS.com or call 1-855-755-0494.

What is AVEED?

AVEED is a prescription medicine that contains testosterone. AVEED is used to treat adult males who have low or no testosterone due to certain medical conditions.

AVEED is only for adult males who need testosterone replacement therapy and when the benefit of receiving AVEED is more than the risk of POME and anaphylaxis.

Your healthcare provider will test your blood before you start and while you are taking AVEED.

It is not known if AVEED is safe or effective to treat men who have low testosterone due to aging.

It is not known if AVEED is safe and effective for use in children younger than 18 years old. Improper use of AVEED may affect bone growth in children.

AVEED is a controlled substance (CIII) because it contains testosterone that can be a target for people who abuse prescription medicines.

AVEED is not meant for use in women.

Who should not receive AVEED?

Do not receive AVEED if you:

- have breast cancer
- have or might have prostate cancer
- are pregnant or may become pregnant or are breastfeeding. AVEED may harm your unborn or breastfeeding baby.
- are allergic to AVEED or to any of the ingredients in AVEED. See the end of this leaflet for a complete list of ingredients in AVEED.

Talk to your doctor before receiving this medicine if you have any of the above conditions.

What should I tell my doctor before receiving AVEED?

Before receiving AVEED, tell your doctor if you:

- have breast cancer
- have or might have prostate cancer
- have urinary problems due to an enlarged prostate
- have heart problems
- have liver or kidney problems
- have problems breathing while you sleep (sleep apnea)
- have any other medical conditions

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Receiving AVEED with certain other medicines can affect each other. Especially tell your doctor if you take:

- insulin
- medicines that decrease blood clotting
- corticosteroids

Ask your doctor or pharmacist for a list of these medicines, if you are not sure.

Know the medicines you take. Keep a list of your medicines and show them to your doctor and pharmacist when you get a new medicine.

How will I receive AVEED?

See **“What is the most important information I should know about AVEED?”**

Your doctor will inject AVEED deep into the muscle of your buttock. You will get 1 injection when you start, 1 injection 4 weeks later and then 1 injection every 10 weeks.

Your doctor will test your blood before you receive and while you are receiving AVEED.

What are the possible side effects of AVEED?

AVEED can cause serious side effects including:

- see **“What is the most important information I should know about AVEED?”**
- **if you already have enlargement of your prostate gland, your signs and symptoms can get worse** while receiving AVEED. This can include:
 - increased urination at night
 - trouble starting your urine stream
 - having to pass urine many times during the day
 - having an urge that you have to go to the bathroom right away
 - having a urine accident
 - being unable to pass urine or weak urine flow
- changes in certain blood tests
- **possible increased risk of prostate cancer.** Your doctor should check you for prostate cancer or any other prostate problems before you receive and while you are receiving AVEED.
- **blood clots in the legs or lungs.** Signs and symptoms of a blood clot in your leg can include leg pain, swelling or redness. Signs and symptoms of a blood clot in your lungs can include difficulty breathing or chest pain.
- **possible increased risk of heart attack or stroke.**
- **in large doses AVEED may lower your sperm count.**
- **liver problems.** Symptoms of liver problems may include:
 - nausea or vomiting
 - yellowing of your skin or whites of your eyes
 - dark urine
 - pain on the right side of your stomach area (abdominal pain)
- **swelling of your ankles, feet, or body, with or without heart failure.** This may cause serious problems for people who have heart, kidney, or liver disease.
- **enlarged or painful breasts.**
- **have problems breathing while you sleep (sleep apnea).**

Call your doctor right away if you have any of the serious side effects listed above.

The most common side effects of AVEED include:

- acne
- pain at the injection site
- increased prostate specific antigen (a test used to screen for prostate cancer)
- increased estradiol level
- low testosterone level
- feeling tired
- irritability
- increased red blood cell count
- difficulty sleeping
- mood swings

Other side effects include more erections than are normal for you or erections that last for a long time.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects with AVEED. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about AVEED

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

This Medication Guide summarizes the most important information about AVEED. If you would like more information, talk with your doctor. You can ask your doctor or nurse for information about AVEED that is written for health professionals. For more information, go to www.AVEEDUSA.com or call 1-800-462-3636.

What are the ingredients in AVEED?

Active ingredient: testosterone undecanoate

Inactive ingredients: benzyl benzoate, refined castor oil

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured for:
Endo Pharmaceuticals Solutions Inc.
Malvern, PA 19355

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Approved: 05/2015

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 022219/S-009

OTHER REVIEW(S)

Division of Bone, Reproductive and Urologic Products

**SAFETY REGULATORY PROJECT MANAGER LABELING REVIEW
FDAAA-Safety Labeling Change**

NDA Supplement	Drug Name	Applicant	Date of Safety Labeling Change Notification letter	Date of Original PAS supplement	Date of Labeling Amendment #1
021015 S-43	AndroGel® 1%	AbbVie, Inc.	8/10/2016	9/9/2016	N/A
022309 S-17	Androgel 1.62%	AbbVie, Inc.	8/10/2016	9/9/2016	N/A
020489 S-34	Androderm®	Watson Laboratories, Inc.	8/10/2016	9/9/2016	9/27/2016
022504 S-14	Axiron®	Eli Lilly and Company	8/10/2016	9/8/2016	9/28/2016
021543 S-12	Striant®	Auxillium	8/10/2016	9/1/2016	9/23/2016
021454 S-24	Testim®	Auxilium	8/10/2016	9/1/2016	9/23/2016
202763 S-04	Testosterone Gel 1%	ANI	8/10/2016	9/2/2016	9/23/2016
022219 S-09	Aveed®	Endo	8/10/2016	9/1/2016	9/23/2016
09165 S-34	Delatestryl®	Endo	8/10/2016	9/1/2016	9/23/2016
203098 S-09	Testosterone Gel 1%	Perrigo	8/10/2016	8/29/2016	9/28/2016
204399 S-04	Vogelxo®	Upsher- Smith	8/10/2016	9/9/2016	9/29/2016
205488 S-02	Natesto®	Aytu	8/10/2016	9/9/2016	10/17/2016
021463 S-19	Fortesta®	Endo	8/10/2016	9/1/2016	9/23/2016

