

Initial REMS Approval: 03/2014

NDA 22-219 AVEED™ (testosterone undecanoate) CIII

Class of Drug: Androgen

Endo Pharmaceuticals Solutions Inc.
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**RISK EVALUATION
AND MITIGATION STRATEGY (REMS)**

I. GOALS:

The goals and the objectives of the AVEED REMS are to mitigate the negative outcomes associated with AVEED-induced pulmonary oil microembolism (POME) and anaphylaxis by:

- Ensuring that AVEED is dispensed only in certified healthcare settings that have immediate access on-site to equipment and personnel trained to manage POME and anaphylaxis;
- Informing healthcare providers that AVEED can cause POME and anaphylaxis, which have the potential to lead to serious medical consequences (e.g., respiratory distress and syncope);
- Informing healthcare providers about the safe use of AVEED, including proper administration technique and patient observation; and
- Informing patients about the risks of POME and anaphylaxis associated with AVEED and the importance of remaining at the healthcare setting for 30 minutes after each injection.

II. REMS ELEMENTS:

A. Elements to Assure Safe Use

1. Healthcare providers who prescribe AVEED are specially certified.

- a. Endo Pharmaceuticals Solutions Inc. (Endo) will ensure healthcare providers who prescribe¹ AVEED are specially certified.
- b. To become specially certified to prescribe AVEED, healthcare providers must:
 - i. Review the Prescribing Information for AVEED;

¹ For the purposes of this REMS, the term “prescribe” and “prescription” include medication orders.

- ii. Complete the *AVEED REMS Education Program for Healthcare Providers (with Knowledge Assessment)*;
 - iii. Agree to provide a copy of the *What You Need To Know About AVEED Treatment: A Patient Guide* to each patient and review it with patients to inform them about the risks associated with AVEED, including POME and anaphylaxis, and the need to remain at the healthcare setting for 30 minutes following each AVEED injection;
 - iv. Acknowledge that they understand how to administer AVEED properly;
 - v. Acknowledge that they understand how to manage POME and anaphylaxis;
 - vi. Acknowledge that their healthcare setting must be a certified healthcare setting enrolled in the AVEED REMS Program;
 - vii. Agree that each patient will be observed in their certified healthcare setting for 30 minutes after each AVEED injection; and
 - viii. Complete and sign the *Healthcare Provider Enrollment Form* and submit it to the AVEED REMS Program.
- c. Endo will:
- i. Ensure that healthcare providers complete the *AVEED REMS Education Program for Healthcare Providers (with Knowledge Assessment)* and complete the *AVEED REMS Healthcare Provider Enrollment Form* before activating healthcare providers' certification in the AVEED REMS Program.
 - ii. Ensure that healthcare providers are notified when they have been certified by the AVEED REMS Program.
 - iii. Maintain a validated, secure database of healthcare providers who are certified to prescribe AVEED in the AVEED REMS Program. Endo will ensure that the healthcare providers' certification requirements are met and may de-certify non-compliant healthcare providers if the requirements do not continue to be met.
 - iv. Ensure that the *AVEED REMS Education Program for Healthcare Providers (with Knowledge Assessment)*, *AVEED REMS Healthcare Provider Enrollment Form*, *What You Need To Know About AVEED Treatment: A Patient Guide*, and *AVEED REMS Program: An Introduction* are available on the AVEED REMS Program Website (www.AveedREMS.com) or from Endo's toll-free medical information line (1-800-462-3636) or from the AVEED REMS Program Call Center (1-855-755-0494).
 - v. Provide an Introductory Information Sheet titled *AVEED REMS Program: An Introduction* to healthcare providers who inquire about how to become certified.

The following materials are part of the REMS and are appended:

- i. *AVEED REMS Education Program for Healthcare Providers (with Knowledge Assessment)*;
- ii. *AVEED REMS Healthcare Provider Enrollment Form*;

- iii. *AVEED REMS Program: An Introduction*;
- iv. *What You Need To Know About AVEED Treatment: A Patient Guide*; and
- v. AVEED REMS Program website.

2. AVEED is dispensed² only in certain healthcare settings that are specially certified.

- a. Endo will:
 - i. Ensure that AVEED is only distributed to and dispensed in healthcare settings that are specially certified.
 - ii. Ensure that healthcare settings are re-certified in the AVEED REMS Program every two years.
 - iii. Provide the Information Sheet titled *AVEED REMS Program: An Introduction* to representatives of healthcare settings who inquire about how to become certified.
- b. To become certified, each healthcare setting must designate an Authorized Representative for each location to coordinate the healthcare setting's activities and assure compliance with the AVEED REMS Program. The Authorized Representative must:
 - i. Review the *AVEED REMS Education Program for Healthcare Settings*;
 - ii. Complete and sign the *AVEED REMS Healthcare Settings Enrollment Form* and agree to establish processes to ensure that:
 - a.) All healthcare providers at the healthcare setting who will prescribe AVEED are specially certified prior to prescribing AVEED;
 - b.) All non-prescribing healthcare providers who dispense AVEED are trained and an up-to-date record of training is maintained;
 - c.) The healthcare setting is equipped with the necessary equipment and personnel to manage POME and anaphylaxis;
 - d.) Each patient is counseled about the risks of POME and anaphylaxis and provided with the *What You Need To Know About AVEED Treatment: A Patient Guide*; and
 - e.) Each patient is observed within the healthcare setting for 30 minutes following each injection;
 - iii. Maintain a record of current certified healthcare providers;
 - iv. Agree not to loan, sell, or transfer AVEED to another healthcare setting, pharmacy, healthcare provider, institution, or distributor, except in the case where the transfer is to another certified healthcare setting (unique ship-to site address) with the same Authorized Representative;
 - v. Monitor and maintain processes and procedures to implement the above requirements; and

² For the purposes of this REMS, "dispense" includes dispensing for administration by a healthcare provider.

