

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022219Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: February 28, 2014

Reviewer(s): Suzanne Robottom, Phar.D.  
Division of Risk Management (DRISK)

Kate Heinrich Oswell, M.A.  
Health Communications Analyst, DRISK

Team Leader: Cynthia LaCivita, Phar.D., DRISK

Division Director: Claudia Manzo, Phar.D., DRISK

Subject: Evaluation of proposed REMS - Final review

Drug Name(s): (b) (4) (testosterone undecanoate)

Therapeutic Class: androgen

Dosage and Route: 750 mg / 3mL by intramuscular injection every 10 weeks

Application Type/Number: NDA 22219

Applicant/sponsor: Endo Pharmaceutical Solutions Inc

OSE RCM #: 2013-2138

## 1 INTRODUCTION

This review documents DRISK's final evaluation of the proposed risk evaluation and mitigation strategy (REMS) for testosterone undecanoate NDA 22219 received on August 29, 2013, amended on February 28, 2014, and submitted in response to the Division of Bone Reproductive and Urologic Products (DBRUP) Complete Response (CR) letter issued May 29, 2013.

This review is written by the Division of Risk Management (DRISK), in consultation with the Office of Prescription Drug Promotion (OPDP).

## 2 MATERIALS REVIEWED

- Proposed REMS. Submitted February 28, 2014.

### **DRISK Review related to the February 25, 2014 email submission**

- Robottom S. DRISK REMS review signed in DARRTS February 27, 2014 by Robottom S and LaCivita C.
  - Comments on and revisions to the REMS Document, all REMS materials, and the REMS Supporting Document.

### **DRISK Review related to the February 10, 2014 email submission**

- Robottom S. DRISK REMS review signed in DARRTS February 22, 2014 by Robottom S and LaCivita C.
  - Comments on and revisions to the REMS Document, all REMS materials, and the REMS Supporting Document.

### **DRISK reviews related to the August 29, 2013 submission**

- Robottom S. DRISK REMS review signed in DARRTS on February 11, 2014 by Robottom S and Willy M.
  - Comments on the REMS Assessment Plan
- Robottom S. DRISK REMS review signed in DAARTS February 4, 2014 by Robottom S and Willy M.
  - Revised REMS Document, Introductory Information Sheet
- Robottom S. DRISK REMS review signed in DARRTS January 30, 2014 by Robottom S and Manzo C.
  - Comments on the Healthcare Provider Enrollment Form, Healthcare Setting Enrollment Form, What You Need to Know About (b) (4) A Patient Guide, REMS Education Program for Healthcare Providers, REMS Education Program for Healthcare Settings, website template.

## 3 RECOMMENDATION

The amended proposed REMS and Supporting Document submitted on February 28, 2014 incorporates the comments DBRUP and DRISK conveyed in the previous reviews and via email on February 27, 2014.

DRISK finds the REMS and REMS Supporting Document to be acceptable. DRISK recommends approval of the (b) (4) REMS.

#### **ATTACHMENTS**

- REMS Document
- Healthcare Provider Enrollment Form
- Healthcare Settings Enrollment Form
- (b) (4) *REMS Program: An Introduction*
- *AVEED REMS Education Program for Healthcare Providers*
- *AVEED REMS Education Program for Healthcare Settings*
- *What You Need To Know about (b) (4) Treatment: A Patient Guide*
- (b) (4) REMS website

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/s/  
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02/28/2014

CLAUDIA B MANZO  
02/28/2014  
concur

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: February 26, 2014

Reviewer(s): Suzanne Robottom, Pharm.D.  
Division of Risk Management (DRISK)

Kate Heinrich Oswell, M.A.  
Health Communications Analyst, DRISK

Team Leader: Cynthia LaCivita, Pharm.D., DRISK

Division Director: Claudia Manzo, Pharm.D., DRISK

Subject: Evaluation of proposed REMS

Drug Name(s): Aveed (testosterone undecanoate)

Therapeutic Class: androgen

Dosage and Route: 750 mg / 3mL by intramuscular injection every 10 weeks

Application Type/Number: NDA 22219

Applicant/sponsor: Endo Pharmaceutical Solutions Inc

OSE RCM #: 2013-2138

## 1 INTRODUCTION

This is a review of Endo Pharmaceutical Solutions Inc's proposed risk evaluation and mitigation strategy (REMS) for testosterone undecanoate (Aveed) submitted via email on February 25, 2014 as a revision to the August 29, 2013 complete response.

This review is written by the Division of Risk Management (DRISK), in consultation with the Office of Prescription Drug Promotion (OPDP).

## 2 MATERIALS REVIEWED

- Proposed REMS. Submitted via email February 25, 2014
- OPDP REMS Consult Review; signed in DARRTS on February 19, 2014 by Tran T-H B.

### **DRISK Review related to the February 10, 2014 email submission**

- Robottom S. DRISK REMS review signed in DARRTS February 22, 2014 by Robottom S and LaCivita C.
  - Comments on and revisions to the REMS Document, all REMS materials, and the REMS Supporting Document.

### **DRISK reviews related to the August 29, 2013 submission**

- Robottom S. DRISK REMS review signed in DARRTS on February 11, 2014 by Robottom S and Willy M.
  - Comments on the REMS Assessment Plan
- Robottom S. DRISK REMS review signed in DAARTS February 4, 2014 by Robottom S and Willy M.
  - Revised REMS Document, Introductory Information Sheet
- Robottom S. DRISK REMS review signed in DARRTS January 30, 2014 by Robottom S and Manzo C.
  - Comments on the Healthcare Provider Enrollment Form, Healthcare Setting Enrollment Form, What You Need to Know About Aveed: A Patient Guide, REMS Education Program for Healthcare Providers, REMS Education Program for Healthcare Settings, website template.

## 3 COMMENTS TO THE REVIEW DIVISION

DRISK notes that OPDP provided the following comments:

- These statements minimize the risk of Aveed. We recommend revising these statements.
  - HCP Education Program and HCS Education Program:
    - “The **majority** of these events lasted a few minutes and resolved with supportive measures” (emphasis added). “The **majority** of cases reported occurred during or within 30 minutes of the injection” (emphasis added).

*Reviewer Comment: With regard to the first statement, DRISK did not accept OPDP's comment because this issue is adequately addressed in the full presentation of risk information in this section of each education piece. The statement "The majority of these events lasted a few minutes and resolved with supportive measures," is included in the Prescribing Information and we include the next statement from the Prescribing Information, "Some events lasted up to several hours and in some cases, emergency care and/or hospitalization were required." We believe these two statements from the Prescribing Information present a complete presentation of the risks.*

*With regard to the second statement, "The majority of cases reported occurred during or within 30 minutes of the injection," DRISK did not accept OPDP's comment because during discussions with the review team, it was expressed that this was an accurate statement based on what is known about the time of onset of these reactions. Providing healthcare providers a rationale for the recommended 30 minute observation period may improve the likelihood that prescribers implement this measure. In addition, the training materials instruct healthcare providers to tell patients who to contact if they experience any signs or symptoms after leaving the healthcare setting. Therefore, we find it is acceptable to leave this statement in the Education Program.*

- These statements fail to adequately communicate the REMS goals which state, "Informing healthcare providers that AVEED can cause POME and anaphylaxis, which have the **potential to lead to** (b) (4) (emphasis added).
  - HCS Enrollment Form
    - "I understand the risks of serious pulmonary oil microembolism (POME) reactions and anaphylaxis following the administration of AVEED."
  - Webpage
    - "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 Introduction Piece
    - "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."

*Reviewer Comment: DRISK did not accept OPDP's comment because the complete risk messages are adequately addressed in the REMS training materials for both HCPs and Healthcare Setting authorized representatives. As this REMS program has a requirement for mandatory training to become certified in the REMS program, we do not believe that shortening the risk message from a communications perspective in the other materials will minimize the overall risk concept to REMS participants.*



#### 4 COMMENTS FOR THE APPLICANT

We consider this our final round of comments on the proposed Aved REMS providing you adequately address and incorporate our comments and revisions without any further changes or revisions.

The sections below include some highlights of our comments.

##### **REMS Document:**

1. Page 1: Include the month/year next to “initial REMS Approval: (b) (4)”
2. Page 2 – II.A.1.b.viii: Italicize “Healthcare Provider Enrollment Form.”

NOTE: Comments revisions on the materials are provided in the pdf version (not in the Word version attached to the REMS Document) with the exception of the Website landing pages.

See attached.

##### **Aved REMS website – landing pages found in the REMS document**

- Home page: no edits.
- HCP landing page:
  1. We agree that it is important that HCPs understand that healthcare settings must be enrolled in order to be able to receive Aved. (b) (4)

We suggest:

- Delete this as Step 1.
- Revise this step to "Step 4" or make it a "note" or "\*" at the bottom/end of the steps.
- Revise text to state: (b) (4)

**Make this a global change throughout all materials that include this presentation.**

2. Revise the following two statements (additional text is underlined) for clarity:

(b) (4) Non-prescribing Healthcare Providers who will administer Aved must be trained on the Aved REMS Education Program for Healthcare Providers.”

“Enrollment is not required for non-prescribing Healthcare Providers who will administer Aved.”

- HCS landing page: no edits.

#### **Healthcare Provider Enrollment Form**

1. Note above comment regarding revision of the “STEPS.”
2. Minor edits. See attached.

#### **Healthcare Settings Enrollment Form**

1. Minor edits. See attached.

#### **Aveed REMS Program: An Introduction**

1. Note above comment regarding revision of the “STEPS.”
2. Minor edits. See attached.

#### **AVEED REMS Education Program for Healthcare Providers**

1. Revise the following statement. (b) (4)  
[REDACTED] All patients must be observed for the 30mins regardless of signs or symptoms.

**Original:** [REDACTED] (b) (4)

**Revised:** "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."

2. Note the above comment regarding revision of the “STEPS.”
3. Minor edits. See attached.

#### **AVEED REMS Education Program for Healthcare Settings**

1. Note the above comment regarding revision of the statement, (b) (4)  
[REDACTED]
2. Minor edits. See attached.

#### **What You Need To Know About Aveed Treatment: A Patient Guide**

1. No edits. Not attached.

#### **Supporting Document**

1. Thank you for making edits to the Supporting Document to maintain consistency with the REMS Document and materials. Please continue to ensure that changes in the above materials are revised in the Supporting Document.

#### **Website Screenshots in the REMS Supporting Document**

1. Overall, the website is well done. We found the screen shots on pages 32 – 37 confusing. We advise that you
  - Include only the final versions (e.g., release 2) in the Supporting Document.
  - Include the same 3 landing pages (Home, HCP, and HCS) consistent with the screen shots appended to the REMS Document.
  - Remove (b) (4)

Pages 38 (Forms and Resources) onward are acceptable.

(b) (4)

## ATTACHMENTS

- REMS Document
  - Aveed REMS website – landing pages
- Healthcare Provider Enrollment Form
- Healthcare Settings Enrollment Form
- *Aveed REMS Program: An Introduction*
- *AVEED REMS Education Program for Healthcare Providers*
- *AVEED REMS Education Program for Healthcare Settings*
- REMS Supporting Document

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02/26/2014

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02/27/2014  
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**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: February 21, 2014

Reviewer(s): Suzanne Robottom, Pharm.D.  
Division of Risk Management (DRISK)

Kate Heinrich Oswell, M.A.  
Health Communications Analyst, DRISK

Team Leader: Cynthia LaCivita, Pharm.D., DRISK

Subject: Review of Endo Pharmaceutical Solutions' proposed  
REMS

Drug Name(s): Aveed (testosterone undecanoate)

Therapeutic Class: androgen

Dosage and Route: 750 mg/3 mL by intramuscular injection every 10 weeks

Application Type/Number: NDA 22219

Applicant/sponsor: Endo Pharmaceutical Solutions Inc

OSE RCM #: 2013-2138

## **1 INTRODUCTION**

This is a review of Endo Pharmaceutical Solutions Inc proposed risk evaluation and mitigation strategy (REMS) for testosterone undecanoate (Aveed) submitted via email on February 10, 2014 as an amendment to the August 29, 2013 complete response.

## **2 MATERIALS REVIEWED**

- Endo's proposed REMS. Submitted via email on February 10, 2014

### **Other DRISK reviews related to the August 29, 2013 submission**

- Robottom S. DRISK REMS review signed on February 11, 2014 by Robottom S and Willy M.
  - Assessment plan
- Robottom S. DRISK REMS review signed February 4, 2014 by Robottom S and Willy M.
  - Revised REMS Document, Introductory Information Sheet
- Robottom S. DRISK REMS review signed January 30, 2014 by Robottom S and Manzo C.
  - Healthcare Provider Enrollment Form, Healthcare Setting Enrollment Form, What You Need to Know About Aveed: A Patient Guide, REMS Education Program for Healthcare Providers, REMS Education Program for Healthcare Settings, website template.

## **3 RECOMMENDATIONS FOR THE REVIEW DIVISION**

The following comments on the Aveed REMS proposal should be sent to the applicant. Please advise the applicant to resubmit the REMS (e.g., REMS document and all REMS materials) and the revised REMS Supporting Document as soon as possible.

## **4 COMMENTS FOR THE APPLICANT**

Revise the materials to reflect any additional agreed-upon revisions to the labeling.

Once you have received comments on all the materials, we request that you re-submit the REMS materials via email for a final review.

All final REMS materials can be submitted via the gateway once they have been fully agreed upon by the Agency.

In general, the materials are well done. Please review each document carefully for all our comments and revisions. The sections below include some highlights of our comments.

### **1. REMS DOCUMENT**

We accepted the majority of your edits. Please note the following comments embedded in the REMS document regarding:

- Goals: We revised the goal sub-bullet to state: "... 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);..." this revisions should be a global change (i.e., REMS Supporting Document, HCP Enrollment Form).
- Aveed REMS Program: An Introduction: In addition to the call center, this piece can be provided through other healthcare provider interactions (e.g., sales force, medical information, meeting booths).
- Website: Attach three landing pages to the REMS document. (1) the main, homepage for the Aveed REMS website,(2) the healthcare provider landing page, and (3) the healthcare setting landing pages. No other pages need to be attached to the REMS document. In the REMS document, you do not need to specify that (b) (4).

These screenshots of the website should be an appendix to the REMS Supporting Document

- We revised the REMS document and all materials (with the exception of the Patient Guide; please maintain "office") to use "in the healthcare setting" uniformly. Please ensure this is a global change.
- Transferring Aveed to other healthcare facilities (2.b.iv): The revision is acceptable.

Please see the revised REMS Document (track changes; in Word). Please note we did not edit the materials following the REMS document. Comments on the REMS materials are provided in the individual mock-up pdfs.

## 2. REMS EDUCATION PROGRAM FOR HEALTHCARE PROVIDERS

- With regard to the following text on page 2:

(b) (4)

(b) (4)

(b) (4)

Therefore, please delete it. In parallel, delete this text (b) (4)

- Please revise the page breaks in this document to correspond to the different sections of information covered in the piece. The page breaks in the pdf version (compared to the web-based version) are awkward. We recommend incorporating similar breaks in the pdf version to mirror the web-based version.

- Knowledge Assessment Question 8: Revise the question as follows.

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

- Please see the complete set of comments/mark-up in the mock-up pdf.

### **3. REMS EDUCATION PROGRAM FOR HEALTHCARE SETTINGS**

- Please apply the applicable comments provided in the “REMS Education Program for HCPs”
- On page 1, revise the “Steps for Healthcare Setting Certification” to include 4 steps. “Step 1: Designate an authorized representative.” Maintain the other 3 steps as written.
- Please see the complete set of comments/mark-up in the mock-up pdf.

### **4. AVEED REMS PROGRAM: AN INTRODUCTION**

- Please see the complete set of comments/mark-up in the mock-up pdf.

### **5. WHAT YOU NEED TO KNOW ABOUT AVEED TREATMENT: A PATIENT GUIDE**

- Page 1 – Instructions to Patients/Healthcare Providers: Because of the amount of text in this section, the reverse text white font is difficult to read.

We acknowledge that this color scheme is consistent with the presentation in the other pieces. However, those pieces had less reverse text and more blank space in the orange background.

We recommend changing to a darker colored font to make the text more legible.

- Please see the complete set of comments/mark-up in the mock-up pdf.

### **6. HEALTHCARE PROVIDER ENROLLMENT FORM**



- Your interim proposal to capture healthcare provider specialty is acceptable.
- We anticipate that this form may be printed in black and white or faxed. We are concerned that some of the light-colored text will not be visible if printed in black and white or if the form is provided via fax.

We recommend you verify that the text is easily readable by practitioners if provided in black and white. We want to avoid any issues with delays in enrollment due to these type of issues.

- Please see the comments/mark-up in the mock-up pdf.

## **7. HEALTHCARE SETTING ENROLLMENT FORM**

- Your explanation for tracking healthcare provider certification and training for non-prescribing healthcare provider is acceptable.
- Your interim proposal to capture healthcare setting type is acceptable.
- Page 1 – Instructions: Revise to ensure that these steps are consistent with the 4 steps in the Introduction piece and REMS Education Program for Healthcare Settings.

Because of the amount of text in this section, the reverse text white font is difficult to read.

We acknowledge that this color scheme is consistent with the presentation in the other pieces. However, some of those pieces have less reverse text and more blank space in the orange background.

We recommend changing to a darker colored font to make the text more legible.

- Please see the complete set of comments/mark-up in the mock-up pdf.