Background and Summary Description:

On January 24, 2014, the Controlled Substance Staff (CSS) completed a consult review for a labeling supplement for Aved. CSS recommended revisions for Section 9 (Abuse and Dependence) of the Aved label and all other testosterone product labels stating that the section contained inadequate risk information. CSS also recommended that the Division consult Office of Surveillance and Epidemiology (OSE) to receive current and updated information, for all testosterone products, on abuse-related safety data, including abuse, misuse, overdose, and addiction. At a February 5, 2014, meeting between the Division, OSE, and CSS, it was decided that a comprehensive review, of abuse-related safety concerns should be conducted for all testosterone replacement therapy (TRT) products, under a Tracked Safety Issue (TSI).

On April 4, 2014, TSI #1351 was opened under the safety issue name, *Testosterone Abuse/Misuse and Dependence*. During the TSI review period, the reviewers decided that the assessment should also include abuse of testosterone when taken with other androgen-anabolic steroids (AAS). The Division of Pharmacovigilance I (DPVI), conducted a search of FDA's Adverse Event Reporting System (FAERS) in order to review cases of serious adverse events reported in association with abuse of testosterone and AAS. DPV provided the several cases that they found in their search to the Clinical Team within the Division. The clinical review concluded, based on their review of the individual cases, that all the testosterone product labels should be revised to include a description of the serious and non-serious events reported in association with testosterone + AAS abuse, dependence, and withdrawal. On August 10, 2016, Safety Labeling Change (SLC) notification letters were issued for all 13 testosterone products listed above.

August 10, 2016, FDAAA Safety Labeling Change (SLC) Notification Letters:

Below contains the requested additions and modifications to the Physician Inserts (PIs) (additions are underlined, and deletions are ~~striketrough~~):

HIGHLIGHTS

RECENT MAJOR CHANGES

Warnings and Precautions (5.X) XX/2016

FULL PRESCRIBING INFORMATION

a) new Warning following the "Cardiovascular Risk" warning and prior to the "Use in Women" warning:

5. (b) 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. (b) (4)

[see Drug Abuse and Dependence (9)].

If testosterone abuse is suspected, check serum testosterone concentrations to ensure they are within therapeutic range. Counsel patients concerning the serious adverse reactions associated with (b) (4). Conversely, consider the possibility of testosterone and anabolic androgenic steroid abuse in (b) (4) who present with serious cardiovascular or psychiatric adverse events.

b) Section 9 revised as follows:

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

(b) (4) contains testosterone, a Schedule III controlled substance in the Controlled Substances Act.

9.2 Abuse

(b) (4)

9.3 Dependence

(b) (4)

9.1 Controlled Substance

(b) (4) 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 (b) (4) in combination with other anabolic androgenic steroids (AAS), (b) (4) There have been reports of misuse by men taking higher doses of legally obtained testosterone than prescribed and continuing testosterone despite adverse events or against medical advice.

(b) (4)

Abuse-Related Adverse Reactions

Serious adverse reactions, (b) (4) 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, (b) (4)

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.

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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

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.

*Please note that the requested language is exactly the same for the non-PLR product, (b) (4), except that there is no numbering, i.e., 9.x.

On September 11, 2016, the sponsor for Androgel 1% and 1.62%, Abbvie, proposed alternate language, which the Division and CSS agreed was acceptable. On September 15, 2016, the Division requested that all of the sponsors amend their original labeling supplements with the alternate language; which they all agreed to.

Modified Text Agreed To By All Sponsors (shown in red font):

Differences in labeling between the August 2016 SLC letter and the final label agreed to by all sponsors are shown here (WARNINGS AND PRECAUTIONS (section 5), DRUG USE AND DEPENDENCE (section 9), additions shown as underline, and deletion as ~~strikethrough~~).

5. (b) 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. (b) (4) **Anabolic androgenic steroid** (b) (4) 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 (b) (4). Conversely, consider the possibility of testosterone and anabolic androgenic steroid abuse in **suspected** patients who present with serious cardiovascular or psychiatric adverse events.

9.1 Controlled Substance

(b) (4) 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. (b) (4)

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 by men taking higher doses of legally obtained testosterone than prescribed and continuing testosterone despite adverse events or against medical advice.

(b) (4)

Abuse-Related Adverse Reactions

Serious adverse reactions have been reported in individuals who abuse anabolic androgenic steroids and include (b) (4) 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, (b) (4)

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. (b) (4)

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

Review

The final agreed upon labeling, for all the aforementioned testosterone products, were received by October 17, 2016, and are consistent with the agreed upon labeling changes.

Recommendations

The proposed labeling changes for all 13 testosterone products are consistent with the safety labeling changes requested, as amended, on August 10, 2016, and recommended by DBRUP. Approval letters for all 13 products should be issued.

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/s/

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10/20/2016

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10/20/2016