CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

022219Orig1s005

Trade Name: AVEED

Generic or Proper Name: testosterone undecanoate

Sponsor: Endo Pharmaceuticals, Inc.

Approval Date: 05/11/2015

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

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NDA 022219/S-005

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022219/S-005

SUPPLEMENT APPROVAL

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

Dear Ms. Clark:

Please refer to your Supplemental New Drug Application (sNDA) dated and received March 6, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Aveed (testosterone undecanoate) injection.

We acknowledge receipt of your amendment dated April 10, 2015.

We also refer to our letter dated, February 9, 2015, 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. This information pertains to the appropriate indicated population for testosterone replacement therapy and the potential risk of major adverse cardiovascular events associated with testosterone replacement therapy.

This supplemental new drug application provides for revisions to the labeling for testosterone injection, consistent with our February 9, 2015, letter and electronic communication dated March 27, 2015. Labeling revisions to the prescribing information are as follows:

- Indications and Usage: addition of a Limitation of Use statement concerning "age-related" hypogonadism and removal of "idiopathic" from hypogonadotropic hypogonadism
- Dosage and Administration: addition of a recommendation to measure and ensure that serum testosterone concentrations are below the normal range to confirm the diagnosis of hypogonadism prior to initiating testosterone replacement therapy
- Warnings and Precautions: addition of a new Warning regarding the possible increased risk of major adverse cardiovascular events
- Revisions to the Adverse Reactions/Postmarketing Experience section

The Medication Guide was also revised to reflect these changes accordingly.

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, and Medication Guide), 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 includes 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:

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

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 or by fax to 301-847-8444.

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
05/11/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022219/S-005

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----------

Indications and Usage (1)	5/2015
Dosage and Administration (2)	5/2015
Dosage and Administration (2.2)	3/2015
Warnings and Precautions (5.5)	6/2014
Warnings and Precautions (5.6)	5/2015

----------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 (5.8).
- Edema with or without congestive heart failure may be a complication in patients with preexisting cardiac, renal, or hepatic disease (5.10).
- Sleep apnea may occur in those with risk factors (5.12).
- Monitor prostatic specific antigen (PSA), hemoglobin, hematocrit, and lipid concentrations periodically (5.3, 5.4, 5.13).

----------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 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: 05/2015

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: SERIOUS PULMONARY OIL MICROEMBOLISM (POME) REACTIONS AND ANAPHYLAXIS

*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.

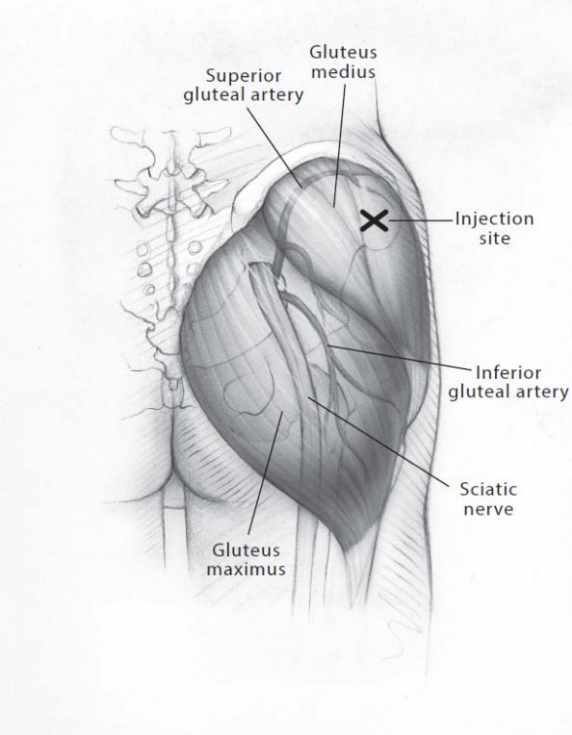
Carefully remove the gray plastic cap from the top of the vial by lifting it up from the edges with your fingers or by pushing the bottom edge of the cap upward using the top of your thumb. Remove only the gray plastic cap while leaving the aluminum metal ring and crimp seal around the gray rubber stopper 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 Use in Women
Due to lack of controlled evaluations in women and potential virilizing effects, Aveed is not indicated for use in women.

5.8 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.

5.9 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.

5.10 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.

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

5.12 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.

5.13 Lipids
Changes in serum lipid profile may require dose adjustment of lipid lowering drugs or discontinuation of testosterone therapy.

5.14 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.

5.15 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 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 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: Aveed 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, Aveed is contraindicated in nursing women because of the potential for serious adverse reactions in nursing infants.

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 the153 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 (5.3)]*.

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 undecanoate, a Schedule III controlled substance in the Controlled Substances Act.

9.2 Abuse

Anabolic steroids, such as testosterone, are abused. Abuse is often associated with adverse physical and psychological effects.

9.3 Dependence

Although drug dependence has not been documented in individuals using therapeutic doses of anabolic steroids for approved indications, dependence has been observed in some individuals abusing high doses of anabolic steroids. In general, anabolic steroid dependence is characterized by any three of the following:

- Taking more drug than intended
- Continued drug use despite medical and social problems

- Significant time spent in obtaining adequate amounts of drug
- Desire for anabolic steroids when supplies of the drugs are interrupted
- Difficulty in discontinuing use of the drug despite desires and attempts to do so
- Experience of a withdrawal syndrome upon discontinuation of anabolic steroid use.

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.

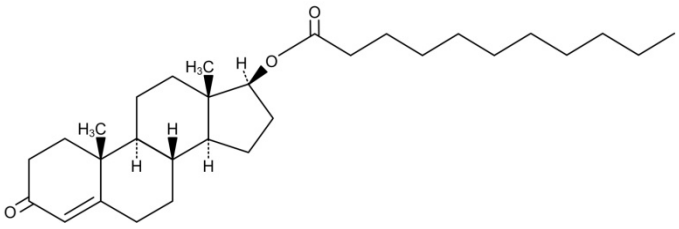
Treatment of overdosage would consist of discontinuation of Aveed together with appropriate symptomatic and supportive care.

11 DESCRIPTION

Aveed (testosterone undecanoate) injection contains testosterone undecanoate (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 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

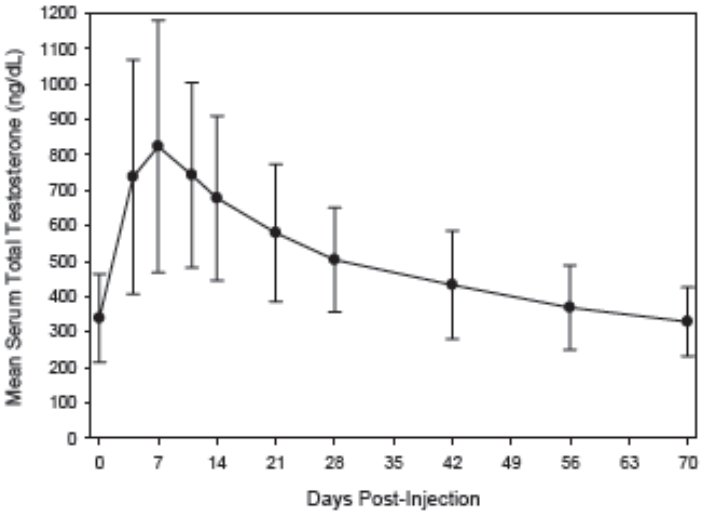
Aveed 750 mg delivers physiologic amounts of testosterone, producing circulation testosterone concentrations that approximate normal concentrations (300-1000 ng/dL) seen in healthy men.

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 (±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/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

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/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 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 ºC (77 ºF); excursions permitted to 15 - 30 ºC (59 - 86 ºF) [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.

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

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

AVEED is a registered trademark of Endo Pharmaceuticals Inc.

Approved: 05/2015

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022219/S-005

OFFICE DIRECTOR MEMO

Tracked Safety Issue (TSI) Decisional Memorandum

Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

NDA/BLA	Multiple NDAs (see Appendix A)
Drug name	Testosterone
TSI #	865
TSI open date*	December 17, 2013
Safety Issue Name	Cardiac Disorders
Signatory Authority	Christine P. Nguyen, MD Deputy Director for Safety Division of Bone, Reproductive, and Urologic Products (DBRUP) Through Hylton V. Joffe, MD, MMSc Director DBRUP
Date	May 11, 2015

*TSI 865 was initially opened in January 2010, closed in January 2011, and reopened in December 2013

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CDTL = Cross Discipline Team Leader
DB = Division of Biostatistics
DCRP = Division of Cardiovascular and Renal Products
DEPI = Division of Epidemiology
DPV = Division of Pharmacovigilance
OB = Office of Biostatistics
OPDP = Office of Prescription Drug Promotion
OSE = Office of Surveillance and Epidemiology

Table of Contents

1. Executive Summary

FDA-approved testosterone products are indicated as hormone replacement in men with primary or secondary hypogonadism. Traditionally, hypogonadism requiring testosterone replacement therapy (TRT) is a consequence of well-defined conditions known to cause absent or low testosterone production ("classic" hypogonadism). In recent years, TRT use has increased significantly among middle-age and older men who appear to have low serum testosterone concentrations for no reason other than age, and who may be experiencing symptoms of aging that overlap with those of classic hypogonadism. FDA refers to this phenomenon as "age-related" hypogonadism. Men ages 40 to 74 years now comprise over 80% of TRT users, and it is likely that many of them are prescribed TRT for age-related hypogonadism. In addition, data based on insurance claims indicated that approximately 25% of new users of TRT did not have evidence of serum testosterone testing prior to initiating therapy. The clinical benefits and long-term risks of treatment in this largest group of TRT users are largely unknown. Evidence from some recently published large observational studies in aging men suggests a potential cardiovascular (CV) safety signal associated with TRT. The combination of the extensive use of TRT for age-related hypogonadism, without clear evidence of efficacy or safety for this condition, and the recent CV safety signal pose an important public health concern.

FDA has undertaken a comprehensive evaluation of TRT use in the US and the evidence informing the CV safety signal associated with TRT under Tracked Safety Issue (TSI) 865[1]. The Division of Bone, Reproductive, and Urologic Products (DBRUP) also reviewed the regulatory approval paradigm for TRT to clarify the clinical evidence generated by the phase 3 trials supporting the marketing approval of TRT products. In collaboration with DBRUP, the Division of Epidemiology II (DEPI II) assessed the drug utilization trend and available published evidence on TRT and cardiovascular safety. The teams presented their findings at the joint Advisory Committee (AC) meeting of the Bone, Reproductive, and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on September 17, 2014.

