

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022219Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 022219	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Aved Established/Proper Name: testosterone undecanoate Dosage Form: intramuscular injection Strengths: 750 mg/3 mL (250 mg/mL)		
Applicant: Endo Pharmaceutical Solutions		
Date of Receipt: August 29, 2013 (Resubmission). Original submission date received: August 28, 2007.		
PDUFA Goal Date: February 28, 2014	Action Goal Date (if different): March 5, 2014	
RPM: Jeannie Roule		
Proposed Indication(s): Replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Published Literature	Non-Clinical Labeling

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The applicant is relying on previous findings of the potential toxicities of testosterone in nonclinical species and provided references that support the current language in Sections 8.1 and 13.1 of their label. The testosterone in this drug product is equivalent to the testosterone in the submitted references, and was evaluated at or above the proposed human doses.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO”, proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES NO
If “YES”, please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES NO
If “YES”, please list which drug(s) and answer question d) i. below.
If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO
(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO" to (a) proceed to question #11.
If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"
If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s): See attached.

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “NO” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): See attached

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If “NO”, list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s):
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]? YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt. YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

Appl No	Proprietary Name
A083976	TESTRED
A080767	METHYLTESTOSTERONE
A084310	METHYLTESTOSTERONE
A086450	ANDROID 10
A087147	ANDROID 25
N020489	ANDRODERM
N021015	ANDROGEL 1%
N022309	ANDROGEL 1.62%
N021454	TESTIM
A080911	TESTOPEL
N022504	AXIRON
N021463	FORTESTA
N 202763	TESTOSTERONE GEL
N203098	TESTOSTERONE GEL
N021543	STRIANT
A090387	TESTOSTERONE CYPIONATE
A090387	TESTOSTERONE CYPIONATE
A040530	TESTOSTERONE CYPIONATE
A085635	DEPO-TESTOSTERONE
A085635	DEPO-TESTOSTERONE
A040615	TESTOSTERONE CYPIONATE
A040615	TESTOSTERONE CYPIONATE
A040652	TESTOSTERONE CYPIONATE
A086030	TESTOSTERONE CYPIONATE
N009165	DELATESTRYL
A040575	TESTOSTERONE ENANTHATE
A040647	TESTOSTERONE ENANTHATE
A085598	TESTOSTERONE ENANTHATE

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/s/

JEANNIE M ROULE
03/05/2014



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: Feb 14, 2014

To: Hylton V. Joffe, M.D., Director
Division of Reproductive and Urologic Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Alicja Lerner, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: **NDA 22-219**
Name: AVEED (testosterone undecanoate intramuscular injection)
Indication: 1) Primary hypogonadism (congenital or acquired).
2) Hypogonadotropic hypogonadism (congenital or acquired)
Dosage: 3 ml (750mg) intramuscularly at initiation, at 4 weeks, and every 10 weeks thereafter
Company: Endo Pharmaceuticals

Materials reviewed: Label is in EDR

ADDENDUM

This is an addendum to a previously submitted CSS consult (Jan 24, 2014) which constituted a response to a consult request from the Division of Reproductive and Urologic Products regarding review of the label for Aveed (NDA 22-219), testosterone undecanoate injection, for intramuscular use.

Safety issues and labeling recommendations discussed in the CSS review dated January 24, 2014, related to abuse and misuse of testosterone. The recommendations were discussed with OND (DBRUP and SEALD) and OSE on February 5, 2014. It was decided that the misuse/abuse safety concerns apply to all testosterone products, and are not limited to Aveed.

Therefore, CSS's recommended labeling changes will not be instituted at this time. OND and OSE will conduct reviews on the evidence of testosterone misuse and abuse. CSS will collaborate with OND and OSE on the assessment of this evidence outside the review of the

CSS Consult: NDA 120055 Aveed (testosterone undecanoate intramuscular injections)

Aveed application, and final regulatory decision (s) will most likely apply to all testosterone products, including Aveed.

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/s/

ALICJA LERNER
02/14/2014

MICHAEL KLEIN
02/18/2014

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: February 12, 2014

To: Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
Division of Bone, Reproductive, and Urologic Products (DBRUP)

From: Trung-Hieu Brian Tran, Pharm.D./ M.B.A.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Christine Corser, Pharm.D., RAC
Regulatory Review Officer
Office of Prescription Drug Promotion

Subject: **NDA: 022219**
AVEED™ (testosterone undecanoate) injection, for intramuscular
use CIII

This consult is in response to DBRUP's September 18, 2013 request for OPDP's review on the proposed PI and PPI for AVEED™ (testosterone undecanoate) injection, for intramuscular use CIII.

OPDP appreciates the opportunity to provide comments on the PI and PPI. OPDP's comments on the PI are based on the substantially complete version of the PI titled, "PI clean from Sponsor Jan 31 2014.doc," which was received via email from DBRUP on February 3, 2014.

Please see the attached PI with our comments incorporated therein. Comments on the PPI will be provided under separate covers.

If you have any questions, please contact Trung-Hieu Brian Tran, (240) 402-0281, or trung-hieu.tran@fda.hhs.gov.

13 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

TRUNG-HIEU B TRAN
02/12/2014

**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**

**Label and Labeling Amendment
Memorandum**

Date: February 11, 2014

Reviewer: Justine Harris, RPh, Safety Evaluator
Division of Medication Error Prevention and Analysis

Acting Team Leader: Lisa Vo Khosla, PharmD, M.H.A.
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Aveed (testosterone undecanoate) Injection
750 mg/ 3 mL (250 mg/ mL)

Application Type/Number: NDA 22219

Applicant: Endo Pharmaceuticals Solutions, Inc.

OSE RCM #: 2013-2138

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Appendix A. .. DMEPA Revisions to Aveed (testosterone decanoate) injection Dosage and Administration Section of Insert Labeling (in Track Changes)..... 4

1 INTRODUCTION

This memo is an amendment to the Aveed (NDA 22219) labels and labeling review (OSE RCM# 2013-2138) in response to further consultation from the Division of Bone, Reproductive, and Urologic Products (DBRUP) to improve clarity in the Dosage and Administration section of the professional insert labeling

2 DISCUSSION

DMEPA reviewed the Aveed professional insert labeling submitted by the Applicant on August 29, 2013. Based on our assessment, we have identified areas of needed improvement to the professional insert labeling and have made additional recommendations in section 3 to mitigate medication errors and promote the safe use of the product. The recommended revisions include changes to the organization of the dosing and administration section to better retrieve dosing, preparation and administration information. These recommendations are reflected in Appendix A and are in addition to the recommendations made in OSE RCM# 2013-2138 dated October 18, 2013.

3 RECOMMENDATIONS AND CONCLUSIONS

We conclude that the proposed Dosage and Administration section of the professional insert labeling can be improved to increase the readability and prominence of important information to promote the safe use of the product.

If you have further questions or need clarifications, please contact, OSE Project Manager, Shawnetta Jackson at (301) 796- 4952.