- vi. Agree to be audited to ensure compliance with the AVEED REMS Program.

The following materials are part of the REMS and are appended:

- i. *AVEED REMS Education Program for Healthcare Settings*; and
- ii. *AVEED REMS Healthcare Setting Enrollment Form*.

B. Implementation System

An implementation system will be established for the AVEED REMS Program to monitor and evaluate whether the elements to assure safe use are meeting the program's goals.

Endo will:

1. Ensure that healthcare settings that dispense AVEED are specially certified.
2. Maintain, monitor, and evaluate the implementation of the AVEED REMS Program:
 - a. Endo will maintain a validated, secure database of all certified healthcare settings.
 - b. Endo will send confirmation of certification to each certified healthcare setting.
 - c. The database of certified healthcare providers will be accessible by the Authorized Representative at the certified healthcare setting.
 - d. Endo will maintain an AVEED REMS Program Call Center (1-855-755-0494) to respond to questions from healthcare providers and healthcare settings.
 - e. Endo will ensure that all materials listed in or appended to the AVEED REMS are available through the AVEED REMS Program website (www.AveedREMS.com) or through the AVEED REMS Program Call Center (1-855-755-0494).
 - f. Endo will maintain a website to facilitate operation of the AVEED REMS Program, which will serve as one method by which healthcare providers and healthcare setting Authorized Representatives can receive education and enroll in the AVEED REMS Program.
 - g. Endo will audit all certified healthcare settings within 180 days after the healthcare setting is certified to ensure they have implemented the AVEED REMS Program as directed. Thereafter, Endo will include the certified healthcare settings in the company's annual audit plan.
3. Ensure that wholesalers/distributors verify healthcare setting certification prior to distributing AVEED.
4. Ensure that wholesalers/distributors maintain distribution records of all shipments of AVEED.
5. Take reasonable steps to improve implementation of these elements and to maintain compliance with the AVEED REMS program requirements, as applicable.

C. Timetable for Submissions of Assessments

Endo will submit REMS Assessments to FDA at 6 months and 12 months from the date of REMS approval, and then annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Endo will submit each assessment so that it will be received by the FDA on or before the due date.

AVEED[™] REMS Healthcare Provider Enrollment Form

Instructions

AVEED is only available through the AVEED Risk Evaluation and Mitigation Strategy (REMS) Program. In order to prescribe AVEED, a healthcare provider must:

1. Ensure that your healthcare setting is enrolled. You cannot complete certification until your healthcare setting is enrolled.
2. Review the AVEED REMS Education Program for Healthcare Providers, including the Prescribing Information.
3. Successfully complete the AVEED REMS Knowledge Assessment.
4. Complete and submit this one-time AVEED REMS Healthcare Provider Enrollment Form.

For online enrollment processing, please go to **www.AveedREMS.com**.

For enrollment via fax, please complete all required fields on the next page and fax the page to **1-855-755-0495**. You will receive enrollment confirmation via your preferred method of communication (email or fax) within two business days.

For questions regarding the AVEED REMS Program, please either visit **www.AveedREMS.com** or call the AVEED REMS Program at **1-855-755-0494**.

Enrollment is not required for non-prescribing healthcare providers who will administer AVEED.

Healthcare Provider Responsibilities

By completing this form, I attest that:

- I understand that AVEED is only available through the AVEED REMS Program and that I must comply with the program requirements in order to prescribe and administer AVEED.
- I completed the AVEED REMS Education Program, including review of the AVEED Prescribing Information, and successfully completed the AVEED REMS Knowledge Assessment.
- I understand how to inject AVEED properly.
- I understand the risks of serious pulmonary oil microembolism (POME) reactions and anaphylaxis following the administration of AVEED, which have the potential to lead to serious medical consequences (e.g., respiratory distress and syncope), and how to manage these risks.
- Prior to initiating treatment and before each injection, I agree to provide a copy of "What You Need To Know About AVEED Treatment: A Patient Guide" to each patient and review it with them to inform them about the risk of serious POME reactions and anaphylaxis and the need to remain in my healthcare setting for **30 minutes** following each AVEED injection.
- I acknowledge that my healthcare setting must be a certified healthcare setting.
- I understand that each patient must be observed in the healthcare setting for **30 minutes** following each AVEED injection in order to provide appropriate medical treatment in the event of serious POME reactions or anaphylaxis following the administration of AVEED.
- I agree that personnel from the AVEED REMS Program may contact me to gather further information or resolve discrepancies or to provide other information related to the AVEED REMS Program.
- I understand that Endo Pharmaceuticals Solutions Inc. (Endo), its agents and contractors, such as the distributors, may contact me via phone, mail or email to survey me on the effectiveness of the program requirements for the AVEED REMS Program.
- I understand the importance of reporting serious events of POME and anaphylaxis following AVEED treatment.

To report suspected adverse events contact Endo at 1-800-462-3636, FDA at 1-800-FDA-1088 or **www.fda.gov/medwatch/report.htm**.

HEALTHCARE PROVIDER INFORMATION (*REQUIRED FIELDS):

M.D. D.O. Physician Assistant Nurse Practitioner Other _____

SPECIALTY:

Endocrinology Primary Care Urology Other _____

First Name* (please print) MI Last Name* (please print) Email Address*

Phone Number* Ext DEA Number* State License Number and State

Prescriber NPI* Fax Number*

Healthcare Setting Name*

Address*

City* State* Zip*

Preferred Method of Communication* (please select **one**)

Email Fax

I understand that this enrollment and certification only applies to me, and does not apply to any healthcare setting that employs me or in which I may have an interest.