FDA convened the joint AC meeting to discuss the two major issues concerning the class of TRT: 1) the appropriate indicated population, based on the data included in TRT marketing applications, and 2) the potential of a CV safety signal associated with its use. The AC panel concluded that testosterone, as replacement therapy, should be indicated only in men with "classic" hypogonadism, and not in those with "age-related" hypogonadism. The panel voted 20 to 1 in favor of revising the TRT class indication to reflect the appropriate intended population. Regarding CV safety, the AC panel acknowledged that the quality and quantity of the data were limited, but believed that the totality of the evidence suggested a weak signal of CV risk. The AC panel recommended that information about the potential for an increased risk of adverse CV outcomes associated with TRT be included in labeling. A majority of AC members (16 of 21) voted to require a CV safety trial if TRT were to be indicated for age-related hypogonadism. Another four AC members voted that such a safety trial should be required regardless of the approved indication, because they expected that TRT use for age-related hypogonadism would persist in clinical practice, despite labeling changes and public education. The one AC member who voted "no" to the question about a need for a CV safety trial still believed that a CV safety trial was warranted, but based his vote on the wording of the question which asked if testosterone sponsors

[1] A Tracked Safety Issue is an FDA-initiated application in FDA's DARRTS system to track and document FDA's review of significant safety issues associated with marketed drugs that require input from several FDA Divisions, Offices, another FDA Center, and/or that require a regulatory briefing, Drug Safety Oversight Board meeting, or advisory committee meeting for their evaluation.

should conduct the trial. He stated that such a study should instead be funded by the federal government and not by regulated industry.

DBRUP and DEPI II have carefully reviewed the data and considered the AC's deliberations and recommendations. Substantial evidence of clinical benefit of TRT for age-related hypogonadism is currently lacking. In this context, the CV safety signal, however tenuous, becomes a significant public health question, especially given the fact that most of TRT users are likely men with age-related hypogonadism. The review teams recommended that labeling be revised to convey that 1) the efficacy and safety of TRT for age-related hypogonadism have not been established, 2) serum T concentrations should be appropriately measured to confirm the diagnosis of hypogonadism prior to initiating treatment, and 3) a signal of CV risk with TRT has been reported in some studies, although the totality of evidence to date has been inconclusive. Lastly, the teams recommended requiring a postmarket cardiovascular outcomes trial (CVOT) to provide the type of evidence necessary for FDA to make an informed regulatory decision regarding CV risks associated with TRT. I concur with these recommendations.

2. Introduction and Regulatory Approval Paradigm of TRT

Androgens, including testosterone, have multiple physiologic functions in the male. They are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. In adult males, testosterone plays a role in maintaining muscle mass and strength, fat distribution, bone mass, red blood cell production, male hair pattern, libido, and spermatogenesis. [2]

Deficiency of endogenous testosterone production can result from injury to the testes (e.g., testicular damage due to chemotherapy, genetic or congenital testicular abnormalities) or the hypothalamus/pituitary (e.g., damage from a pituitary tumor, pituitary surgery, or brain irradiation). Low or absent serum testosterone concentrations can be replaced satisfactorily regardless of whether the deficiency is due to testicular (primary hypogonadism) or hypothalamic/pituitary disorders (secondary hypogonadism). These patients require replacement with exogenous testosterone for normal development and maintenance of secondary sexual characteristics and maintenance of bone and muscle mass.

FDA has approved testosterone products since the 1950s as hormone replacement therapy in men for conditions associated with a deficiency or absence of endogenous testosterone. In the US, TRT products are available in multiple formulations, including topical gels (for example, AndroGel 1%, Testim), a topical solution (Axiron), a transdermal system (Androderm), a buccal system (Striant), an intranasal gel (Natesto), intramuscular injections (testosterone enanthate, testosterone cypionate, and testosterone undecanoate), oral methyltestosterone, and subcutaneously implanted pellets (Testopel).

The current TRT class indication follows:

"*DRUG is indicated for 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 conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testes syndrome, orchiectomy, Klinefelter's*

[2] Bagatell, CJ, Bremner WJ. Androgens in Men – Uses and Abuses. NEngl J Med 1996; 334:707-715.

syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (FSH, LH) above the normal range.

- *Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing (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.*"

Because the intended use of testosterone is replacement therapy, FDA has only required for marketing approval that an investigational testosterone product is safe for use and reliably increases deficient serum T concentrations in adult hypogonadal males to the normal range, defined as serum T concentrations observed in healthy, young men. The primary efficacy endpoint is the percentage of subjects with an average serum testosterone concentration (Cavg) within the normal range following completion of all dose-titration (if titration is part of the regimen), and while on a stable testosterone dose at steady-state exposure. FDA also requires success on three secondary endpoints related to the percentage of patients meeting certain Cmax thresholds. These secondary endpoints ensure that the testosterone product does not produce supraphysiologic T concentrations (referred to as Cmax "outliers"). For example, no study subjects should have a Cmax concentration > 2500 ng/dL with testosterone treatment.

The pivotal safety and efficacy study of an investigational TRT is generally an open-label, single-arm study in approximately 150 to 200 hypogonadal men, with a treatment duration ranging from 26 to 52 weeks. The study population typically consists of adult men at least 18 years old, with primary or secondary hypogonadism, and average morning serum total testosterone concentrations below the normal range for healthy eugonadal adult males (these studies typically require testosterone < 300 ng/dL). In the majority of subjects in Phase 3 TRT trials, a specific etiology for the diagnosis of hypogonadism has not been determined (i.e., "idiopathic" hypogonadism), and it is likely that most of these subjects have this condition as a consequence of aging. Inclusion of such patients in the Phase 3 trials facilitates enrollment and improves trial feasibility, because these patients are more common than those who have a specific underlying etiology for their hypogonadism (i.e., classic hypogonadism). Such trials can adequately establish efficacy by meeting the regulatory requirement of demonstrating an increase in serum T to the normal range, an efficacy endpoint that should not be materially impacted by the underlying etiology for the low serum testosterone concentrations. FDA has not required that a TRT product ameliorate or improve any specific hypogonadal clinical sign or symptom as a condition of approval.

Based on the class indication and the regulatory approval paradigm for TRT, the intended population for TRT is men who have well-recognized causes of hypogonadism (for example, those with Klinefelter's syndrome, pituitary injury). In adult men with such well-defined etiologies for their hypogonadism, replacement of deficient endogenous testosterone to within the eugonadal range is a well-established and accepted standard of care. For instance, replacing testosterone in these patients is necessary for the development or maintenance of secondary sexual characteristics. Therefore, for this patient population, the current regulatory approval paradigm for TRT is a reasonable approach, and the need to evaluate clinical endpoints in phase 3 studies does not appear to be necessary. The labeled indication lists a number of specific etiologies of male hypogonadism; however, it does not clearly differentiate between etiologies that are well-defined (i.e., "classic" hypogonadism) versus etiologies that are vague (i.e., "*idiopathic" gonadotropin or luteinizing hormone-releasing deficiency*), where hypogonadal-like signs and symptoms associated with low serum T concentrations could be a consequence of other

medical conditions or of aging itself.

3. Age-related hypogonadism

In recent years, a controversial treatment population that could broadly fit under the category of "*idiopathic"* hypogonadotropic hypogonadism has emerged. This population consists of aging men who have low serum T concentrations for no apparent reason other than age, and who experience signs and symptoms that overlap with those of hypogonadism. FDA refers to this condition as "age-related" hypogonadism.

Evidence from cross-sectional and longitudinal studies indicates that serum T concentrations decrease as men age. The largest cross-sectional study to date, the European Male Aging study, evaluated 3220 community-dwelling men ages 40 to 79 years and reported that total testosterone falls approximately 0.4% per year, while free testosterone concentration falls 1.3% per year.[3] The Baltimore Longitudinal Study of Aging in 890 men reported that serum testosterone concentrations decrease at a fairly constant rate from age 20 to 80 years, independent of other clinical variables. Although this decline is usually modest, serum T concentrations can fall below the lower limit of the normal range for younger, healthy men. The Baltimore study indicated that the percentage of study subjects with total T concentrations in the hypogonadal range (the study defined this range as total testosterone <325 ng/dL) was 20, 30, and 50 percent for men in their 60s, 70s, and 80s, respectively.[4] Furthermore, aging men often experience many of the signs and symptoms associated with hypogonadism, including decreases in energy level, sexual function, bone mineral density, muscle mass and strength, and increases in fat mass. Multiple factors other than decreased testosterone may contribute to these undesirable changes, including low growth hormone and insulin-like growth factor 1 levels, poor nutrition, smoking, excessive alcohol intake, inactivity, certain illnesses, certain medications, genetic disposition, and perhaps aging itself. Thus, it is uncertain whether the signs and symptoms experienced by aging men are simply a consequence of the age-related decline in endogenous testosterone or whether these signs and symptoms are due to other factors. Without definitive evidence that raising testosterone concentrations in these men is beneficial and safe, the need to replace testosterone in aging men remains debatable.

In 2002, the National Institute on Aging and the National Cancer Institute commissioned the National Academies Institute of Medicine (IOM) to assess the state of clinical knowledge on testosterone therapy and provide recommendations on future research. This request was born out of evidence that growing numbers of middle-aged and older men were using TRT to delay or avert signs and symptoms of aging. At the time, findings from large placebo-controlled trials of hormone replacement therapy in postmenopausal women (Women's Health Initiatives) showed that hormone replacement, once thought to be beneficial as treatment and preventive measures in postmenopausal women, was, in fact, unfavorable in the overall balance of benefits and risks.

The IOM expert committee conducted a systemic review of the medical literature on TRT, focusing on placebo-controlled trials conducted in older men. In its 2004 report, the committee noted that there was a paucity of randomized controlled trials, especially in middle-aged and older men. Their literature review identified only 31 placebo-controlled trials of testosterone therapy in older men. Among those trials, the largest sample size was 108 participants. The duration of therapy in 25 of the 31 trials was 6

[3] Wu FC, Tajar A, Pye SR, et al. Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. J Clin Endocrinol Metab. 2008;93(7):2737.