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/s/

JUSTINE HARRIS
02/11/2014

LISA V KHOSLA
02/11/2014

**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**

Label, Labeling, and Packaging Memorandum

Date: February 11, 2014

Reviewer: Justine Harris, RPh, Safety Evaluator
Division of Medication Error Prevention and Analysis

Team Leader: Lisa Vo Khosla, PharmD, M.H.A.
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Aveed (Testosterone Undecanoate) Injection
750mg/3 mL (250 mg/ mL)

Application Type/Number: NDA 22219

Applicant: Endo Pharmaceutical Solutions, Inc.

OSE RCM #: 2013-2138-1

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1 INTRODUCTION

This memorandum evaluates the revised container labels and carton labeling for Aved (testosterone undecanoate) Injection submitted on February 10, 2014 (see Appendix A). The Division of Medication Error Prevention and Analysis (DMEPA) initially reviewed the container labels and carton labeling in OSE Review 2013-2138, dated October 17, 2013.

2 MATERIALS REVIEWED

DMEPA evaluated the revised container labels and carton labeling submitted on February 10, 2014. We compared the revised labels and labeling against our recommendations in OSE Review 2013-2138, dated October 17, 2013, to assess whether the revised labels and labeling address our concerns from a medication error perspective.

3 CONCLUSIONS AND RECOMMENDATIONS

Our review of the revised container labels and carton labeling determined the Applicant has implemented all of our recommendations and we find the revisions acceptable. Therefore, we have no further recommendations.

If you have further questions or need clarifications, please contact OSE Project Manager, Shawnetta Jackson at 301-796-4952.

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page.

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/s/

JUSTINE HARRIS
02/11/2014

LISA V KHOSLA
02/11/2014

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title¹	AVEED™ (testosterone undecanoate) injection, for intramuscular use CIII
Applicant	Endo Pharmaceuticals Solutions Inc.
Application/Supplement Number	NDA 22219
Type of Application	Original
Indication(s)	For testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone: <ul style="list-style-type: none"> • Primary hypogonadism (congenital or acquired) • Hypogonadotropic hypogonadism (congenital or acquired)
Office/Division	ODEIII/DBRUP
Division Project Manager	Jeannie Roule
Date FDA Received Application	August 29, 2013
Goal Date	February 28, 2014
Date PI Received by SEALD	February 10, 2014
SEALD Review Date	February 10, 2014
SEALD Labeling Reviewer	Abimbola Adebowale
Acting SEALD Division Director	Sandra Kweder

¹ Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word “must” denotes that the item is a regulatory requirement, while the word “should” denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO:** The PI does not meet the requirement for this item (**deficiency**).
- **YES:** The PI meets the requirement for this item (**not a deficiency**).
- **N/A:** This item does not apply to the specific PI under review (**not applicable**).

Selected Requirements of Prescribing Information

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

- NO** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment: *There is no horizontal line separating the TOC from the FPI. Insert.*

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- NO** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format

Selected Requirements of Prescribing Information

is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: The summarized statement in the second paragraph of the Indications and Usage section of HL does not reference the section or subsection (e.g., (1)) of the Full Prescribing Information (FPI) that contains more detailed information.

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Selected Requirements of Prescribing Information

Initial U.S. Approval in Highlights

- NO** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.
***Comment:** The Initial U.S. Approval in Highlights should read as “Initial U.S. Approval: 1953” and not “Initial U.S. Approval: Year 1953.”*

Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.
Comment:
- YES** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.
Comment:
- YES** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.
Comment:
- YES** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).
Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.
Comment:
- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.
Comment:
- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).
Comment:

Indications and Usage in Highlights

Selected Requirements of Prescribing Information

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *The bolded revision date at the end of HL should read as “Revised: 02/2014” instead of “Revised: xx/2014.”*

Contents: Table of Contents (TOC)

Selected Requirements of Prescribing Information

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- NO** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment: *The same heading for the BW that appears in HL and the FPI is not present at the beginning of the TOC. Insert the same heading for the BW at the beginning of the TOC in upper case letters and bolded.*
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- NO** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment: *Subsection heading “6.2 Postmarketing experience” in the TOC is not in title case (i.e., “6.2 Postmarketing Experience”). Change to title case.*
- NO** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Match the following subsection headings in the TOC with those in the FPI:
Comment: *The TOC subsection heading “6.2 Postmarketing experience” does not match the FPI subsection heading “6.2 Postmarketing Experience.”
The TOC section heading “7 DRUG INTERACTIONS” does not match the FPI subsection heading (b) (4)*
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

Selected Requirements of Prescribing Information

- NO** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: Section heading currently written as (b) (4) in the FPI should read as “7 DRUG INTERACTIONS” as shown in the table above.

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see *Warnings and Precautions (5.2)*]” or “[see *Warnings and Precautions (5.2)*]”.

Comment:

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

Selected Requirements of Prescribing Information

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- YES** 36. In the BW, all text should be **bolded**.

Comment:

- YES** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- YES** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

Selected Requirements of Prescribing Information

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

ABIMBOLA O ADEBOWALE
02/10/2014

ERIC R BRODSKY
02/10/2014

I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, acting SEALD Division Director.

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

PATIENT LABELING REVIEW

Date: February 04, 2014

To: Hylton Joffe, MD
Director
Division of Bone, Reproductive, and Urologic Products (DBRUP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Melissa Hulett, MSBA, BSN, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Trung-Hieu Brian Tran, PharmD, MBA
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): AVEED (testosterone undecanoate)

Dosage Form and Route: Injection, for intramuscular use

Application Type/Number: NDA 22-219

Applicant: Endo Pharmaceuticals

1 INTRODUCTION

On August 29, 2013, Endo Pharmaceuticals re-submitted submitted for the Agency's review a New Drug Application (NDA 22-219) for AVEED (testosterone undecanoate) injection, for intramuscular use, indicated for testosterone replacement therapy in adult males for conditions associated with an absence or deficiency of endogenous testosterone. NDA 22-219 was originally submitted on August 24, 2007, but was issued a Complete Response (CR) letter by the Agency on December 02, 2009, and May 29, 2013, respectively, citing Risk Evaluation and Mitigation Strategy (REMS) deficiencies.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Bone, Reproductive, and Urologic Products (DBRUP) on September 18, 2013, and September 18, 2013, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for AVEED (testosterone undecanoate) injection, for intramuscular use.

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DBRUP under separate cover.

2 MATERIAL REVIEWED

- Draft AVEED (testosterone undecanoate) MG received on August 29, 2013 and received by DMPP on January 28, 2014.
- Draft AVEED (testosterone undecanoate) MG received on August 29, 2013 and received by OPDP on January 28, 2014.
- Draft AVEED (testosterone undecanoate) Prescribing Information (PI) received on August 29, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on January 28, 2014.
- Draft AVEED (testosterone undecanoate) Prescribing Information (PI) received on August 29, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on January 28, 2014.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more

accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

11 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page.