Healthcare Provider Signature* Date* (MM/DD/YYYY)

AVEED™ REMS Healthcare Setting Enrollment Form

Instructions

AVEED is only available through the AVEED Risk Evaluation and Mitigation Strategy (REMS) Program. In order to dispense and administer AVEED, each healthcare setting must:

1. Designate an Authorized Representative.
2. Review the AVEED REMS Education Program for Healthcare Settings, including the Prescribing Information.
3. Complete and sign the Healthcare Setting Enrollment Form. This Enrollment must be renewed every 2 years.
4. Implement the necessary staff training and processes to comply with the AVEED REMS Program requirements.

For online enrollment, please go to www.AveedREMS.com.

For enrollment via fax, please complete all required fields on the next page and fax the page to **1-855-755-0495**. You will receive enrollment confirmation via your preferred method of communication (email or fax) within two business days.

For questions regarding the AVEED REMS Program, please either visit www.AveedREMS.com or call the AVEED REMS Program at **1-855-755-0494**.

Authorized Representative Responsibilities

I am the Authorized Representative designated by my healthcare setting to coordinate the activities of the AVEED REMS Program. I agree to comply with the following program requirements:

- I understand that my healthcare setting must be certified with the AVEED REMS Program to order or administer AVEED.
- I have completed the AVEED REMS Education Program for Healthcare Settings.
- I understand the risks of serious pulmonary oil microembolism (POME) reactions and anaphylaxis following the administration of AVEED.
- I understand this healthcare setting must renew its enrollment in the AVEED REMS Program every two years from the date of initial enrollment.
- This healthcare setting has the necessary on-site equipment and personnel to manage POME or anaphylaxis.
- This healthcare setting will establish procedures and protocols that are subject to audit, to help ensure compliance with the safe use conditions required in the AVEED REMS Program, including the following:
 - All Healthcare Providers (HCPs) who prescribe AVEED in my healthcare setting are specially certified.
 - All non-prescribing HCPs who administer AVEED in my healthcare setting are trained and a record regarding such training must be maintained.
 - Prior to initiating treatment and before each injection, review with and provide a copy of “What You Need To Know About AVEED Treatment: A Patient Guide” to each patient to inform them about the risks of serious POME reactions and anaphylaxis.
 - To observe each patient administered AVEED for **30 minutes** at my healthcare setting following each injection in order to provide appropriate medical treatment in the event of serious POME reactions or anaphylaxis following the administration of AVEED.
- Not to loan, sell or transfer AVEED to another pharmacy, healthcare setting, prescriber, institution or distributor, except in the case where the transfer is to another certified healthcare setting (unique ship-to site address) where I am also the Authorized Representative.
- This healthcare setting must not dispense AVEED for home or patient self-administration.
- To make available to Endo Pharmaceuticals Solutions Inc. (Endo), and/or a designated third party or the FDA, documentation to verify understanding of, and adherence to, the requirements of the AVEED REMS Program.

HEALTHCARE SETTING INFORMATION (* REQUIRED FIELDS)

Healthcare Setting Name*

DEA Number* [On file with distributor account]

Address*

City*

State*

ZIP*

Setting Type:

Group practice

Independent practice

Institution

Other _____

Phone Number*

Fax Number*

Email Address

AUTHORIZED REPRESENTATIVE INFORMATION (* REQUIRED FIELDS)

M.D.

D.O.

Nurse

Physician Assistant

Practice Manager

Other _____

First Name* (please print)

MI

Last Name* (please print)

Title

Email Address*

Phone Number* Ext

Fax Number*

Preferred Method of Communication*

(please select **one**)

Email

Fax

I understand that this enrollment only applies to me as the designated Authorized Representative of this healthcare setting. I will complete a separate enrollment form for each healthcare setting (unique ship-to site address) for which my designation and responsibilities extend. Failure to enroll a healthcare setting and have certified healthcare providers in the AVEED REMS program will result in the inability to receive shipments of AVEED.

Healthcare Setting Authorized Representative Signature*

Date* [MM/DD/YYYY]

AVEED™ REMS Program: An Introduction

What is the AVEED REMS (Risk Evaluation and Mitigation Strategy) Program?

A REMS is a strategy to manage known or potential risks associated with a drug, and is required by the FDA to ensure that the benefits of the drug outweigh its risks. AVEED is available only under a restricted program called the AVEED REMS Program because of the risks of serious pulmonary oil microembolism (POME) reactions and anaphylaxis.

AVEED REMS Program Requirements

Healthcare settings must be certified in the AVEED REMS Program to be able to order AVEED. One representative needs to enroll per healthcare setting (the “Authorized Representative”).

Prescribing Healthcare Providers must be certified in the AVEED REMS Program to be able to prescribe AVEED. Prescribing healthcare providers cannot complete certification until their healthcare setting is enrolled.

Non-Prescribing Healthcare Providers who will administer AVEED to patients must be trained on the *AVEED REMS Education for Healthcare Providers*.