[4] Harman SM, et al. Baltimore Longitudinal Study of Aging. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. J Clin Endocrinol Metab. 2001; 86(2):724.

months or less; only one placebo-controlled trial lasted longer than a year. These trials evaluated TRT effects on bone mineral density, body composition and strength, physical function, cognitive function, mood and depression, sexual function, quality of life, and cardiovascular-related and prostate safety outcomes. TRT's effects on these specific health measures were generally inconsistent, except for a trend of improvement in body composition (increases in lean body mass, decreases in fat mass) and increases in hematocrit. The IOM committee concluded that assessments of TRT's risks and benefits in aging men were limited, and the value of TRT in these men was uncertain.[5]

The 2010 Endocrine Society Clinical Practice Guidelines for Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes recommended against a general policy of offering TRT to all older men with low serum testosterone concentrations. The Guidelines suggested individualizing therapy to older men based on laboratory confirmation of low serum testosterone concentrations and clinically significant symptoms of androgen deficiency. The Guidelines, however, acknowledged that the treatment effect of TRT in this population is ill-defined and advised that physicians discuss the uncertainty of benefits and risks of TRT with these patients.[6]

To date, no large-scale, long-term clinical trials have been conducted to elucidate the benefits and risks of TRT in aging men. Based on the current state of knowledge, important questions remain: What is the extent to which hypogonadism occurs as part of the normal aging process? To what extent are the lower serum T levels in aging men clinically significant? Are typical changes with age in physiologic function consistent with hypogonadism requiring testosterone replacement therapy? Are there benefits to treating aging men? What are the risks of treatment?

4. Drug Utilization of TRT

Despite important uncertainties about the treatment effects of TRT in men with age-related hypogonadism, this patient population appears to constitute the majority of patients receiving TRT. The 2004 IOM report on testosterone therapy stated, "In recent years there has been growing concern about an increase in the use of testosterone by middle-aged and older men who have borderline testosterone levels—or even normal testosterone levels—in the absence of adequate scientific information about its risks and benefits." According to the IOM report, a cumulative 500 percent increase in prescription sales of testosterone was reported from 1993 to 2000. This trend has continued over the past decade, with several-fold increase in testosterone prescriptions from the early 2000's to 2011.[7] This past decade also saw widespread direct-to-consumer advertisement for TRT and non-branded disease awareness campaigns of 'low T' that imply benefits of TRT for health-related quality of life issues, such as improved sexual and physical function, targeted at aging men.

For Tracked Safety Issue (TSI) 865, the DEPI Drug Utilization review team examined drug use databases and analyzed US outpatient drug utilization trends for TRT from 2008 to 2013 stratified by age groups (0-39 years, 40-64 years, 65-74 years, and 75 years and older), concurrent use of TRT and select CV medications, claims for testosterone laboratory testing, and duration of drug use. Key findings follow:

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[5] Liverman, C, Blazer, D. (ed). Testosterone and Aging: Clinical Research Directions. Committee on Assessing the Need for Clinical Trials of Testosterone Replacement Therapy. National Academies Press, 2004

[6] 2010 Endocrine Society Clinical Practice Guidelines for Testosterone Therapy Adult Men with Androgen Deficiency Syndromes

[7] Baillargeon J, et al. Research Letter: Trends in Androgen Prescribing in the United States. JAMA Internal Medicine 2013: 173(15): 1465-1466.

- The use of TRT has increased significantly in the time period examined.
    - From 2009 to 2013, sales of TRT in terms of kilograms of active ingredient saw an increase of 66%, with approximately 8,500 kilograms sold in 2009 to 14,000 kilograms sold in 2013. Topical TRT products accounted for the greatest proportion of sales (71% of total sales), followed by injectable products (24%).[8]
    - In 2010, 1.3 million unique patients received an outpatient prescription for testosterone from a retail pharmacy, and by 2013, this number had risen to 2.3 million patients (76% increase). In 2013, the largest group of these TRT users is men 40 to 64 years of age, accounting for 69% of men who received a TRT prescription. The second largest age group receiving a TRT prescription is men 65 – 74 years old (14%), followed by men 0-39 years old (13%) and by men age 75 years and older (4%). Men ages 40 to 64 years also had the largest relative increase in TRT prescriptions, from approximately 850,000 in 2010, to 1.5 million patients in 2013 (78% increase).[9]

- Fifty-seven percent (57%) of patients prescribed TRT were also concurrently receiving prescriptions for one or more cardiovascular medications, such as anti-hypertensives, statins, and nitrates.
- Based on an office-based physician survey database, the leading diagnosis associated with a TRT prescription across all age groups was 'testicular hypofunction, not elsewhere classified' (International Classification of Diseases, Ninth Revision code 257.20).
- In a sample of commercially insured patients, 21% of patients who received a prescription for TRT did not have a claim for laboratory testing for testosterone at any time prior to or during TRT treatment. Another 6% of patients did not have a claim for testosterone laboratory testing prior to the first TRT prescription (but did have laboratory testing after receiving TRT prescription).[10] This is particularly concerning because the diagnosis of hypogonadism requires documented evidence of consistently low or absent serum testosterone concentrations prior to initiating TRT.
- In FDA's duration of use analysis, over a 5-year period examined, the mean and median cumulative duration of use was 6 months and 3 months, respectively.[10] This duration of use would not be expected for men with classic hypogonadism, who typically require lifelong testosterone replacement therapy.

Comment: *The Drug Utilization team's analyses provided the current landscape of the pattern of TRT use in the U.S. In summary, the use of TRT has increased considerably over the most recent 5 year-period examined. A significant majority of men prescribed TRT (~85%) are those between the ages of 40 and 74 years, and over one-half of TRT users are also concurrently prescribed CV medication(s). The most common diagnostic code associated with a TRT prescription (testicular hypofunction, not elsewhere specified) does not specify one of the well-recognized causes of hypogonadism. The average duration of use is relatively brief. In a sample of commercially insured patients from one database, approximately 25% of men who received TRT prescription did not have evidence of serum testing of T concentrations prior to the first TRT prescription. These findings portray a treatment population in current clinical practice consistent with age-related hypogonadism rather than classic hypogonadism.*

[8] Source: IMS Health, IMS National Sales Perspectives™. Years 2009 – 2013. Extracted April 2014

[9] Source: Symphony Health Solutions' Anonymous Patient Longitudinal Database. Years 2010 - 2013. Extracted May 2015

[10] Source: IMS Health Plan Claims Database. Reporting years 2008 – 2013. Extracted June 2014

5. Cardiovascular Safety of TRT

It is within the current context of the expanded use of TRT, particularly in those with age-related hypogonadism, that recent publications have reported a possible increased risk of adverse CV outcomes with TRT.

FDA evaluated this same safety signal under TSI 865 in 2010, following the premature discontinuation (due to CV safety concerns) of a randomized, double-blind, parallel group, placebo controlled efficacy trial of TRT in approximately 200 frail older men. Compared to placebo, the testosterone-treated group experienced a higher incidence of a variety of adverse events (25% in testosterone group vs. 5% in placebo) related to the cardiovascular system (e.g., peripheral edema, cardiac arrhythmias, myocardial infarction, stroke).[11] The Division of Cardiovascular and Renal Products (DCRP) reviewed these safety findings and concluded that the trial had several significant limitations, such as imbalances in baseline CV risk factors, pooling of diverse on-treatment CV events, and uncertainty regarding complete ascertainment of CV events that precluded a reliable assessment of the role of testosterone therapy in the CV events. DCRP's review also questioned whether the study results apply to the indicated population of TRT, namely those with classic hypogonadism. DBRUP also consulted FDA's Division of Epidemiology (DEPI) to review three published articles that addressed CV risks associated with testosterone therapy in hypogonadal patients (two meta-analyses of randomized, placebo-controlled clinical trials and one systematic qualitative review). DEPI concluded that the findings from these studies did not support an association between TRT and an increased risk of adverse cardiovascular outcomes. In January 2011, DBRUP determined that the overall safety information informing CV risk with testosterone therapy was insufficient to warrant a regulatory action and closed TSI 865.

In December 2013, FDA decided to reassess the potential risk of adverse CV outcomes associated with TRT under TSI 865 prompted by the publication of new observational studies suggesting such risk (see the FDA Drug Safety Communication published January 31, 2014).[12] The first new observational study included men who were undergoing coronary angiography for the assessment of coronary artery disease and who had low serum testosterone. Some of the men received TRT while others did not. This study reported a 30 percent increased risk of adverse cardiovascular events in patients who were prescribed testosterone therapy compared to non-users.[13] A second recent observational study reported a 2-fold increased risk of myocardial infarction (MI) in men 65 years and older, and nearly a 3-fold increase risk in younger men with pre-existing heart disease, in the first 90 days following a first prescription for TRT compared to the pre-TRT period.[14] Xu et al. published results of a meta-analysis of randomized, controlled trials (RCTs) of testosterone therapy and CV-related adverse events (CREs). Combining the results of 27 published RCTs analyzed at trial level, the meta-analysis found that testosterone therapy was associated with an increased odds ratio (OR=1.5) of CREs. Furthermore, the authors noted that the risk estimate was greater in non-industry funded studies than those funded by pharmaceutical companies (odds ratio 2.06 vs. 0.89).[15]

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[11] Basaria, et al. Adverse events associated with testosterone administration. N Engl J Med. 2010;363(2):109-122.

[12] FDA Drug Safety Communication: FDA evaluating risk of stroke, heart attack and death with FDA-approved testosterone products. January 31, 2014. http://www.fda.gov/downloads/Drugs/DrugSafety/UCM383909.pdf

[13] Vigen, R., et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA, 2013; 310, 1829-1836

[14] Finkel WD, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLoS ONE, 2014; 9(1): e85805.

[15] Xu, et al. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. BMC Med, 2013; 11, 108.

DEPI II, in collaboration with the Division of Biostatistics 7 (DB7) and in consultation with DCRP, reviewed the evidence from the above three studies, a 2014 meta-analysis of randomized placebo-controlled trials (Corona, 2014), and three retrospective cohort studies identified from a thorough literature search (Shores, 2012; Muraleedharan, 2013; Baillargeon 2014). In other words, FDA reviewed 5 retrospective cohort studies and 2 meta-analyses that informed CV safety with TRT. See reviews by the respective disciplines and by the CDTL of TSI 865 (David Moeny) for further details. The following discussion provides salient high level details and critical limitations of these studies.