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/s/

SHAWNA L HUTCHINS
02/04/2014

TRUNG-HIEU B TRAN
02/04/2014

MELISSA I HULETT
02/05/2014



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: Jan 31, 2014

To: Hylton V. Joffe, M.D., Director
Division of Reproductive and Urologic Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Alicja Lerner, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: **NDA 22-219**
Name: AVEED (testosterone undecanoate intramuscular injections)
Indication: 1) Primary hypogonadism (congenital or acquired).
2) Hypogonadotropic hypogonadism (congenital or acquired)
Dosage: 3 ml (750mg) intramuscularly at initiation, at 4 weeks, and every 10 weeks thereafter
Company: Endo Pharmaceuticals

Materials reviewed: Label is in EDR

Amendment

CSS would like to propose a small change to the suggested in the memo from Jan 24 2014 label language in the section 9.2 Abuse, sub-section *Potential Abuse-Related Adverse Reactions* to add “**homicides**” to the psychiatric adverse events.

The section should be changed to the following:

Potential Abuse-Related Adverse Reactions (listed by the order of severity)

Potential adverse reactions of abuse of high dose testosterone in combination with other anabolic steroids include cardiovascular complications, such as cardiomyopathy with impaired systolic and diastolic function, left ventricular hypertrophy, myocardial infarctions, myocardial fibrosis; cerebrovascular complications including strokes, and transient ischemic attacks; convulsions; sleep apnea; dyslipidemias e.g. lowering of HDL cholesterol and psychiatric

CSS Consult: NDA 120055 Aved (testosterone undecanoate intramuscular injections)

*effects: mood disorders: major depression, mania and hypomania with irritability, psychotic symptoms, hostility, aggression, violence, suicides, **and homicides**. In men, anabolic steroid abuse causes prolonged suppression of the hypothalamic-pituitary-testicular axis (e.g., testicular atrophy, subfertility, or infertility). Adverse reactions that occur in women include hirsutism, virilization, clitoral enlargement, breast atrophy, and menstrual irregularity.*

Following references are discussing in detail homicides and near homicides.
The reason for the addendum is that not all references requested by CSS were received by the review deadline.

References:

Conacher GN, Workman DG. Violent crime possibly associated with anabolic steroid use. Am J Psychiatry. 1989 May;146(5):679.

Corrigan B. Anabolic steroids and the mind. Med J Aust. 1996 Aug 19;165(4):222-6.

Hall RC, Hall RC, Chapman MJ. Psychiatric complications of anabolic steroid abuse. Psychosomatics. 2005 Jul-Aug;46(4):285-90.

Pope HG Jr, Katz DL. Homicide and near-homicide by anabolic steroid users. J Clin Psychiatry. 1990 Jan;51(1):28-31.

Pope HG Jr, Kouri EM, Powell KF, Campbell C, Katz DL. Anabolic-androgenic steroid use among 133 prisoners. Compr Psychiatry. 1996 Sep-Oct;37(5):322-7. PMID: 8879906

Thiblin I, Kristiansson M, Rajs J. Anabolic androgenic steroids and behavioural patterns among violent offenders. The Journal of Forensic Psychiatry, 8:2, 299-310, DOI: 10.1080/09585189708412012

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/s/

ALICJA LERNER
01/31/2014

MICHAEL KLEIN
02/04/2014



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: Jan 24, 2014

To: Hylton V. Joffe, M.D., Director
Division of Reproductive and Urologic Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Alicja Lerner, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: **NDA 22-219**
Name: AVEED (testosterone undecanoate intramuscular injections)
Indication: 1) Primary hypogonadism (congenital or acquired).
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Dosage: 3 ml (750mg) intramuscularly at initiation, at 4 weeks, and every 10 weeks thereafter
Company: Endo Pharmaceuticals

Materials reviewed: Label is in EDR

Table of Contents

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I. BACKGROUND

This memorandum responds to a consult request from the Division of Reproductive and Urologic Products regarding review of the label for Aveed (NDA 22-219), testosterone undecanoate injection, for intramuscular use.

This drug was initially approved in the U.S. in 1953. The drug is indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of

endogenous testosterone: 1) Primary hypogonadism (congenital or acquired), and 2) Hypogonadotropic hypogonadism (congenital or acquired). The drug is available only through a restricted program called the Aveed REMS Program.

Testosterone was discovered by the famous neurologist Charles-Eduard Brown-Séquard who first injected testosterone into humans (himself) in 1889. However, isolation and characterization of testosterone did not occur until the 1930s in Germany. Testosterone was widely prescribed to treat depression in psychiatric patients, and as a cure for the “male climacteric” and for decades, testosterone continued to be prescribed largely for the treatment of male hypogonadism.

Abuse of testosterone and related drugs (anabolic-androgenic steroids, AAS) started first in the 1950s by athletes who discovered that the drug leads to a gain in muscle mass. The abuse of AAS quickly began to spread through the elite athletic community as a “doping” drug. By the 1960s, AAS was banned in the Olympics. In the 1980s, AAS abuse/misuse began to break out of the elite athletic community and bodybuilders into wider public use. The spread of interest in illicit AAS use was stimulated by an increasing Western cultural importance of male muscular body image (Leit et al., 2002). Increasing abuse/misuse has continued to the present in spite of legislation enacted to counter AAS abuse/misuse:

- 1) 101st U.S. Congress, 1990 (testosterone and anabolic steroids became controlled substances and were placed into Schedule III).
- 2) 108th U.S. Congress, 2004 (expanded the list of anabolic steroids controlled in Schedule III and allowed for DEA to administratively add new steroids to Schedule III)
- 3) NIDA educational efforts, 2000.
- 4) U.S. Drug Enforcement Administration, 2007 (DEA placed boldione, desoxymethyltestosterone, and 19-nor-4,9 (10)-androstadienedione into Schedule III, and had large enforcement actions).

In recent years, testosterone misuse and abuse continues. The media is seemingly encouraging its prescribing by physicians for “male aging” or “andropause”, that can lead to prescription testosterone misuse (Handelsman, 2006). According to Handelsman (2013), in *“the absence of any new indications, off-label testosterone prescribing has increased in most countries in 2000-2011, especially over the last half of the period. The increased testosterone prescribing appears to be primarily for older men and driven by clinical guidelines that endorse testosterone prescribing for age-related functional androgen deficiency (andropause). By eliminating the fundamental distinction between pathological and functional androgen deficiency, these guidelines tacitly promote increased testosterone prescribing, bypassing the requirement for high-quality clinical evidence of safety and efficacy and creating dramatic increases in prescription of testosterone products.”*

According to Pope et al. (2013), among Americans currently age 13-50 years, 2.9-4.0 million have used AAS and within this group, roughly 1 million may have experienced AAS dependence. The syndrome of AAS dependence is well-recognized and described and about 23-30% of AAS users appear to develop a dependence syndrome characterized by chronic AAS use despite adverse effects on physical, psychosocial or occupational functioning (Ip et al., 2012; Kanayama et al., 2009, 2010; Pope et al., 2010). Chronic users exhibit a well-documented AAS

withdrawal syndrome after drug discontinuation (Medras et al., 2001; Wood 2008; Brower, 2009; Kanayama et al., 2009, 2010). See proposed drug labeling for a description of the syndrome.