Safe Use Actions You Must Implement for AVEED

- Ensure all healthcare providers who prescribe AVEED at your healthcare setting are certified in the AVEED REMS program
- Ensure all non-prescribing healthcare providers who administer AVEED are trained on:
 - Serious POME reactions and anaphylaxis
 - Proper administration of AVEED
 - Patient counseling
 - 30 minute post-injection patient observation
- Establish a process to ensure all patients are counseled about AVEED and receive *What You Need To Know About AVEED Treatment: A Patient Guide*
- **Establish a process to ensure each patient is observed for 30 minutes at the healthcare setting after each AVEED injection**
- Have the necessary equipment and personnel on-site to manage serious POME reactions or anaphylaxis
- Ensure a patient is NEVER provided AVEED for home or self-injection

Steps for Healthcare Setting Certification

1. Designate an Authorized Representative. This may be a prescribing or non-prescribing healthcare provider, practice manager or any responsible individual in the healthcare setting.
2. Review *AVEED REMS Education Program for Healthcare Settings*, including the Prescribing Information.
3. Complete and sign the Healthcare Setting Enrollment Form. This Enrollment must be renewed every 2 years.
4. Implement the necessary staff training and processes to comply with the AVEED REMS Program requirements.

Steps for Healthcare Provider Certification

1. Ensure that your healthcare setting is enrolled. Prescribing healthcare providers will not be able to complete certification until their healthcare setting is enrolled.
2. Review *AVEED REMS Education Program for Healthcare Providers*, including the Prescribing Information.
3. Successfully complete the 10 question Knowledge Assessment.
4. Complete and sign the one-time Healthcare Provider Enrollment Form.

Where to Find REMS Program Information and Resources

The AVEED REMS Education Program, Healthcare Setting Enrollment Form, and other AVEED REMS Program tools are available online at www.AveedREMS.com or by contacting the AVEED REMS Program at 1-855-755-0494 to request materials.

AVEED[™] REMS Education Program for Healthcare Providers

This Education Program Includes Information About:

- AVEED REMS Program requirements
- Serious POME reactions and anaphylaxis with AVEED injection
- Proper administration of AVEED
- Counseling your patient
- Required Knowledge Assessment

What is the AVEED REMS (Risk Evaluation and Mitigation Strategy) Program?

A REMS is a strategy to manage known or potential risks associated with a drug, and is required by the FDA to ensure that the benefits of the drug outweigh its risks. AVEED is available only under a restricted program called the AVEED REMS Program because of the risks of serious pulmonary oil microembolism (POME) reactions and anaphylaxis. The AVEED REMS Education Program is designed to train healthcare providers (HCPs) who prescribe and/or administer AVEED about these risks.

- **Prescribing Healthcare Providers** must be certified in the AVEED REMS Program to be able to prescribe AVEED. Prescribing Healthcare Providers cannot complete certification until their healthcare setting is enrolled.
- **Healthcare settings** must be certified in the AVEED REMS Program to be able to order AVEED.
- **Non-Prescribing Healthcare Providers** who will administer AVEED to patients must review the AVEED REMS Education Program for Healthcare Providers before injecting AVEED.

Steps for Healthcare Provider Certification:

- 1 Ensure that your healthcare setting is enrolled. You will not be able to complete certification until your healthcare setting is enrolled.
- 2 Review the AVEED REMS Education Program, including the Prescribing Information
- 3 Successfully complete the 10 question Knowledge Assessment
- 4 Complete and sign the one-time Healthcare Provider Enrollment Form

The AVEED REMS Education Program, Knowledge Assessment, Healthcare Provider Enrollment Form, and other AVEED REMS Program tools are available online at www.AveedREMS.com or by contacting the AVEED REMS Program at 1-855-755-0494 to request materials.

You can review the educational materials, enroll, and complete the knowledge assessment online at www.AveedREMS.com or review the printed versions and fax your enrollment form and knowledge assessment.

You will not be able to prescribe AVEED without completing your certification in the AVEED REMS Program.

Healthcare Setting Certification

Each healthcare setting must also be certified in the AVEED REMS Program to be able to order, dispense, and administer AVEED. Visit www.AveedREMS.com for more information on healthcare setting certification.

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)

AVEED should only be used in patients who require testosterone replacement therapy and in whom the benefits of the product outweigh the serious risks of POME and anaphylaxis.

Serious Risks of POME and Anaphylaxis

With each AVEED injection, there is a potential for serious POME reactions or anaphylaxis to occur. These reactions can occur after any injection of AVEED during the course of therapy, including after the first dose.

The signs and symptoms of serious POME reactions and anaphylaxis overlap. It is important to observe patients in your healthcare setting for 30 minutes after each AVEED injection to determine whether medical intervention is necessary.

Serious POME reactions

POME occurring after an AVEED injection is believed to be caused by tiny droplets of oil, in which the testosterone undecanoate has been dissolved, that have traveled to the lungs.

- POME is **not** a blood clot
- There is a risk of POME occurring with each injection of AVEED

Symptoms of POME

The following symptoms of POME have been reported with AVEED:

- | | | |
|-----------------|---|---------------------|
| - cough | ⋮ | - throat tightening |
| - urge to cough | | - chest pain |
| - dyspnea | | - dizziness |
| - hyperhidrosis | | - syncope |

- The majority of these events lasted a few minutes and resolved with supportive measures
- Some of the events lasted up to several hours and in some cases, emergency care and/or hospitalization were required

Anaphylaxis

Episodes of anaphylaxis, including life-threatening reactions, have been reported to occur following AVEED injection.