5.1 Retrospective cohort studies

The five retrospective cohort studies are summarized in Appendix B and Appendix C. It is important to note that these studies differed in key aspects of their study designs. They used different databases, including U.S. commercial claims, Veterans Affairs medical data (2 studies, 1 with linkage to external data sources), clinic and hospital medical records in the United Kingdom, and U.S. Medicare. The definition of a CV outcome also varied, with some evaluating a composite CV endpoint (all-cause mortality, MI and stroke [Vigen]) or non-fatal MI (Finkle), while others studied a single endpoint of all-cause mortality (Shores, Muraleedharan), or hospitalization for MI (Baillargeon). The study patient populations were also dissimilar.

Taken together, findings from these 5 studies did not show a consistent trend in the effect of TRT on CV-related outcomes. Two studies found statistically significant CV harm with TRT (Vigen and Finkle), two studies found statistically significant all-cause mortality benefit with TRT (Shores and Muraleedharan) and one study found no significant change in risk of hospitalization for MI (Baillargeon).

> The Vigen study, conducted from 2005 to 2011, evaluated 8,709 male veterans post angiography with low testosterone levels (T levels less than 300 ng/dL) and found an increased risk in men who initiated TRT (N=1,223) compared to those who did not initiate TRT (N=7,486) for the composite cardiovascular outcome of MI, stroke, and death (hazard ratio of 1.29 [1.04, 1.58]).
>
> The Finkle study, evaluated over 55,000 TRT users in a large commercial claims database from 2006 to 2010 and found an increased risk of non-fatal MI in the 90-day post-TRT prescription period compared to the pre-TRT period (relative risk 1.36 [1.03, 1.81]). In particular, men 65 years and older had a doubling of risk for non-fatal MI with TRT (relative risk 2.19, [1.27, 3.77]) regardless of their history of heart disease, and men younger than 65 years with pre-existing heart disease had an approximate 3-fold increase in such risk (relative risk 2.90, [1.49, 5.62]).
>
> The Shores study, conducted from 2001 to 2005 in approximately 1,000 US male veterans older than 40 years old with low testosterone, found a decreased risk of all-cause mortality with TRT (N=398) compared to no TRT (N=633) (hazard ratio 0.61 [0.42, 0.88]).[16]
>
> The Muraleedharan study evaluated type 2 diabetic men in the United Kingdom from 2000 to 2005. The primary analysis assessed mortality in men with endogenous low serum testosterone concentrations compared to those with normal testosterone concentrations. The authors also performed a subgroup analysis of mortality in hypogonadal men treated with TRT compared to hypogonadal men not treated with TRT. In this subgroup, the authors found an increased risk of

[16] Shores MM, et al. Testosterone treatment and mortality in men with low testosterone levels. J Clin Endocrinol Metab 2012;97:2050-2058.

all-cause mortality in untreated hypogonadal men (N=174) compared to those on TRT (N=64) (HR 2.30 [1.30, 3.90]).[17]

The Baillargeon study, conducted in males older than 65 years enrolled in Medicare from 1997 to 2005, found that there was no overall increase in risk of hospitalization for MI when comparing those treated with TRT (N=6,455) to those with no treatment (N=19,065) (hazard ratio of 0.84 [0.69 -1.02]).[18]

Some studies explored factors that may predict TRT use. In the Shores and Muraleedharan studies where laboratory data were available for analysis, lower testosterone level was a predictor for TRT; in the Shores study, increased body mass index and younger age were also predictors of TRT use. The Baillargeon study did not use testosterone levels to select the cohort as no lab data were available from the claims data source, but clinical indication for TRT prescription (e.g., fatigue, hypogonadism, osteoporosis, sexual dysfunction) and increased comorbidity load were associated with TRT treatment. The findings from these three studies might indicate that testosterone was being used to treat men with lower baseline testosterone levels, or men with symptoms of hypogonadism, or both.

Comment: *Findings on factors that may predict TRT use suggest that men with low T levels prescribed TRT may differ from those who did not receive TRT. This makes it difficult to decipher the role of TRT in the differences in CV-related outcomes between TRT users and non-users for a given study.*

The results from the five retrospective cohort studies are difficult to integrate in a meaningful manner. The studies relied on diverse data sources, patient populations, formulations of testosterone, follow-up times, cardiovascular outcomes, and statistical methods to adjust for confounders or time varying covariates. Thus, none of the studies replicates the design of another study. It is unclear whether the differences in methodology, population characteristics, adverse outcome of interest, or random chance led to differences in findings.

Two major limitations with some or all of the five studies are particularly noteworthy. The first is the lack of data on clinical decision making involved in prescribing TRT, such as indication for TRT and disease severity. As mentioned, men prescribed TRT may differ in significant ways from those who did not receive TRT; therefore, these study results may be biased due to confounding by indication. An additional challenge related to this first limitation is the fact that there is no alternative treatment to TRT for male hypogonadism. In pharmacoepidemiology studies, it is preferable that the comparator group be exposed to an alternative drug treating the same disease as the drug being evaluated. In studies using a non-exposed comparator, the possibility of unmeasured confounding exists, despite having data on baseline characteristics and utilizing complex statistical modeling. The second limitation is the inability of these studies to separate the effect of TRT on CV risk from those of serum testosterone levels on CV risk. Testosterone levels over time affect both TRT dose prescribed and biomarkers associated with CV risk (e.g., serum HDL). In turn, TRT dose, adherence and effectiveness can affect testosterone levels over time. In order to examine both effects, a study would need to measure serum testosterone concentrations at baseline and during the study period for both the exposed and control patients.

[17] Muraleedharan V, et al. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. Eur J Endocrinol 2013;169:725-733.

[18] Baillargeon J, et al. Risk of Myocardial Infarction in Older Men Receiving Testosterone Therapy. Ann Pharmacother 2014

DEPI II and DB7 concluded that caution should be applied when interpreting the results of these 5 observational studies. The teams considered these studies to be reasonably well conducted retrospective observational studies and the cardiovascular outcomes of MI, stroke, and mortality are endpoints with high positive predictive values in claims, medical records databases and death registries. Nevertheless, because of differences in study design, conduct, and analysis, one cannot integrate in a meaningful manner the studies' findings into a single summary risk estimate. Further, due to the studies' major limitations, one could not reliably judge the role of TRT in these CV outcomes.

5.2 Meta-analyses of randomized controlled trials

***Xu et al*:** Combining the results of 27 published RCTs representing 2,994 men and 180 cardiovascular-related events (CREs), the authors found that TRT was associated with an increased odds of a CRE (OR 1.5 [1.1, 2.1]). When the analysis was restricted to serious CREs, the estimate was similar. The effect of testosterone therapy varied with source of funding (p-value for interaction 0.03). In non-industry funded trials, the odds ratio was greater (OR 2.1 [1.3, 3.2]) than in pharmaceutical industry-funded trials (OR 0.9 [0.5 to 1.6]).

DEPI II and DB7 noted the following limitations of the meta-analysis: Inconsistent and incomplete reporting of adverse events; substantial heterogeneity in the design and conduct of the component trials, and types of cardiovascular-related outcomes reported; potential bias resulting from selection of component trials; and variable quality of the trials, including ascertainment of cardiovascular safety outcomes. Both DBRUP and DCRP had specific concerns about the heterogeneity of the events pooled together as "CV-related" adverse outcomes. Such pooling of adverse events with widely varying severity and pathophysiology (for example, MI, esophageal rupture, and peripheral edema are pooled in the composite outcome) renders the aggregate result clinically uninterpretable. The noted discrepancy in CRE risk estimate based on funding source (non-industry versus industry funded) was based on a post-hoc analysis. The observed difference may have been due to chance or to differences in study design or adverse event reporting. DEPI II concluded that, because of substantial methodological limitations, this study has not provided convincing evidence of drug causality. Nevertheless, the results do contribute to the CV safety signal that may warrant additional investigation.

***Corona et al*:**[19] Whereas Xu et al. used a broadly-defined composite outcome of CV-related events, the Corona analysis focused on major adverse cardiac events (MACE), defined by the authors as CV death, non-fatal acute myocardial infarction and stroke, and acute coronary syndrome and/or heart failure reported as serious adverse events. Combining the results of 26 published RCTs, representing 3,236 men (N=1895 on testosterone; N=1341 on placebo) and 51 MACE, the authors found that TRT was not associated with an increased incidence of MACE relative to placebo (MH-OR 1.01 [0.57, 1.77]). Trial-level subgroup analyses also found no increases in MACE incidence associated with testosterone treatment in specific patient populations (e.g. trials restricted to patients with pre-existing CVD, associated diseases, frailty, or metabolic disease). Of note, 24 of the 26 trials analyzed in the Corona meta-analysis were also included in the Xu meta-analysis.

As with the case with the Xu study, DEPI II noted substantial limitations and potential biases in the Corona study inherent to the use of published data from trials not designed as CV safety studies. These

[19] Corona, et al. Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis. Expert Opin.Drug Saf., 2014; *13,* 1327-1351.

limitations and biases include undefined safety ascertainment procedures, lack of adjudication, and incomplete or selective reporting of events. Possible study arm imbalances in cardiac risk factors and high or unbalanced discontinuation rates in some trials created further uncertainty in the study's findings. Subgroup analyses were underpowered and were limited by the lack of patient-level data. Finally, given the subjective judgment inherent to the selection of composite studies to be included in a meta-analysis, author affiliations with industry cannot be ruled out as a possible bias factor. Therefore, given the above limitations, this study could not reliably exclude the role of TRT in adverse CV outcomes.

Comment: *I agree with DEPI's assessment of the available data informing CV safety associated with TRT. The role of TRT in the risk of adverse cardiovascular events is uncertain. As mentioned above, the available studies generating these data have major limitations. These studies differ in their fundamental study elements, such that their findings cannot be reliably compared or summarized as a whole. Because of their heterogeneity and significant limitations, the available epidemiological studies and meta-analyses are limited in their ability to provide the evidence needed to adequately answer the question of whether TRT confers an increased CV risk.*

Biologic plausibility: There is biologic plausibility underlying a contributory role of TRT in adverse CV outcomes. Current TRT class labeling contains the warnings on the following undesirable CV biomarkers: water retention and edema, adverse effects on lipids (mainly a decrease in HDL), polycythemia, and sleep apnea. Aging men with their co-morbidities may also be more vulnerable to these risks than younger men.

