

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022219Orig1s000

OTHER ACTION LETTERS



NDA 022219

COMPLETE RESPONSE

Endo Pharmaceuticals Inc.
Attention: Paula Clark
Director, Regulatory Affairs
100 Endo Boulevard
Chadds Ford, PA 19317

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 testosterone undecanoate injection.

We acknowledge receipt of your amendments dated November 29, December 11, 19, and 20, 2012, January 14, 15, February 1, 12, and 27, March 4, and 25, and April 30, 2013.

The November 29, 2012, submission constituted a complete response to our December 2, 2009, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

As described in our letter dated December 2, 2009, in accordance with section 505-1 of the FDCA, we have determined that a risk evaluation and mitigation strategy (REMS) is necessary for testosterone undecanoate injection to ensure that the benefits of the drug outweigh the risks of severe post-injection anaphylactic reactions and pulmonary oil microembolism (POME). We acknowledge the submission of your proposed REMS on November 29, 2012, which contains a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

We have determined that your proposed REMS does not adequately address the risks described above. Because your application cannot be approved without an approved REMS, you must revise your proposed REMS and submit it as part of your response to the deficiency cited in this letter. We will continue discussion of your revised proposed REMS after your complete response to this action letter has been submitted.

Your proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that testosterone undecanoate injection poses 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 testosterone undecanoate injection. FDA has determined that testosterone undecanoate injection is a product that 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 testosterone undecanoate injection.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed testosterone undecanoate injection. The Medication Guide should be available through the REMS website.

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.

Your proposed REMS submission should include two parts: a “Proposed REMS” and a “REMS Supporting Document.” Attached is a template for the Proposed REMS that you should complete with concise, specific information (see Appendix A). Include information in the template that is specific to your proposed REMS for testosterone undecanoate injection. Additionally, all relevant proposed REMS materials including educational and communication materials should be appended to the proposed REMS. Once FDA finds the content acceptable and if the drug is approved, we will include these documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS Supporting Document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

If you do not submit electronically, please send 5 copies of your proposed REMS as an amendment to your application. Prominently identify the proposed REMS submission with the following wording in bold capital letters at the top of the first page of the submission:

PROPOSED REMS FOR NDA 22219

On the first page of subsequent submissions related to the proposed REMS, prominently identify the submission with the following wording in bold, capital letters at the top of the first page:

NDA 22219 / PROPOSED REMS - AMENDMENT

LABELING

The intended population for testosterone undecanoate injection should be better defined to reflect the input from the April 2013 Advisory Committee and to ensure that the benefits outweigh the risks. To that end, address the following revisions to the indication of testosterone undecanoate injection:

1. Revise your proposed language for the **INDICATION** section as follows:

“Testosterone undecanoate injection is an androgen indicated 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)

Testosterone undecanoate injection should be used in patients who require therapy and in whom the benefits (b) (4) outweigh the serious risks of pulmonary microembolism and anaphylaxis.”

We reserve additional comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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

Sincerely,

{See appended electronic signature page}

Audrey Gassman M.D.
Deputy Director
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

AUDREY L GASSMAN
05/29/2013



NDA 022219

COMPLETE RESPONSE

Endo Pharmaceutical Solutions, Inc.
Attention: Mark Roessel
Vice President, Regulatory Affairs
100 Endo Boulevard
Chadds Ford, PA 19317

Dear Mr. Roessel:

Please refer to your new drug application (NDA) dated August 24, 2007, received August 28, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for testosterone undecanoate injection.

We acknowledge receipt of your submissions dated July 2 and September 5, 2008, March 2, 13, and 27, April 21, 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, 2009.

The March 2, 2009, amendment constituted a complete response to our June 27, 2008, action letter.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address the deficiency.

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).

These immediate post-injection adverse reactions have 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, we do 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, you 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.

We are amenable to future discussion of this application at a meeting of the Reproductive Health Drugs Advisory Committee to include discussion of whether the demonstrated benefits of treatment with testosterone undecanoate injection outweigh the risks associated with its use in the target population.

RISK EVALUATION AND MITIGATION STRATEGIES (REMS) REQUIREMENTS

Section 505-1 of the FDCA authorizes 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)).

In accordance with section 505-1 of the FDCA, we have determined that a REMS will be necessary for Aveed (testosterone undecanoate) injection, if it is approved, to ensure that the benefits of the drug outweigh the risks of immediate post-injection anaphylactic reactions and pulmonary oil microemboli (POME). The REMS, once approved, will create enforceable obligations.

Your proposed REMS, included in your submission dated March 2, 2009, and amended on August 24, 2009, is not sufficient to ensure that the benefits of Aveed (testosterone undecanoate) injection outweigh the risks associated with use of Aveed (testosterone undecanoate) injection.