## **8. WEBSITE – SCREEN SHOTS**

We reviewed the landing pages included in the REMS supporting document (submitted February 10, 2014) and the website word document submitted via email on February 14, 2014.

- The formatting of the website is acceptable unless otherwise noted. Any content edits on the print-version of the educational materials and enrollment forms need to be incorporated into the web-based equivalent.
- Incorporate revisions below to address our comments. A revised version of the screenshots is not attached.

### **AVEED REMS Homepage Landing Page**

- Consider adding the “My Account” tab back to the top of the Landing Page.

### **Healthcare Provider Certification Landing Page**

- We prefer the version of the HCP webpage sent in on Friday February 14, 2014 that allows for non-prescribers to access the training more easily. After the bullet “Non-Prescribing Healthcare Providers must also be trained on the AVEED REMS Education Program for Healthcare Providers,” include the following statements: “Enrollment is not required for Non-Prescribing Healthcare Providers. Click below to complete the training online.”
- Consider adding the “My Account” tab back to the top of the Landing Page.

### **Healthcare Setting Certification Landing Page**

- Consider adding the “My Account” tab back to the top of the Landing Page.

### **Healthcare Provider Education Pages**

- At the bottom of the “start page,” the button to forward to the next page states

(b) (4)

- Reformat this page so that there is a page break after the section: *What is the AVEED REMS?*

- Rename the button on bottom of both of these pages (b) (4)

- Remove the following language under the section (b) (4)

(b) (4)




### **Healthcare Provider Enrollment Pages**

We recognize that in the first submission of your supporting document on August 29, 2013 you included screen shots of the process to become certified, including website registration, responsibilities, and enrollment including the electronic signature. However, with the last submission of screen shots of February 14, 2014, the screen shots showing the certification process were not included.

Therefore we are missing important screen shots to show the complete process of registration and the complete enrollment process as depicted in the printed Enrollment Form.

- Resubmit screenshots (as an appendix to the Supporting Document) showing the complete process a healthcare provider would be taken through for online certification. Include specific screenshots showing website registration, the Education Program including the knowledge assessment, and enrollment including the electronic signature after reviewing the responsibilities.
- Please note that the phone number on the print form is required, but it is not required on the online version.

#### **Healthcare Setting Education Pages**

- At the bottom of the “start page,” the button to forward to the next page states (b) (4)  

  - Reformat this page so that there is a page break after the section: *What is the AVEED REMS?*
  - Rename the button on bottom of both of these pages (b) (4)
- On the “start page” for Healthcare Settings, the heading (b) (4)  
 should be modified to “Steps for Healthcare Setting Certification.”
  - Include the additional Step; Step 1- Designate an Authorized Representative and maintain the current steps as Steps 2, 3, and 4 as stated in our comments on the *REMS Education Program for Healthcare Settings* print version.
- Remove the following language under the section (b) (4)  


(b) (4)  


#### **Healthcare Setting Enrollment Pages**

We recognize that in the first submission of your supporting document on August 29, 2013 you included screen shots of the process to become certified, including

website registration and enrollment including the electronic signature. However, with the last submission of screen shots of February 14, 2014, the screen shots showing the certification process were not included. Therefore we are missing important screen shots to show the process of registration and the complete enrollment process.

- Resubmit screenshots (as an appendix to the Supporting Document) showing the complete process an authorized representative would be taken through for certification. Include specific screenshots showing website registration, the Education Program and enrollment including the electronic signature after reviewing the responsibilities.
- The data fields from the print version of the form and the online version do not match up and some data fields are not included on the online version. For example, “Setting Type” is included under the Authorized Healthcare Setting Representative section on the online version, but under the Healthcare Setting Information section on the print version. Also, the contact information for the Healthcare Setting (phone, fax and email) is missing on the online version of the form.

## **9. REMS SUPPORTING DOCUMENT**

- Page 3 - See revisions to the Background section. These revisions make this section consistent with the Aveed Prescribing Information.
- Page 5 - See revision to the Goals to be consistent with the REMS Document.
- Page 19 – Assessment Plan: See revisions to the Assessment Plan. These revisions are consistent with our previous comments. It does not appear that the assessment was revised to include the scope of the REMS Assessment.
- Please see the revised REMS Supporting Document (track changes; in Word).

## **10. GENERAL COMMENTS**

Resubmission Requirements and Instructions: Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

Format Request: Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single MS Word document.

## **ATTACHMENTS**

- Revised REMS Document (track changes)
- REMS Education Program For Healthcare Providers
- REMS Education Program For Healthcare Settings
- Aveed REMS Program: An Introduction
- Healthcare Provider Enrollment Form
- Healthcare Setting Enrollment Form
- What You Need To Know About Aveed Treatment: A Patient Guide
- Revised REMS Supporting Document (track changes)

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02/21/2014

CYNTHIA L LACIVITA  
02/22/2014  
Concur

## **Risk Evaluation and Mitigation Strategy (REMS) Memorandum Addendum**

**U.S. FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
Office of Drug Evaluation III  
Division of Bone, Reproductive and Urologic Products**

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<b>NDA/BLA #s:</b>	22-219
<b>Products:</b>	Aveed (testosterone undecanoate) injection
<b>APPLICANT:</b>	Endo Pharmaceuticals Inc.
<b>FROM:</b>	Christine P. Nguyen, M.D.
<b>DATE:</b>	February 19, 2014

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This addendum updates the REMS memorandum dated May 28, 2013, and signed by Christine P. Nguyen. The May 2013 memo stated that a Medication Guide and Elements to Assure Safe Use (ETASUs) would be required under the REMS program for Aveed to adequately mitigate the risks of post-injection serious pulmonary microembolization (POME) and anaphylaxis. The elements to assure safe use are that healthcare providers who prescribe or dispense testosterone undecanoate are specially certified and health care settings that dispense testosterone undecanoate are specially certified, and an implementation system.

In the Complete Response letter issued on May 29, 2013, the Division of Bone, Reproductive, and Urologic Products stated that Aveed's REMS program must provide for a Medication Guide and ETASUs described above, and a timetable of assessment to ensure that the benefits of the drug outweigh the risks of post-injection serious POME and anaphylactic reactions. The sponsor submitted a Complete Response on August 29, 2013, proposing a revised REMS program that includes a Medication Guide, a communication plan, the required ETASUs, and a timetable of REMS assessment.

Medication Guide: After further discussions between OND and OSE, it was determined that the Medication Guide will be maintained as a part of labeling under 21 CFR 208 and a concise patient counseling document to specifically address the risk of serious post-injection reactions will be developed and included as part of the REMS. This document will serve as the primary REMS patient education tool and healthcare providers must agree, as part of the REMS healthcare provider and healthcare setting certification, to provide it to each patient.

Communication Plan: The May 29, 2013, Complete Response letter did not require Endo to submit a proposed communication plan. However, Endo included a proposed communication plan (consisting of a Dear Healthcare Provider (b) (4) ) as part of their August 29, 2013, CR submission.

Because Aveed is another testosterone therapy and the third injectable testosterone ester to be approved, OND and OSE considered that a more targeted communication approach was more practical and less burdensome. OND and OSE agreed that a concise, one-page general introductory information piece to communicate the risks and Aveed REMS program information as a component under the ETASUs, is sufficient. This introductory piece will be available to

healthcare providers and healthcare settings requesting general information about Aveed and the Aveed REMS program.

Therefore, the Aveed REMS program consists of Elements to Assure Safe Use, including that healthcare providers who prescribe or dispense Aveed (testosterone undecanoate) are specially certified and healthcare settings that dispense Aveed are specially certified, an implementation system, and a timetable of assessment.



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/s/  
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CHRISTINE P NGUYEN  
02/20/2014

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review - ADDENDUM**

Date: February 11, 2014

Reviewer(s): Suzanne Robottom, Pharm.D.  
Division of Risk Management (DRISK)

Subject: Review of the Endo's proposed REMS – Assessment Plan

Team Leader: Cynthia LaCivita, Pharm.D.  
DRISK

Division Director: Claudia Manzo, Pharm.D.  
DRISK

Drug Name(s): testosterone undecanoate (Aveed)

Therapeutic Class: androgen

Dosage and Route: 750 mg/ 3mL by intramuscular injection every 10 weeks

Application Type/Number: NDA 22219

Applicant/sponsor: Endo Pharmaceuticals Solutions Inc

OSE RCM #: 2013-2138

## **1 INTRODUCTION**

This is an **addendum** to the January 30, 2013 DRISK review of Endo's proposed risk evaluation and mitigation strategy (REMS) for Aveed (testosterone undecanoate) NDA 22219 received on August 29, 2013 and submitted in response to the Division of Bone Reproductive and Urologic Products (DBRUP) Complete Response (CR) letter issued May 29, 2013.

This addendum includes a revised REMS Assessment Plan

## **2 MATERIALS REVIEWED**

- Endo's proposed REMS submitted August 29, 2013. (Sequence No 0024)

## **3 RECOMMENDATIONS FOR THE REVIEW DIVISION**

The following comments on the Aveed REMS proposal should be sent to the applicant.

## **4 COMMENTS FOR THE APPLICANT**

### **1. REMS ASSESSMENT**

Please see the revised REMS Assessment.

#### **A. REMS Program Outreach**

The following data will be tabulated for each reporting period and cumulatively:

1. Number of Introductory Information Sheets (Aveed REMS Program: An Introduction) provided to prescribers and stratified by method of distribution and recipient.
2. Number of unique visits to the Aveed REMS website

#### **B. Program Utilization Statistics**

The following data will be tabulated for each reporting period and cumulatively:

1. Prescribing healthcare providers
  - a. Number of prescribing healthcare providers enrolled and stratified by medical specialty and method of enrollment (i.e., online or via fax)
  - b. Number of healthcare providers with incomplete enrollment

- c. Number of attempts needed for healthcare providers to complete the Knowledge Assessment and summary of most frequently missed questions.
  - d. Number of healthcare providers who were unable to enroll because they were unable to complete the knowledge assessment.
- 2. Non-prescribing healthcare providers
    - a. Number of non-prescribing healthcare providers who completed education using the Aveed REMS Program website.
  - 3. Healthcare Settings
    - a. Number of healthcare settings enrolled stratified by type of practice setting and method of enrollment (i.e., online or via fax)
    - b. Number of healthcare settings with incomplete enrollment
  - 4. Number of entities distributing Aveed
  - 5. Number of shipments sent to non-certified healthcare settings or to certified healthcare settings that do not have certified healthcare providers.

### **C. Program Infrastructure and Performance**

The following metrics on program infrastructure and performance will be tabulated for each reporting period:

- 1. Summary of Call Center frequently asked questions
- 2. Summary of program problems reported
- 3. Description of corrective actions taken to address program or system problems
- 4. Number of prescribers inactivated for noncompliance with the AVEED REMS Program requirements. Include a summary of reasons for inactivation.
- 5. Number of healthcare settings inactivated for noncompliance with the AVEED REMS Program. Include a summary of reasons for inactivation.

6. Summary of audits performed during the reporting period including but not limited to:
  - a. an overview of the site-audit plan
  - b. the number of site-audits performed
  - c. summary report of the processes healthcare settings are implementing to be in compliance with the AVEED REMS Program requirements
  - d. summary report of serious or critical deviations found and corrective action taken.

## **E. Knowledge Evaluations**

Endo will conduct healthcare provider (both prescribing and non-prescribing healthcare provider) and patient surveys at 1 and 2 years after initial approval of the REMS. If the product does not launch within 6 months of approval, surveys will be conducted at 2 and 3 years after initial approval of the REMS. The surveys will evaluate:

1. Healthcare provider understanding of the serious risks (serious POME reactions and anaphylaxis) of AVEED and need for and compliance with the 30 minute observation period
2. Patient understanding of the serious risks (serious POME reactions and anaphylaxis) of AVEED and need for and compliance with the 30-minute observation period

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

## **2. Developing your Survey Methodology and Surveys**

The following comments are to assist you in drafting your survey methodology and survey.

Submit for review the detailed plan you propose to use to evaluate patients', healthcare providers' understanding about the safe use of Aveed. You may submit the proposed plan after approval of the REMS, however submit it at least 90 days before you conduct the evaluation. Code the submission "REMS Correspondence." If the plan is to conduct

the required assessment using a survey, make sure the submission includes all methodology and instruments used to evaluate the knowledge about the risks associated with and safe use of Aveed.

1. Recruit respondents using a multi-modal approach. For example, you might recruit respondents through physicians' offices, pharmacies, managed care providers, consumer panels, or on-line.

Explain how often you perform non-respondent follow-up or reminders.

If you use an incentive or honorarium, provide details on what is offered and the estimated dollar value.

Explain how you select recruitment sites.

Submit for review any recruitment advertisements.

2. Describe the rationale for your sample size. Report the 95% confidence interval around the expected level(s) of patient knowledge for each key risk(s).
3. Define the expected number of people to be contacted to obtain the proposed sample size, and how the sample is determined (selection criteria).
4. Ensure the sample is demographically representative of the population who use the drug (patients), prescribe the drug (doctors), or dispense the drug (nurses, doctors), regardless of the condition for which they use or prescribe it.
5. When possible and appropriate, ensure the sample is diverse in terms of age, race, ethnicity, sex, socio-economic status, education level, and geographically.
6. List the inclusion criteria for patients and healthcare providers. For example, eligible *patient* respondents must be:
  - Age 18 or older
  - Currently taking Aveed or have taken the drug in the past 3 months
  - Not currently participating in a clinical trial involving Aveed
  - Not a healthcare provider

Submit any screener instruments, and describe any quotas of sub-populations used.

7. Explain how you administer surveys and the intended frequency.

Offer respondents multiple options for completing the survey. Be sure to include an option for the lower literacy population. For example, respondents might complete surveys online or through email, in writing or by mail, over the phone, and in person.

Explain how you train surveyors.

8. Explain how you control for limitations or bias associated with the methodology and survey instrument(s).
9. Submit for review the introductory text used to inform respondents about the purpose of the survey.

Tell potential respondents that their answers will not affect their ability to receive or take (patients), prescribe (doctors), or dispense (nurses, doctors) Aved, and that their answers and personal information will be kept confidential and anonymous.

All text, including questions and answers, are to be non-promotional in language and tone.

10. Clarify in your methodology that respondents are eligible for one wave of the survey only.
11. Analyze results on an item-by-item or variable-by-variable basis. You may present the data using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables).

You may stratify the data by any relevant variable, and also in aggregate. Submit with your assessments all methodology and instruments utilized.

12. Submit all methodology and instruments utilized with your assessments.

## Patient Survey

13. The assessment evaluates the effectiveness of the REMS in achieving the goal by evaluating patients' knowledge of the serious risks associated with use of the drug.

Do not offer respondents an opportunity to read or see *What You Need To Know About AVEED Treatment: A Patient Guide*, the Medication Guide, Package Insert, or any other related educational materials again prior to taking the survey.

14. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in *What You Need To Know About AVEED Treatment: A Patient Guide*.
15. Ensure the patient knowledge survey includes questions that ask about the specific risks or safety information conveyed in *What You Need To Know About AVEED Treatment: A Patient Guide* to determine if the patient understands the information and knows what to do if they experience an adverse event.

Ensure the risk-specific questions are not biased or leading, and that multiple choice questions include an instruction to "select all that apply." Answer options should include an appropriate number of foils. Ensure that each question has an "I don't know" answer option.

Randomize the order of the multiple choice responses on each survey.

16. Order questions so the risk-specific questions are asked first, followed by questions about receipt of *What You Need To Know About AVEED Treatment: A Patient Guide*. Collect demographic questions last or as part of any screener questions.

Do not allow respondents the opportunity or ability to go back to previous questions in the survey.

Explain if and when any education will be offered for incorrect responses.

17. Include questions about receipt of *What You Need To Know About AVEED Treatment: A Patient Guide* in the patient survey.



18. Prior to the questions about receipt of *What You Need To Know About AVEED Treatment: A Patient Guide*, include text that describes this patient education piece. For example,

Now we are going to ask you some questions about *What You Need To Know About AVEED Treatment: A Patient Guide* you may have received with Aveed. *What You Need To Know About AVEED Treatment: A Patient Guide* is a paper handout that contains important information about certain risks associated with use of Aveed. [include more descriptive information here.]

19. Use the following (or similar) questions to assess receipt and use of *What You Need To Know About AVEED Treatment: A Patient Guide*.

- Who gave you *What You Need To Know About AVEED Treatment: A Patient Guide* for Aveed? (Select all that apply)
  - a) My doctor or someone in my doctor's office
  - b) Someone else - please explain: \_\_\_\_\_
  - c) I did not get a *What You Need To Know About AVEED Treatment: A Patient Guide*
- Did you read *What You Need To Know About AVEED Treatment: A Patient Guide*
  - a) All,
  - b) Most,
  - c) Some,
  - d) None
- Did you understand what you read in *What You Need To Know About AVEED Treatment: A Patient Guide*?
  - a) All,
  - b) Most,
  - c) Some,
  - d) None
- Did someone offer to explain to you the information in *What You Need To Know About AVEED Treatment: A Patient Guide*?
  - a) Yes, my doctor or someone in my doctor's office
  - b) Yes, someone else – please explain: \_\_\_\_\_
  - c) No

- Did you accept the offer? Yes or No
- Did you understand the explanation that was given to you?
  - a) All,
  - b) Most,
  - c) Some,
  - d) None
- Did or do you have any questions about *What You Need To Know About AVEED Treatment: A Patient Guide*? Yes or No (If Yes, list your question(s) below)  
 Note: Group/code this open text field prior to submitting to FDA

### **Healthcare Provider Survey**

20. The assessment evaluates how effective the REMS is in achieving the goal(s) by evaluating healthcare providers' knowledge of the risks and safe use associated with Aveed.

