DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022219/S-008

SUPPLEMENT APPROVAL

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

Dear Ms. Clark:

Please refer to your Supplemental New Drug Application (sNDA) dated and received June 30, 2106, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Aveed® (testosterone undecanoate) injection.

This Prior Approval supplemental new drug application proposes modifications to the approved risk evaluation and mitigation strategy (REMS) for Aveed to establish a single shared system (SSS) REMS for testosterone undecanoate products.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter.

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.

Because none of these criteria apply to your application, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Aveed (testosterone undecanoate) was originally approved on March 5, 2014. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modification to the REMS establishes a SSS REMS for the elements to assure safe use required for the reference listed drug (RLD) Aveed and ANDAs referencing Aveed, called the Testosterone Undecanoate REMS Program, which will become applicable on the date of full approval of the first ANDA referencing Aveed. The modification being approved results in a two-part REMS consisting of: (1) the requirements

of the previously approved Aveed REMS; and (2) the new single, shared system for testosterone undecanoate products. The requirements of the previously approved AVEED REMS will remain applicable until full approval of the first ANDA, at which time, they will automatically be replaced by the requirements of the single, shared system .

Your proposed modified REMS, submitted on June 30, 2016, amended and appended to this letter, is approved. The modified REMS consists of the two-part REMS document described above, the REMS supporting documents, all appended materials for the modified REMS, and a timetable for submission of assessments.

The timetable for submission of assessments of the modified REMS is the same as that approved in the Aveed REMS on March 5, 2014, until the full approval of the first ANDA referencing Aveed. Upon full approval of the first ANDA referencing Aveed, you must submit REMS assessments to the FDA 6 months and 12 months from the effective date of the SSS, and annually thereafter.

1. There are no changes to the assessment plan described in our March 5, 2014, letter.

2. The SSS assessment plan must include, but is not limited to, the following:

A. REMS Program Transition Status (to be provided in the 6 month assessment report only)

a. Dates when Testosterone Undecanoate REMS Program materials became available to healthcare providers and healthcare settings on the website and via the REMS call center.
b. Dates when healthcare providers and healthcare settings could become certified online and by fax.
c. Automatic data transition:
    i. Total number of healthcare providers automatically transitioned into the Testosterone Undecanoate REMS Program and date the transition was completed.
    ii. Number of pharmacies automatically transitioned into the Testosterone Undecanoate REMS Program and date the transition was completed.
    iii. Total number of healthcare settings transferred into the Testosterone Undecanoate REMS Program and date the transition was completed.
d. Date when the Testosterone Undecanoate REMS website went live

B. REMS Program Outreach (to be provided in the 6 and 12 month assessments only)

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

1. Number of Introductory Information Sheets *(Testosterone Undecanoate REMS Program: An Introduction)* provided to prescribers and stratified by method of distribution and recipient.

2. Number of unique visits to the Testosterone Undecanoate REMS website

3. Dates of distribution of the *Dear Healthcare Provider Letter and the Dear Healthcare Setting Letter* and the numbers sent on each date. Provide a list of the documents included with each distribution including the revision date.

4. Number of undeliverable and returned communications for each distribution date, by method of distribution.

C. Program Utilization Statistics

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

1. Prescribing healthcare providers

   i. Number of prescribing healthcare providers enrolled and stratified by medical specialty and method of enrollment (i.e., online or via fax)

   ii. Number of healthcare providers with incomplete enrollment

   iii. Number of attempts needed for healthcare providers to complete the Knowledge Assessment and summary of most frequently missed questions.

   iv. Number of healthcare providers who were unable to enroll because they were unable to complete the Knowledge Assessment.

2. Non-prescribing healthcare providers

   i. Number of non-prescribing healthcare providers who completed education using the Testosterone Undecanoate REMS Program website.

3. Healthcare Settings

   i. Number of healthcare settings enrolled stratified by type of practice setting and method of enrollment (i.e., online or via fax)

ii. Number of healthcare settings with incomplete enrollment

iii. Number of healthcare settings verified annually for an accurate Authorized Representative of record. In addition, provide the number of healthcare settings with changed Authorized Representatives and the number of healthcare settings with no Authorized Representative on record during annual verification

4. Number of entities distributing testosterone undecanoate

5. Number of shipments and vials of testosterone undecanoate sent

6. Number of shipments sent to non-certified healthcare settings or to certified healthcare settings that do not have certified prescribing healthcare providers stratified by distribution source.

D. REMS Support Center Report

The following metrics 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

E. REMS Program Compliance (to begin at the 12-month assessment and continuing annually thereafter)

The following metrics will be tabulated for each reporting period:

1. Number of prescribers who were temporarily suspended and number of prescribers who had certification revoked permanently for noncompliance with the AVEED REMS Program requirements during the current reporting period and cumulatively. Include a detailed summary of reasons for suspension or revoked certification.

2. Number of prescribers that were reactivated during the current reporting period and cumulatively.

3. Number of healthcare settings that were suspended or had certification revoked for noncompliance with the Testosterone Undecanoate REMS Program requirements during the current reporting period and cumulatively. Include a detailed summary of reasons for suspension or revoked certification.

4. Number of healthcare setting that were reactivated during the current reporting period and cumulatively.

5. Summary of audits performed during the reporting period including but not limited to:

   i. an overview of the site-audit plan

   ii. the number of site-audits performed

   iii. summary report of the processes and procedures healthcare settings are implementing to be in compliance with the Testosterone Undecanoate REMS Program requirements

   iv. summary report of serious or critical deviations found and corrective action taken.

F. Knowledge Evaluations

Testosterone undecanoate Sponsors will conduct healthcare provider (both prescribing and non-prescribing healthcare provider) and patient surveys at 12 months and then annually following approval of the Testosterone Undecanoate REMS. The scope, methodology, and survey questionnaires that will be used in this evaluation will be provided in the Survey Protocol. The surveys will evaluate:

1. Healthcare provider understanding of the serious risks (serious POME reactions and anaphylaxis) of testosterone undecanoate and need for and compliance with the 30 minute observation period

2. Patient understanding of the serious risks (serious POME reactions and anaphylaxis) of testosterone undecanoate 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 1 or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.
e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

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 22219 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.

We remind you that section 505-1(f)(8) of 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.

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

NDA 22219 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 22219/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 22219/S-000 PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 22219/S-000 PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 22219/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 22219

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. 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 in Word format.

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

REPORTING REQUIREMENTS

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

If you have any questions, call Meredith Alpert, MS, Safety Regulatory Project Manager, at (301) 796-1218.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINE P NGUYEN
12/09/2016