Additionally, testosterone and other AAS are being misused and abused in the pediatric population especially by young athletes, including both males and females (Yesalis et al., 2000; Kerr et al., 2007; Holland-Hall 2007). The majority of abusers begin AAS use by age 16 years and obtain their drugs illegally and physicians supply a significant number of these abusers (Hall et al., 2005).

According to Arvary et al. (2000) and Kanayama et al. (2003), testosterone and other AAS are considered to be “gateway drugs”, which means that they promote, facilitate and lead to further abuse of other drugs with substantial associated morbidity and mortality (.

The majority of abuse/misuse/overdose related AEs is described for testosterone and other AAS as the abusers commonly combine different steroids (“stacking”) in cycles of increasing and decreasing concentrations (“pyramiding”) (Wood, 2005; Hall et al., 2005). The abusers use complicated multidrug regimens combining oral and intramuscular preparations that progressively increase in dose until 40 to 100 times physiologic levels of testosterone are reached; this is called “stacking.”

In fact, the Advisory Council on the Misuse of Drugs (ACMD) in the United Kingdom issued a report on anabolic steroid misuse, entitled ‘Consideration of the Anabolic Steroids’ (2010 UK Advisory Council on the Misuse of Drugs on anabolic-steroids). The report states that there are *“increasing concerns at the use of anabolic steroids by the general public, and in particular young people. These substances have become ‘popular’ in relation to body building and image enhancement and there is some evidence that such use is increasing”*.

A vast body of published scientific data documents side effects from illicit AAS use and a small fraction of which is referenced below, to include the following:

- Cardiovascular toxicity:
 - cardiomyopathy characterized by impaired systolic and diastolic function (Bagish et al., 2010 ; Rothmann et al., 2011; Youssef et al., 2011; Higgins et al., 2012), and cardiac hypertrophy-left ventricular hypertrophy (Higgins et al., 2012)
 - myocardial fibrosis (Di Paolo et al., 2007)
 - myocardial infarction (Bowman, 1990; Ferenchick et al., 1992; Huie, 1994; Fineschi et al., 2001, 2007)
- Cerebrovascular accidents:
 - strokes and transient ischemic attacks (Nagelberg et al., 1986; Santamarina et al., 2008; Youssef et al., 2011; Shimada et al., 2012)
- Hypertension (Hall et al., 2005)
- Thromboembolic events (Youssef et al., 2011)
- Lipid abnormalities:
 - AAS-related decreases in high-density lipoprotein cholesterol (HDL) (Higgins et al., 2012), and increases of low-density lipoprotein cholesterol (LDL) represent a major risk factor for coronary heart disease

- AAS-induced atherosclerosis is suspected in chronic AAS users (Santora et al., 2006)
- Hepatotoxicity:
 - Including hepatic neoplasms, hepatocellular hyperplasia and hepatocellular adenomas, hepatocellular and intrahepatic cholestasis, peliosis hepatic (hemorrhagic liver cysts) which can lead to liver failure (Soe et al., 1992; Bagatell et al., 1996; Hall et al., 2005)
- Acne (Hall et al., 2005)
- Decreased testicular size and azoospermia and male contraception (Bagatell et al., 1996)
- Neuroendocrine effects:
 - Suppression of the hypothalamic-pituitary-testicular (HPT) axis and hypogonadism after stopping AAS abruptly after chronic use (Kanayama et al., 2010)
- Hirsutism, amenorrhea and virilization in women (Bagatell et al., 1996)
- Gynecomastia (Bagatell et al., 1996; Kanayama et al., 2009; Ip et al., 2012)
- Psychiatric effects:
 - Mood disorders: major depression, mania and hypomania with irritability, hostility, aggressiveness, euphoria, grandiose beliefs, hyperactivity, and reckless or dangerous behavior (Hall et al., 2005).
 - Psychotic symptoms (Pope et al., 1987, 1994)
 - Acute confusional/delirious states. (Freinhar et al., 1985; Katz and Pope, 1994; Thilblin et al., 1999)
 - Suicides (Thilblin et al., 1999; Petersson et al., 2006)
 - Aggression, violence including criminal behavior and homicides (Hall et al., 2005; Thilblin and Parklo, 2002)
- Convulsions (Petersson et al., 2006, 2007)
- Sleep apnea (Bagatell et al., 1996; Hall et al., 2005)
- Premature mortality due to sudden cardiac death, myocardial infarction, suicides (Parssinen et al., 2000, Fineschi et al., 2001; Petersson et al., 2006; Di Paolo et al., 2007)

Testosterone and other AAS also cause the development of dependence and during the withdrawal period after AAS discontinuation following symptoms were reported:

- Major depression, and suicides (Thilblin et al., 1999)
- Anhedonia (Hall et al., 2005)
- Fatigue
- Suppression of the hypothalamic-pituitary-testicular (HPT) axis and hypogonadotropic hypogonadism after stopping AAS after chronic use (Brower 2009; Kanayama et al., 2012))
- Insomnia
- Anorexia
- Decreased libido
- Headache
- Muscle and joint pain

- Desire to take more steroids

II. CONCLUSIONS

1. Section **9 Drug Abuse and Dependence** of the label for Aveed NDA 22219 does not provide the consumers (physicians and patients) current information related to abuse/misuse of this drug, or provide updated safety data related to abuse, misuse, overdose, dependency and withdrawal symptoms.
2. The proposed language in the label under Section 9 Drug Abuse and Dependence is provided in section Labeling issues.

III. RECOMMENDATIONS

1. Introduce in Section **9 Drug Abuse and Dependence** of the label for Aveed (NDA 22-219) a description of the abuse potential of the drug product based on information in the public domain.
2. Sections 9.2 Abuse, 9.3 Dependence, should include the most current safety findings as related to abuse, misuse, overdose and dependence including withdrawal symptoms of testosterone.
3. OSE should be contacted to provide the current and updated information on abuse-related safety data for testosterone products, which includes abuse, misuse, overdose, and addiction.

IV. LABELING ISSUES

CSS proposed changes for the AVEED label.

9.2 Abuse

Drug abuse is intentional non-therapeutic use of a drug, even once, for its rewarding psychological and physiological effects. Testosterone, typically in combination with other anabolic steroids, is abused by athletes (pending OSE review) with the intent of gaining a competitive advantage in sports and is abused by bodybuilders with the intent to increase muscle mass, decrease fat mass, and improve body appearance. Abuse has been seen in young adult men and male adolescents, though AAS are abused in adults, also.