5.3 Actions by regulators and the professional societies on TRT and CV Risks

FDA: In February 2014, Public Citizen submitted a citizen petition requesting the addition of a boxed warning for CV risk for the class of TRT products and a delay in approval of a pending TRT NDA. This type of citizen petition (a "Q" petition) required a final response from FDA within 150 days. In July 2014, the Agency denied the citizen petition's request, as the review of the CV safety issue was still ongoing and the evidence provided by the petitioner did not justify the addition of a boxed warning for CV risks at the time.[20]

Health Canada (HC): In July 2014, Health Canada completed a safety review on testosterone replacement products. This review concluded that there is accumulating evidence (from published scientific literature and case reports received by Health Canada and foreign regulators) for serious and possible life-threatening heart and blood vessel problems such as heart attack, stroke, blood clot in the lungs or legs; and increased or irregular heart rate with the use of testosterone replacement products. Although these studies have limitations, HC believed that the available evidence suggests the possibility that cardiovascular problems, other than those already identified in labeling, may occur with the use of TRT. The agency also expressed concerns that the use of TRT in Canada has been increasing, and not always within the approved patient population. HC is working with manufacturers to update labeling to include a broad warning of 'cardiac and vascular risks' encompassing heart attack, stroke, blood clots in the lungs or legs, and increased or irregular heart rate.

European Medicines Agency (EMA): In October 2014, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) concluded that it did not find consistent evidence that TRT increases the risk of heart

20 http://www.citizen.org/documents/2184_FDA%20Denial%20of%20Petition_July%2016,%202014.pdf

problems. While some studies including three recently published studies did suggest an increased risk of heart problems in men using testosterone,[10,11,12] these studies had limitations, and other studies did not confirm this risk[13,14,15]. The PRAC recommended that TRT should only be used where low or absent testosterone has been confirmed by signs and symptoms and laboratory tests. The Coordination Group for Mutual Recognition and Decentralised Procedures concurred with the PRAC's recommendations, which will be implemented by the member states according to each state's individual timelines. The EU product information for all testosterone-containing medicines will be updated to include this recommendation, as well as warnings against use in men suffering from severe heart, liver or kidney problems. In addition, information regarding the limited data on safety and effectiveness of TRT in patients over 65 years old, and fact that testosterone levels decrease with age and that age-specific testosterone reference values do not exist will be highlighted in the product information.

Comment: *HC and the EMA reviewed essentially the same published evidence as FDA did for TSI 865. The different conclusions reached by HC and EMA not only underscore the conflicting data informing CV risks associated with TRT use, but also perhaps reflects differences in how TRT is actually being used in Canada compared to Europe. In its assessment, HC cited concerns of overuse or inappropriate use of TRT in aging men in Canada, whereas the EMA did not mention such concerns of TRT pattern of use in Europe. In general, regulatory decisions regarding a drug's safety do not only consider the evidence of safety in isolation. Such decisions are made based on the overall assessment of the drug's benefits and risks, within the context of the patient population using the drug. It may be that the differences in the context of TRT use between Canada and Europe contributed to HC and the EMA's disparate conclusions and regulatory action on the same safety issue.*

The Endocrine Society: In February 2014, the Endocrine Society issued a statement citing the Finkle, Vigen and Basaria studies as grounds for heightened concerns about the safety of TRT in older men with pre-existing heart disease. [11,13,14] The Endocrine Society advised that, "until evidence from large randomized controlled trials becomes available, patients should be made aware of the potential risk of CV events, especially middle age to older men who are taking or considering taking testosterone for age-related decline in testosterone concentrations and symptoms."

The American Urological Association (AUA): In February 2014, the AUA issued a position statement on TRT. It acknowledged that the evidence on CV outcomes with TRT is contradictory. The AUA stated that the diagnosis of hypogonadism should be determined by physicians appropriately trained to diagnose and treat this condition; that benefits and risks should be discussed with patients prior to treatment; and that patients on TRT should be appropriately monitored. The AUA statement concluded by encouraging increased educational awareness on the benefits and risks of TRT for both patients and healthcare providers.

6. Joint Advisory Committees meeting September 2014

A joint Advisory Committee meeting of BRUDAC and DsARM was convened on September 17, 2014, to discuss two main controversies surrounding TRT. The first issue was the identification of the appropriate patient population for whom TRT is indicated, based on the drug approval paradigm and other clinical evidence, and the second issue was the potential risk of major adverse cardiovascular events (MACE) associated with TRT use.

Appropriate indicated patient population: The AC panel was asked to consider whether the available scientific evidence and regulatory approval paradigm demonstrate the benefits of TRT in the types of patients currently being prescribed TRT in clinical practice. FDA staff presented the clinical drug development paradigm currently used to support FDA approval of a TRT product (section 2 of this memo), drug utilization trend (section 4 of this memo), and 'Low T' disease aware campaign targeted at middle age to older men suffering from common complaints of sexual dysfunction, reduced stamina and strength, and impaired cognition and concentration.

The following discussion point and voting question were posed to the joint AC Committees:

Discussion: The current approach to establishing the efficacy and safety of testosterone products for marketing approval is based upon pharmacokinetic assessments of serum testosterone concentrations and an acceptable safety profile. The product must be able to reliably raise low serum testosterone concentrations into the normal range for healthy, eugonadal men. FDA does not require a demonstration that testosterone products ameliorate or improve any specific hypogonadal sign or symptom.

- Describe the specific patient populations for which approval is supported based on data generated from this current approach.
- Discuss changes that would be needed in the current development paradigm to support an indication for testosterone replacement therapy in men with "age-related" hypogonadism.

Voting question: Should the FDA revise the current indication for testosterone therapies?

AC Discussion/Vote:
The joint AC committee agreed that the use of TRT in men with inherited or acquired loss of testosterone production in conjunction with a recognized disease condition ("classical hypogonadism") was supported by data. There was general consensus that the current paradigm for drug development is not capable of generating data in support of TRT for "age-related hypogonadism" nor has efficacy of TRT been established to treat such a condition. Some committee members expressed a concern that age-related hypogonadism had not yet been established as a disease condition, although two members opined that testosterone therapy may be justified in select older men with significant hypogonadal signs/symptoms and documented 'very low' serum testosterone concentrations (e.g., less than 100 ng/dL). However, even these two committee members recognized the need for additional research to assess the effectiveness of testosterone therapy for this patient population. The AC panel concluded that controlled clinical trials using meaningful clinical endpoints would be needed if a sponsor were to seek an indication for age-related hypogonadism in the future.

There was virtual unanimous agreement that FDA should revise the current indication for the class of testosterone replacement therapies (20 yes, 1 no). Committee members stated that the indication should limit testosterone replacement therapy to men with classical hypogonadism and clarify that the efficacy and safety of TRT for age-related hypogonadism have not been established. Further, the Committees recommended that labeling reflect the importance of proper testing of serum testosterone concentrations to confirm the diagnosis of hypogonadism.

Potential CV risk with TRT*:* The Committees were asked to discuss the potential for the risk of MACE attributable to TRT, taking into account the quality and strength of the evidence of CV safety with TRT. The AC panel was also asked to advise on whether to further evaluate the potential for CV risk with TRT. The FDA staff presented their review and assessment of the 5 retrospective cohort studies and the Xu

meta-analysis study (section 5 of this memo; the Corona article was published in August 2014 and could not be reviewed in time for the September AC meeting).

The following discussions point and voting question were posed to the joint AC Committees:

Discussion: Discuss whether the totality of the data indicates a cardiovascular safety signal associated with the use of testosterone therapy. Include in your discussion:

a. The strength of the signal.
b. Whether you believe the signal is restricted to a certain subset of the population using testosterone products (e.g., older men) or whether it applies to all users.
c. Whether the current evidence concerning the association of major adverse cardiovascular events and testosterone replacement therapy warrants inclusion in labeling.

Voting question:
Should FDA require sponsors of testosterone products to conduct a study (e.g., observational study, controlled clinical trial) to further assess a potential cardiovascular risk with the use of testosterone replacement therapy?

a. No, a study should not be required
b. Yes, but only for certain indication(s) for testosterone therapy. When explaining your vote, please specify which indication(s) should prompt the need for a cardiovascular study.
c. Yes, regardless of the indication for testosterone therapy

Please provide a rationale for your vote. If you voted yes (option B or C), discuss the type of study that should be required (e.g., observational study, controlled clinical trial). Include a discussion of the study population that should be enrolled as well as an acceptable degree of risk that would need to be excluded.

AC Discussion/Vote:
The AC panel acknowledged that the available studies informing CV safety with TRT are limited in design, quality, and scope. Nonetheless, the AC panel believed that a weak signal of CV risk has emerged from the recent large epidemiological studies; the biologic plausibility for CV-related adverse events (e.g., water retention, erythrocytosis) with TRT adds support to this signal. Thus, committee members expressed that the need for high quality studies evaluating CV safety of TRT was critical. Committee members further recommended that randomized controlled trials, rather than observational studies, be conducted to adequately address the question of CV risk with TRT. Although a majority (16 of 21) voted that such a trial be required for only certain indications, and specifically for an indication of age-related hypogonadism, some (4 of 21) believed that such trial should be required regardless of indication. This latter group believed that the use of TRT for age-related hypogonadism would continue despite labeling changes. The one committee member who voted "no" clarified that his vote was based on the wording of the question, which asks whether sponsors should conduct the study. He stated that such a study is needed but should be funded by NIH and not by the industry sponsors.

The committee members recommended that the labeling include a precautionary statement about the potential cardiovascular risk of testosterone therapy. Such warning should describe the known information about this potential risk, so that the prescriber and patients can be fully informed in their decision of whether to use or continue to use TRT.