The assessment does not assess healthcare providers' comprehension of the educational materials.

Do not offer respondents an opportunity to read or see any educational materials (prescribing information, communications, promotional materials, websites, videos, etc.) again prior to taking the survey.

21. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in any educational materials.
22. Ensure the healthcare provider knowledge survey includes a section with questions asking about the specific risks and safety information conveyed in the educational materials.

Ensure questions are not biased or leading, and that multiple choice questions include an instruction to "select all that apply." Answer options should include an appropriate number of foils. Ensure each question has an "I don't know" answer option.

Randomize the order of the multiple choice responses on each survey.

23. Order the survey questions so the risk-specific questions are asked first, followed by questions about receipt of the educational materials. Collect demographic questions last or as part of any screener questions.

Do not allow respondents the opportunity or ability to go back to previous questions in the survey.

Explain if and when any education will be offered for incorrect responses.

24. Use the following (or similar) questions to assess receipt and use of the educational materials.

- Prior to today, which of the following were you aware of or received with regard to Aveed? (Select all that apply)

<b>Educational Material</b>	<b>Aware</b>	<b>Received</b>
Full Prescribing Information	<input type="checkbox"/>	<input type="checkbox"/>
<i>Aveed REMS Program: An Introduction</i>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Aveed REMS Education Program for Healthcare Providers</i>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Aveed REMS Education Program for Healthcare Settings</i>	<input type="checkbox"/>	<input type="checkbox"/>
Something else - please explain:	<input type="checkbox"/>	<input type="checkbox"/>
None of the above	<input type="checkbox"/>	<input type="checkbox"/>

- Did you read the Full Prescribing Information?
  - a) All,
  - b) Most,
  - c) Some,
  - d) None
  - e) I did not receive the Aveed Full Prescribing Information
- Did you read the *Aveed REMS Program: An Introduction*?
  - a) All,
  - b) Most,
  - c) Some,

- d) None
  - e) I did not receive the *Aveed REMS Program: An Introduction*
- Did you read the *Aveed REMS Education Program for Healthcare Providers/Healthcare Settings*?
  - a) All,
  - b) Most,
  - c) Some,
  - d) None
  - e) I did not receive the *Aveed REMS Education Program for Healthcare Providers/Healthcare Settings*
- Do you have any questions about any of the educational materials related to Aveed? Yes or No (If Yes, list your question(s) below) Note: Group/code this open text field prior to submitting to FDA

### 3. GENERAL COMMENTS

Resubmission Requirements and Instructions: Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

Format Request: Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single MS Word document.

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/s/  
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SUZANNE C BERKMAN ROBOTOM  
02/11/2014

MARY E WILLY  
02/11/2014  
I concur

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review - ADDENDUM**

Date: February 4, 2014

Reviewer(s): Suzanne Robottom, Pharm.D.  
Division of Risk Management (DRISK)

Subject: Review of the Endo's proposed REMS – REMS Document  
& Introductory Information Sheet

Team Leader: Cynthia LaCivita, Pharm.D.  
DRISK

Division Director: Claudia Manzo, Pharm.D.  
DRISK

Drug Name(s): testosterone undecanoate (Aveed)

Therapeutic Class: androgen

Dosage and Route: 750 mg/ 3mL by intramuscular injection every 10 weeks

Application Type/Number: NDA 22219

Applicant/sponsor: Endo Pharmaceuticals Solutions Inc

OSE RCM #: 2013-2138

## **1 INTRODUCTION**

This is an **addendum** to the January 30, 2013 DRISK review of Endo's proposed risk evaluation and mitigation strategy (REMS) for Aveed (testosterone undecanoate) NDA 22219 received on August 29, 2013 and submitted in response to the Division of Bone Reproductive and Urologic Products (DBRUP) Complete Response (CR) letter issued May 29, 2013.

This addendum includes:

- a revised REMS document with track changes, and
- an education piece titled "AVEED REMS Program: An Introduction."

## **2 MATERIALS REVIEWED**

- Endo's proposed REMS Document submitted August 29, 2013. (Sequence No 0024)

## **3 RECOMMENDATIONS FOR THE REVIEW DIVISION**

The following comments on the Aveed REMS proposal should be sent to the applicant. Please advise the applicant to resubmit the REMS (e.g., REMS document and all REMS materials) and the REMS Supporting Document as soon as possible.

The comments below are based on DRISK's preliminary review of the REMS proposal for Aveed. Appended to this addendum are the revised REMS document and an education piece titled "AVEE REMS Program: An Introduction."

## **4 COMMENTS FOR THE APPLICANT**

### **1. REMS DOCUMENT**

Please see the revised REMS document with comments and track changes.

To ensure the safe use of Aveed, it is necessary for Aveed only to be available for dispensing and administration by a healthcare provider in a healthcare facility and not dispensed directly to a patient. The REMS, as revised and appended, requires that Endo ensure that Aveed can only be dispensed in healthcare settings that are certified.

How you distribute Aveed to ensure compliance with the Controlled Substance Act is a matter under the purview of the Drug Enforcement Agency.

#### **A. MEDICATION GUIDE**

Remove the Medication Guide from the REMS. The Medication Guide will be part of labeling.

Comment on the Medication Guide will be provided under separate cover.

#### **B. COMMUNICATION PLAN**

Remove the Communication Plan from the REMS. This will remove the "Dear Healthcare Provider Letter," (b) (4)

(b) (4) We recommend a single introductory information piece be distributed as part of the elements to assure safe use to communicate information about the risks and REMS program requirements.

Please see the attached “Aveed REMS Program: An Introduction.”

## **2. REMS SUPPORTING DOCUMENT**

The REMS Supporting Document must be consistent with all changes made to the REMS document.

## **3. GENERAL COMMENTS**

Resubmission Requirements and Instructions: Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

Format Request: Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single MS Word document.

## **ATTACHMENTS**

- **Revised REMS document**
- **Aveed REMS Program: An Introduction**

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/s/  
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SUZANNE C BERKMAN ROBOTOM  
02/04/2014

MARY E WILLY  
02/05/2014  
I concur and sign for Claudia Manzo

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: January 30, 2014

Reviewer(s): Suzanne Robottom, Pharm.D.  
Division of Risk Management (DRISK)

Subject: Review of the Endo's proposed REMS

Team Leader: Cynthia LaCivita, Pharm.D.  
DRISK

Division Director: Claudia Manzo, Pharm.D.  
DRISK

Drug Name(s): testosterone undecanoate (Aveed)

Therapeutic Class: androgen

Dosage and Route: 750 mg/ 3mL by intramuscular injection every 10 weeks

Application Type/Number: NDA 22219

Applicant/sponsor: Endo Pharmaceuticals Solutions Inc

OSE RCM #: 2013-2138

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## 1 INTRODUCTION

This is a review of Endo's proposed risk evaluation and mitigation strategy (REMS) for Aveed (testosterone undecanoate (TU)) NDA 22219 received on August 29, 2013 and submitted in response to the Division of Bone Reproductive and Urologic Products (DBRUP) Complete Response (CR) letter issued May 29, 2013.

DRISK and DBRUP determined a REMS was necessary to address the risks of serious pulmonary oil microembolism (POME) reactions and anaphylaxis associated with TU.

For an analysis of the benefits, risks, and risk management options for TU, please refer to the DRISK review signed in DARRTS on May 29, 2013.

### 1.1 BACKGROUND

TU is under review for 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)

The proposed dosing of TU consists of an initial intramuscular injection of 3 mL (750 mg), a second 3 mL dose injected 4 weeks later, and then 3 mL injected every 10 weeks thereafter.

A joint meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and the Reproductive Health Drugs (RHD) Advisory Committee was held on April 18, 2013 to discuss the application. The Committee vote was split (9-9) in response to "...do you believe that TU is safe for the proposed indication?" The Committee voted 17-1 that labeling alone was not sufficient to ameliorate the risk of severe post-injection reactions.

In subsequent discussions within the Agency, there was recognition that some patients may prefer a longer acting Testosterone Replacement Therapy injectable product particularly those who require lifelong testosterone therapy. DRISK and DBRUP, with concurrence from the CDER senior management, agreed that prescribers and patients should be informed of the risks, and after thoughtful consideration, the decision to use this product should be between the patient and prescriber. TU should be administered only in healthcare settings able to manage serious POME and anaphylaxis reactions and the patient should be observed following the injection for a period of time as described in the label (e.g., for at least 30 minutes).

On May 29, 2013 DBRUP issued a CR letter citing the need for a REMS with elements to assure safe use as outlined below:

- **Medication Guide**

- **Elements to Assure Safe Use (ETASU):** We have determined that elements to assure safe use are necessary to mitigate the risks and severe complications related to post-injection reactions (POME and anaphylaxis) as will be listed in the labeling. In addition, we have determined that a Medication Guide and a communication plan alone are not sufficient to mitigate the serious risks. Your REMS must include tools to manage these risks, including at least the following:
  1. **Healthcare providers who prescribe or dispense testosterone undecanoate are specially certified.**
    - A. Develop an educational program that will train prescribers about the risk of severe post-injection reactions, measures necessary to mitigate these risks, and tools to prompt a discussion between patients and prescribers about the risks.
    - B. In order for the health care providers to be certified, each prescriber must undergo the educational training program and enroll in your REMS program.
    - C. Maintain a list of the prescribers who have obtained the certification.
  2. **Healthcare settings that dispense testosterone undecanoate injection are specially certified.**
    - A. In order for a health care setting to be certified, an authorized representative will complete a REMS enrollment form and agree to ensure that all health care providers who prescribe or dispense testosterone undecanoate injection are certified, that staff are properly trained and comply with all program requirements, that the health care setting is able to manage POME and anaphylaxis reactions, order testosterone undecanoate injection only from distributors enrolled in your REMS program, and have procedures in place to ensure compliance with the REMS requirements.
    - B. Maintain a list of the healthcare settings who have obtained the certification.
- **Implementation System:**

The REMS must include an implementation system to monitor and evaluate the implementation of the elements to assure safe use (outlined above) required under 505-1(f)(3). Include an intervention plan to address any findings of non-compliance with the elements to assure safe use and to address any findings that suggest an increase in risk.
- **Timetable for Submission of Assessments:**

The proposed REMS must include a timetable for submission of assessments that shall be 6 months and 1 year from the date of the 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.

Each assessment must assess the extent to which the elements to assure safe use of your REMS are meeting the goals of your REMS and whether the goals or elements should be modified.

## **2 MATERIALS REVIEWED**

- Endo's proposed REMS submitted August 29, 2013. (Sequence No 0024)
- DBRUP NDA 22219 Complete Response Letter dated May 29, 2013
- Robottom S. DRISK REMS Options review for NDA 22219. Signed in DARRTS on May 29, 2013 by Robottom S and Manzo C.

The proposed REMS document for Aveed was reviewed and compared to the approved REMS with ETASU for Adasuve (approved December 21, 2012), Juxtapid (approved December 21, 2012), and Xiaflex (approved December 6, 2013).

## **3 SUMMARY OF APPLICANT'S PROPOSED REMS**

Endo submitted a REMS with ETASU consistent, in principle, with the REMS outlined in the May 29, 2013 CR letter. The proposed REMS describes requirements for prescribers and healthcare settings to certify in order to prescribe, procure, and administer TU.

### **3.1 Goals**

Endo proposed the following goals for the Aveed REMS:

- Healthcare professionals (HCPs) and patients understand the risks of injection-based pulmonary oil microembolism (POME) and anaphylaxis following the administration of AVEED
- Patients remain at the healthcare setting for 30 minutes following injection to allow for early recognition and management of injection-based POME or anaphylaxis following the administration of AVEED

*Reviewer Comments: The goals of the REMS must be revised to include the overarching goal of mitigating the negative outcomes associated with AVEED-induced POME and AVEED-induced anaphylaxis followed by measureable objectives. This approach reflects DRISK's most current thinking and framework for writing goals based on the experience gained over the last several years of reviewing REMS and analyzing if the REMS is meeting its goals via the REMS assessments.*

*The revised REMS document will be available in an addendum to this review.*

### 3.2 Medication Guide

Endo has included the Medication Guide (MG) as an element of the REMS

*Reviewer Comments: The May 29, 2013 CR letter stated that the proposed REMS should include a MG as an element of the REMS. DRISK consulted both DBRUP and Office of Medical Policy Patient Labeling Team and together agreed that the Medication Guide should be maintained as part of labeling and that a concise patient counseling tool should be developed and included as part of the REMS. This tool will serve as the primary, REMS education piece for patients to explain the risks addressed through the REMS in a readable and consumer-friendly format.*

### 3.3 Communication Plan

Endo proposed a communication plan as an element of the REMS to support implementation of the Aveed REMS which includes a one-time letter to urologists, endocrinologists, and designated primary care physicians.

*Reviewer Comments: The May 29, 2013 CR did not require Endo to submit a proposed communication plan as part of the Aveed REMS. However, Endo included a communication plan (consisting of a Dear Healthcare Provider (b) (4) ) as part of their August 29, 2013 submission.*

*Given that Aveed is another testosterone treatment and it is not expected to be used broadly across a wide variety of specialty areas, we considered a more targeted communication approach was more practical and less burdensome than wide dissemination of a Dear Healthcare Provider letter. Therefore, DRISK recommends removing the proposed communication plan and create a short, introductory information sheet to communicate information about the risks and REMS program requirements. DRISK recommends the information sheet be distributed to healthcare providers either via sales representatives, at the time of first discussion of Aveed, or at the time a healthcare provider attempts to order Aveed and is not certified, or if a healthcare provider requests information about how to become certified.*

*The introductory information sheet supports both the prescriber and the healthcare setting certification requirements and, as such, should be included as part of those corresponding elements to ensure that any future abbreviated new drug applicants (ANDAs) would distribute a similar piece in a similar manner.*

*The Introductory Information Sheet will be available in an addendum to this review.*

### 3.4 Elements to assure safe use (ETASU)

The proposed REMS include the following ETASU that includes:

- Healthcare providers who prescribe or dispense testosterone undecanoate are specially certified.
- Healthcare settings that dispense testosterone undecanoate injection are specially certified.

*Reviewer Comments: The proposed ETASU are consistent with what was outlined in the CR letter, however the elements as described in the REMS document and enrollment forms will require revisions to align with the Agency's current thinking.*

*The revised REMS document will be available in an addendum to this review.*

- **Controlled Substance Distribution**

Testosterone is a controlled, Schedule III substance. As such in addition to requiring a REMS as part of approval to address serious risks, TU must also be procured, stored, and dispensed in compliance with the Controlled Substance Act (CSA). Endo's initial REMS proposal includes a distribution plan utilizing two mechanisms to distribute Aveed through 1) specialty distributors shipping Aveed in bulk directly to the certified healthcare settings, and 2) specialty pharmacies shipping filled Aveed prescriptions to the prescriber and not the patient named on the prescription. To maximize the safe use of Aveed, we agree that it is necessary for Aveed only to be available for dispensing and administration by a healthcare provider in a healthcare facility and not dispensed directly to a patient. However, because Aveed would be a Schedule III drug subject to the CSA, it is our understanding that a pharmacy filling a prescription must dispense/ship Aveed directly to the patient. Therefore, Endo must ensure that distribution of Aveed must address both the safe use conditions determined necessary for Aveed and be in compliance with the CSA.

This issue was brought to Endo's attention on December 19, 2013. Endo stated that they met with representatives from the Drug Enforcement Agency on January 14, 2014. After the meeting, they stated to DBRUP via email that they "are completely confident that our potential engagement of either or both types of distributors proposed in our REMS submission will meet both the safe use conditions required for approval AND the requirements of the CSA."

Per the usual REMS review process, the Office Chief Counsel (OCC) reviewed the REMS document. OCC does not believe the REMS document, as revised, is in conflict with the CSA. The REMS does not include certification of pharmacies or distributors. However, the REMS document states that Aveed can only be dispensed in healthcare settings that are certified which is the primary safe use condition for Aveed. Therefore, any entity distributing Aveed, must distribute Aveed to a certified healthcare setting.

*Reviewer Comment: The revised REMS document will be available in an addendum to this review.*

### **3.5 Implementation System**

Endo has included an implementation system for the AVEED REMS Program to monitor and evaluate whether the elements to assure safe use are meeting the program's goals.

*Reviewer Comments: The proposed implementation system will require revisions to align with the Agency's current thinking regarding monitoring and evaluating whether the elements to assure safe use are meeting the program goals.*

### **3.6 Timetable for Submission 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.

*Reviewer Comments: This is acceptable.*

#### **4 CONCLUSION**

While the proposed REMS, in principle, is consistent with the REMS outlined in the May 29, 2013 CR, the REMS document and materials require revision to be consistent with CDER's most current thinking on REMS and the final labeling for TU. Additional comments and/or final recommendations for approval will be captured in subsequent reviews.

#### **5 RECOMMENDATIONS FOR THE REVIEW DIVISION**

The following comments on the Aveed REMS proposal should be sent to the applicant. Please advise the applicant to resubmit the REMS (e.g., REMS document and all REMS materials) and the REMS Supporting Document once they have received comments on all the pieces.

The comments below are based on DRISK's preliminary review of the REMS proposal for Aveed. Appended to this review are some of the REMS materials with track changes.

