

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**022219Orig1s000**

***Trade Name:*** Aveed

***Generic Name:*** Testosterone Undecanoate

***Sponsor:*** Endo Pharmaceuticals, Inc.

***Approval Date:*** March 5, 2014

***Indications:*** Replacement Therapy in Males for Conditions Associated with a Deficiency or Absence of Endogenous Testosterone.

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**022219Orig1s000**

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***APPLICATION NUMBER:***

**022219Orig1s000**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 022219

**NDA APPROVAL**

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

Dear Ms. Clark:

Please refer to your New Drug Application (NDA) dated August 24, 2007, received August 28, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Aveed (testosterone undecanoate) injection.

We acknowledge receipt of your submissions dated October 8 and December 5, 20, and 28, 2007, February 8, 11, 15, and 26, March 12 and 31, April 2 and 30, May 13, 15, 19, 23, 27, and 28, June 10 and 13(2), July 2, August 8 and September 5, 2008, March 2 (2), 13, and 27, April 21, May 13, June 8, 15, and 22, July 21 and 23, August 11, 13, 14, 24, 27, and 29, September 11, 16, and 22, October 6, 12, and 21, and November 19 and 30 (2), and December 10, 2009, March 31, April 21, June 14, and November 4 (2), 2010, February 16, May 26, June 3, August 17, September 30, November 10 and December 19, 2011, November 29, December 11, 19, and 20, 2012, January 14, and 15, February 1, 12, and 27, March 4, and 25, and April 30, May 21, June 18, August 29, and September 20, 2013, January 10, 13, and 17, February 6, 10, 24, 25, 27 and 28, 2014.

The August 29, 2013, submission constituted a complete response to our May 29, 2013, action letter.

This new drug application provides for the use of Aveed (testosterone undecanoate) injection for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. Aveed should only be used in patients who require testosterone replacement therapy and in whom the benefits of the product outweigh the serious risks of pulmonary oil microembolism and anaphylaxis.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

### **WAIVER OF HIGHLIGHTS SECTION**

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

### **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and immediate container labels that are identical to the carton and immediate container labels submitted on February 24, 2014, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 022219.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because the necessary studies are impossible or highly impracticable and because Aved is unlikely to be used in a substantial number of all pediatric age groups for which a waiver is being requested.

## **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (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)]. The details of the REMS requirements for Aveed were outlined in our complete response letter dated May 29, 2013, which stated the REMS must include a Medication Guide and elements to assure safe use (ETASU). However, we have since determined that a Medication Guide is not necessary to ensure the benefits of Aveed (testosterone undecanoate) outweigh its risks, as a tool of the REMS under section 505-1.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Aveed (testosterone undecanoate) to ensure the benefits of the drug outweigh the risks of post-injection serious pulmonary oil microembolism (POME) reactions and anaphylaxis.

Pursuant to 505-1(f)(1), we have also determined that Aveed (testosterone undecanoate) can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate the risks of post-injection serious POME reactions and anaphylaxis that are listed in the labeling. The elements to assure safe use will ensure that the benefits of the drug outweigh the risk of post-injection serious POME reactions and anaphylaxis by ensuring that healthcare providers who prescribe Aveed (testosterone undecanoate) are specially certified and that Aveed (testosterone undecanoate) is dispensed only in certain healthcare settings that are specially certified.

We remind you that section 505-1(f)(8) of the FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Your proposed REMS, submitted on February 28, 2014, and appended to this letter, is approved. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Aveed (testosterone undecanoate) into interstate commerce.

The REMS assessment plan should include, but is not limited to, the following:

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

Endo will tabulate the following data for each reporting period and cumulatively:

1. Number of introductory information sheets (*Aveed REMS Program: An Introduction*) provided to prescribers, sorted by method of distribution (e.g., website, REMS call center, etc.) and recipient; and
2. Number of unique visits to the Aveed REMS website.

## **B. Program Utilization Statistics**

Endo will tabulate the following data for each reporting period and cumulatively:

1. Prescribing healthcare providers:
  - a. Number of prescribing healthcare providers enrolled, sorted 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; and
  - 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, sorted by type of practice setting and method of enrollment (i.e., online or via fax); and
  - 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**

Endo will tabulate the following metrics on program infrastructure and performance 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 of certified healthcare settings 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 and procedures certified healthcare settings have implemented to be in compliance with the Aveed REMS Program requirements; and
  - d. summary report of serious or critical deviations found and corrective action taken.

## **D. 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; and
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.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 022219 REMS CORRESPONDENCE  
(insert concise description of content in bold capital letters, e.g.,  
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT  
METHODOLOGY)**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 022219 REMS ASSESSMENT**

**NEW SUPPLEMENT FOR NDA 022219  
PROPOSED REMS MODIFICATION**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)  
FOR NDA 022219  
REMS ASSESSMENT  
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

**PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

**REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

In addition, you will conduct enhanced pharmacovigilance for Aveed for pulmonary microembolism (POME) and anaphylaxis adverse events of special interest. Submit expedited post-marketing reports of POME and anaphylaxis resulting in serious adverse events from both U.S. and foreign sources as 15-day Alert reports. Provide periodic and cumulative summaries and analysis of all serious U.S. and foreign reports of POME and anaphylaxis since approval of Aveed with the quarterly safety reports. The enhanced pharmacovigilance will be reassessed 3 years after the marketing of Aveed.

If you have any questions, call Jeannie Roule, Regulatory Project Manager, at (301) 796-3993.

Sincerely,

*{See appended electronic signature page}*

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

Enclosures:

Content of Labeling  
Carton and Container Labeling  
REMS

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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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CHRISTINE P NGUYEN  
03/05/2014