7. Overall conclusions and recommendations

FDA-approved testosterone products are intended to replace absent or low endogenous testosterone concentrations caused by well-defined underlying etiologies. Over the past decade, the number of patients treated with testosterone has increased steadily, from hundreds of thousands into the millions. This market is dominated by middle aged to older men, most of whom are likely using TRT to treat age-related debilities such as diminished sexual capacity, loss of muscle mass and strength, and decline in cognitive function. Whether TRT provides clinically meaningful benefits in these men remain unknown. On the other hand, TRT is associated with some well-recognized risks and, recently, the potential signal of adverse CV outcomes has emerged.

After a careful review of the evidence and the AC panel's input, DBRUP and DEPI II concluded that labeling revisions and a CV safety trial were warranted for the class of TRT products.

Labeling Revisions: The teams recommend that the class INDICATION be revised to remove the term 'idiopathic' from the list of possible etiologies of secondary hypogonadism to prevent the misconception that 'idiopathic' can apply to all clinical situations where an etiology for hypogonadism has not been clearly defined, including age-related changes. The INDICATION will also include a limitation of use stating that safety and efficacy of TRT in men with age-related hypogonadism have not been established. The addition of this information to labeling is important as it accurately informs the extant evidence of potential benefits and harms of TRT in aging men. To address the concern that some men are being treated with TRT without confirmation of low serum testosterone concentrations, which is a key component of the diagnosis of hypogonadism, the DOSAGE AND ADMINISTRATION section of labeling will be revised to reflect the need for confirmatory laboratory testing of serum testosterone concentrations prior to initiating treatment. Lastly, a new WARNING of possible cardiovascular risk will be added to describe that some, but not all, studies have reported a signal for adverse CV outcomes associated with TRT. The aforementioned changes were applied to the labeling for all TRT products.

The Clinical Pharmacology and Clinical Studies sections for certain TRT products include text that could be construed as implied claims of benefit. For example, the Clinical Pharmacology section describes signs and symptoms of hypogonadism, such as sexual desire/function, fatigue, and depressed mood, which may imply that these symptoms will improve with testosterone, even though none of the TRT products carry such an indication. Similarly, the Clinical Studies section for some TRT products discusses improvement in body composition and libido/sexual function with TRT, even though substantial evidence of such benefit is lacking. The teams have recommended revisions to these two sections of labeling to ensure consistency with the approved indication.

Postmarketing Requirement Safety Trial: A majority of the advisory committee members recommended that a cardiovascular safety trial be required only with certain approved uses of testosterone, such as age-related hypogonadism. Although labeling changes will convey that the benefit and safety of testosterone have not been established for age-related hypogonadism, healthcare providers are still able to prescribe testosterone for uses that are not FDA approved, including age-related hypogonadism. FDA does not regulate off-label use, which is considered the practice of medicine. Therefore, the question of cardiovascular risk of testosterone in aging men remains relevant. Given the extensive use of testosterone in aging men, the unknown impact of labeling changes in limiting unapproved use in age-related hypogonadism, and the lack of substantial evidence of testosterone's benefits and risks for age-related hypogonadism, the cardiovascular safety signal in aging men is an important public health concern that warrants a thorough evaluation.

As discussed at the AC meeting, observational studies are unlikely to adequately resolve the question of whether TRT imparts a heightened risk of major adverse CV outcomes. For this specific safety question, these types of studies have significant inherent limitations that are difficult to overcome, such as the lack of an appropriate comparator, incomplete data on serum testosterone concentrations, and inadequate ascertainment of prescribing decision. The studies reporting CV risks with TRT have found risk estimate magnitudes of less than 2-fold. The potential for confounding by undiscernible or uncontrollable biases in observational studies will likely outweigh the magnitude of the relative CV risk of TRT, rendering results that are difficult to interpret. Therefore, the teams recommended a class postmarket required (PMR) placebo-controlled clinical trial with the primary objective of determining the effect of TRT on the incidence of major adverse cardiovascular outcomes (MACE). Key secondary endpoints should evaluate other important safety outcomes and clinical efficacy measures.

Comment: *We acknowledge the unique dilemma posed by conducting a safety trial in a population in whom the benefits of TRT have not been clearly established. It is also not known whether TRT definitively confers an increased CV risk. This situation is one of scientific uncertainty about both the harms and benefits of TRT in aging men - a clinical equipoise. According to the 2012 IOM report on Ethical and Scientific Issues in Studying the Safety of Approved Drugs, FDA is justified to require a postmarket safety trial if (1) a responsible regulatory decision cannot be made on the basis of existing evidence or evidence that could be obtained from new observational studies, (2) a trial can be properly designed and implemented to inform a responsible regulatory decision, (3) FDA will use the trial results in making a regulatory decision in a timely fashion, and (4) the trial can be carried out in a manner that provides sufficient protection of and respect for research participants. Interpretable data from a well-controlled clinical trial are necessary to provide the type of data which the Agency needs to rely upon to make responsible regulatory decisions regarding the safe and effective use of TRT in men, and especially in the largest group of men using TRT. FDA is experienced working with a variety of sponsors across various drug products on the design, conduct, analysis, and review of safety trials that evaluate MACE outcomes as the primary objective. Regarding ethical concerns of study subjects experiencing no benefit from TRT, there is equipoise for both benefit and risk and, even if no benefit is ultimately shown, participants could still benefit through improved clinical care in a trial setting. Potential study subjects could be fully informed as to why the study is required and why it is still ethically acceptable to ask them to participate (the risks and benefits of TRT are considered on equilibrium based on current evidence), provide voluntary informed consent, and be adequately protected against undue risks. Given the size and projected growth of the aging male population, public health interests would be served to characterize the treatment effects of TRT before more men are treated at considerable uncertainty of safety or benefit.*

Recommended Regulatory Action: I concur with the teams' recommendations. I recommend that safety labeling revisions and the PMR cardiovascular safety trial be required under the FDA Amendments Act (FDAAA) for the class of TRT products (**see ADDENDUM**).

ADDENDUM:

On February 9, 2015, FDA issued a Notification Letter informing holders of approved TRT NDAs of the labeling changes and PMR required under FDAAA. These requirements are described below.

PMR: Sponsors are required to conduct a randomized, double-blind, placebo-controlled clinical trial to evaluate the effect of testosterone replacement therapy on the incidence of major adverse cardiovascular events in men. We recommend that this trial also assess other important safety and efficacy outcomes associated with testosterone therapy. The proposed timetable follows:

Final Protocol Submission: 06/2016
Trial Completion: 06/2021
Final Report Submission: 06/2022

Comment: On March 9, 2015, FDA held a teleconference with all the sponsors required to conduct the PMR. FDA informed the sponsors of the expectations regarding the design, conduct, and analysis of the PMR and encouraged that sponsors collaborate in fulfilling the PMR. FDA requested that a study synopsis and an initial study protocol be submitted for review by July and October, 2015, respectively.

Labeling Changes: For all TRT products, labeling changes affected the following sections: Indications and Usage, Dosage and Administration, Warnings and Precautions, and Adverse Reactions/Postmarketing Experience. For selected TRT products, the Clinical Pharmacology and Clinical Trials sections also required labeling changes.

The changes described below pertain to the FULL PRESCRIBING INFORMATION, although summary statements of these changes were also added to HIGHLIGHTS. Additions are noted by underline and deletions are noted by ~~strikethrough.~~

INDICATIONS AND USAGE:

Hypogonadotropic hypogonadism (congenital or acquired): ~~idiopathic~~ gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency…

Limitations of use:
Safety and efficacy of DRUG in men with [redacted] (b) (4)

DOSAGE AND ADMINISTRATION:

Prior to initiating DRUG, 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.

WARNINGS AND PRECAUTIONS:

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 DRUG.

ADVERSE REACTIONS
Postmarketing Experience: Cardiovascular Disorders – Myocardial infarction, stroke

Some TRT products have text in the Clinical Pharmacology section that could be construed as implied claims of benefit. This text was revised as follows:

CLINICAL PHARMACOLOGY:
Mechanism of Action
…. Testosterone and DHT are necessary for the normal development of secondary sex characteristics. ~~Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone concentrations. Signs/symptoms associated with male hypogonadism include erectile dysfunction and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics and osteoporosis.~~

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).

For two TRT products (Androgel 1% and Testim), portions of the Clinical Studies section that include efficacy claims unsupported by substantial evidence were deleted.

CLINICAL STUDIES (Androgel 1%)
~~AndroGel 1% 50 mg/day and 100 mg/day resulted in significant increases over time in total body mass and total body lean mass, while total body fat mass and the percent body fat decreased significantly. These changes were maintained for 180 days of treatment during the original study.~~
~~Changes in the 75 mg dose group were similar. Bone mineral density in both hip and spine increased significantly from Baseline to Day 180 with AndroGel 1% 100 mg.~~

~~AndroGel 1% treatment at 50 mg/day and 100 mg/day for 90 days produced significant improvement in libido (measured by sexual motivation, sexual activity and enjoyment of sexual activity as assessed by patient responses to a questionnaire). The degree of penile erection as subjectively estimated by the patients, increased with AndroGel 1% treatment, as did the subjective score for "satisfactory duration of erection." AndroGel 1% treatment at 50 mg/day and 100 mg/day produced positive effects on mood and fatigue. Similar changes were seen after 180 days of treatment and in the group treated with the 75 mg dose.~~

CLINICAL STUDIES (Testim)
~~At Day 30, patients receiving Testim 100 mg daily showed significant improvement from baseline in multiple sexual function parameters as measured by patient questionnaires when compared to placebo. These parameters included sexual motivation, sexual desire, sexual activity and spontaneous erections. For Testim 100 mg, improvements in sexual motivation, spontaneous erections, and sexual desire were maintained through Day 90. Sexual enjoyment and satisfaction with erection duration were improved compared to baseline but these improvements were not significant compared to the placebo group.~~

~~In Testim-treated patients, the number of days in which sexual activity was reported to occur increased by 123% from baseline at Day 30 and was still increased from baseline by 59% at Day 90. The number of days with spontaneous erections increased by 137% at Day 30 and was maintained at 78% at Day 90 for Testim-treated patients compared to baseline.~~

~~Table 3 summarizes the changes in body composition at Day 90 for patients receiving Testim 50 mg or 100 mg as measured by standardized whole body DEXA (Dual-Energy Xray Absorptiometry) scanning.~~
(Delete Table 3 below):

Table 3: Effect of Testim on Lean Body Mass, Total Fat Mass and % Body Fat

Days of Treatment	Lean Body Mass (Muscle) (kg)	Total Fat Mass (kg)	% Body Fat
Baseline	61.6	29.4	30.9
Day 90	63.3	28.6	29.8
Change from Baseline	↑1.6	↓0.8	↓1.1

~~At Day 90, mean increases from baseline in lean body mass and mean decreases from baseline in total fat mass and percent body fat in Testim-treated patients were significant when compared to placebo-treated patients~~.