Behaviors Associated with Addiction

Continued abuse of testosterone and other anabolic steroids, leading to addiction is characterized by the following behaviors:

- Taking greater dosages than prescribed
- Continued drug use despite medical and social problems due to drug use
- Spending significant time to obtain the drug when supplies of the drug are interrupted

- Giving a higher priority to drug use than other obligations
- Having difficulty in discontinuing the drug despite desires and attempts to do so
- Experiencing a withdrawal syndrome upon abrupt discontinuation of use

Potential Abuse-Related Adverse Reactions (listed by the order of severity)

Potential adverse reactions of abuse of high dose testosterone in combination with other anabolic steroids include cardiovascular complications, such as cardiomyopathy with impaired systolic and diastolic function, left ventricular hypertrophy, myocardial infarctions, myocardial fibrosis; cerebrovascular complications including strokes, and transient ischemic attacks; convulsions; sleep apnea; dyslipidemias e.g. lowering of HDL cholesterol and psychiatric effects: mood disorders: major depression, mania and hypomania with irritability, psychotic symptoms, hostility, aggression, violence and suicides. In men, anabolic steroid abuse causes prolonged suppression of the hypothalamic-pituitary-testicular axis (e.g., testicular atrophy, subfertility, or infertility. Adverse reactions that occur in women include hirsutism, virilization, clitoral enlargement, breast atrophy, and menstrual irregularity.

9.3 Dependence

Physical dependence is characterized by withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug. Although drug dependence has not been documented in individuals using approved doses of testosterone for approved indications, dependence has been observed in some individuals who abused higher doses of testosterone in combination with other anabolic steroids. The withdrawal syndrome can last for weeks or months and is characterized by depressed mood, major depressions, and suicides, fatigue, craving, restlessness, anorexia, insomnia, and decreased libido and suppression of the hypothalamic-pituitary-testicular (HPT) axis and hypogonadotropic hypogonadism.

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/s/

ALICJA LERNER
01/24/2014

MICHAEL KLEIN
01/24/2014

**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**

Label, Labeling and Packaging Review

Date: October 17, 2013

Reviewer: Justine Harris, RPh, Safety Evaluator
Division of Medication Error Prevention and Analysis

Team Leader: James Schlick, RPh, MBA, Team Leader
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Aveed (Testosterone Undecanoate) Injection
750 mg/3 mL (250 mg/mL)

Application Type/Number: NDA 022219

Applicant: Endo Pharmaceutical Solutions, Inc.

OSE RCM #: 2013-2138

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1 INTRODUCTION

This review evaluates the proposed REMS, insert labeling (to include Medication Guide) carton labeling, and container labels for Aveed NDA 022219 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

This is the fourth review cycle for this New Drug Application (NDA) 022219. The Division provided Endo with a CR Letter stemming from their review of the NDA resubmission in correspondence dated May 29, 2013. The Division determined that a revised risk evaluation and mitigation strategy (REMS) is necessary to ensure the benefits of the drug outweigh the risks of severe post-injection anaphylactic reactions and pulmonary oil microembolism (POME). Endo submitted revised REMS for review on August 29, 2013.

1.2 PRODUCT INFORMATION

The following product information is provided in the December 20, 2012 proprietary name submission.

- Active Ingredient: Testosterone Undecanoate
- Indication of Use: Replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone (i.e., primary hypogonadism and hypogonadotropic hypogonadism).
- Route of Administration: Intramuscular injection into the gluteal muscle
- Dosage Form: Sterile injectable solution
- Strength: 750 mg/3 mL (250 mg/mL)
- Dose and Frequency: Inject 3 mL (750 mg) intramuscularly at initiation, at 4 weeks, and every 10 weeks thereafter. Following injection, the patient should remain in the health care facility or physician's office for 30 minutes in order to provide for early recognition and management of an anaphylactic reaction or an injection-based pulmonary oil microembolism.
- How Supplied: Single-Use amber glass vial containing 750 mg/3 mL testosterone undecanoate sterile injectable solution.
- Storage: Controlled room temperature 25°C (77°F); excursions permitted to 15-30°C (59-86°F)
- Container and Closure Systems: Amber glass, single use vial with silver-colored crimp seal and gray plastic cap.
- Schedule III

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,¹ the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted August 29, 2013 (Appendix A)
- Carton Labeling submitted August 29, 2013 (Appendix B)
- REMS, Insert Labeling and Medication Guides, traditional and 1- page versions, submitted August 29, 2013

2.2 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed the container labels, carton and insert labeling, and medication guide under OSE Review #2009-510, dated August 11, 2009 and the revised labels and labeling under OSE Review #2009-510, dated August 13, 2009 and OSE Review #2009-510, dated August 14, 2009, and the revised label and labeling under OSE 2012-2947, dated April 30, 2013. We looked at the reviews to ensure all our recommendations were implemented, addressed our concerns from a medication error perspective, and that our recommendations have not changed due to lessons learned from post-marketing experience.

3 CONCLUSIONS AND RECOMMENDATIONS

The Applicant incorporated most of the recommendations from OSE Review # 2012-2947, dated April 30, 2013. However, our evaluation noted areas where information on the proposed container labels, carton, and insert labeling can be improved to minimize the potential for medication errors. We provide recommendations in *Section 3.1* Comments to the Applicant.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Shawnetta Jackson, project manager, at 301-796-4952.

3.1 COMMENTS TO THE APPLICANT

A. Container Label and Carton Labeling

1. Revise the presentation of the proprietary name to use title case font (e.g., Avedo). Words set in upper and lower case form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all capital letters.
2. Use bold font to make the presentation of the strength per total volume (i.e. 750 mg/3 mL) more prominent on the container label and carton labeling than the strength per milliliter presentation (250 mg/mL). This may prevent confusion when the practitioner is attempting to ascertain the total contents of the vial, thus, mitigating the risk of medication error.
3. Revise the presentation of the concentration to use a capital 'L' for the volume (i.e., 250 mg/mL) on the container label.

4 REFERENCES

1. **Mena-Grillasca, C., OSE Review #2009-510**, Label and Labeling Review for Aveed (Testosterone Undecanoate) Injection, August 11, 2009
2. **Mena-Grillasca, C., OSE Review #2009-510**, Label and Labeling Review for Aveed (Testosterone Undecanoate) Injection, August 12, 2009
3. **Mena-Grillasca, C., OSE Review #2009-510**, Label and Labeling Review for Aveed (Testosterone Undecanoate) Injection, August 14, 2009
4. **Park, Alison, OSE Review # 2012-2947**, Label, and Labeling Review for Aveed (Testosterone Undecanoate) Injection, April 30, 2013

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JUSTINE HARRIS
10/18/2013

JAMES H SCHLICK
10/18/2013

**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**

Label, Labeling and Packaging Review

Date: April 30, 2013

Reviewer: Alison Park, Pharm.D., Safety Evaluator
Division of Medication Error Prevention and Analysis

Team Leader: Zachary Oleszczuk, Pharm.D., Team Leader
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh, Division Director
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Aveed (Testosterone Undecanoate) Injection
750 mg/3 mL (250 mg/mL)

Application Type/Number: NDA 022219

Applicant: Endo Pharmaceutical Solutions, Inc.