#### **6 COMMENTS FOR THE APPLICANT**

##### **1. REMS DOCUMENT**

The revised REMS document will be provided under separate cover.

##### **o Enrollment**

- o Clarify if a prescriber can begin the online enrollment process and resume the process or if he/she must restart the process.
- o Explain how the Healthcare Provider Enrollment and Healthcare Setting Enrollment will work. For example, how will you ensure that Aveed will not be shipped until a healthcare setting is certified and has a prescriber certified?

##### **2. MATERIALS**

We appreciate your efforts to provide consumer-tested materials. In effort to condense the materials and use language consistent with the label, we have revised the materials keeping in mind the valuable feedback from the pretesting.

Please note that the Aveed-specific content of the revised materials is consistent with the FDA-revised labeling you received on January 28, 2014.

##### **A. Patient Materials**

- o You propose to educate patients through (b) (4) the Medication Guide (b) (4)

(b) (4) We recommend a single, patient-directed piece focused on the risks addressed through the REMS.

- Please see the attached patient counseling tool titled “What You Need To Know About AVEED Treatment: A Patient Guide.” We remind you that What You Need To Know About AVEED Treatment: A Patient Guide must be consistent with final labeling. Therefore, we expect additional changes.

## **B. Healthcare Provider/Prescriber Materials**

- We recommend (b) (4)
- Please see the revised “REMS Education Program for Healthcare Providers.”
- (b) (4)
  - i. Revise the title of this form to “Healthcare Provider Enrollment Form.”
  - ii. See the revised form.

## **C. Healthcare Setting Materials**

- We recommend (b) (4)  
“REMS Education Program for Healthcare Settings” (b) (4)
- Please see the revised “REMS Education Program for Healthcare Settings.”
- Please see the revised “Healthcare Setting Enrollment Form.”

## **D. Website**

- Submit the REMS program website for review.
  - Ensure the REMS website, is independent of link to the promotional and/or commercial website and non-REMS materials about the product. Do not include a link from the REMS website back to the [www.aveed.com](http://www.aveed.com) website. The REMS website should also be accessible directly through a search engine.
  - Submit screen shots and actual layout for the Aveed REMS website.
  - We remind you to use bullets, moderate white space, shorter line lengths, and fewer lines of text when possible when developing your website. The following is a link to helpful guidelines developed by HHS that you may consider in developing your website.  
[http://www.usability.gov/sites/default/files/documents/guidelines\\_book.pdf?post=yes](http://www.usability.gov/sites/default/files/documents/guidelines_book.pdf?post=yes)

- See proposed REMS website template attached which includes a template landing page, healthcare provider page, and healthcare setting page.

### **3. REMS SUPPORTING DOCUMENT**

The REMS Supporting Document must be consistent with all changes made to the REMS document.

### **4. GENERAL COMMENTS**

Resubmission Requirements and Instructions: Once you have received comments on all the pieces submit the amended REMS (e.g., REMS document and all REMS materials) and the amended REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

Format Request: Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single MS Word document.

### **ATTACHMENTS**

- **Healthcare Provider Enrollment Form**
- **Healthcare Setting Enrollment Form**
- **What You Need To Know About AVEED Treatment: A Patient Guide**
- **REMS Education Program for Healthcare Providers**
- **REMS Education Program for Healthcare Settings**
- **Website template**

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**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Options Review**

Date: May 29, 2013

Reviewer(s): Suzanne Robottom, Pharm.D.  
Division of Risk Management (DRISK)

Team Leader: Cynthia LaCivita, Pharm.D.  
DRISK

Division Director: Claudia Manzo, Pharm.D.  
DRISK

Drug Name(s): Testosterone undecanoate

Therapeutic Class: Androgen

Dosage and Route: 750 mg / 3mL by intramuscular injection every 10 weeks

Application Type/Number: 22219

Applicant/sponsor: Endo Pharmaceuticals

OSE RCM #: 2012-2947; 2013-252

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## EXECUTIVE SUMMARY

This review provides an analysis of the risk management options and the sponsor's proposed Risk Evaluation and Mitigation Strategy (REMS) submitted on November 29, 2012 to address the risk of pulmonary oil microembolism (POME) and anaphylaxis adverse events associated with testosterone undecanoate (TU) injection.

The Division of Bone, Reproductive, and Urologic Products (DBRUP) has maintained that the primary reason for lack of approval was and continues to be that the benefits of TU (taken in light of the availability of alternative products for the indication) do not outweigh the risk of serious POME and anaphylaxis events. A joint meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and the Reproductive Health Drugs (RHD) Advisory Committee was held on April 18, 2013 to discuss the application. The Committee vote was split (9-9) in response to "...do you believe that TU is safe for the proposed indication?" The Committee voted 17-1 that labeling alone was not sufficient to ameliorate the risk of severe post-injection reactions.

In subsequent discussions within the Agency, there was recognition that some patients may prefer a longer-acting Testosterone Replacement Therapy (TRT) injectable product particularly those who require lifelong testosterone therapy. All agreed that prescribers and patients should be informed of the risks, and, after thoughtful consideration, the decision to use this product should be between the patient and prescriber. TU should be administered only in healthcare settings equipped with appropriate resuscitative equipment and the patient should be observed following the injection for a period of time as described in the label (e.g., for at least 30 minutes). To accomplish this, DRISK proposed the following REMS with ETASU:

- Medication Guide
- Certification of healthcare providers
- Dispensing TU only in certain healthcare settings that are certified
- Certification of wholesalers/distributors to ensure that only certified prescribers and healthcare settings receive testosterone undecanoate.

DRISK agrees that these risks associated with TU can be serious and unpredictable. Therefore, these reactions cannot be prevented. A REMS with ETASU as outlined above may help to reduce poor outcomes in patients who experience post-injection reactions. While not in full agreement that a REMS with ETASU is appropriate for TU, DRISK aligns with DBRUP's proposal to narrow the indicated population, include a Boxed Warning in the label, and require a REMS with ETASU (outlined above) to inform prescribers and patients of the risks and require healthcare setting where TU is administered be equipped to manage POME and anaphylaxis.

## 1 INTRODUCTION

This review provides an analysis of the risk management options and the sponsor's proposed REMS submitted on November 29, 2012 to address the risk of severe post-injection reactions, specifically pulmonary oil microembolism (POME) and anaphylaxis adverse events associated with TU injection.

### 1.1 BACKGROUND

TU is under review for 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)

The proposed dosing of TU consists of an initial intramuscular injection of 3 mL (750 mg), a second 3 mL dose injected 4 weeks later, and then 3 mL injected every 10 weeks thereafter. The sponsor recommends a healthcare provider inject TU slowly over 30 to 60 seconds into the gluteus medius muscle, avoid intravascular injection, and that the patient be observed for 30 minutes after the injection.

Each single use vial contains 3 mL of 250 mg/mL testosterone undecanoate solution in a mixture of refined castor oil (885 mg) and benzyl benzoate (1,500 mg).

The product has been approved outside of the United States since 2003. In Europe, it is available as a 1000 mg/4mL solution for injection.

## **1.2 REGULATORY HISTORY**

This is the third cycle review for this product.

Review of the original application and second cycle submission resulted in “Complete Response”<sup>1</sup> letters for clinical deficiencies. DBRUP has maintained that the primary reason for lack of approval was and continues to be that the benefits of TU (taken in light of the availability of alternative products for the indication) do not outweigh the risk of serious pulmonary oil microembolism (POME) and anaphylaxis events. While the etiology of POME is not entirely known, it is thought to be due, in large part, to the castor oil component of the formulation. It is the castor oil component that allows for its administration every 10 weeks. Other testosterone injectable products are available in the U.S. but these formulations are administered every 2 to 4 weeks. Anaphylaxis may be a result from any component of a formulation.

In an attempt to resolve what was felt to be an impasse between DBRUP and the Applicant regarding the risk/benefit profile for TU, DBRUP decided to discuss the safety concerns with an Advisory Committee. Endo submitted TU for the third cycle review on November 29, 2012. A joint meeting of the DSaRM and the RHD Advisory Committee was held on April 18, 2013.

For a complete regulatory history from the date of the original application, refer to the risk management options review signed by Dr. Amarilys Vega on September 30, 2011 and Dr. Guodong Fang’s clinical review signed May 20, 2013.

## **2 MATERIALS REVIEWED**

- Fang G. Clinical Review. Signed May 20, 2013 by Fang G and Hirsch M.
- Kornegay C. Briefing Document – Epidemiology: Evaluation and Anaphylaxis and Pulmonary Oil Microembolism Reporting Rates. Signed March 28, 2013 by Kornegay C, Greene P, Chai G, Money D, Governale L, and Ouellet-Hellstrom R.
- Chin S. DPARP Medical Officer Consultation. Signed March 22, 2013 by Chin S, Durmowicz A, and Chowdhury B.
- FDA-prepared background package for the April 18, 2013 joint Drug Safety and Risk Management and Reproductive Health Drugs Advisory Committee.
- Endo’s proposed REMS submitted November 29, 2012.
- Vega A. REMS Review. September 30, 2011 by Vega A and Karwoski C.

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<sup>1</sup> The June 27, 2008 action letter for the original application was an “approvable” letter.



### 3 BENEFIT/RISK CHARACTERIZATION

#### 3.1 HYPOGONADISM AND TREATMENT

Hypogonadism in men results from a deficiency or absence of endogenous testosterone.

Primary and secondary hypogonadism are chronic conditions. Patients can be treated indefinitely (years to decades) with TRT. Patients can be maintained on the same product throughout treatment. Some men using transdermal testosterone may be switched to parenteral testosterone if their testosterone concentrations are not adequately replaced.

There are a variety of TRT products approved including intramuscular agents (testosterone enanthate, testosterone cypionate),<sup>2</sup> subcutaneous pellets (Testopel), transdermal film (AndroDerm, Testoderm), topical gels (AndroGel, Fortesta, Testim), topical solutions (Axiron), oral medications (methyltestosterone), and mucoadhesive agents (Striant).

According to U.S. office-based physician survey data, *injectable* testosterone products were most commonly mentioned for use by general practice and internal medicine physicians, accounting for 58% of drug use occurrences for years 2009-2012. Urologists accounted for 26% of drug use occurrences for injectable testosterone products during the same time.<sup>3</sup>

Drug utilization estimates indicate that sales of TRT products have been growing. Sales of testosterone injectable products increased 3-fold from (b) (4) vials sold in 2008 to approximately (b) (4) vials sold in year 2012. According to IMS National Sales Perspectives, the number of patients with at least one prescription claim for an *injectable* testosterone product more than doubled from approximately (b) (4) patients in year 2009 to (b) (4) patients in year 2012.<sup>4</sup>

#### 3.2 EXPECTED BENEFIT

TU confers the expected benefit<sup>5</sup> for TRT product approval and requires fewer injections per year compared to other injectable testosterone products. Patients would be expected to receive an injection every 10 weeks compared to every 2 to 4 weeks with the currently approved injectable testosterone products.

#### 3.3 SEVERITY OF RISK

TU is associated with severe post injection reactions, specifically POME and anaphylaxis. This section provides a summary of these risks. Clinical differentiation of these events is difficult. No deaths were reported however, some cases required hospitalization and/or emergency department visit.

For a comprehensive evaluation of these risks, case summaries, and FDA adjudication, refer to Dr. Guodong Fang's clinical review and Dr. Stacy Chin's DPARP<sup>6</sup> medical officer consultation. Dr. Cynthia Kornegay's review provides an analysis of the challenges in determining an incidence of these risks using post-marketing data.

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<sup>2</sup> Testosterone propionate is not currently marketed.

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=TESTOSTERONE%20PROPIONATE>. Accessed February 26, 2013.

<sup>3</sup> Email communication dated May 7, 2013 from Grace Chai.

<sup>4</sup> Kornegay C. Briefing Document – Epidemiology: Evaluation and Anaphylaxis and Pulmonary Oil Microembolism Reporting Rates. Signed March 28, 2013 by Kornegay C, Greene P, Chai G, Money D, Governale L, and Ouellet-Hellstrom R.

<sup>5</sup> DBRUP has relied on pharmacokinetic data from a single, open-label, uncontrolled study as demonstration of efficacy for approval of a testosterone product for replacement therapy.

<sup>6</sup> Division of Pulmonary, Allergy, and Rheumatology Products.

### 3.3.1 Pulmonary Oil Microembolism (POME)

POME is thought to be due to lymphovascular microembolization of oil (castor oil component in the injection solution) to the lung causing short-duration reactions characterized by; the need to cough, coughing, dyspnea, and/or respiratory distress.<sup>7</sup> These can be mild to severe. The long-term consequences of repeated POME events are unknown. One reason they may be observed more often with TU is due to the relatively greater injection volume relative to other products that contain castor oil.<sup>8</sup> POME may be less likely when oil-based products are injected carefully and slowly and when smaller volumes are injected.<sup>9</sup> However, case reports describe events occurring during the injection using proper injection technique.

### 3.3.2 Anaphylaxis

Any component of the formulation may cause anaphylaxis. In particular, benzoates as a class are recognized to produce immediate reactions that are either anaphylactoid or anaphylactic.<sup>8</sup> Rate or volume of intramuscular injection would not be expected to influence the rate of anaphylaxis.<sup>7</sup>

## 4 RISK MANAGEMENT OPTIONS

### 4.1 ENDO'S PROPOSED REMS

To address the risk of serious post-injection reactions, Endo proposes a REMS consisting of a MG and communication plan (CP). The CP includes a single Dear Healthcare provider letter. The letter is to be distributed to the following:

- urologists, endocrinologists, and designated primary care physicians, nurses, and physician assistants who prescribe or who are likely to prescribe/administer TU
- members of the following professional societies
  - The American Urological Association
  - The Endocrine Society
  - The Sexual Medicine Society of North America

Endo proposes to distribute the letter via US mail or electronically at the time of product approval and 6 months post-approval to the above audiences. In addition, sales representatives will provide it during their first sales call. Endo proposes to review order records and distribute the letter to any identified healthcare provider who has not received the communication for the first 12 months post-approval.

*Reviewer Comment: Efforts to inform patients and prescribers about the risk of life-threatening post-injection reactions associated with TU, the need for access to resuscitation equipment, the need to observe of patients for a period of time following the injection, and proper administration technique could be required. There is often little incentive for prescribers to review materials that are not required within a REMS, given the demands on their time and competing priorities.*

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<sup>7</sup> Lee C. Division of Pulmonary and Allergy Drug Products medical officer consultation response. Signed April 21, 2008 by Lee C and Chowdhury B.

<sup>8</sup> Durmowicz A. Division of Pulmonary and Allergy Drug Products medical officer consultation response. Signed June 13, 2011 by Durmowicz A and Chowdhury B.

<sup>9</sup> Chin S. DPARP Medical Officer Consultation. Signed March 22, 2013 by Chin S, Durmowicz A, and Chowdhury B.

## **4.2 ADDITIONAL RISK MANAGEMENT OPTIONS**

For a comprehensive evaluation of the risk management options, refer to Dr. Amarilys Vega's September 30, 2011 review.

### **4.2.1.1 Reformulation**

If these reactions are due to the excipients, the most effective mechanism to prevent the resulting serious adverse reactions remains product reformulation. However, this would require the Sponsor to redevelop the product beginning with Phase 1 trials.

Without reformulation, the risk does not lend itself to a definitive plan to prevent these adverse events, so the focus of any risk management plan must be on minimizing the severity and sequelae of the event.

### **4.2.1.2 Prescribing Restrictions**

Active strategies to better ensure these safe use measures can be required and could include:

- Limiting prescribing to those prescribers who are enrolled and certified in a REMS program. The prescriber would confirm understanding of the risk and attest that they can manage the resulting adverse events. Distributors and/or pharmacies would need to be enrolled/certified to ensure that TU was only dispensed to those certified prescribers.
- Enrolling patients to ensure that they understand the risk before beginning treatment. Patient enrollment would be cumbersome for TU because the product will be distributed directly to prescribers, not by pharmacies to patients.

## **5 DISCUSSION**

DRISK was consulted in 2011 to evaluate the risk management options and recommend a strategy for testosterone undecanoate. What is known regarding the safety issue, factors to consider, and risk management options is largely unchanged.

- The frequency of occurrence and severity of an identified serious adverse event are two factors that are considered when making decisions about the need for and rigor of a risk management strategy for a product. Due to limitations on the data provided by Endo, FDA is not able to definitively determine the incidence of serious post-injection reactions. The reported post-injection reactions are serious and life-threatening in some cases.
- The drug's benefit and available therapies are also factors to consider. There is no evidence that TU addresses an unmet medical need or provides substantial benefit over existing, available treatment options. There are a variety of other TRT options and dosage forms available including Testopel – testosterone pellets implanted every 3 to 6 months.
- The disease and patient population must also be considered, as well as what is considered acceptable treatment risks for a disease or condition. Hypogonadism and its complications are important but are generally not considered life-threatening conditions. Depending on the underlying cause, patients may be relatively healthy, making it less acceptable to expose them to serious medication risks.
- Because it is not possible to predict who or when patients will experience a serious post-injection adverse event, risk management strategies will unlikely prevent the event from occurring. Therefore, the risk management approaches are limited to informing prescribers and patients about the risk or restricting distribution of TU to prescribers who attest to understanding the risk, practice in healthcare settings with proper medical equipment to manage the event, and are capable (or have staff/colleagues

capable and immediately accessible) of managing the event, and only administer TU to patients who are counseled about the risks/benefits and agree to treatment.