Strategies That May Mitigate These Risks:

- Take proper precautions and avoid injecting AVEED intravascularly
- Inject AVEED slowly (over 60 to 90 seconds)
- AVEED should not be used or should be discontinued in men with any known hypersensitivity to AVEED or to any of its ingredients (testosterone undecanoate, refined castor oil, benzyl benzoate)
- **30 Minute Post-Injection Patient Observation**
 - Observe patients in your healthcare setting for a period of 30 minutes after each AVEED injection to provide appropriate medical treatment in the event of serious POME reactions or anaphylaxis
 - The majority of cases reported occurred during or within 30 minutes of the injection
- Your healthcare setting must have immediate access on-site to equipment and personnel trained to manage serious POME reactions and anaphylaxis

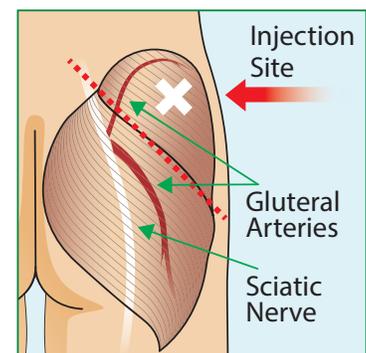
Proper Administration

AVEED is for intramuscular use only. Intravascular injection may lead to POME.

Only healthcare providers trained in the proper injection technique for AVEED should administer AVEED.

Proper Injection Technique for AVEED Intramuscular Injection

1. 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.
2. 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 to aspirate for blood. **IF BLOOD APPEARS IN THE SYRINGE DO NOT PROCEED WITH THE INJECTION**, as this is an indication that a blood vessel may have been punctured. Immediately withdraw the needle completely and replace it.
3. 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.
4. **Observe the patient in the healthcare setting for 30 minutes after the injection in order to provide appropriate medical treatment in the event of a serious POME reaction or anaphylaxis.**



Patient Counseling

With each injection of AVEED:

- Review the AVEED Patient Counseling Tool (“What You Need to Know about AVEED Treatment: A Patient Guide”) with patients and caregivers.
- Give the Patient Counseling Tool to the patient to read during their 30 minute wait in your healthcare setting.

Explain to patients:

- The importance of providing an accurate medical history about any previous allergic reactions to AVEED or its components (testosterone undecanoate, castor oil and benzyl benzoate)
- AVEED can only be administered by a trained HCP in a certified healthcare setting
- The risks of serious POME reactions and anaphylaxis associated with AVEED
- POME is not a blood clot
- How to recognize the symptoms of serious POME reactions and anaphylaxis
- Report signs and symptoms to the healthcare setting staff immediately. These include:

<ul style="list-style-type: none"> - swelling of your face, tongue, or throat - hoarseness or trouble speaking - difficulty breathing - feeling flushed - itching or rash including hives 	<ul style="list-style-type: none"> - coughing or urge to cough - tightening in your throat - numbness and tingling in your arms - dizziness - feeling very sweaty 	<ul style="list-style-type: none"> - chest pain - feeling unwell - fainting - pain in your stomach - vomiting or throwing up
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- **The importance of waiting in the healthcare setting for 30 minutes post-injection to provide for appropriate medical treatment in the event of a serious POME reaction or anaphylaxis.**
- The AVEED REMS Patient Counseling Tool contains an AVEED Injection Tracking Sheet. The purpose of this sheet is that the patient’s injection time and scheduled departure time – 30 minutes apart – can be recorded by the HCP and given to the patient. The patient will then know when they have waited 30 minutes and can leave the healthcare setting accordingly. Explain the importance of this tool to your patients and encourage them to use it every time.

<i>Healthcare Professional to Complete</i>		
Time I received the Injection	How long I need to wait in the office	Time I can leave the office
	30 Minutes	

- Who to contact immediately if they experience any of the above signs or symptoms after leaving the healthcare setting
- Both serious POME reactions and anaphylaxis can occur after any injection of AVEED during the course of therapy, including after the first dose
- Who they should contact with any questions they may have regarding AVEED

Reporting of Adverse Events

Report suspected adverse events to Endo Pharmaceuticals at 1-800-462-3636. You also may report adverse event information to the FDA MedWatch Reporting System at 1-800-FDA-1088.

All AVEED REMS documents are available at www.AveedREMS.com, or call the AVEED REMS Program at 1-855-755-0494.

The completion of the AVEED REMS Education Program and enrollment process is NOT a substitute for reading the AVEED Full Prescribing Information and AVEED Medication Guide.

Other Resources for Healthcare Providers

The AVEED REMS Program does not include training on how to manage POME and anaphylaxis.

HCPs should also be familiar with current standards for the treatment of anaphylaxis. Treatment guidelines are provided by the following organizations:

- The American Academy of Allergy, Asthma and Immunology (AAAAI)
(<http://www.aaaai.org/home.aspx>)
- National Institute of Allergy and Infectious Diseases (NIAID)
(<http://www.niaid.nih.gov/Pages/default.aspx>)
- World Allergy Organization (WAO)
(<http://www.worldallergy.org/anaphylaxis/>)

Knowledge Assessment

Complete all 10 questions.

To become a certified healthcare provider in the AVEED REMS Program you will need to answer ALL questions correctly.

- Complete the Knowledge Assessment, populate and sign the one-time Healthcare Provider Enrollment Form online at www.AveedREMS.com

OR

- Fax your responses to all 10 Knowledge Assessment questions and a completed and signed one-time Healthcare Provider Enrollment Form to 1-855-755-0495

If you complete the Knowledge Assessment and Enrollment Form online, correspondence from the AVEED REMS Program confirming your enrollment and certification in the AVEED REMS Program will be sent via the preferred communication method (email or fax) selected on your enrollment.