OSE RCM #: 2012-2947

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1 INTRODUCTION

This review evaluates the proposed container label, carton, and insert labeling for Aved NDA 022219 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

This is the third review cycle for this New Drug Application (NDA) 022219. The original Applicant, Indevus Pharmaceuticals, received an Approvable Letter on June 27, 2008 due to a chemistry, manufacturing and control (CMC) deficiency and due to safety concerns related to immediate post-injection adverse reactions. On March 2, 2009, the Applicant submitted a Complete Response which addressed the CMC deficiencies but did not address the safety issues related to post-injection adverse reactions. On December 2, 2009, the current Applicant, Endo Pharmaceuticals Solutions Inc., received a Complete Response (CR) for this NDA due to the reports of serious, immediate, potentially life-threatening post-injection adverse reactions. On November 29, 2012, Endo Pharmaceuticals Solutions Inc., submitted their response to the complete response letter.

The proposed name, Aved, was found conditionally acceptable in OSE Review #2012-2995 dated March 14, 2013, and the Applicant, Endo Pharmaceuticals Solution Inc, was notified via letter on March 15, 2013.

1.2 PRODUCT INFORMATION

The following product information is provided in the December 20, 2012 proprietary name submission.

- Active Ingredient: Testosterone Undecanoate
- Indication of Use: Replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone (i.e., primary hypogonadism and hypogonadotropic hypogonadism).
- Route of Administration: Intramuscular injection into the gluteal muscle
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- Dose and Frequency: Inject 3 mL (750 mg) intramuscularly at initiation, at 4 weeks, and every 10 weeks thereafter. Following injection, the patient should remain in the health care facility or physicians office for 30 minutes in order to provide for early recognition and management of an anaphylactic reaction or an injection-based pulmonary oil microembolism.
- How Supplied: Single-Use amber glass vial containing 750 mg/3 mL testosterone undecanoate sterile injectable solution.
- Storage: Controlled room temp 25°C (77°F); excursions permitted to 15-30°C (59-86°F)
- Container and Closure Systems: Amber glass, single use vial with silver-colored crimp seal and gray plastic cap.

- Schedule III

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,¹ the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted November 29, 2012 (Appendix A)
- Carton Labeling submitted November 29, 2012 (Appendix B)
- Insert Labeling and Medication Guide submitted November 29, 2012

2.2 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed the container labels, carton and insert labeling, and medication guide under OSE Review #2009-510, dated August 11, 2009 and the revised labels and labeling under OSE Review #2009-510, dated August 13, 2009 and OSE Review #2009-510, dated August 14, 2009, and we looked at the reviews to ensure all our recommendation were implemented, address our concerns from a medication error perspective, and that our recommendations have not changed due to lessons learned from postmarketing experience.

3 CONCLUSIONS AND RECOMMENDATIONS

The Applicant incorporated most of the recommendations from OSE Review #2009-510, dated August 11, 2009, August 13, 2009, and August 14, 2009. However, our evaluation noted areas where information on the proposed container labels, carton and insert labeling can be improved to minimize the potential for medication errors. We provide recommendations in *Section 3.1* Comments to the Division and *Section 3.2* Comments to the Applicant.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Shawnetta Jackson, project manager, at 301-796-4952.

3.1 COMMENTS TO THE APPLICANT

A. Container Label and Carton Labeling

1. Revise the presentation of the proprietary name to use title case font (e.g., Aveed). Words set in upper and lower case form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all capital letters.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2. Ensure the presentation of the established name is at least half the size of the proprietary name in accordance to 21 CFR 201.10(g)(2), which requires that the established name shall be printed in letters that are at least half as large and with a prominence commensurate to the proprietary name, taking into consideration all pertinent factors, including typography, layout, contrast and other printing features.
3. Make the presentation of the strength more prominent by bolding on the container label and carton labeling.
4. Revise the presentation of the concentration to use a capital 'L' for the volume (i.e., 250 mg/mL) on the container label.

4 REFERENCES

1. **Mena-Grillasca, C., OSE Review #2009-510**, Label and Labeling Review for Aved (Testosterone Undecanoate) Injection, August 11, 2009
2. **Mena-Grillasca, C., OSE Review #2009-510**, Label and Labeling Review for Aved (Testosterone Undecanoate) Injection, August 12, 2009
3. **Mena-Grillasca, C., OSE Review #2009-510**, Label and Labeling Review for Aved (Testosterone Undecanoate) Injection, August 14, 2009

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/s/

ALISON J PARK
04/30/2013

CAROL A HOLQUIST
04/30/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)**

**Briefing Document - Epidemiology: Evaluation of Anaphylaxis and Pulmonary
Oil Microembolism Reporting and Incidence Rates**

Date: 27 March, 2013

Reviewer(s): Cynthia Kornegay, Ph.D.,
Patty Greene, Pharm.D.
Division of Epidemiology II

Team Leaders David Moeny, M.P.H., R. Ph.,
Grace Chai, Pharm.D.,
Division of Epidemiology II

Associate Director Rita Ouellet-Hellstrom, Ph.D., M.P.H.
Division of Epidemiology II

Deputy Director: Laura A. Governale, Pharm.D., MBA
Division of Epidemiology II

Subject Evaluation of reporting and incidence rates for
pulmonary oil microembolism and anaphylaxis
associated with injectable testosterone undecanoate

Drug Name(s): Aveed® (testosterone undecanoate)

Application Type/Number: NDA 022-219

Applicant/sponsor: Endo Pharmaceuticals Solutions, Inc.

OSE RCM #: 2013-252

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EXECUTIVE SUMMARY

Aveed® (testosterone undecanoate, TU) is a testosterone replacement product intended for use as a 750 mg/3 ml injection in adult males for conditions associated with testosterone deficiency. TU has been available worldwide since November 2003 as a 1000 mg / 4ml injection product (Nebido) with an indication of confirmed male hypogonadism, but is not approved in the U.S. On April 18th, 2013, an advisory committee meeting will discuss issues related to the U.S. approval of Aveed. Currently, there are two other injectable testosterone products approved in the U.S.; testosterone enanthate (approved in 1953) and testosterone cypionate (approved in 1979). If approved, Aveed will allow for a longer time between injections.

In 2009, FDA issued a “Complete Response” to Endo Pharmaceuticals Solutions (Endo) for Aveed due to cases of anaphylaxis or pulmonary oil microembolism (POME) that occurred worldwide in the postmarketing period for Nebido. There were between five and eight potential cases in the TU clinical trials, and an additional 66 potential cases reported in the postmarketing period. In response, Endo provided POME and anaphylaxis reporting rates based on worldwide sales of TU. OSE/DEPI was asked to evaluate the validity of these reporting rates, to put these rates into context, and provide an estimate of the use of injectable testosterone in the U.S..

While reporting rates are simple to construct and seemingly intuitive to understand, there are several underlying conditions for both the numerator and denominator that must be met for a valid and interpretable metric. The biggest concern is identifying the appropriate population at risk. To construct a rate, both the cases and the population at risk must be from the same population. This is not the case with TU reporting rates; the cases are from a spontaneous reporting system and the population at risk is represented by sales information. The reporting rates submitted by Endo are actually measuring an association, which does not translate necessarily to a direct relationship between the event and the drug. In summary, there is no way to validate, interpret, or place Endo’s reporting rates into context.