We will continue discussion of your proposed REMS and will notify you about the elements that will be required in the REMS, after your complete response to this action letter has been submitted.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

SAFETY UPDATE

When you respond to the above deficiency, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A

resubmission must fully address the deficiency listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22219

ORIG-1

ENDO
PHARMACEUTICA
LS INC

NEBIDO

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/s/

SCOTT E MONROE

12/02/2009



NDA 22-219

Indevus Pharmaceuticals, Inc.
Attention: John Berryman
Vice President, Regulatory Affairs
33 Hayden Avenue
Lexington, MA 02421-7971

Dear Mr. Berryman:

Please refer to your August 28, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for testosterone undecanoate intramuscular 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, and June 10 and 13(2), 2008.

We further refer to your amendment dated February 22, 2008, containing your request [REDACTED] (b) (4) [REDACTED] for us to use the 750 mg loading dose regimen, used in Part C of Study IP157-001, as the primary basis for our review of your application.

This application proposes the use of testosterone undecanoate intramuscular injection for replacement therapy 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 (FSH, 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.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, it will be necessary for you to address the following deficiencies.

Clinical Deficiencies

Reports of serious post-injection respiratory and allergic adverse reactions in men who have received testosterone undecanoate intramuscular injection raise significant safety concerns regarding the risk/benefit profile for the use of testosterone undecanoate intramuscular injection for the proposed indication. The drug-related respiratory events, generally described as a sudden need to cough in the immediate post-injection period, have been reported in two patients in the testosterone undecanoate

intramuscular injection clinical trials and in approximately 60 patients in the postmarketing period in Europe. In some of the cases, laryngeal tightness, respiratory distress, circulatory collapse, cyanosis, and loss of consciousness were also reported as part of the event. Pulmonary oil microembolism (POME), based upon the castor oil in the depot injection, appears to be causative for most of these cases. In at least four other cases, however, signs and symptoms of a clinically serious systemic allergic reaction have been reported, including two cases meeting criteria for anaphylaxis.

1. The likely incidence of these serious POME and allergic reactions in men who would be treated with testosterone undecanoate intramuscular injection, should the drug product be approved for marketing, is not known. A precise estimate of the likely incidence of these serious adverse events is needed to make a meaningful risk/benefit assessment for the use of testosterone undecanoate intramuscular injection for the proposed indication.
2. The application does not include information regarding the underlying etiology of the anaphylaxis-like reactions. It is not known if these reactions are secondary to the active drug substance or excipients in the drug product, including the castor oil vehicle.
3. The application does not include an adequate plan to minimize or manage the risk of developing these potentially life-threatening events (both POME and anaphylaxis-like events).

Chemistry, Manufacturing, and Controls (CMC) Deficiency

Deficiencies were identified in the Drug Master File (DMF) # (b) (4) for the drug product. A letter outlining the deficiencies has been provided to the DMF holder.

Information Needed to Resolve the Clinical Deficiencies

1. *Detailed safety information from clinical studies to determine the incidence of serious post-injection POME and allergic reactions.*

At a minimum, the safety database should include (1) all subjects treated in Stage 2 of all parts of Study IP157-001, (2) all subjects in (a) Study NE0601 (IPASS), (b) the Non-Interventional Study (NIS), and (c) Study 42306, and (3) all additional foreign data of which you are aware. We consider the information that you provided in your submissions of June 10 and 13, 2008, to be preliminary. Depending on the findings and the number of subjects and the number of injections of testosterone undecanoate from the studies listed above, the safety database may need to include data from additional clinical studies. You should propose the size of the safety database (i.e., total number of subjects exposed to testosterone undecanoate intramuscular injection and total number of injections) and the rationale for the size of the proposed safety database.

2. *Information from clinical investigations intended to characterize the nature and etiology of the anaphylaxis-like events with testosterone undecanoate intramuscular injection.*

This information could be obtained by (1) skin testing procedures to the product and its excipients and (2) *in vitro* testing for the presence of specific IgG and IgE antibodies to both active and excipient components of the drug product.

3. *A plan to minimize the risks associated with the clinical use of testosterone undecanoate intramuscular injection, namely, to reduce the incidence and/or severity of the serious POME and anaphylaxis-like adverse events.*

Information Needed to Resolve the CMC Deficiency

All deficiencies identified in DMF # (b) (4) must be satisfactorily resolved and submitted to the DMF to support your application.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required. When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
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 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or a telephone conference with us to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

NDA 22-219

Page 4

If you have any questions, call Eufrecina DeGuia, Regulatory Health Project Manager, at (301) 796-0881.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.

Director

Division of Reproductive and Urologic Products

Office of Drug Evaluation III

Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
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/s/

Scott Monroe

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