- Finally, the impact of additional safe use measures on the healthcare system must be considered. A REMS cannot prevent post-injection reactions associated with the use of TU (although it could mitigate serious outcomes associated with the event through education coupled with access to appropriate supportive measures and treatment). A strategy that restricts access by requiring enrollment of prescribers, distributors/ pharmacies, and potentially patients imposes substantial burden to these stakeholders.

During the April 18, 2013 the DSaRM and RHD Advisory Committee meeting,<sup>10</sup> DRISK presented these factors and discussed the merits of restricting distribution; considering the burdens to prescribers, pharmacists, and patients, in light of testosterone undecanoate's benefits and risks. We stated our concern that implementing any one of these restrictive measures or some combination of them for testosterone undecanoate imposes excessive burden for stakeholders for a drug with limited additional benefit compared to the other treatment options. The Committee vote was split (9-9) in response to "...do you believe that TU is safe for the proposed indication?" Committee members who agreed it was safe expressed concern that TU was being held to a higher standard compared to the other testosterone injectables, these are known risks of other approved products, there is a need for additional longer-acting treatments particularly for patients with prolonged hypogonadism, some patients, in particular, may run out of injection sites, and the post-marketing experience in Europe with no deaths reported is reassuring. Those who voted that they did not believe it was safe, cited insufficient safety data, echoed the Agency's concerns, and expressed concern that the majority of use will be driven by the "low T" population. The Committee voted 17-1 that labeling alone was not sufficient to ameliorate the risk of severe post-injection reactions. Many members recognized the reactions are unpredictable. There was general consensus to strengthen the REMS to ensure prescribers are educated about the risks, the need to have access to appropriate resuscitation equipment, and/or ensure patients are educated about the risks. Some members recommended narrowing the indication and limiting use in patients with cardiovascular and pulmonary disease.

In subsequent discussions within the Agency there was recognition that some patients may prefer a longer-acting TRT injectable product particularly in patients who require prolonged testosterone therapy but prescribers and patients should be informed of the risks, and, after thoughtful consideration, the decision to use this product should be between the patient and prescriber. It should be administered in healthcare settings equipped with appropriate resuscitative equipment and the patient should be observed following the injection for an appropriate time period as described in the label (e.g., at least 30 minutes). To accomplish this, DRISK proposed the following REMS with ETASU:

- Medication Guide – to be provided to the patient to ensure that the patient is aware of the serious risks (relative to benefits) of TU and has all the necessary information to make an informed decision to use or continue to use TU.
- ETASU – certification of healthcare providers to ensure that health care providers who prescribe testosterone undecanoate are informed about the risks of POME and anaphylaxis and have access to on-site equipment and personnel in order to manage these reactions.
- ETASU – dispensing testosterone undecanoate only in certain healthcare settings that are certified to ensure testosterone undecanoate will only be dispensed in healthcare settings with the appropriate equipment on-site and by certified prescribers.

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<sup>10</sup> Summary minutes of the joint meeting of the Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee. April 18, 2013.

- Implementation system - certification of wholesalers/distributors to ensure that only certified prescribers and healthcare settings receive testosterone undecanoate.

The critical limitations of this restricted distribution system are:

- No safe use strategies can definitively prevent the post-injection reactions from occurring.
- Prescribers who are not certified will have access to TU but should be practicing in a setting that has attested to having the necessary equipment to manage the reactions.

## **6 CONCLUSION**

DRISK agrees that these risks associated with TU can be serious and unpredictable. Therefore, these reactions cannot be prevented. A REMS with ETASU may help to reduce poor outcomes in patients who experience the post-injection reactions. While not in full agreement that a REMS with ETASU is appropriate for TU, DRISK aligns with DBRUP's proposal to narrow the indicated population, include a Boxed Warning in the label, and require a REMS with ETASU (outlined above) to inform prescribers and patients of the risks and require healthcare setting where TU is administered be equipped to manage POME and anaphylaxis.

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CLAUDIA B MANZO  
05/29/2013  
concur

**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**REMS Review**

**Date:** September 19, 2011

**To:** Scott Monroe, M.D., Director  
Division of Reproductive and Urologic Products (DRUP)

**Through:** Claudia Karwoski, Pharm.D., Director  
Division of Risk Management (DRISK)

**From:** **Amarilys Vega**, M.D., M.P.H.  
Risk Management Analyst, DRISK

**Cynthia LaCivita**, Pharm.D.  
Risk Management Analyst Team Leader, DRISK

**Subject:** Review of Proposed REMS for Aveed<sup>®</sup> (Testosterone undecanoate injection)

**Drug Name (Established Name):** Aveed<sup>®</sup> (testosterone undecanoate injection)

**Therapeutic Class:** Androgen

**Dosage and Route:** 750 mg/3 mL (250 mg/mL) for intramuscular (IM) injection

**Application Type/Number:** NDA 22-219

**Applicant:** ENDO Pharmaceuticals Solutions Inc.

**OSE RCM #:** 2011-1429

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## 1. Introduction

This review provides an analysis of the risk management options and the sponsor's proposed Risk Evaluation and Mitigation Strategy (REMS) to address the risk of Pulmonary Oil Microembolism (POME) and anaphylaxis-like adverse events associated with Aveed<sup>®</sup> (testosterone undecanoate injection). This review also states the REMS Oversight Committee guidance to the review team on how to proceed with the application.

## 2. Background

Aveed is currently authorized as Nebido<sup>®</sup> in 90 countries and marketed in 72 countries. The manufacturer of Aveed is seeking an indication as a testosterone replacement therapy (TRT) in adult males for conditions associated with a deficiency or absence of endogenous testosterone including:<sup>1</sup>

- Primary hypogonadism (congenital or acquired) - testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchidectomy, Klinefelter's 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 hormone (LHRH) deficiency, as might be caused by pituitary hypothalamic injury from tumors, trauma, or radiation. These men have low serum testosterone concentrations but have gonadotropins in the normal or low range.

The proposed dosing of Aveed consists of an initial intramuscular injection of 3 mL (750 mg), a second 3 mL dose injected 4 weeks later, and then 3 mL injected every 10 weeks thereafter. Each single use vial contains 3 mL of 250 mg/mL testosterone undecanoate solution in a mixture of refined castor oil (885 mg) and benzyl benzoate (1,500 mg).

### *Regulatory History*

The regulatory history, in pertinent part, is as follows:

- **August 24, 2007:** Original application received by FDA
- **June 27, 2008** – DRUP issued an “Approvable” letter listing chemistry, manufacturing, and clinical deficiencies. There were reports of serious post-injection respiratory and allergic adverse reactions in men who have received testosterone undecanoate intramuscular injection consistent with Pulmonary Oil Microembolism (POME) and anaphylaxis-like adverse events. FDA requested the applicant provide additional safety information from the clinical studies to determine the incidence of serious post-injection POME and allergic reactions and to characterize the nature and etiology of the anaphylaxis-like events with Aveed.
- **March 2, 2009** - The applicant submitted a Complete Response, which included a proposed REMS consisting of a Medication Guide (MG) and a communication plan (CP).

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<sup>1</sup> Aveed product labeling, August 28, 2009 ([\\fdswa150\NONECTD\N22219\N\\_000\2009-08-27\us\114-label\1142-final-label](#)).

- **December 2, 2009** – DRUP issued a Complete Response (CR) letter listing the following reasons, in pertinent part, for the action:
  - **Clinical Deficiency** – Continuing safety concerns regarding reports of serious, immediate, life-threatening post-injection adverse reactions and their impact on the risk/benefit profile. FDA advised the Endo Pharmaceuticals, to consider the following two potential remedial actions:
    1. Identify which components of the drug product may be contributing to the serious, immediate post-injection adverse reactions, reformulate the product, and demonstrate that these reactions have been reduced or mitigated; or
    2. Identify a population of adult males who require TRT and in whom the additional potential risks associated with the use of testosterone undecanoate injection as currently formulated would be acceptable.

The letter stated that the proposed REMS was not sufficient to ensure that the benefits of Aveed injection outweigh the risks associated with use of Aveed, but did not specify what would be sufficient.

- **May 24, 2010** – The sponsor met with FDA to discuss a path forward. The sponsor proposed that the risk-benefit profile for Aveed might be acceptable if distribution was restricted (through a REMS with elements to assure safe use (ETASU)) and if the indication was narrowed. The FDA replied that a narrowed target population with restricted distribution (through a REMS with ETASU) was a possible way forward.<sup>2</sup>
- **February 16, 2011 & May 26, 2011** – The sponsor requested a type C meeting. The sponsor was seeking the broader TRT indication and submitted a proposal for a REMS with ETASU.
- **June 17, 2011** - REMS Oversight Committee (ROC) meeting to discuss Endo's proposed REMS with ETASU.
- **June 27, 2011** - A Type C meeting with the sponsor and the Agency. The FDA stated that a REMS with ETASU was not appropriate in this particular situation.

### 3. Materials Reviewed

DRISK reviewed the following documents:

- ENDO, Aveed, Type-C Briefing Package, submitted February 16, 2011 and updated version from May 26, 2011
- ENDO, Aveed, FDA/ENDO Meeting Minutes from March 24, 2010, finalized by FDA June 22, 2010
- DRISK, Defer Comment Memo, dated January 15, 2010
- Aveed, reviews by Carolyn L. Yancey, MD, Risk Management Analyst, DRISK, dated August 5 and August 27, 2010, RCM # 2009-560
- Mark Hirsch, MD, Aveed Cross-Discipline Team Leader Memo, dated November 30, 2009.

<sup>2</sup> Endo's meeting minutes from the May 24, 2010 meeting with FDA

(b) (4)

- Hina Mehta, Pharm.D. Drug Use Data Analyst, Division of Epidemiology: Androgel® (testosterone) BPCA Drug Use Review, February 4, 2009.
- Aved product labeling, August 28, 2009 ([\\fdswa150\NONECTD\N22219\N 000\2009-08-27\us\114-label\1142-final-label](#)).
- REMS Oversight Committee, June 17, 2010 meeting minutes.

## 4. Benefit/Risk Characterization

### 4.1. Expected Benefit

The sponsor proposed the following indication for Aved: for TRT in adult males for conditions associated with a deficiency or absence of endogenous testosterone, including primary and secondary hypogonadism.<sup>3</sup>

Aved does confer the expected benefit for a TRT product with the need for fewer injections per year compared to other injectable testosterone products. Patients receive an injection every 10 weeks compared to every 2 to 4 weeks.

### 4.2. Severity of the Risk

Aved is associated with (1) POME and (2) anaphylaxis. POME is attributed to the castor oil in Aved, while anaphylaxis could be due to the excipient benzyl benzoate, or to the castor oil; both are known allergens. The reported reactions occurred during or within minutes from the time of the intramuscular injection and have been reported to occur after any dose.<sup>4</sup> Clinical differentiation of anaphylactic reactions vs. POME is extremely difficult.

- POME - signs and symptoms reported include flushing, sweating, sensation of warmth, and chest tightness, sudden urge to cough during or soon after injection, and usually accompanied by dyspnea. In some cases, severe difficulty breathing and severe cough were reported, and in a few cases, respiratory distress, cardiovascular collapse and loss of consciousness were reported. Some patients required supportive therapy and resuscitation, and some were hospitalized. Many were treated as if a serious allergic reaction was occurring.<sup>4</sup>
- Anaphylactic reactions – signs and symptoms reported included shortness of breath, difficulty breathing, flushing, sensation of warmth, rash, urticaria, tightening of the throat, closing up of the throat, tickling and fullness in the throat, cardiovascular collapse, and loss of consciousness. Most of these patients received standard treatment for an anaphylactic reaction (i.e., epinephrine, steroid, antihistamine).<sup>4</sup>

No deaths have been reported; however, some patients required resuscitation and/or hospitalization. Post-injection reactions have been reported after any dose.

<sup>3</sup> Aved product labeling, August 28, 2009 ([\\fdswa150\NONECTD\N22219\N 000\2009-08-27\us\114-label\1142-final-label](#)).

<sup>4</sup> Mark Hirsch, MD, Aved Cross-Discipline Team Leader Memo, dated November 30, 2009.

## ***Incidence***<sup>5</sup>

- Clinical trial data: Endo estimates that the incidence of post-injection reactions in clinical trials is 5 in 3,509 patients (0.14%) and the incidence of serious post-injection reactions in clinical trials is 1 in 3,509 patients (0.03%).

DRUP reviewers indicated that in 6 additional cases (collapse, syncope, circulatory collapse, etc.), details were unavailable and these cases may have represented additional serious post-injection reactions. If these 6 cases are included, the clinical trial incidence for serious post-injection reactions would be 0.14% (vs. 0.03%).<sup>4</sup>

- Post-marketing reports: The sponsor provides several estimates of a “postmarketing reporting rate”.
  - Based upon a December 22, 2009 report, the FDA estimate of 106 post-injection reactions and sponsor’s statement that (b) (4) doses have been “dispensed”; the sponsor calculated a post-marketing reporting rate of 0.0064% (95% CI, 0.0048%, 0.0080%). Based on the assumption of 5 injections per patient per year, the reporting rate per total number of patients exposed would be 0.032%.

In preparation for the June 27, 2011 Guidance meeting, the sponsor informed FDA of a total of 400 post-injection reaction reports (160 POME and 240 anaphylaxis) among (b) (4) ampoules sold. The Sponsor agrees that all 160 POME cases should be included in the analysis, but they include only 23 of the 240 reported anaphylactic reactions. Therefore, the Sponsor calculated post-marketing reported rates of 0.0068% and 0.001% for POME and anaphylactic reactions, respectively.

Based on 5 injections per year, using these data, the reporting rates per total number of patients exposed would be 0.034% and 0.005% for POME and anaphylaxis, respectively.

If the total number of cases reported is used for the numerator ( $n=400$ ), then the reporting rate for post-injection reactions would be 0.017%. Based on 5 injections per year, using these data, the reporting rate per total number of patients exposed would be 0.085%, or approximately 1 in 1,200 patients per year. This estimate does not account for underreporting or for ampoules sold but not administered.

### **4.3. Risk in context of drugs in class, prescribers’ familiarity with risk, and management**

Safety data from clinical trials and postmarketing safety reports indicate that Aveed is comparable to other products used for TRT – except for the occurrence of immediate post-injection, potentially life-threatening reactions.<sup>4</sup>

Other products used for TRT include intramuscular testosterone cypionate and testosterone enanthate, testosterone subcutaneous pellets, the Androderm testosterone transdermal system, the Striant testosterone buccal bioadhesive system, testosterone topical gels (e.g., AndroGel 1%, Testim, etc.), and testosterone topical solution (Axiron). Methyltestosterone is also available for replacement therapy, but its known hepatotoxicity limits clinical use.

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<sup>5</sup> ENDO, Aveed, Type-C Briefing Package, submitted February 16, 2011 and updated version from May 26, 2011

- Three of these products (testosterone cypionate, testosterone enanthate and methyltestosterone) are labeled (in the Adverse Reactions section) for anaphylaxis and/or anaphylactoid reactions. A search of FDA Adverse Event Reporting System (AERS) database conducted in September of 2009 revealed only a small number of anaphylaxis events for testosterone cypionate (1 case of anaphylactic reaction and 8 cases of anaphylactoid reactions). Another AERS search conducted in May 2007 showed no cases of anaphylaxis for intramuscular testosterone enanthate.<sup>6</sup>
- One of these products (testosterone cypionate injections) also contains benzyl benzoate and is labeled for anaphylactic reactions but does not have a REMS.<sup>7</sup> It is worth noting that the total volume in a unit dose of Aveed is 3 mL ( (b) (4) 1,500 mg of benzyl benzoate) while the volume of benzyl benzoate in the average dose of testosterone cypionate is much lower (average dose of testosterone cypionate contains 0.15 mL (b) (4) benzyl benzoate).

In 2009, a drug use review was completed for Androgel.<sup>8</sup> This review included analysis by prescribing specialty for topical testosterone formulations dispensed through retail pharmacies. General practitioners, family practitioners, and osteopaths were the top prescribers of Androgel (28.1%) followed by internal medicine (23.4%) and urologists (16.2%). While of some value, this information is limited since it focused on the topical testosterone formulations. It is unknown if prescribing patterns differ for a formulation that requires healthcare provider administration. Future reviews should include an updated drug use analysis focused on the intramuscular formulations.

While we assume that most physicians and other healthcare providers are familiar with the signs and symptoms of anaphylaxis, they may not be confident in their ability to respond to an event without additional medical assistance. For example, a physician may know the standard treatment (e.g., epinephrine) but may not know the appropriate dose to give if a pre-loaded syringe was not available. Further, it is not known if it is routine practice in offices and/or clinics of the anticipated prescribing populations to have the appropriate medical equipment necessary to manage these adverse events. We assume that there is a wide range of readiness.

#### 4.4. How is the risk managed across other products and/or diseases?

Table 1 provides an overview of the drugs that are associated with anaphylaxis or immediate post-injection reactions for which FDA considered and/or required a REMS to address the risk. The incidence rate of serious post-injection reactions for Aveed is comparable to that of Xolair, used in the treatment of severe and persistent asthma. The more serious the conditions treated and the higher the incidence rates of the post-injection reactions, the more rigorous the risk management options.

<sup>6</sup> Email communication with Mark Hirsch, MD, July 21, 2011.