In addition to reporting rates, Endo, provided incidence rates for POME and anaphylaxis based on clinical and postmarketing studies of TU. Although incidence rates are typically presented as person-time, that denominator is misleading in this case since these events occur immediately post-injection, so patients are not at risk during most of the time between injections. Incidence rates per 10,000 injections are a more appropriate metric to quantify POME and anaphylaxis occurrence.

There was one POME case in the study group that received a dose of 750 mg TU (a 3 ml injection), and 8 cases in the group of patients who received a dose of 1000 mg TU (a 4 ml injection). This translates to incidence rates of 3.2 and 4.7 POME cases per 10,000 injections, respectively. There were two cases of anaphylaxis in the in the 1000 mg dose group, for a rate of 1.2 cases per 10,000 TU injections (or 32.4 cases per 10,000 treatment-years of exposure).

When the POME incidence rates were compared to two postmarketing TU studies, the rates remained consistent (4.8 and 5.1 POME cases per 10,000 injections. Although a definitive rate of drug-related anaphylaxis is difficult to establish, the rate seen in the TU clinical and postmarketing trials is significantly higher than published rates of 0.8 to 5 cases per 10,000 treatment-years (15). While Endo is aware of these rates, none of the reviewed documents indicate that a serious attempt was made to reduce or eliminate either POME or anaphylaxis beyond reducing the proposed dose for the U.S. market.

In summary, Endo's failure to characterize TU use accurately especially for the 750 mg product, the consistent high POME and anaphylaxis incidence rates reported in the clinical and postmarketing databases, and Endo's unwillingness to acknowledge or effectively address possible increased rates is concerning. It is unlikely that the incidence of either POME or anaphylaxis associated with TU has decreased in the postmarketing period. The risk of serious and life-threatening events should be carefully weighed against the benefit of a potentially longer injection-free period, particularly given the availability of multiple alternatives to TU, including other injectable testosterone preparations and other dose forms.

1 INTRODUCTION

Aveed® (testosterone undecanoate, TU) is a testosterone replacement product intended for use as a 750 mg/3 ml injection in adult males for conditions associated with testosterone deficiency. TU is authorized to be marketed in 90 countries and is available in 72 countries worldwide as a 1000 mg / 4ml injection product marketed as Nebido. It is not approved for use in the U.S. An upcoming advisory committee meeting, on April 18th, 2013, will discuss issues related to the U.S. approval of Aveed.

Nebido is given as an intramuscular injection approximately every 12-14 weeks. In the European Union (EU), the dose is 1000 mg or 4 ml per injection. The proposed dose in the U.S. is 750 mg or 3 mg per injection, given at the start of therapy, 4 weeks later, and approximately every 10 weeks thereafter. There are currently two other injectable testosterone products approved for use in the U.S., Delatestryl® (testosterone enanthate) and Depo Testosterone® (testosterone cypionate). The dose regimen for testosterone replacement for both of these drugs is 50 mg – 400 mg per injection (every two to four weeks).

Male testosterone deficiency is commonly a symptom of a condition called hypogonadism, which can be either primary or secondary. Primary hypogonadism (PH) is caused by testicular disease, and can be caused by congenital disorders, testicular cancer (or its treatment), infection, or high doses of certain antibiotics (4, 8). The estimated prevalence of primary hypogonadism is one in 10,000 men (8).

Secondary hypogonadism, or hypogonadotropic hypogonadism (HH), is a more common disorder. In contrast to PH, it stems from a congenital or acquired impairment of the pituitary gland (8). Causes of acquired HH include age, obesity, type II diabetes, strenuous exercise, eating disorders, malnutrition, traumatic brain injury, chronic diseases, and cancer(8). As testosterone levels decrease with age, the prevalence of HH increases(12). Morley et al compared three studies of hypogonadism, and found that in men aged 40 to 59 years, the prevalence was between 2% and 30%(12). However, in men aged 70 to 79 years, the prevalence ranged from 34% to 70%. Giagulli et al estimated that while 30% of men between the ages of 40 and 60 have HH, only 6% to 12% are symptomatic. In addition, approximately 5% of all men with some form of hypogonadism are treated(4).

Symptoms of hypogonadism (either primary or secondary) vary widely in type and severity depending on the age at which the condition manifests. Prenatal hypogonadism can result in micropenis, hypospadias, or cryptorchidism. If the condition strikes in the early teens, it may manifest as delayed puberty, eunuchoidal body type, scant body hair, a high-pitched voice, or small testicles, penis, and prostate. Adult-onset hypogonadal symptoms include loss of libido, body hair, energy, muscle mass, and strength, low sperm count and shrinking testes, gynecomastia, weight gain, depression, sleep disturbance, hot flushes, osteoporosis and low-trauma fractures, and an inability to concentrate. The standard treatment for both primary and secondary hypogonadism is testosterone replacement therapy (4, 8, 12).

Worldwide, injectable TU marketed as Nebido was approved in 2003 for the treatment of testosterone therapy in confirmed male hypogonadism. (Oral TU has been available worldwide since the mid-1970's (6). Each single-dose vial of Nebido contains 1000 mg of TU in a 4 ml dose. The other ingredients are castor oil and benzyl benzoate, a preservative. Long-term, Nebido is administered as a gluteal injection every 10-14 weeks after the initial doses, while the proposed dose schedule is every 10 weeks for Aveed. TU is not intended for use in children, adolescents, or women, and should only be used after the patient's hypogonadism has been confirmed with laboratory tests(1).

For reference, in the US, two other injectable testosterone products, Delastryl® (testosterone enanthate or TE), and Depo-Testosterone® (testosterone cypionate or TC), are currently available. TE was approved in the US in 1953. A 5 ml, multi-dose vial holds up to 5 doses of TE at 200 mg/ml. Other ingredients are sesame oil and chlorobutanol, a preservative. TE indicated for hypogonadism and delayed puberty in males, and inoperable metastatic mammary breast cancer in females. TE is administered every two to four weeks, depending on dosage and indication, into the gluteal muscle. TE is a pregnancy category X and a schedule III controlled substance. It carries warnings for hypercalcemia, hepatic conditions (including cancer), prostate hyperplasia and cancer, edema, gynecomastia, and compromised adult stature when used for delayed puberty(3).

TC was approved in the US in 1979. TC is available in 10 ml, multi-dose vials with 200 mg of TC per ml. Additional ingredients are cottonseed oil, benzyl benzoate, and benzyl alcohol as a preservative. The only indications for TC are the treatment of primary or hypogonadal (i.e., secondary) hypogonadism in men. TC carries the same warnings and classifications as TE as well as an additional warning against the use to enhance athletic performance(14).

The primary safety concerns associated with injectable TU, TE, and TC are the acceleration of sub-clinical prostate cancer and benign prostatic hyperplasia.

Appendix 1 provides a table that summarizes the characteristics of all three injectable testosterone preparations.