If you return the Knowledge Assessment and Enrollment Form via fax, you will receive correspondence from the AVEED REMS Program via the preferred communication method (email or fax) selected on your enrollment form within two business days. Correspondence may include:

- How to retake the Knowledge Assessment, if necessary
- How to correct missing or invalid information provided on the Enrollment Form and resubmit to the AVEED REMS Program for re-processing, if necessary
- A confirmation of your enrollment and certification in the AVEED REMS Program (which requires no further action)

Questions 1-5 Multiple Choice. Select only **one** answer for each question.

QUESTION 1

Which of the following would be an appropriate patient for AVEED?

- A. 45-year-old female with a history of androgen insensitivity syndrome
- B. 16-year-old male with symptoms of delayed puberty and hypogonadism
- C. 40-year-old male with history of congenital hypogonadism complaining of fatigue and decreased libido
- D. 54-year-old male with a family history of prostate cancer and complaining of decreased urine output

QUESTION 2

Which of the following symptoms most accurately describes a patient experiencing an episode of post-injection pulmonary oil microembolism (POME)?

- A. Severe palpitations and diaphoresis one week post AVEED injection
- B. Headache, nausea, or vomiting prior to AVEED injection
- C. Rash, skin irritation, and erythema surrounding the injection site
- D. Cough, dyspnea, chest pain, and dizziness 5 minutes post-injection

QUESTION 3

Why should a patient wait in the healthcare setting for 30 minutes following each AVEED injection?

- A. To make sure their insurance information is accurate
- B. To provide them with follow-up appointment information
- C. To provide appropriate medical treatment in the event of a serious POME reaction or anaphylaxis.
- D. To ensure that they do not eat for 30 minutes after an injection

QUESTION 4

What is the proper injection route and injection site for AVEED?

- A. Intramuscular injection in the gluteus muscle
- B. Intramuscular injection in the deltoid
- C. Intravascular injection in the gluteus muscle
- D. None of the above

If you plan on faxing this Knowledge Assessment to the Program please provide your Prescriber NPI so we can associate your progress with your stakeholder record. You can provide this information below.

Prescriber NPI: _____

QUESTION 5

Prior to administering an AVEED injection, you must counsel the patient using the Patient Counseling Tool “What You Need to Know about AVEED Treatment: A Patient Guide” and the AVEED Medication Guide on all of the following EXCEPT:

- A. The risks of serious POME and anaphylaxis associated with AVEED
- B. Techniques for aseptic self-injection of AVEED
- C. The importance of waiting 30 minutes post-injection in the healthcare setting in order to provide appropriate medical treatment in the event of a serious POME reaction or anaphylaxis
- D. Signs and symptoms of an adverse reaction and how to report them

Questions 6-10 (True or False)

QUESTION 6

In order to administer AVEED, my healthcare setting must also be certified.

T F

QUESTION 7

As a patient continues receiving AVEED injections, their risk of experiencing pulmonary oil microembolism (POME) or anaphylaxis decreases.

T F

QUESTION 8

If a patient experiences a hypersensitivity reaction (e.g., angioedema and/or hives) following an AVEED injection, it is appropriate to continue therapy with AVEED.

T F

QUESTION 9

Patients who feel comfortable with self-administering AVEED may do so after receiving their initial injection in the healthcare setting.

T F

QUESTION 10

It is a requirement of the AVEED REMS to review the Patient Counseling Tool “What you need to know about AVEED Treatment: A Patient Guide” with patients and provide them with a copy prior to each injection of AVEED.

T F

If you plan on faxing this Knowledge Assessment to the Program please provide your Prescriber NPI so we can associate your progress with your stakeholder record. You can provide this information below.

Prescriber NPI: _____

AVEED[™] REMS Education Program for Healthcare Settings

This Educational Piece Includes Information About:

- Serious POME reactions and anaphylaxis with AVEED Injection
- AVEED REMS Program requirements to implement in your healthcare setting
- Ordering AVEED

The REMS Education Program for Healthcare Providers Includes Additional Information About:

- Steps for healthcare PROVIDER certification
- Proper administration of AVEED
- Patient counseling

What is the AVEED REMS (Risk Evaluation and Mitigation Strategy) Program?

A REMS is a strategy to manage known or potential risks associated with a drug, and is required by the FDA to ensure that the benefits of the drug outweigh its risks. AVEED is available only under a restricted program called the AVEED REMS Program because of the risks of serious pulmonary oil microembolism (POME) reactions and anaphylaxis. The AVEED REMS Education Program for Healthcare Settings is designed to train healthcare setting Authorized Representatives on these serious risks, and AVEED REMS Program requirements to order AVEED for their healthcare setting.

- **Healthcare settings** must be certified in the AVEED REMS Program to be able to order AVEED.
- **Prescribing Healthcare Providers** must be certified in the AVEED REMS Program to be able to prescribe AVEED.
- **Non-Prescribing Healthcare Providers** who will administer AVEED to patients must review the AVEED REMS Education for Healthcare Providers before injecting AVEED.

Steps for Healthcare Setting Certification

- 1** Designate an Authorized Representative
- 2** Review the AVEED REMS Education Program for Healthcare Settings, including the Prescribing Information
- 3** Complete and sign the Healthcare Setting Enrollment Form. This Enrollment must be renewed every 2 years
- 4** Implement the necessary staff training and processes to comply with the AVEED REMS Program requirements

The AVEED REMS Education Program, Healthcare Setting Enrollment Form, and other AVEED REMS Program tools are available online at www.AveedREMS.com or by contacting the AVEED REMS Program at 1-855-755-0494 to request materials.

You can review the educational materials and enroll online at www.AveedREMS.com, or review the printed versions and fax your enrollment form to the AVEED REMS Program at 1-855-755-0495.