<sup>7</sup> Testosterone cypionate ADVERSE EVENTS section of label: Allergic: Hypersensitivity, including skin manifestations and anaphylactoid reactions. Estradiol valerate, ADVERSE EVENTS section of label: urticaria, angioedema, anaphylactoid/anaphylactic reactions.

<sup>8</sup> Hina Mehta, Pharm.D., Drug Use Data Analyst, Division of Epidemiology: Androgel® (testosterone) BPCA Drug Use Review, February 4, 2009.

Table 1. Drugs associated with anaphylaxis or immediate post-injection reactions for which FDA considered and/or required a REMS						
Drug Name	Approval Date	Indication & Route of Admin	Boxed Warning	Anaphylaxis or Post-injection Reaction Rate <sup>9</sup>		REMS
				Clinical Trials	Postmarketing	
Aveed	Pending	TRT IM by HCP <sup>10</sup>		0.14%	Evaluation in progress	Under discussion
Xolair	6/20/03	Severe and persistent asthma SC <sup>11</sup>	Yes	0.1%	0.2%	MG
Plenaxis	11/25/03	Palliative treatment of men with advanced symptomatic prostate cancer IM by HCP	Yes	1.1–3.7%	NA	MG, ETASU
Rozerem	7/22/05	Insomnia PO <sup>12</sup>	No	NA	NA	MG
Krystexxa	9/14/10	Chronic gout IV <sup>13</sup>	Yes	6.5%	NA	MG, CP
Kalbitor	12/01/09	Hereditary Angioedema SC by HCP	Yes	3.9%	NA	MG, CP
Zyprexa Relprevv	12/11/09	Schizophrenia IM by HCP	Yes	<0.1% injections ~2 % patients	NA	MG, CP, ETASU
Asclera	3/30/10	Spider veins IV	No	0%	NA <sup>14</sup>	None
Lumizyme	5/24/10	Pompe Disease IV	Yes	6.7%	NA	CP, ETASU

<sup>9</sup> Reaction rates included in product label.

<sup>10</sup> Healthcare Provider (HCP)

<sup>11</sup> Subcutaneous

<sup>12</sup> Oral

<sup>13</sup> Intravenous

<sup>14</sup> Khin Maung U, M.D., Asclera Cross-Discipline Team Leader Review, dated December 18, 2009 - The data in the NDA did not show any patient with anaphylaxis. However, there are postmarketing case reports of anaphylaxis from other countries using other forms/doses/concentrations/volumes and for other diseases (large varicose veins or "medical" uses to stop bleeding from esophageal varices, gastric and duodenal ulcer, etc.). Endo refers to this product to point out that it has no REMS, although it is labeled for anaphylaxis.

#### 4.5. Size of the Population

The estimated number of male patients in the United States with hypogonadism is 4 to 5 million.<sup>15</sup> In 2009, a drug use review was completed by FDA; based on retail pharmacy sales data in 2007, more than (b) (4) unique patients received a prescription for a testosterone product. Currently, the testosterone gel products have, by far, the largest market share among testosterone-containing products. It is unknown what percent of TRT patients would be prescribed Aveed.

#### 4.6. Seriousness of the Disease

Hypogonadism in men is a serious disease resulting from a lack of endogenous testosterone. The aim of testosterone therapy in men with hypogonadism is to restore or normalize male secondary sexual characteristics (such as beard, body hair, voice) and male sexual behavior, and to promote normal male somatic development (muscle mass, bone). The consequences of long-term testosterone deficiency in hypogonadal men may include decreased muscle mass and strength, decreased sexual function, and osteoporosis.

#### 4.7. Duration of Treatment

Primary and secondary hypogonadism are chronic conditions. Patients are treated indefinitely (years/decades) with TRT. Patients can be maintained on the same product throughout treatment. Some men using transdermal testosterone are switched to parenteral testosterone if their testosterone concentrations are not adequately replaced.

### 5. Risk Management Options

The review team believed the goal of the REMS would be to *minimize the serious complications resulting from post-injection reactions associated with Aveed*. The risk does not lend itself to a definitive plan to *prevent* adverse events so, the focus must be minimizing the severity and sequelae of the event.

In conjunction with labeling, the following options were considered:

1. Medication Guide
2. REMS with Communication Plan or ETASU A/Prescriber Certification (not linked to drug distribution)
3. REMS with ETASU: Prescriber and Pharmacy Certification (Applicant's proposed REMS; linked to drug distribution)
4. REMS with ETASU: Prescriber and Pharmacy Certification with Patient Enrollment
5. Not approve

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<sup>15</sup> Kaufman, M. REMS Memorandum for AndroGel, signed April 22, 2009

### 5.1. Option 1: No REMS, labeling only with PPI or Medication Guide

Option 1: No REMS, labeling only with PPI or Medication Guide	
Advantages	Disadvantages
<ul style="list-style-type: none"><li>• Least burdensome approach</li><li>• No impact on drug distribution</li><li>• Patients receive FDA-approved information about risk</li><li>• Minimal impact on medical and pharmacy practice (in comparison to other more restrictive REMS elements)</li></ul>	<ul style="list-style-type: none"><li>• No additional required material targeted to Healthcare Providers</li><li>• No active assurance that prescribers have discussed the risks with patients before administration, or observe patient for at least 30 minutes post-injection</li></ul>
<b>Anticipated Consequences</b> <ul style="list-style-type: none"><li>• Likely that not all patients will be provided the Medication Guide.</li><li>• None to very limited impact on prescribing behavior and ensuring prescribers are informed and prepared to manage the serious adverse event.</li><li>• Difficult to assess the impact of labeling. Spontaneous adverse event reports are the most likely source of information.</li></ul>	



## 5.2. Option 2: REMS with Communication Plan or ETASU with Prescriber Training (not linked to drug distribution)

<b>Option 2: REMS with Communication Plan or ETASU with Prescriber Training (not linked to drug distribution)</b>	
<p>Communication Plan or ETASU A/Prescriber Training would consist of materials educating prescribers about:</p> <ul style="list-style-type: none"> <li>• approved indication</li> <li>• the risk of life-threatening post-injection reactions</li> <li>• proper administration technique for Aveed</li> <li>• purpose and need for a 30 minute patient wait time post-Aveed administration</li> <li>• procedure for reporting adverse events when they occur</li> <li>• Patient Management Algorithm for immediate post-injection reactions</li> </ul>	
<b>Advantages</b>	<b>Disadvantages</b>
<ul style="list-style-type: none"> <li>• Same advantages as option 1</li> <li>• Does not limit a prescribers ability to prescribe if they choose not to participate</li> <li>• Assessment would include analysis of HCP and patient knowledge of risks and have quantitative data (prescribers complete training; especially if Endo chooses to distribute drug through specialty pharmacies only)</li> </ul>	<ul style="list-style-type: none"> <li>• No incentive to participate unless tied to continuing medical education or ability to prescribe</li> <li>• Difficult to assess impact on minimizing the risk (emphasis would be on assessing prescribers understanding or knowledge)</li> </ul>
<b>Anticipated Consequences</b>	
<ul style="list-style-type: none"> <li>• Participation will be low unless an incentive is put into place.</li> <li>• Need to define “success,” develop threshold and contingency plan if “success” is not achieved. Spontaneous adverse event reports and HCPs and patient surveys are the most likely sources of information regarding REMS performance.</li> </ul>	

**5.3. Option 3: REMS with ETASU: Prescriber and Pharmacy Certification  
(Applicant's Proposal; linked to drug distribution)**

<b>Option 3: REMS with ETASU: Prescriber and Pharmacy Certification (Applicant's Proposal; linked to drug distribution)</b>	
The training would be consistent with what is outlined in Option 2 above and be required for HCPs to order Aveed. Pharmacies would only accept/dispense prescriptions written by certified prescribers.	
<b>Advantages (over option 2)</b>	<b>Disadvantages</b>
<ul style="list-style-type: none"> <li>• Definitive data that prescribers complete training</li> <li>• Ensures prescribers are aware of the risks, proper injection techniques, need for a 30 minutes observation period, required office equipment, and proper management of life-threatening adverse events</li> </ul>	<ul style="list-style-type: none"> <li>• Administrative aspects of enrolling in REMS can be burdensome to prescribers</li> <li>• Requires another ETASU (pharmacy certification) to ensure that pharmacies know to check for certification(sponsor proposes using specialty pharmacies so this is minimal additional burden from the pharmacy perspective)</li> <li>• No assurance patient is informed or observed for 30 minutes</li> <li>• Will have an impact on product distribution</li> </ul>
<b>Anticipated Consequences</b> <ul style="list-style-type: none"> <li>• Treatment delays (both intended and unnecessary).</li> <li>• Limit the number of providers who can prescribe, leaving certain patients without access to this drug (other treatment options are available)</li> <li>• Backlash from medical community.</li> </ul>	

#### 5.4. Option 4: REMS with ETASU: Prescriber and Pharmacy Certification with Documentation of Safe Use Conditions

Option 4: REMS with ETASU: Prescriber and Pharmacy Certification with Documentation of Safe Use Conditions	
<p>In addition, to prescriber and pharmacy certification, a patient component could be incorporated. This would consist of a patient-prescriber acknowledgement (or informed consent) regarding the risks associated with Aveed. The REMS could be structured to either link or not link the acknowledgement to drug distribution.</p> <ul style="list-style-type: none"> <li>→ <i>Linked</i>: To ensure that patients had signed the acknowledgement would require that Aveed be ordered on a “per patient” basis. Endo plans to distribute Aveed directly to HCPs (which is typical for many injectables). Therefore, “per patient ordering” would be additionally burdensome.</li> <li>→ <i>Not Linked</i>: Alternatively, Endo could be required to audit practices to determine if the acknowledgements are being utilized. In this scenario, this risk management tool would rely on voluntary compliance so there is not prospective assurance of prescriber/patient discussion.</li> </ul>	
Advantages	Disadvantages
<ul style="list-style-type: none"> <li>Ensures patients are aware of the risks</li> </ul>	<ul style="list-style-type: none"> <li>Most burdensome approach</li> </ul>
<p><b>Anticipated Consequences</b></p> <ul style="list-style-type: none"> <li>Additional cause for treatment delays (both intended and unnecessary)</li> <li>Limit the number of providers who can prescribe, leaving certain patients without access to this drug (other treatment options are available)</li> <li>Backlash from medical community</li> </ul>	

#### 5.5. Option 5: Not approve and advise sponsors to reformulate

Advising Endo to reformulate the drug product would address the root of the problem if the benzyl benzoate and castor oil are causing these reactions. This was one of two options provided to the sponsor in the 12/02/09 CR letter. However, this would require the sponsor to redevelop the product beginning with Phase 1 trials.

#### 5.6. Additional information

The following information would provide additional context to the analysis of this safety question: (1) testosterone replacement therapy market analysis, (2) data on private practitioners’ readiness to manage life-threatening reactions, and (3) a complete analysis of all postmarketing post-injection reaction reports.

## 6. Discussion

The Sponsor contends that the actual reporting rates of postmarketing POME and anaphylactic reactions for Aveed are low; however, FDA review of postmarketing post-injection reactions is ongoing.

This safety issue and REMS options were discussed with members of the REMS Oversight Committee (ROC) on June 17, 2011. DRISK and DRUP requested that the ROC members provide guidance regarding the appropriateness of a REMS with ETASU for Aveed. In considering the appropriate risk management approach for Aveed, the ROC took into consideration the severity of the post-injection reactions; the incidence rates reported in clinical trials and postmarketing reporting rates; availability of other treatment alternatives; the current knowledge regarding the etiology of these reactions; and the feasibility of narrowing the indication for Aveed to improve the risk:benefit balance.

ROC members acknowledged that, although the nature of the post-injection reactions is very serious, the frequency of occurrence of post-injection reactions in clinical trials and the reporting rates of postmarketing case reports is low.

If these reactions are indeed due to the excipients, the most effective mechanism to prevent the risk is reformulation. However, this would require the Sponsor to redevelop the product beginning with Phase 1 trials. Narrowing the indication alone can reduce the total number of serious post-injection reactions by decreasing the number of patients treated with Aveed, if prescribing behavior is consistent with the approved indication, or if an ETASU is designed to enforce compliance with use in a narrow population. Given the above mentioned factors, the fact that a REMS with ETASU cannot prevent post-injection reactions associated with the use of Aveed (although it could minimize serious outcomes associated with the event), and the fact that the product's sole additional benefit is more convenient dosing, the ROC recommended that this product's approval not rely on the implementation of a REMS with ETASU but rather on Aveed's inherent risk:benefit balance. If approved, the risk of post-injection reactions should be managed through product labeling only.

## 7. Recommendations

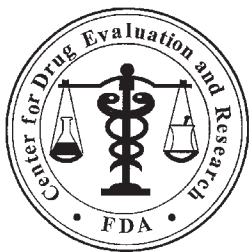
- The implementation of a REMS with ETASU is not recommended for Aveed.
- The management of the risk of post-injection reactions must be through product labeling.

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/s/  
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AMARILYS VEGA  
09/30/2011

CLAUDIA B KARWOSKI  
09/30/2011  
concur



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: January 15, 2010

To: Scott Monroe, MD  
Director, Division of Reproductive and Urologic Products (DRUP)

Through: Claudia Karwoski, Pharm.D.  
Director, Division of Risk Management (DRISK)

From: Carolyn L. Yancey, MD, FAAP, Risk Management Analyst,  
DRISK  
Gita Toyserkani, PharmD, Acting Team Leader, DRISK  
Mary Willy, PhD, Deputy Director, DRISK

Subject: Defer Comment Memo for the proposed REMS for AVEED®  
based upon additional clinical safety information submitted on  
August 31, 2009

Drug Trade Name: AVEED® (b) (4)

Established Name: Testosterone undecanoate injection

Dosage and Route: 750 mg/3 mL (250 mg/ mL) for intramuscular (IM) injection

Submission Number: SN-000/RP (02Mar09); Post-marketing cases of potential  
anaphylaxis (11Sept09)

Application Type/Number: NDA 22-219/ SN #19 Complete Response to the Approvable letter  
(submitted 2Mar09); Additional clinical safety information (SN #  
34, received 11Sept09); Complete Response Letter (COR-NDA  
ACTION #07 sent 02Dec09)

Applicant/sponsor: Endo Pharmaceuticals, Inc. (formerly Indevus Pharmaceuticals,  
Inc.)

OSE RCM #: 2009-560

The Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology (OSE) was consulted to review the proposed Risk Mitigation and Evaluation Strategy (REMS) for AVEED® submitted on March 2, 2009. The DRISK review of the original proposed REMS and the amended proposal (August 24, 2009) was completed on August 28, 2009, and concluded, at that time, that the REMS proposal was acceptable to ensure that the benefits of AVEED® (testosterone undecanoate) intramuscular injection outweigh the risks associated with its use.

On August 31, 2009, the applicant submitted substantial additional clinical safety information to the Agency. Based upon the additional clinical safety information, the DRUP concluded that there remains a severe and serious life-threatening risk with administration of this product and that the proposed REMS for AVEED® is insufficient to ensure that the benefits of AVEED® outweigh the risks associated with use of this product.

Due to outstanding Clinical Deficiencies, DRUP issued a Complete Response (CR) letter on December 2, 2009 stating that the application cannot be approved in its present form for the following reasons:

- **Clinical Deficiency**

There are reports of serious, immediate post-injection adverse reactions in men who have received testosterone undecanoate intramuscular injections. Although the exact etiology of these adverse reactions has yet to be determined, some of the reactions included clinical features consistent with anaphylaxis or angioedema. Other reported reactions appeared to be more consistent with pulmonary oil microemboli (POME).

The immediate post-injection adverse reactions included one or more of the following findings: respiratory distress, throat tightening or closing, wheezing, cough, flushing, and/or rash. Some patients lost consciousness during the events. Some were urgently resuscitated with oxygen, fluids, epinephrine, steroids, and/or antihistamines, and some were hospitalized.

Based on the reports of these serious, immediate, potentially life-threatening post-injection adverse reactions, DRUP does not believe that the demonstrated benefits of the drug outweigh the additional potential risks associated with the use of testosterone undecanoate injection.

- **Information Needed to Address the Clinical Deficiency**

To demonstrate that the benefits of treatment with testosterone undecanoate injection outweigh the additional potential risks associated with its use, the applicant may consider the following approaches:

1. Identify which components of the drug product may be contributing to the serious, immediate post-injection adverse reactions, reformulate the product, and demonstrate that these reactions have been reduced or mitigated; or
2. Identify a population of adult males who require testosterone replacement therapy and in whom the additional potential risks associated with the use of testosterone undecanoate Injection, as currently formulated, would be acceptable.

DRISK defers any further risk management review and comments until the applicant resubmits a complete response to the CR letter issued on December 2, 2009.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22219	ORIG-1	ENDO PHARMACEUTICA LS INC	NEBIDO

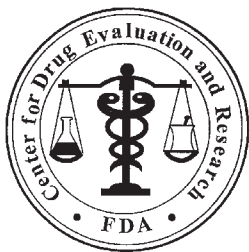
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/s/

CAROLYN L YANCEY  
01/15/2010  
Defer REMS Comment Memo AVEED

CLAUDIA B KARWOSKI  
01/19/2010  
concur





**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: September 25, 2009

To: Scott Monroe, M.D., Director  
**Division of Reproductive and Urologic Products (DRUP)**

Through: Claudia Karwoski, PharmD, Director  
**Division of Risk Management (DRISK)**

From: Jodi Duckhorn, M.A., Senior Social Science Reviewer  
**Division of Risk Management (DRISK)**  
Brian Gordon, M.A., Social Science Reviewer  
**Division of Risk Management (DRISK)**

Subject: DRISK Review of Proposed REMS assessment methodology  
and survey instruments

Drug Name(s): AVEED (testosterone undecanoate injection)

Application Type/Number: NDA 22-219

Applicant/sponsor: Endo Pharmaceuticals Inc.

