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” have not been established.
- Safety and efficacy of AVEED® in males less than 18 years old have not been established.

IMPORTANT SAFETY INFORMATION about AVEED®

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.
- 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.
- 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.

CONTRAINDICATIONS

- Men with carcinoma of the breast or known or suspected carcinoma of the prostate.
- Women who are or may become pregnant, or who are breastfeeding. Testosterone can cause fetal harm when administered to a pregnant woman. 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.
- Men with known hypersensitivity to AVEED or any of its ingredients (testosterone undecanoate, refined castor oil, benzyl benzoate).
WARNINGS AND PRECAUTIONS

• 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.

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.
• **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.

• **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.

• **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.

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

• **Cardiovascular Risk** - Some postmarketing studies have shown an increased risk of major adverse cardiovascular events (MACE) with use of testosterone replacement therapy. Patients should be informed of this possible risk when deciding to use or to continue to use AVEED.

• **Use in Women** - Due to lack of controlled evaluations in women and potential virilizing effects, AVEED is not indicated for use in women.

• **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.

• **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 hepatitis, hepatic neoplasms, cholestatic hepatitis, and jaundice). Peliosis hepatitis 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.
• **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.

• **Gynecomastia** - Gynecomastia occasionally develops and occasionally persists in patients being treated for hypogonadism.

• **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.

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

• **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.

• **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.

• **Laboratory Monitoring** - Monitor prostatic specific antigen (PSA), hemoglobin, hematocrit, and lipid concentrations at the start of treatment and periodically thereafter.

**ADVERSE REACTIONS**

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, injection site pain, prostate specific antigen increased, hypogonadism, estradiol increased, fatigue, irritability, hemoglobin increased, insomnia, and mood swings.

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.

• **Postmarketing Experience**

  **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.

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.

**DRUG INTERACTIONS**

• **Insulin** - Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, may necessitate a decrease in the dose of anti-diabetic medication.
• **Oral Anticoagulants** - Changes in anticoagulant activity may be seen with androgens, therefore more frequent monitoring of international normalized ratio (INR) and prothrombin time are recommended in patients taking warfarin, especially at the initiation and termination of androgen therapy.

• **Corticosteroids** - The concurrent use of testosterone with corticosteroids may result in increased fluid retention and requires careful monitoring, particularly in patients with cardiac, renal or hepatic disease.

**USE IN SPECIFIC POPULATIONS**

• **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. There are insufficient long-term safety data in geriatric patients to assess the potential risks of cardiovascular disease and prostate cancer.

**DRUG ABUSE**

AVEED contains testosterone undecanoate, a Schedule III controlled substance in the Controlled Substances Act. Anabolic steroids, such as testosterone, are abused. Abuse is often associated with adverse physical and psychological effects.

Please see accompanying full Prescribing Information, including Boxed Warning.
IMPORTANT SAFETY INFORMATION FOR CONSUMERS

What is the most important information I should know about AVEED® (testosterone undecanoate) injection, for intramuscular use CIII?

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.

**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.

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 allergic to AVEED or to any of the ingredients in AVEED (testosterone undecanoate, castor oil, benzyl benzoate), are pregnant, may become pregnant, or are breastfeeding.

- AVEED may harm your unborn or breastfeeding baby.

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

How will I receive 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.
- 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.
- 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, or 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).
- blood clots in the legs or lungs. This can include pain, swelling or redness of your legs, difficulty breathing, or chest pain.
- possible increased risk of heart attack, death, or stroke.
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, or 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.

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

Please see full Prescribing Information, including Boxed Warning and Medication Guide for patients.