Your healthcare setting will not be able to order AVEED unless you meet these two requirements:

1. Your healthcare setting is certified
2. Healthcare providers who prescribe AVEED at your healthcare setting are certified in the AVEED REMS Program

Who Can Be An Authorized Representative?

An Authorized Representative at the healthcare setting can be a:

- Prescribing healthcare providers
- Non-prescribing healthcare providers
- Practice manager
- Or, any responsible individual in the healthcare setting

Please check with your manager to ensure the appropriate person represents the healthcare setting and attests to the enrollment requirements as stated on the Healthcare Setting Enrollment Form.

- One representative needs to enroll per healthcare setting (the “Authorized Representative”). One Authorized Representative can manage more than one healthcare setting.
- Please note, there are no AVEED REMS requirements for staff at a healthcare setting that will not be involved with prescribing or administering AVEED.

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)

AVEED should only be used in patients who require testosterone replacement therapy and in whom the benefits of the product outweigh the serious risks of POME and anaphylaxis.

Serious Risks of POME and Anaphylaxis

With each AVEED injection, there is a potential for serious POME reactions or anaphylaxis to occur. These reactions can occur after any injection of AVEED during the course of therapy, including after the first dose.

The signs and symptoms of serious POME reactions and anaphylaxis overlap. It is important to observe patients in your healthcare setting for 30 minutes after each AVEED injection to determine whether medical intervention is necessary.

Serious POME reactions

POME occurring after an AVEED injection is believed to be caused by tiny droplets of oil, in which the testosterone undecanoate has been dissolved, that have traveled to the lungs.

- POME is **not** a blood clot
- There is a risk of POME occurring with each injection of AVEED

Symptoms of POME

The following symptoms of POME have been reported with AVEED:

- | | |
|-----------------|---------------------|
| - cough | - throat tightening |
| - urge to cough | - chest pain |
| - dyspnea | - dizziness |
| - hyperhidrosis | - syncope |

- The majority of these events lasted a few minutes and resolved with supportive measures
- Some of the events lasted up to several hours and in some cases, emergency care and/or hospitalization were required

Anaphylaxis

Episodes of anaphylaxis, including life-threatening reactions, have been reported to occur following AVEED injection.

Strategies to implement in your healthcare setting to mitigate these risks:

- Ensure all healthcare providers who prescribe AVEED are certified in the AVEED REMS program
 - Maintain up-to-date records
- Ensure all non-prescribing healthcare providers who administer AVEED are trained on:
 - Serious POME reactions and anaphylaxis
 - Patient counseling
 - 30 minute post-injection patient observation
 - Proper administration of AVEED
- Maintain an up-to-date record of training
- Establish a process to ensure all patients are counseled about AVEED and receive “What You Need To Know About AVEED Treatment: A Patient Guide”
- **Establish a process to ensure each patient is observed for 30 minutes at your healthcare setting after each AVEED injection**
- Have the necessary equipment and personnel on-site to manage serious POME reactions or anaphylaxis
- Ensure a patient is NEVER provided AVEED for home or self-injection

How Do I Order AVEED?

Contact the AVEED REMS Program at 1-855-755-0494.

All AVEED REMS documents are available at www.AveedREMS.com, or call the AVEED REMS Program at 1-855-755-0494.

The completion of the AVEED REMS Education Program and enrollment process is NOT a substitute for reading the AVEED Full Prescribing Information and AVEED Medication Guide.

What You Need to Know About AVEED™ Treatment: A Patient Guide

Patients: Your doctor or nurse will go over this Patient Guide with you. It is important to ask any questions you might have prior to each time AVEED is given to you. Keep this guide for important safety information about the serious risks and reactions of AVEED.

Healthcare Providers: Review this Patient Guide with your patient each time an injection is given and provide your patient a copy to take home. Record the patient’s injection time and scheduled departure from your office (30 minutes apart) on the back of this sheet.

What is AVEED?

AVEED is a prescription medicine that contains testosterone. AVEED is used to treat adult males who have a condition called hypogonadism. You and your healthcare provider have determined that AVEED is an appropriate treatment for you.

AVEED is only available at your doctor’s office, clinic, or hospital. It is not a medicine you will give yourself at home because of the serious risks of AVEED.

What is the Most Serious Risk Information about AVEED Treatment?

- AVEED can cause a serious lung problem called a **pulmonary oil microembolism (POME)**. POME is NOT a blood clot. AVEED contains castor oil and POME is believed to be caused by tiny droplets of castor oil that may travel to the lungs.
- AVEED may also cause a severe allergic reaction called **anaphylaxis**.

These reactions can occur with any AVEED injection during your treatment, even if you have not had a reaction occur before.

You need to stay in the doctor’s office, clinic, or hospital for 30 minutes after receiving each AVEED injection to be sure that you are not experiencing these serious side effects.

What are the Signs of POME or Anaphylaxis After Receiving AVEED?

Prompt emergency medical attention is important if you have signs or symptoms of a serious side effect after receiving an AVEED injection.

After receiving an injection of AVEED, tell your doctor or nurse if you have any of the following signs or symptoms during the 30-minute wait. Your doctor or nurse will instruct you about getting emergency medical attention if these signs or symptoms occur after leaving the doctor’s office:

- | | | |
|--|--------------------------------------|---------------------------|
| - swelling of your face, tongue, or throat | - coughing or urge to cough | - chest pain |
| - hoarseness or trouble speaking | - tightening in your throat | - feeling unwell |
| - difficulty breathing | - numbness and tingling in your arms | - fainting |
| - feeling flushed | - dizziness | - pain in your stomach |
| - itching or rash including hives | - feeling very sweaty | - vomiting or throwing up |

These are **NOT** all the possible side effects of AVEED. Refer to the AVEED Medication Guide that you were given or talk to your doctor or nurse for medical advice about other side effects.