Sponsors of approved NDA holders accepted all the above labeling changes, with the exception of the following:

> Limitations of use:
> Safety and efficacy of DRUG in men with age-related hypogonadism have not been established. Age-related hypogonadism refers to men with serum testosterone concentrations below the normal range for no apparent reason other than age, and who experience signs and symptoms of aging that overlap with those of hypogonadism.

The final agreed upon changes to this section follow:

> Limitation of Use:
> Safety and efficacy of DRUG in men with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established.

***Comment*:** *After receiving the sponsors' feedback, the teams concluded that "age-related hypogonadism," which is also known as "late-onset hypogonadism" among the professional groups with expertise in this area, is not a well-defined clinical condition at this time. Therefore, it would be premature to define age-related hypogonadism in labeling.*

8. Appendices

Appendix A: FDA-approved Testosterone Replacement Therapy covered under TSI 865

NDA #	Tradename	Formulation
21015	Androgel 1%	Topical gel
22309	Androgel 1.62%	Topical gel
21454	Testim	Topical gel
21463	Fortesta	Topical gel
203098	Testosterone gel (Perrigo)	Topical gel
202763	Testosterone gel (Teva)	Topical gel
204399	Vogelxo	Topical gel
22504	Axiron	Topical gel
20489	Androderm	Transdermal patch
22219	Aveed	Intramuscular injection
09165	Delatestryl	Intramuscular injection
205488	Natesto	Intranasal solution
21543	Striant	Buccal tablet

Appendix B: Summary of study designs of the observational Studies

Table 1 – Summary of study designs

Design Features	Finkle et al., 2014	Vigen et al., 2013	Shores et al., 2012	Muraleedharan et al., 2013	Baillargeon et al., 2014
Objectives/ Aims/Scope	TRT and non-fatal MI in males	TRT and [all-cause mortality, MI and stroke] in males with low T[1] who underwent angiography	TRT and Mortality, in male veterans with low T[1]	TRT and mortality in males with low T[1] and type II diabetics	TRT and MI in older males
Exposure/ Intervention	Testosterone (gels, topicals, injections, micronized)	Testosterone (patch, gels, injections)	Testosterone	Testosterone (gels, buccal tablets, injections)	Intramuscular testosterone
Outcome(s)	Non-fatal MI (first event)	Composite: All-cause mortality, MI and stroke (first event)	Mortality	All-cause mortality	Hospitalization for MI (first event)
Comparisons of interest	(a) Self-control cohort: time pre TRT vs. time post TRT (b) TRT vs. PDE5-I	Users to non-users	Users to non-users	Users to non-users	Users of TRT to non-users (1:3)
Strengths	Large sample size Self-controlled cohort study can control for measured and unmeasured confounders	Large sample size Testosterone levels used to select the cohort	Testosterone levels used to select the cohort	Claims and medical records data Testosterone levels used to select the cohort	Large Sample Size Long follow up period Representation of all US geographic regions
Limitations	Testosterone levels not available in this database Reasons for initiating treatment unknown Short follow up time Possible prescribing bias in self-control cohort Lack of comparability of TRT to PDE5I in parallel cohort Unclear propensity weighting scheme in parallel cohort	Unknown cause of death Reasons for initiating treatment unknown Possible selection bias due to exclusion of events pre-TRT Possible misclassification bias of exposure Time on treatment not accounted for in ITT analysis	Excluded more recent data Small sample size Reasons for initiating treatment unknown Time on treatment not accounted for in ITT analysis	Excluded more recent data Small sample size Possible misclassification bias of exposure Time on treatment not accounted for in ITT analysis	Excluded more recent data Included only injections and not more recent formulations of TRT Could not include testosterone level (as baseline factor to define hypogonadism or risk factor for MI)

Abbreviations: TRT=Testosterone replacement therapy, MI=Myocardial infarction, Low T= Low testosterone, PDE5-I = phosphodiesterase 5 inhibitor, ITT=Intention to treat

Source: FDA Briefing Package, p. 28/209 (taken from Dr. Monique Falconer's review, Table 1, p. 7/9)

Appendix C: Summary comparisons of study design features and results of the observational studies

Table 2: Summary comparisons of study design features and results

Design Features	Finkle, 2014	Vigen, 2013	Shores, 2012	Muraleedharan, 2013	Baillargeon, 2014
Design Type	Retrospective self-control cohort (SCC) Retrospective cohort with parallel group (TRT & PDE5-I)	Retrospective cohort	Retrospective cohort	Retrospective cohort (TIMES2 trial follow-up)	Retrospective cohort
Data Source	Commercial claims database (MarketScan) in the US	VA clinical database in the US	VA clinical database, with linkage to outside death index data	Clinic and hospital medical records in the UK	5% national sample of Medicare in the US
Time Period	2006-2010	2005-2011	2001-2005	2000-2005	1997-2005
Study outcome	Non-fatal MI (first event)	Composite: All-cause mortality, MI and stroke (first event)	All-cause mortality	All-cause mortality deaths within 6 months of start to follow up excluded	Hospitalization for MI (first event)
Exposure cohorts/ Sample Size	⊕TRT: n=55,598 ⊕PDE5-I: n=167,279 (weighted 141,031)	⊕TRT: n=1,223 ∅TRT: n=7,486	⊕TRT: n=398 ∅TRT: n=633	⊕TRT: n=64 ∅TRT: n=174	⊕TRT: n=6,455 ∅TRT: n=19,065
Criterion (Selection) Standards	Males with ≥ 22 months continuous database enrollment and 90-days post treatment initiation	Male veterans post angiography, with low T (<300ng/dL)	Male veterans >40 years old with low T (<250ng/dL)	Type 2 diabetic males with low T (<300ng/dL) and at least 1 year of TRT	Males > 65 years enrolled in Medicare Part A and Part B for at least 12 months and no end-stage renal disease
Statistical Methods	Pre-TRT: 1 year; Post-TRT: 90 days SCC: Post/pre RR Parallel cohort: Propensity score weighting ATT(5) to estimate RR and weighted Poisson regression to estimate ratio of rate ratios (RRR)	Cox regression with stabilized inverse probability of treatment weights HR (95%CI); Weighted Kaplan Meier survival curves	Cox regression, with Time-varying TRT HR (95%CI); Unadjusted Kaplan Meier Curves; (Propensity score analysis [exploratory analysis])	Cox regression analysis HR (95%CI); Kaplan Meier Curves	Cohort selection: matching on author's developed MI prognostic score at baseline Analysis of outcome: Cox regression analysis HR (95% CI)
Follow up (FU) and Treatment Duration (TD)	FU: ≤ 90 days after 1st Rx	FU, Average: 27.5 months Average TRT TD: ~ 10-months	Average FU: 40 months Average TRT TD: 20-months	Average FU: 6 years Average TRT duration: 42-months (85% of cohort >24 months)	Average FU: ~ 3.5 years Median number of injections in study: 2.5
Primary Results Risk Estimate and (95% CI)	Post/Pre TRT, RR Overall: 1.36 (1.03, 1.81) <65 years: 1.17 (0.84, 1.63) ≥65 years: 2.19 (1.27, 3.77)	Intent to Treat 1.29 (1.04 , 1.58)	Intent to Treat: HR 0.61 (0.42, 0.88)	Intent to Treat HR 0.43 (0.26, 0.77)	Intent to Treat: HR (0.84 (0.69 – 1.02)

Abbreviations: SCC=Self Control Cohort, VA = Veterans Affairs, UK=United Kingdom, MI=Myocardial infarction, TRT=Testosterone replacement therapy, Low T= Low testosterone, PDE5-I= Phosphodiesterase 5 inhibitor, FU= follow up, RR= Rate Ratio, HR=Hazard Ratio, MI=Myocardial Infarction, TD=Treatment duration

Source: FDA Briefing Package, p. 29/209 (taken from Dr. Monique Falconer's review, Table 2, p. 8/10)

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/s/

CHRISTINE P NGUYEN
05/11/2015

HYLTON V JOFFE
05/11/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022219/S-005

OTHER REVIEW(S)

Division of Bone, Reproductive and Urologic Products

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	Date of Labeling Amendment #2	REMS modification
021015 S-40	AndroGel® 1%	AbbVie, Inc.	2/9/15	3/10/15	4/10/15		yes
022309 S-14	Androgel 1.62%	AbbVie, Inc.	2/9/15	3/10/15	4/10/15		yes
020489 S-33	Androderm®	Watson Laboratories, Inc.	2/9/15	3/9/15	4/10/15		no
022504 S-12	Axiron®	Eli Lilly and Company	2/9/15	3/11/15	4/10/15		yes
021543 S-11	Striant®	Auxillium	2/9/15	3/9/15	4/10/15		no
021454 S-23	Testim®	Auxilium	2/9/15	3/9/15	4/10/15		yes
202763 S-03	Testosterone Gel 1%	Teva	2/9/15	3/4/15	4/22/15		yes
022219 S-05	Aveed	Endo	2/9/15	3/6/15	4/10/15		no
09165 S-33	Delatestryl®	Endo	2/9/15	3/6/15	4/10/15		no
203098 S-06	Testosterone Gel 1%	Perrigo	2/9/15	2/24/15	4/22/15		yes
204399 S-02	Vogelxo	Upsher-Smith	2/9/15	3/6/15	4/24/15		yes
205488 S-01	Natesto	Endo Ventures	2/9/15	3/6/15	4/10/15		no
021463 S-17	Fortesta	Endo	2/9/15	3/6/15	4/10/15		yes

Background and Summary Description:

In December 2013, Tracked Safety Issue #865 was opened for a multi-disciplinary review of the safety signal of adverse cardiovascular (CV) events associated with testosterone replacement therapy (TRT). Concurrently, FDA also evaluated the expanded use of TRT in middle-aged and older men, in whom the need for treatment with TRT is uncertain. In September 2014, FDA convened a joint Advisory Committee (AC) meeting of the Bone, Reproductive, and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss the appropriate indicated population for TRT and the CV safety signal. After reviewing the evidence of CV safety and considering the AC panel's recommendations, FDA concluded that labeling revisions to address the indicated population and CV safety were warranted for the class of TRT products. Refer to the Cross-Discipline Team Leader's memo (David Moeny, dated, December 11, 2014) and the Decisional Memo (Christine Nguyen, dated May 11, 2015) for more details.

