I. GOALS:

The goals and 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 prescribe\(^1\) 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 dispensed\(^2\) 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](http://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.