OSE RCM #: 2009-560

## **1 INTRODUCTION**

This memorandum is in response to a request by the Division of Reproductive and Urologic Products (DRUP) for the Division of Risk Management (DRISK) to review the proposed methodology and survey instruments that will be used to assess the effectiveness of the Risk Evaluation and Mitigation Strategy (REMS) for AVEED (testosterone undecanoate). Please send these comments to the Applicant. The proposed REMS and Medication Guide were reviewed by DRISK and provided to DRUP under separate covers.

## **2 MATERIAL REVIEWED**

- AVEED (testosterone undecanoate) Risk Evaluation and Mitigation Strategy (REMS) submitted on August 24, 2009
- AVEED (testosterone undecanoate) Risk Evaluation and Mitigation Strategy (REMS) Supporting Document submitted on August 24, 2009

## **3 CONCLUSIONS AND RECOMMENDATIONS**

### **Healthcare Provider Survey:**

- Clarify if there are limits on the number of physicians and nurses that can participate from a large practice (more than five physicians)
- Clarify how the list of AVEED prescribers and their contact information will be generated
- In addition to email, please fax the initial survey request to AVEED prescribers who did not provide an email address
- Move questions #3a and #3b to the demographic section at the end of the survey
- Add an answer choice of “I don’t know” to questions #11a and #11b
- Replace question #8 with True/False and multiple choice questions about AVEED. For example:
  - A serious injection-based pulmonary oil reaction can occur if AVEED is not administered properly. True/False/I don’t know
  - Which of the following is true about AVEED (select all that apply):
    - The method of injection should be subcutaneous
    - May be injected into the upper-outer quadrant of the buttocks
    - May be injected into the upper thigh
    - Potential for an allergic reaction occurs only with the first injection
    - The method of injection should be intramuscular
    - Should only be administered in a healthcare setting
    - Patients can self-administer at home following the first injection
    - I don’t know

- Following an injection of AVEED, patients should be monitored in the healthcare facility for signs of a possible allergic reaction for how long?
  - 15 minutes
  - 30 minutes
  - 60 minutes
  - Patients can leave immediately
  - I don't know
- Remove questions #9 and #19

**Patient survey:**

- Clarify if there is a limit on the number of patients that can participate from one practice or physician
- Report the number of prescribers who received invitations to distribute as part of the analysis
- Explain the rationale of eliminating patients who have not had an injection in the past 10 weeks
- If the sample size is not achieved, provide details about the distribution of the second invitation. Will physicians receive more invitations to distribute to patients?
- If the sample size is not achieved after the second invitation, provide details about the online panels and explain their function
- Re-word question #4 to read “Are you currently being treated or have you been treated with AVEED? Yes/No/I don't know
- Re-word question #7. For example:
  - How is AVEED given to patients? (Select all that apply)
    - A shot in the arm
    - A shot in the buttocks
    - A shot in the leg
    - A shot in the shoulder
    - I don't know
- Add additional answer choices to question #8. For example:
  - I need to wait in the doctor's office for 15 minutes after getting a shot
  - I need to wait in the doctor's office for 45 minutes after getting a shot
  - I need to wait in the doctor's office for 1 hour after getting a shot
  - I don't know
- In question #10 replace the answer choice (b) (4) with “To see if I need another shot of AVEED”

- Put question #13 before question #12
- Replace question #14 with a series of True/False/I don't know statements. For example:
  - Two possible serious side effects of AVEED are an allergic reaction and tiny droplets of oil can get into my lungs. True/False/I don't know
  - After my first shot of AVEED at the doctor's office, I can give myself shots of AVEED at home. True/False/I don't know
- Prior to the demographic section of the survey, explain what the Medication Guide is and add questions that ask if a patient received and read the Medication Guide. For example:
  - Have you ever received the Medication Guide for AVEED?
    - Yes
    - No
    - I don't know
  - Did you receive the Medication Guide for AVEED each time you received a shot of AVEED?
    - Yes
    - No
    - I don't know
  - Did you read the Medication Guide?
    - All
    - Most
    - Some
    - None
    - I did not get a Medication Guide
  - Did you understand what you read in the Medication Guide?
    - All
    - Most
    - Some
    - None
    - I did not get a Medication Guide
  - Did your healthcare provider offer to explain to you the information in the Medication Guide?
    - Yes
    - No
    - I did not receive the Medication Guide
  - Did or do you have any question about the Medication Guide? Yes or No (If Yes, list your question below) Note: This is an open text field that should be grouped/coded by the sponsor prior to submitting to FDA

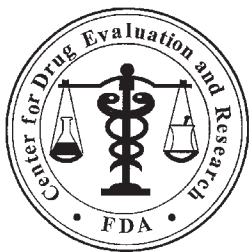
Please let us know if you have any questions

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/s/  
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BRIAN A GORDON  
09/25/2009

CLAUDIA B KARWOSKI  
09/25/2009



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: August 27, 2009

To: Scott Monroe, MD  
Director, Division of Reproductive and Urologic Products (DRUP)

Thru: Claudia Karwoski, Pharm.D.  
Director, Division of Risk Management (DRISK)

From: - Carolyn L. Yancey, MD, Medical Officer, DRISK  
- Marcia Britt, PhD, Health Education Reviewer, DRISK  
- Brian Gordon, MA, Social Science Reviewer, DRISK  
- Janice Maniwang, PharmD, Regulatory Review Officer, Division of Drug Marketing, Advertising and Communications (DDMAC)  
- Walter Fava, PharmD, Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)  
- Lesley Navin, MSN, Office of Compliance (OC)  
- Suzanne Barone, PhD, OC  
- Mary E. Willy, PhD, Team Leader, DRISK

Drug Class: Androgen

Subject: Review of AVEED® (b) (4) Risk Evaluation and Mitigation Strategy (REMS)

Proposed Trade Name: AVEED® (b) (4)

Established Name: Testosterone undecanoate injection

Dosage and Route: 750 mg/3 mL (250 mg/ mL) for intramuscular (IM) injection

Submission Number: SN-000/RP (submitted March 2, 2009)

Application Type/Number: NDA 22-219 Complete Response to NA Letter

Applicant/sponsor: Endo Pharmaceuticals, Inc. (formerly Indevus Pharmaceuticals, Inc.)

OSE RCM #: 2009-560

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## 1 INTRODUCTION

The original applicant, Indevus Pharmaceuticals, Inc. (Indevus), submitted the new drug application (NDA) 22-219 NEBIDO® to the Food and Drug Administration (FDA), Division of Reproductive and Urologic Products (DRUP) on August 24, 2007 for testosterone undecanoate intramuscular (IM) injection. AVEED® (b) (4) is a formulation of testosterone undecanoate in castor oil and benzyl solution for IM depot injection proposed as a long-acting treatment in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

1. Primary hypogonadism, congenital or acquired, testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchidectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone levels and gonadotropins [follicle stimulating hormone (FSH), luteinizing hormone (LH)] above the normal range.
2. Hypogonadotropic hypogonadism, congenital or acquired, idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation. These patients have low serum testosterone levels but have gonadotropins in the normal or low range.

The original NDA 22-219 NEBIDO® was determined to be approvable by DRUP (Approvable Letter dated June 27, 2008). The approvable letter includes the clinical deficiencies explaining that the applicant must address the requirement for a plan to minimize the risks associated with the clinical use of testosterone undecanoate IM injection, specifically to reduce the incidence and/or severity of the serious POME and anaphylactic adverse events. A Complete Response (CR) for NDA 22-219 was submitted to DRUP on March 2, 2009 and includes a proposed (b) (4) Risk Evaluation and Mitigation Strategy (REMS) and REMS Supporting Document. The trade name for the proposed formulation is resubmitted as AVEED® (b) (4)

This review is in response to a consult request from the DRUP to the Division of Risk Management to review and comment upon the proposed AVEED® REMS (received on August 24, 2009) including a Medication Guide and Communication Plan (CP) with education materials. The Interim Comments from DRISK on August 4, 2009 about the proposed AVEED® REMS and REMS Supporting Document were sent to DRUP to be communicated, in turn, to the applicant. The applicant's health care professional and patient surveys will be reviewed and commented upon separately from this AVEED® REMS review. In general, the AVEED® REMS is to be acceptable.

## 2 BACKGROUND

The original application contained reports of serious post-injection respiratory and allergic adverse reactions in men who have received testosterone undecanoate IM injections. These reports raised significant safety concerns for the DRUP regarding the risk/benefit profile for the use of testosterone undecanoate IM injection for the proposed indication.

As stated, the original NDA 22-219 NEBIDO® application did not include an adequate plan to minimize or to manage the risk of developing either a potentially life-threatening event of POME and or an anaphylactic reaction. The testosterone undecanoate drug-related respiratory events are generally described as a sudden need to cough in the immediate post-injection period. The report-



ed events may include laryngeal tightness, respiratory distress, circulatory collapse, cyanosis and loss of consciousness. The applicant believes a POME event, as characterized though not completely understood, is based upon the castor oil content of the formulation, intended for depot IM injection, inadvertently entering the intravascular space and prompting a pulmonary oil microembolism as described in the clinical events. In worldwide clinical trials involving 2,834 subjects (>16,000 injections), there was one report of serious injection-based pulmonary oil microembolism and one non-serious report. The cause of these events is believed to be pulmonary microembolism of the oily solution.

The original NDA 1) lacked an adequate plan to minimize or to manage the risk of developing either a potentially life-threatening event of pulmonary oil microembolism (POME) and or an anaphylactic reaction and 2) did not include information about the underlying etiology of the reported POME events and the anaphylactic reactions.

The applicant submitted an outline of a proposed (b) (4) REMS for the reported POME events in the pre-meeting briefing package for a Type B meeting (September 24, 2008) with DRUP. In the briefing package, the applicant acknowledged that anaphylaxis is a potential risk (b) (4) and conveyed their willingness to address this potential risk in the labeling and the risk management plan. The Agency response to Question #3 (in the briefing package) about the proposed REMS underscores the importance of managing the risk of anaphylaxis and the event of a POME, including efforts to increase awareness of such reactions and their proper treatment. The Agency advised the applicant that the risk management plan should include a patient observation period of at least 30 minutes after each IM depot injection (b) (4) in a healthcare facility. The rationale for the waiting period of 30 minutes is based upon the reported incidence of a POME event and or the anaphylactic reaction reported in the NDA clinical trials and in the postmarketing surveillance reported cases.

### 3 METHODS AND MATERIALS

The following materials were reviewed from the applicant's electronic NDA 22-219 submission, Agency reviews and comments communicated to the applicant. The materials are listed by the date of the document. Brief summary comments as relate to risk management are reported in the **Appendix, Section A**, Regulatory History with Brief Summary Comments, of this review.

August 24, 2007: NDA 22-219 NEBIDO® (testosterone undecanoate for IM injection) is submitted by Indevus to the FDA (received on August 28, 2007).

November 9, 2007: 74-Day Filing Communication Letter to the applicant identifies four potential review issues and six information requests (IR).

February 12, 2008: Executive Summary of "cough" clinical reports of immediate post-injection "cough reactions".

March 26, 2008: Applicant submits additional information about POME clinical presentation, possible mechanism, safety and sequelae of reported reactions. Applicant submits expert opinions from a pulmonologist, cardiologist and radiologist about POME.

May 9, 2008: Applicant submits postmarketing clinical study proposal (b) (4)

June 27, 2008: Approvable Letter for NDA 22-219 NEBIDO®, SN-000, Amendment 019.

July 2, 2008: Applicant submits letter of intent to amend NDA 22-219 application and resubmit the NDA to the Agency.

September 3, 2008: Pre-meeting (Type B) briefing package includes (b) (4) REMS for the POME event and anaphylactic reaction.

September 24, 2008: Type B meeting, minutes include Agency responses to the proposed (b) (4) REMS.

March 2, 2009: Complete Response to the Approvable Letter (June 27, 2008) is submitted to the Agency. Submission includes the proposed (b) (4) REMS and REMS Supporting Document (dated February 17, 2009).

March 27, 2009: Company name change as Endo Pharmaceuticals, Inc. (Endo) acquires Indevus Pharmaceuticals. All rights to NDA 22-219 are owned by Endo.

May 5, 2009: DDMAC denies proposed proprietary trade name (b) (4)

May 12, 2009: Proposed proprietary trade name, AVEED®, is submitted for review. Agency decision is pending as of this review.

May 19, 2009: DRUP submits comments and information requests to Endo Pharmaceuticals based on CR submission. The proposed trade name, AVEED®, is included in labeling revisions recommended by DRUP.

June 5, 2009: Addendum to original OSE/DRISK Consult request from DRUP (March 30, 2009). DRUP requests review of proposed AVEED® REMS by DRISK.

July 21, 2009: AVEED® Medication Guide is submitted as a converted PPI.

July 28, 2009: Endo and DRUP concur on proposed final labeling for AVEED® (July 2009).

August 4, 2009: Interim Comments from DRISK for the proposed AVEED® REMS and REMS Supporting Document sent to DRUP for written communication to the applicant.

August 24, 2009: Final AVEED® REMS submitted to the Agency.

The AVEED® REMS was reviewed for responsiveness to Agency recommendations communicated to the applicant (Type B meeting on September 24, 2008) and for conformance with the Food and Drug Administration Amendments Act of 2007. The AVEED® REMS was also reviewed for content adequately reflecting the risk/benefit as reported for the significant safety concern of post-injection respiratory and or anaphylactic adverse reactions in men who have received testosterone undecanoate IM injection for the proposed indication.

## 4 RESULTS OF REMS REVIEW

The following REMS proposal submitted on August 24, 2009 reflects revisions based upon interim comments sent to the applicant.

### 4.1 GOALS

#### *Original Proposal*

The Sponsor's original goal of the AVEED® REMS was (b) (4)

#### *Revised Proposal*

The revised Goals are:

(b) (4)

#### *Reviewer Comments:*

In our interim comments we included the following:

1. We recommended that both safety risks, e.g. an anaphylactic reaction and risk of a POME event, must be included in the REMS Goals. It was communicated to the applicant that the second goal be revised to include "anaphylactic reaction" and delete (b) (4) (see the **Appendix, Section B** for AVEED® REMS). The applicant complied with the Goal revisions.
2. We reminded the applicant that the Goals in the AVEED® REMS Supporting Document should reflect the Goals in the AVEED® REMS. The applicant complied with this request.

(b) (4)

## 4.2 REMS ELEMENTS

### 4.2.1 MEDICATION GUIDE

The Sponsor had originally proposed a Patient Package Insert (PPI) but submitted a Medication Guide in response to the Agency's request (communicated at the Type B meeting September 24, 2008). The Medication Guide is an element of the REMS. See the DRISK Patient Labeling (Medication Guide) review by Sharon R. Mills, BSN, RN, CCRP, Patient Labeling Reviewer (August 10, 2009).

*Reviewer Comment:*

1. The applicant clarified (in the August 24, 2009 final REMS submission) that the Medication Guide will be included in each product carton. The Medication Guide will also be made available via sales and/or clinical representatives and the product website, and by request through Endo's toll-free medical information line.

### 4.2.2. COMMUNICATION PLAN

The original proposal included the following:

The Communication Plan (CP), in accordance with FDCA 505-1(e)(3), directed to health care professionals (HCPs) includes education and outreach as well as patient labeling to reinforce important safety information regarding:

- 1) Instructional Video
- 2) Education Brochure

These materials provided instruction for the proper intramuscular administration of AVEED® (e.g., instructional video script (b) (4) and the Education Brochure, (b) (4) ); and the need for a 30 minute waiting period in a healthcare facility for patients after each IM administration of AVEED®.

#### Prescribers

The CP is directed to urologists, endocrinologists, designated primary care physicians, nurses and physician assistants who prescribe or administer AVEED®.

- “Dear Health Care Professional Letter” (DHCPL) will be provided at the product launch.

*Reviewer Comments:*

In our interim comments we included the following:

1. The applicant should include the following statements in the AVEED® REMS CP including a timeline for the frequency of distribution of the DHCPL for the designated number of years.

“In accordance with FDCA 505-1(e)(3), Endo Pharmaceuticals will execute a CP to healthcare professionals to reinforce safety information and education regarding proper administration of AVEED® for the designated year(s) following September 2, 2009 approval of NDA 22-219 for AVEED®. The CP will familiarize targeted prescribers with the risks of anaphylactic reactions and POME events associated with AVEED®”.

In the final submission, the applicant clarified that provider education will begin at product launch and will continue every 4 months for one year after launch. Because the Communication Plan includes only the Dear Healthcare Provider Letter, the requirement to conduct provider education should be revised to clarify that the provider letter will be sent every 4 months for one year after approval of the REMS.

2. See the **Appendix, Section C** of this review for the “Introductory Health Care Professional Letter”.

3. We recommended that the instructional video script, (b) (4) and the Education Brochure, (b) (4) be deleted from the CP materials based on the rationale that the product labeling (July 2009) adequately explains IM injection technique and that IM injection technique is understood by health care providers.

*Note:* DDMAC did not concur with DRISK’s recommendation to remove the video script and education brochure; however, DDMAC remains flexible for the applicant’s final decision (see separate review of the CP by Janice Maniwag, PharmD, Regulatory Review Officer, DDMAC).