On February 9, 2015, DBRUP issued safety labeling change notification letters under the Food and Drug Administration Amendments Act (FDAAA), requiring class changes to various sections of labeling. Corresponding changes were also required in the Medication Guide (MG) or Patient Package Inserts (PPI), for all 13 approved testosterone products. The specific labeling changes are stated below.

Following discussions with each sponsor, one revision to the February 2015 FDAAA letter was made to the Limitation of Use statement regarding age-related hypogonadism (see below in the section entitled 'Modified Text Agreed To By All Sponsors"). All sponsors agreed to the final revised language and submitted the required labeling supplements by April 24, 2015.

February 2015 FDAAA Safety Labeling Change (SLC) Notification Letter:

In HIGHLIGHTS (for labels in PLR format only)

Under INDICATIONS AND USAGE:

- DRUG NAME is ~~an androgen~~ indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone (b) (4)):
- (b) (4) Limitations of use: Safety and efficacy of DRUG NAME in men with age-related hypogonadism have not been established.

Under DOSAGE AND ADMINISTRATION:

- Prior to initiating DRUG NAME, 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.X).

Under WARNINGS AND PRECAUTIONS:

This new bullet follows the 'Venous thromboembolism (VTE)' bullet:

- Some postmarketing studies have shown an increased risk of myocardial infarction and stroke associated with use of testosterone replacement therapy. (5.X)

TABLE OF CONTENTS

- Update the TABLE OF CONTENTS to reflect the changes in the FULL PRESCRIBING INFORMATION.

FULL PRESCRIBING INFORMATION

Under INDICATIONS AND USAGE (where appropriate):

- DRUG NAME ~~an androgen~~ indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

(b) (4)

Under DOSAGE AND ADMINISTRATION (for both PLR and non-PLR labels):

- (b) (4)
- Prior to initiating DRUG NAME, 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.

Under Warnings and Precautions (PLR) or Warnings (non-PLR) add new bullet, as follows:

- 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 DRUG NAME.

Under ADVERSE REACTIONS (for both PLR and non-PLR labels):

- Postmarketing Experience: Add new Organ Class "Cardiovascular disorders:" followed by "myocardial infarction, stroke".

Under CLINICAL PHARMACOLOGY (for selected PLR labels only, when appropriate):

- 12.1 Mechanism of Action: …. Testosterone and DHT are necessary for the normal development of secondary sex characteristics. ~~Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone concentrations. Signs/symptoms associated with male hypogonadism include erectile dysfunction and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics and osteoporosis.~~

  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).

Under CLINICAL STUDIES (only for Androgel 1% and Testim):

- Delete the following portions of the Clinical Studies section that contain efficacy claims unsupported by substantial evidence:

CLINICAL STUDIES (for Androgel 1%)

~~AndroGel 1% 50 mg/day and 100 mg/day resulted in significant increases over time in total body mass and total body lean mass, while total body fat mass and the percent body fat decreased significantly. These changes were maintained for 180 days of treatment during the original study. Changes in the 75 mg dose group were similar. Bone mineral density in both hip and spine increased significantly from Baseline to Day 180 with AndroGel 1% 100 mg.~~

~~AndroGel 1% treatment at 50 mg/day and 100 mg/day for 90 days produced significant improvement in libido (measured by sexual motivation, sexual activity and enjoyment of sexual activity as assessed by patient responses to a questionnaire). The degree of penile erection as subjectively estimated by the patients, increased with AndroGel 1% treatment, as did the subjective score for "satisfactory duration of erection." AndroGel 1% treatment at 50 mg/day and 100 mg/day produced positive effects on mood and fatigue. Similar changes were seen after 180 days of treatment and in the group treated with the 75 mg dose.~~

CLINICAL STUDIES (for Testim)

~~At Day 30, patients receiving Testim 100 mg daily showed significant improvement from baseline in multiple sexual function parameters as measured by patient questionnaires when compared to placebo. These parameters included sexual motivation, sexual desire, sexual activity and spontaneous erections. For Testim 100 mg, improvements in sexual motivation, spontaneous erections, and sexual desire were maintained through Day 90. Sexual enjoyment and satisfaction with erection duration were improved compared to baseline but these improvements were not significant compared to the placebo group.~~

~~In Testim-treated patients, the number of days in which sexual activity was reported to occur increased by 123% from baseline at Day 30 and was still increased from baseline by 59% at Day~~

~~90. The number of days with spontaneous erections increased by 137% at Day 30 and was maintained at 78% at Day 90 for Testim-treated patients compared to baseline.~~

~~Table 3 summarizes the changes in body composition at Day 90 for patients receiving Testim 50 mg or 100 mg as measured by standardized whole body DEXA (Dual-Energy Xray Absorptiometry) scanning.~~

Delete the following table

Table 3: Effect of Testim on Lean Body Mass, Total Fat Mass and % Body Fat			
Days of Treatment	**Lean Body Mass (Muscle) (kg)**	**Total Fat Mass (kg)**	**% Body Fat**
Baseline	61.6	29.4	30.9
Day 90	63.3	28.6	29.8
Change from Baseline	↑1.6	↓0.8	↓1.1

~~At Day 90, mean increases from baseline in lean body mass and mean decreases from baseline in total fat mass and percent body fat in Testim-treated patients were significant when compared to placebo-treated patients~~.

MEDICATION GUIDE (for products with MGs only)

In addition to the changes described above, revise the Medication Guide to include the new safety information for DRUG NAME, as follows:

Under **"What is DRUG NAME?"**

> DRUG NAME is a prescription medicine that contains testosterone. DRUG is used to treat adult males who have low or no testosterone <u>due to certain medical conditions</u>.
>
> Your healthcare provider will test your blood before you start and while you are taking DRUG NAME.
>
> <u>It is not known if DRUG NAME is safe or effective to treat men who have low testosterone due to aging</u>.
>
> It is not known if DRUG NAME is safe or effective in children younger than 18 years old. Improper use of DRUG NAME may affect bone growth in children.

Under **"What are the possible side effects of DRUG NAME?"**

DRUG NAME can cause serious side effects including:

- If you already have enlargement of your prostate gland your signs and symptoms…
- Possible increased risk of prostate cancer…

- 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 DRUG NAME may lower your sperm count.
- Swelling of your ankles, feet, or body, with or without heart failure.
- Enlarged or painful breasts.
- Have problems breathing while you sleep (sleep apnea).

PATIENT PACKAGE INSERT (for products with PPIs):

Under **"What is DRUG NAME?"**

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

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

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

It is not known if DRUG NAME is safe or effective in children younger than 18 years old. Improper use of DRUG NAME may affect bone growth in children.

Under **"What are the possible side effects of DRUG NAME?"**

DRUG NAME can cause serious side effects including:

- If you already have enlargement of your prostate gland your signs and symptoms…
- Possible increased risk of prostate cancer…
- Blood clots in the legs or lungs…
- Possible increased risk of heart attack or stroke.
- In large doses DRUG NAME may lower your sperm count.
- Swelling of your ankles, feet, or body, with or without heart failure.
- Enlarged or painful breasts.
- Have problems breathing while you sleep (sleep apnea).

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

In HIGHLIGHTS under INDICATIONS AND USAGE, Limitations of Use (for labeling in PLR format):

Added Quotes around "age-related hypogonadism"

Added the following text "age-related hypogonadism" (b) (4)) have not been established.

Differences in labeling between the February 2015 SLC letter and the final label agreed to by all sponsors are shown here (Indications and Usage section, Limitation of Use subsection, additions shown as underline, and deletion as ~~strikethrough~~).

- Safety and efficacy of DRUG NAME in men with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established.- (b) (4)

Review

The final agreed upon labeling, for all the aforementioned testosterone products, were received by April 24, 2015, 2015, and are consistent with the agreed upon labeling changes (also see Decisional Memo (Christine Nguyen, dated May 11, 2015)

Recommendations

The proposed labeling changes for all 13 testosterone products are consistent with the safety labeling changes requested on February 9, 2015, and modified via email to the sponsors on March 27 and April 17, 2015, and recommended by DBRUP. Approval letters for all 13 products should be issued.

_____

Meredith Alpert, MS
Safety Regulatory Health Project Manager
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Supervisory Comment/Concurrence:

_____

Suresh Kaul, MD, MPH
Urology Team Leader
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

_____

Mark Hirsch, MD
Urology Team Leader
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

MEREDITH ALPERT
05/11/2015

SURESH KAUL
05/11/2015
Signing for NDA 22504 (Axiron), NDA 203098 (Testosterone 1% Gel), NDA 20489 (Androderm), NDA 204399 (Testosterone Gel 1%).

MARK S HIRSCH
05/11/2015
Signing for the remaining nine NDA supplements.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022219/S-005

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022219/S-005

LABELING DISCUSSION EXTENSION

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

Dear Ms. Clark:

Please refer to your March 6, 2015, Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Aveed (testosterone undecanoate) injection.

On February 9, 2015, we sent a letter invoking our authority under section 505(o)(4) of the FDCA to require changes to the labeling of Aveed based upon new safety information identified since the product was approved. You were directed to submit a supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

On March 6, 2015, we received your prior approval supplement containing your proposed safety related labeling changes, including changes to the Medication Guide. Section 505(o) requires FDA to promptly review the supplement. If we need additional time to harmonize the language across the drug class, we would extend the time to allow potential discussions with you, should the content of the labeling changes need further revisions. These discussions were to be completed within 30 days, unless FDA determined that an extension was warranted.

This letter is to inform you that we have determined that a 30-day extension of the discussion period is warranted to allow us to complete our review and reach agreement on the content of the labeling. Therefore, the discussion period for this supplement ends on May 5, 2015.

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

Sincerely,

{See appended electronic signature page}

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

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
03/24/2015