NDA 022219/S-020

SUPPLEMENT APPROVAL

Endo Operations, Limited
c/o Endo USA, Inc.
Attention: Julie Sims
Director, Regulatory Affairs, CMC
1400 Atwater Drive
Malvern, PA 19355

Dear Julie Sims:

Please refer to your supplemental new drug application (sNDA) dated and, received August 9, 2024, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Aveed (testosterone undecanoate) injection.

This Changes Being Effected sNDA provides for a proposed modification to the approved Aveed risk evaluation and mitigation strategy (REMS). We have completed our review of this supplemental application, and 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 (which includes new salts and new fixed combinations), 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Aveed was originally approved on March 5, 2014, and the most recent REMS modification was approved on May 26, 2022. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modifications to the REMS consists of:

1) Updates to the REMS document, appended REMS materials, website screenshots, and supporting document as a result of the change to the REMS Administrator, and;

2) Incorporation of the Endo name change into the REMS document and appended materials.

Your proposed modified REMS, submitted and received on August 9, 2024, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on March 5, 2014.

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

For each metric, provide the two previous, current, and cumulative reporting periods (if applicable), unless otherwise noted.

A. REMS Program Outreach

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 Implementation and Operations

1. Enrollment Statistics
   a. Prescribing healthcare providers
      i. Number and percentage of prescribing healthcare providers certified and stratified by medical specialty and method of enrollment (i.e., online or via fax)
      ii. Number and percentage of healthcare providers with incomplete certification
   b. Non-prescribing healthcare providers
      i. Number and percentage of non-prescribing healthcare providers who completed education using the Aveed REMS Program website.
   c. Healthcare Settings
      i. Number and percentage of healthcare settings certified, stratified by type of practice setting, geographic location, and method of certification (i.e., online or via fax); and
      ii. Number and percentage of healthcare settings with incomplete certification
   d. Distributors or Wholesalers
      i. Number of entities distributing Aveed.
      ii. Number of shipments and vials of Aveed sent from the specialty pharmacies and distributors. Provide a unique ID number for each specialty pharmacy and specialty distributor.

2. Post Training Prescriber Knowledge Assessment (KA)
   a. Number of healthcare providers who completed post-training KA. Include method of completion and number of attempts needed to complete.
   b. Number of healthcare providers who did not pass the knowledge assessment

3. Call Center
   a. Summary of Call Center frequently asked questions
   b. Summary of program problems reported
   c. Description of corrective actions taken to address program or system problems

4. Compliance
   a. Healthcare Providers
      i. Number of prescribers who were deactivated or 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 deactivated, suspension or revoked certification.
      ii. Number and percentage of prescribers that were reactivated during the current reporting period and cumulatively. Include reasons and what actions were taken to be reactivated.
   b. Healthcare Settings
      i. Number of healthcare settings verified annually for an accurate Authorized Representative of record. Include the number of healthcare settings with changed authorized representatives and the number of deactivations, if any.
      ii. Number and percentage of healthcare settings that were deactivated, temporarily suspended or had certification revoked for noncompliance with the Aveed REMS Program requirements during the current reporting period and cumulatively. Include a detailed summary of reasons (i.e., AR not current, failure to respond to audit, expired enrollment, or opt out) stratify by healthcare setting status (i.e., deactivation, suspension, or revoked certification). Provide a unique ID number for each healthcare setting and the source of the report.
      iii. Number and percentage of healthcare settings that were reactivated during the current reporting period and cumulatively. Include reasons and what actions were taken to be reactivated.
      iv. Summary of audits of certified healthcare settings performed during the reporting period including but not limited to:
         1. An overview of the site-audit plan for newly enrolled as well as existing healthcare setting
         2. The number of site-audits performed;

3. Summary report of the processes and procedures healthcare settings implemented to be in compliance with the Aveed REMS Program requirements; and
4. Summary report of serious or critical deviations found and corrective action taken. Include the number of unique healthcare settings that were associated with serious or critical deviations, the number of unique healthcare settings that took corrective actions, and the number of unique healthcare settings that were deactivated at the end of the reporting period.

c. Distributors/Wholesalers
   i. Number of shipments sent to non-certified healthcare settings or to certified healthcare settings that do not have certified healthcare providers. Provide a unique ID number for each healthcare setting. Include the final disposition of the shipment.

C. Health Outcomes and/or Surrogates of Health Outcomes
   1. As part your annual periodic safety report (e.g., PADER), provide an analysis of US POME and anaphylaxis reports.

D. Knowledge Evaluations
   The Applicant will conduct healthcare provider (both prescribing and non-prescribing healthcare provider) and patient surveys annually. 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.

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 that 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.

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 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 022219 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 022219/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 022219/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 022219/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022219/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 022219

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, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling.*

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

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, contact Meredith Hillig, MS, Safety Regulatory Project Manager, at Meredith.hillig@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Audrey Gassman, MD
Deputy Director
Division of Urologic, Obstetrics, and Gynecology
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Center for Drug Evaluation and Research

ENCLOSURE:

- REMS

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

AUDREY L GASSMAN
10/08/2024 03:32:16 PM