What Can I Do to Help Reduce the Risks of AVEED?

1. Tell your doctor or nurse if you have ever had an allergic reaction to AVEED or any of its ingredients.

The ingredients in AVEED are:

- testosterone undecanoate
- castor oil
- benzyl benzoate

2. After each AVEED injection:

Stay in the doctor's office, clinic, or hospital for 30 minutes after receiving each AVEED injection to be sure that you are not experiencing any serious side effects.

How Often Will I Receive an Injection of AVEED?

You will get 1 injection when you start, 1 injection 4 weeks later, and then 1 injection every 10 weeks thereafter.

Where Can I Get More Information on AVEED?

There is an AVEED Medication Guide that your doctor or nurse will give you each time you receive an AVEED injection. You can also find additional information at www.AveedREMS.com or call the AVEED REMS Program at **1-855-755-0494**.

Injection Tracking Sheet

To ensure that you wait at your doctor's office for 30 minutes after your injection, use this tracking sheet so that you know when it's time to leave.

<i>Healthcare Professional to Complete</i>		
Time I received the Injection	How long I need to wait in the office	Time I can leave the office
	30 Minutes	

AVEED™ REMS Website

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AVEED™ REMS (Risk Evaluation and Mitigation Strategy) Program

What is the AVEED REMS Program?

A REMS is a strategy to manage known or potential serious risks associated with a drug product and is required by the FDA to ensure the benefits of the drug outweigh its risks. The purpose of the AVEED REMS Program is to inform Healthcare Providers, Healthcare Settings and patients about the risks of:

- Serious pulmonary oil microembolism (POME) reactions
- Anaphylaxis

AVEED REMS Program Requirements

- **Training** — for Healthcare Providers and authorized representatives of Healthcare Settings on serious POME reactions and anaphylaxis associated with AVEED, safe use strategies, and REMS Program requirements.
- **Certification** — for [Prescribing](#) Healthcare Providers by completing training, Knowledge Assessment and enrollment into the AVEED REMS Program.
- **Certification** — for [Healthcare Settings](#) by completing training and enrollment into the AVEED REMS Program. Each Healthcare Setting must be certified to be able to order AVEED.
- **Patient counseling** — about the risks of serious POME reactions and anaphylaxis. Healthcare Providers must give patients the Patient Counseling Tool: *"What You Need to Know About AVEED Treatment: A Patient Guide."*
- **Patient observation** — patients must remain in Healthcare Setting for 30 minutes after each AVEED injection.

For additional information about the AVEED REMS Program, please call 1-855-755-0494.

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AVEED™ REMS Program

Healthcare Provider Certification

Prescribing Healthcare Providers must be certified in the AVEED REMS Program in order to prescribe AVEED.

Certification in the AVEED REMS Program includes the following four steps:

- 1 Ensure that your healthcare setting is enrolled. You will not be able to complete certification until your healthcare setting is enrolled.
- 2 Review the AVEED REMS Education Program, including the Prescribing Information
- 3 Successfully complete the 10 question Knowledge Assessment
- 4 Complete and sign the one-time Healthcare Provider Enrollment Form

- You can complete the training and enrollment online by clicking below, or by downloading the print version of the training and faxing your Knowledge Assessment and enrollment form into the AVEED REMS Program at 1-855-755-0495.

[Click here to complete the AVEED REMS Training and Enrollment online](#)

- Non-Prescribing Healthcare Providers must also be trained on the AVEED REMS Education Program for Healthcare Providers.

Enrollment is not required for Non-Prescribing Healthcare Providers. Click below to complete the training online.

[Click here to complete the AVEED REMS Training online](#)

- Your Healthcare Setting must also be certified in the AVEED REMS Program in order for you to prescribe AVEED.

Program Materials for Healthcare Provider

[AVEED REMS Program: An Introduction](#)

[AVEED REMS Education Program for Healthcare Providers](#)

[Healthcare Provider Enrollment Form](#)

[Patient Counseling Tool: What You Need to Know About AVEED Treatment: A Patient Guide](#)

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For additional information about the AVEED REMS Program, please call 1-855-755-0494.

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AVEED™ REMS Program

Healthcare Setting Certification

Healthcare Settings must be certified in the AVEED REMS Program to be able to order AVEED.

To become certified in the AVEED REMS Program, an Authorized Representative of the Healthcare Setting must do the following:

- 1 Designate an Authorized Representative
- 2 Review the AVEED REMS Education Program for Healthcare Settings, including the Prescribing Information
- 3 Complete and sign the Healthcare Setting Enrollment Form. This Enrollment must be renewed every 2 years.
- 4 Implement the necessary staff training and processes to comply with the AVEED REMS Program requirements

- You can complete the training and enrollment online by clicking below, or by downloading the print version of the training and faxing your enrollment form into the AVEED REMS Program at 1-855-755-0495.

[Click here to complete the AVEED REMS Training and Enrollment online](#)

- All Prescribing Healthcare providers must be certified in the AVEED REMS Program in order to prescribe AVEED at your Healthcare Setting.
- Non-Prescribing Healthcare Providers who will administer AVEED to patients must review the AVEED REMS Education for Healthcare Providers before injecting AVEED.

For additional information about the AVEED REMS Program, please call 1-855-755-0494.

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/s/

CHRISTINE P NGUYEN
03/05/2014