The applicant deleted the instructional video script and the Education Brochure from the CP materials.

4. Under FDAAA, the provisions for the CP do not include materials directed to patients. The applicant was informed to exclude all references to patient education from the CP. The applicant has removed all materials directed to patients from the CP materials.

5. The applicant was informed to insert “physician assistants” in the DHCPL as physician assistants were listed in the CP. In the final submission, the applicant revised the list of providers to include physicians assistants.

#### **4.2.3. ELEMENTS TO ASSURE SAFE USE**

The AVEED® REMS does not require Elements to Assure Safe Use (ETASU).

#### **4.2.4. IMPLEMENTATION PLAN**

An implementation plan for ETASUs is not required. See explanation above in Section 4.2.3.

#### **4.2.5. TIMETABLE FOR SUBMISSION OF ASSESSMENTS**

The applicant submitted the timetable for submission of assessments as a REMS Assessment.

1 <sup>st</sup> REMS Assessment at (b) (4) after the approval date:	(b) (4)
2 <sup>nd</sup> REMS Assessment at 3 years after the approval date:	
3 <sup>rd</sup> REMS Assessment at 7 years after the approval date:	

#### *Reviewer Comments:*

In our interim comments we included the following:

1. We advised the applicant to revise the AVEED® REMS to include a “Timetable for Submission Assessments” in accordance with (505-1(d)) as a separate section in the AVEED®

REMS. The applicant complied with this recommendation (see **Appendix, Section B** of this review for the revised AVEED® REMS including the REMS Assessment and Timetable for Submission of Assessment).

2. We advised the applicant that the “Timetable for Submission of Assessments” section should specify the interval that each assessment will cover and the planned date of submission of the assessment to the FDA. We recommend that the reporting interval covered by each assessment conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31 should end no earlier than June 1. This process will facilitate inclusion of as much information as possible while allowing the company reasonable time to prepare the submission (see **Appendix, Section B**).

Additional comment: The language under the timetable for submission of assessments will need to be revised to the following:

Endo Pharmaceuticals will submit REMS Assessments to FDA (b) (4) 3 years, and 7 years from the date of the approval of the REMS. 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 Pharmaceuticals will submit each assessment so that it will be received by the FDA on or before the due date.

Content of the Applicant’s REMS Assessments described in the Supporting Document  
In brief summary, the content of proposed REMS Assessments will include:

- The effectiveness of the REMS will be assessed in a knowledge, attitude and behavior survey of a randomly selected sample of HCPs who prescribe or administer AVEED®.
- The effectiveness of the REMS, specifically the information in the Medication Guide, will be assessed in a knowledge, attitude and behavior survey of a randomly selected sample of patients who receive AVEED® to determine if they understand the benefits and risks of AVEED®.
- The risk of an injection-based pulmonary oil reaction and an anaphylactic reaction will be assessed through a Phase 4 postmarketing observational study of patients receiving AVEED® injections.
- A descriptive epidemiologic analysis of spontaneous postmarketing reports of possible injection-related pulmonary oil reactions and anaphylactic reactions will be conducted by Endo every 6 months to identify any case reports of these events, and to analyze information collected to help determine if AVEED® is being administered properly.

*Reviewer Comments:*

1. The HCP and patient surveys as part of the AVEED® REMS Supporting Document will be reviewed and commented upon at a later time by Brian Gordon, MA, Social Science Reviewer, DRISK.
2. Information needed for assessments (REMS Assessment Plan) is not a required element of the REMS proposal. Nonetheless, this information will be addressed in the REMS approval letter and discussed in the REMS Supporting Document.
3. The Phase 4 postmarketing observational study and descriptive epidemiologic analysis of post-marketing reports are not considered to be part of the REMS assessment.



## 4 CONCLUSION

The AVEED® REMS (received on August 24, 2009) contains the agreed upon REMS components which include a Medication Guide, Communication Plan and a Timetable for Submission of Assessments. The REMS Supporting Document outlines the information that the applicant will employ with HCP and patients to assess the effectiveness of the AVEED® REMS in achieving the specified goals.

The applicant incorporated the OSE/DRISK recommendations and revisions communicated in our Interim Comments (dated August 4, 2009) into their AVEED® REMS. The AVEED® REMS (received on August 24, 2009) is acceptable to OSE/DRISK and would appropriately mitigate, to the extent possible, the risks of an injection-based pulmonary oil reaction (POME) event and assure appropriate recognition and treatment of a potentially serious anaphylactic reaction. Though not applicable to this AVEED® REMS review, additional comments about the REMS Supporting Document are listed under Section 5 .

## 5 COMMENTS TO BE COMMUNICATED

### Comments to DRUP

1. The information needed to assess the effectiveness of the REMS (REMS Assessment Plan) will need to be incorporated into the Approval Letter.
2. Consider whether the proposed (b) (4)

### Comments to Applicant – AVEED® REMS

1. We remind you to clarify how the Medication Guide will be dispensed to patients in your REMS. We recommend inserting the text “Health Care Professionals” will dispense the Medication Guide to each patient before each injection. See **Appendix, Section B**, for this revision in the first paragraph under the Section II. REMS ELEMENTS, Section A. Medication Guide, of your REMS.
2. Regarding your Communication Plan
  - a. Because the Communication Plan includes only the Dear Healthcare Provider Letter, the requirement to conduct provider education should be revised to clarify that the provider letter will sent within 30 days and every 4 months for one year after approval of the REMS.
  - b. Clarify how you will send out this letter.
3. The language under the timetable for submission of assessments will need to be revised to the following:

Endo Pharmaceuticals will submit REMS Assessments to FDA (b) (4) 3 years, and 7 years from the date of the approval of the REMS. 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 Pharmaceuticals will submit each assessment-so that it will be received by the FDA on or before the due date.

4. Please see appended red-lined REMS for additional edits corresponding to these comments. Your proposed REMS may undergo additional revisions as it goes through the clearance process.

Comments to Applicant – AVEED® REMS Supporting Document

The Agency has the following recommendations and clarifications regarding the AVEED® REMS Supporting Document to be communicated to the applicant.

1. You submitted a pharmacovigilance plan and spontaneous postmarketing adverse event reporting under your REMS Supporting Document. Neither of these reports is required under a REMS. Any postmarketing commitments and or postmarketing requirements would be determined by the review division and communicated in the Approval Letter.
2. We remind you that the Goals listed in the AVEED® REMS Supporting Document should be the same Goals as included in the AVEED® REMS.
3. Comments on the HCP and patient surveys as part of the AVEED® REMS Supporting Document will be provided to you at a later time.



## APPENDICES

### A. Regulatory History with Brief Summary Comments

November 9, 2007: Filing Communication 74-day letter to the applicant identified four potential clinical review issues including the immediate post-injection “cough reactions” which include symptoms of cough, urge to cough, dyspnea and respiratory distress.

February 22, 2008: General Correspondence from the applicant suggests that the 750 mg dose (b) (4) is the optimal dosage and administration based upon submitted data. Therefore, the 3 mL vial, 750 mg dose, would be the basis of labeling and review (b) (4). The applicant believes the 750 mg dose would be better for patients in regard to the risk and incidence of immediate-onset cough-type reactions due to pulmonary oil microembolism (POME). It appears that the greater volume of oil delivered in the 4 mL, 1000 mg dose, contributes a significant role in the incidence of the event.

September 24, 2008: Brief summary of Type B meeting minutes.

Agency response to proposed REMS:

“We believe that plans are also warranted to manage the risk of anaphylaxis, including efforts to increase awareness of such reactions as well as their proper treatment. Part of this plan should include patient observation for at least 30 minutes after each injection (b) (4). In addition, you might consider a Medication Guide as part of your risk management program.

“We have reviewed your briefing package which contains an outline of your proposed risk mitigation and assessment activities targeting the POME reactions. This includes labeling, education and outreach, and a Phase 4 study. While these activities represent a good starting point for minimizing and assessing the risk of POME reactions, it should be noted that anaphylaxis and allergic reactions were also of concern to the Agency. These risks are not addressed in your strategy to minimize and assess the product’s risks. The final risk management efforts will largely depend on the risk assessment from your proposed analyses. The meeting package prepared by the sponsor states that there have been two POME events in clinical studies of testosterone undecanoate (b) (4) for a frequency of one in 14,000 injections. The observational study proposed by the sponsor (10,000 patients /42,000 injections) would appear to be powered to detect a POME frequency as low as 7 per 100,000; however, detailed information is needed to assess the adequacy of the sample size.

A final protocol with more detail about the type of data that will be collected and how these data will be collected, particularly in relation to “peri-injection” data would be needed to determine if this study addresses the Agency’s concerns.

Additional Discussion:

“The Sponsor stated that while the 30 minutes post-inject observation period is not included in their European label, they will agree to add it to the proposed U.S. label. The Sponsor asked for the Division’s rationale for a Medication Guide. The Division responded that a Medication Guide provides additional information to patients as compared to a Patient Package Insert (PPI). The risks are explained in a Medication Guide in a very specific format in patient friendly language. This is particularly important if the product being approved raises significant safety concerns. In addition, it may be

useful to periodically assess understanding of the Medication Guide to assess how well the risks of the product are being understood by patients. It is possible that a Medication Guide would be required by the Division (b) (4) after review of the additional safety data”.

The Sponsor asked for an overall assessment and specific comments about their risk management proposal. The Division responded that if indeed the Sponsor accepted the potential risk of anaphylaxis and addressed that risk in their plan, then the overall proposal was very reasonable. No additional specific comments could be made at this time, although there may be additional comments and requests at a later date.

#### **B. AVEED® REMS**



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/s/  
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CAROLYN L YANCEY

08/28/2009

AVEED REMS Review

CLAUDIA B KARWOSKI

08/28/2009

**Risk Evaluation and Mitigation Strategy (REMS) Memorandum**

**U.S. FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
Office of Drug Evaluation III  
Division of Reproductive and Urologic Products**

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<b>NDA:</b>	22-219
<b>PRODUCT:</b>	Aveed™ (testosterone undecanoate) injection
<b>SPONSOR:</b>	Endo Pharmaceuticals
<b>FROM:</b>	Scott Monroe, M.D.
<b>DATE:</b>	August 20, 2009

---

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Aveed to ensure that the benefits of the drug outweigh the risks of injection-based pulmonary oil microemboli (POME) and anaphylactic reactions. In reaching this determination, we considered the following:

- A. The estimated number of male patients in the United States with hypogonadism is 4 to 5 million. Approximately 5 percent of men with this condition will receive testosterone therapy. This estimate is based on *Testosterone and Aging, Clinical Research Directions* (Institute of Medicine of the National Academies, 2004).
- B. Hypogonadism in men is a serious disease resulting from a lack of endogenous testosterone. The aim of testosterone therapy in adult men with hypogonadism is to restore or maintain (1) male secondary sexual characteristics (such as beard, body hair, voice) and sexual behavior and (2) normal male somatic development (muscle mass, bone). The consequences of long-term testosterone deficiency in hypogonadal men may include decreased muscle mass and strength, decreased sexual function, and osteoporosis.

- C. In the phase 3 trial, Aveed was demonstrated to be safe and effective in producing serum total testosterone concentrations within the normal range in the majority of hypogonadal men studied.
- D. Aveed will be used for testosterone replacement therapy in males with conditions associated with a deficiency or absence of endogenous testosterone. Treatment is expected to continue throughout the patient's lifetime.
- E. The following known adverse events are listed in class labeling for testosterone products: gynecomastia, edema, and sleep apnea. In addition to the expected adverse events associated with the use of testosterone products, there have been several postmarketing reports of serious reactions involving urge to cough, dyspnea, malaise, hyperhidrosis, chest pain, dizziness, paresthesia, and syncope during or immediately after the intramuscular injection of testosterone undecanoate 1000 mg (4 mL). The cause of these events is believed to be pulmonary microembolism of the oily solution. Though the majority of these cases lasted only a few minutes and resolved without sequelae, some lasted up to several hours and a few patients required emergency treatment and/or were hospitalized. In addition, there have been several postmarketing reports with intramuscular testosterone undecanoate 1000 mg (4 mL) in which a post injection anaphylactic reaction could not be excluded.
- F. Aveed is not a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Aveed. FDA has determined that Aveed could pose a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Aveed. FDA has determined that (1) Aveed is a product for which patient labeling could help prevent serious adverse effects and (2) has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use, Aveed.

The elements of the REMS will be a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

### REMS Interim Review Comments

<b>Proposed Drug Name:</b>	<b>BLA/NDA:</b>	<b>Date:</b> 04AUG09
AVEED (b) (4) (testosterone undecanoate) Injection	22-219	<b>Comment Set # 1</b>
<b>DRISK Scientific Lead:</b> Carolyn Yancey, MD, Medical Officer, DRISK		<b>Reviewers:</b> Marcia Britt, PhD, Health Education Reviewer, DRISK Sharon Mills, Patient Product Information Reviewer, DRISK Janice Maniwang, PharmD, Regulatory Review Officer, DDMAC Walter Fava, PharmD, DMEPA
<b>RCM #:</b> 2009-560		

#### Materials Reviewed:

- Proposed (b) (4) REMS submission dated February 17, 2009.
- *Pending* Medication Guide review: Sharon Mills, Patient Product Information Reviewer.

#### Introduction:

The comments below are OSE's preliminary review of the proposed AVEED REMS (b) (4) for testosterone undecanoate injection. Please request Endo Pharmaceuticals, Inc. to respond to these revisions and comments as soon as possible.

Attached to this review is an edited (with track changes) Proposed (b) (4) REMS and Dear Healthcare Provider Letter.

#### Proposed REMS Comments:

##### 1. REMS Goals:

The REMS goals are acceptable. (b) (4)  
(see the attached AVEED REMS with tracked changes in Appendix A).

##### 2. Medication Guide:

The sponsor did not include sufficient information about the Medication Guide to review the Medication Guide section of the REMS. The Agency recommends the following language for the (b) (4) Medication Guide section of the REMS. If Endo modifies the Medication Guide text of this REMS section, provide that language to the Agency for review.

The Medication Guide will be provided in accordance with 21 CFR 208 as follows:

A Medication Guide will be dispensed with each (b) (4) injection.

Endo will provide a sufficient quantity of Medication Guides to health care providers that administer (b) (4) to their patients or the patient's representative. Endo will notify and provide health care professionals (HCPs) with updated Medication Guides if they are revised.

Medication Guides will also be made available to health care providers through field-based personnel, in a printable format that can be downloaded from (b) (4) or by contacting Endo at (b) (4)

### 3. Communication Plan:

Revise the Communication Plan (CP) as follows:

a. Remove the intramuscular injection video script entitled (b) (4) and the education brochure (b) (4)

from the REMS. Based on the rationale that the IM injection technique is adequately explained in the Prescribing Information (July 2009) and that IM technique is well known to HCPs, we recommend that you delete the proposed instructional video and educational brochure from your CP materials.

Endo can resubmit these materials to DDMAC as promotional material.

b. The Dear Healthcare Professional Letter (DHCP) (b) (4)  
(b) (4) Please see the attached DHCP letter with tracked changes in Appendix B.

c. Delete all references to "allergic reactions" throughout the REMS (including the Dear Health Care Professional Letter) and the REMS Supporting Document and replace with "anaphylactic reactions" to reflect clinical safety information provided in the proposed final product labeling.

d. Endo should place the following statement into the (b) (4) REMS Communication Plan indicating a timeline for the Dear Health Care Professional Letter:

This provider education is not intended to continue over the lifetime of the product; it will function only to inform targeted prescribers of the possible risk of an anaphylactic reaction and or a pulmonary oil microembolism (POME) event associated with (b) (4) for a period of X years [or months].

### 4. Elements to Assure Safe Use (ETASU):

There are no elements to assure safe use for this proposed REMS.



## 5. Implementation System:

As there are no ETASU, there is no implementation plan.

## 6. Timetable for Assessment of the REMS:

The proposed time intervals for submission of assessments, e.g., 1<sup>st</sup> Assessment at (b) (4) from REMS approval; 2<sup>nd</sup> Assessment at 3 years from REMS approval and, 3<sup>rd</sup> Assessment at 7 years from REMS approval, are acceptable as submitted under FDAAA requirements (see the attached strikethrough version of your proposed (b) (4) REMS).

Revise your proposed (b) (4) REMS to include a “Timetable for Submission Assessments” (505-1(d)) as a separate section (see **Table 1**). The “Timetable for Submission of Assessments” section should specify the interval that each assessment will cover and the planned date of submission of the assessment to the FDA.

The reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment due July 31<sup>st</sup> should conclude no earlier than June 1<sup>st</sup>.

**Table 1.**

	Month/Year of Submission
1 <sup>st</sup> REMS Assessment (b) (4) from approval)	
2 <sup>nd</sup> REMS Assessment (3 years from approval)	
3 <sup>rd</sup> REMS Assessment (7 years from approval)	

## 7. General Comments

Submit a revised Proposed REMS that reflects the following:

- 1) the proposed trade name, AVEED (b) (4) and
- 2) the Medication Guide in place of the Patient Package Insert.

Submit a revised final Proposed AVEED REMS with the appended materials and an AVEED REMS Supporting Document. Please provide a copy with track changes and a WORD version of all revised materials and documents.

7 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page



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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CAROLYN L YANCEY

08/05/2009

MARY E WILLY

08/05/2009

Interim comments; final review will be submitted after reviewing Sponsor's response