If approved, Aveed will allow for longer periods between injections compared to the two currently available testosterone products although shorter than Nebido. FDA issued a "Complete Response" to Endo in 2009 due to cases of anaphylaxis or pulmonary oil microembolism (POME) that occurred worldwide in the postmarketing period for Nebido. There were between five and eight potential cases in the TU clinical trials, and an additional 66 potential cases reported to Endo in the postmarketing period(7). Endo has provided reporting rates for both POME and anaphylaxis based on estimated sales of TU in the documents reviewed for this assessment. OSE/DEPI was asked to evaluate the validity of these reporting rates and provide an estimate of the use of injectable testosterone in the U.S. to put these rates into context.

2 REVIEW METHODS AND MATERIALS

2.1 REPORTING RATES AND INCIDENCE RATES

The following sponsor documents were reviewed for this report:

- Periodic Safety Update Report 9, Nov. 25th 2009 – Nov. 24th 2010 (PSUR 9, dated Jan 2011)
- PSUR 10, Nov. 25th 2010 – Nov. 24th 2011, dated Jan 2012
- PSUR Addendum Report, Nov. 25th 2011 – April 30th 2012, dated Jun 2012
- Aved Summary of Clinical Safety (Section 2.7.4), dated Oct 2012
- Aved Clinical Overview (Section 2.5), dated Nov 2012

FDA background information was obtained from:

- Cross-Discipline Team Leader Memo, NDA 22-219, signed Nov. 30, 2009
- REMS Review, Aved®[®], NDA 22-219, OSE RCM #2011-1429, signed Sep. 30, 2011
- Nebido® EU-Safety Risk Management Plan, dated Jan 2013

In addition, PubMed was searched for articles describing TU studies, as well as case reports involving injectable TU use.

2.2 FDA DRUG USE DATA SOURCES

To assess the feasibility of determining use for the older testosterone products as potential comparators to the TU, the IMS Health, IMS National Sales Perspective™ database was searched. National estimates of the number of packages (eaches) sold for testosterone products by dosage formulation from manufacturers into retail and non-retail markets were retrieved for the years 2008 through 2012. Sales data represent the amount of product sold from manufacturers to the “back door” of various drug distribution outlets such as retail pharmacies, hospitals, clinics, etc.; sales data do not reflect what is being sold or administered to patients directly.

The Source Healthcare Analytics' ProMetis Lx® database was also searched to determine the nationally estimated number of patients with a prescription claim for testosterone cypionate (TC) and testosterone enanthate (TE) injection by patient age and sex in the outpatient retail pharmacy setting for the years 2009 through 2012.

3 REVIEW RESULTS

3.1 US SALES DATA- IMS HEALTH, IMS NATIONAL SALES PERSPECTIVE™

US sales data were not available as far back as 1953 so comparisons of the older products with TU cannot be made. Nonetheless, current information on sales and patient use in the US is provided for context.

Table 1 displays the nationally estimated number of packages (bottles, cartons or vials) sold for testosterone products by dosage formulation from manufacturers to U.S. retail and non-retail channels of distribution between 2008 through 2012.

Although sales of all testosterone products increased by 27% from year 2008 to 2011, there was a decrease (-9%) from year 2011 to 2012, primarily due to a decrease in sales of topical testosterone products. Approximately (b) (4) packages were distributed nationwide for testosterone products in year 2012, a net increase of 16% since year 2008. Sales of testosterone injection products accounted for 6% of total sales in year 2012.

Sales of testosterone injection products increased 3-fold from (b) (4) vials sold in 2008 to approximately (b) (4) vials sold in year 2012. The average percent change in sales by year of testosterone injectable products was approximately 35% during each year between 2008 and 2012 (data not shown). Sales data during year 2012 indicated that approximately 55% of testosterone vials (Eaches) were distributed to outpatient retail pharmacies; 24% were to non-retail settings; and 21% were to mail-order/specialty pharmacies.¹ Since the injectable testosterone is distributed primarily to outpatient pharmacies, outpatient retail pharmacy utilization patterns were used to obtain national patient estimates. Non-retail and mail-order pharmacy data were not included in this analysis.

Table 1: Sales of testosterone products in packages sold (bottles, cartons, or vials), by dosage form, to all U.S. channels of distribution, Y2008-2012

	Year 2008		Year 2009		Year 2010		Year 2011		Year 2012		Y2008-2012	
	Packages (N)	Share %	Packages (N)	Share %	Packages (N)	Share %	Packages (N)	Share %	Packages (N)	Share %	Packages (N)	Share %
TESTOSTERONE TOTAL	(b) (4)											
T TOPICALS												
I INJECTABLES												
J INSERTS/IMPLANTS												
D DERMATOLOGICALS												
O ORALS												
Y ALL OTHERS												

Source: IMS Health, IMS National Sales Perspectives™, Year 2008-2012, extracted January 2013 File: NSPC 2012-2713 Testosterone by form 3-8-13.xls

3.2 US PATIENT-BASED DATA

Table 2 and Figure 1 provide the nationally estimated number of patients with at least one prescription claim for injectable testosterone products, testosterone cypionate (TC) and testosterone enanthate (TE), stratified by patient age, from U.S. outpatient retail pharmacies for years 2009 through 2012. Overall, the number of patients with at least one prescription claim for injectable testosterone product more than doubled from approximately (b) (4) patients in year 2009 to (b) (4) patients in year 2012. Throughout this time period, patients 50+ years of age accounted for slightly more than half of patients using testosterone injections

¹ IMS Health, IMS National Sales Perspectives™. Year 2012. Extracted March 2013. File: NSPC 2013-252 Inj Test by channel 3-4-13.xls

compared to patients 0-49 years of age. Between both age groups, the absolute number of patients, 0-49 years and 50+ years, more than doubled from year 2009 to year 2012.

Table 2: Nationally estimated number of patients with at least one prescription claim for injectable testosterone products, testosterone cypionate and testosterone enanthate, by patient age, in U.S. outpatient retail pharmacies, years 2009-2012

	2009		2010		2011		2012	
	Patient Count	Share	Patient Count	Share	Patient Count	Share	Patient Count	Share
Injectable Testosterone	(b) (4)							
Age 0-49 yrs								
<30 yrs								
30-39 yrs								
40-49 yrs								
Age 50+ yrs								
50-59 yrs								
60-69 yrs								
70+ yrs								
Unspecified Age								

Source Healthcare Analytics' ProMetis Lx[®]. Years 2009-2012. Extracted March 2013. File Name: SHALX 2013-252 Testosterone Inj 3-6-13.xls

Figure 1: Nationally estimated number of patients with at least one prescription claim for injectable testosterone products, testosterone cypionate and testosterone enanthate, in U.S. outpatient retail pharmacies, years 2009-2012



Source Healthcare Analytics' ProMetis Lx[®]. Years 2009-2012. Extracted March 2013.

Table 3 provides the nationally estimated number of patients with at least one prescription claim for injectable testosterone products, stratified by patient age and sex, aggregated for years 2009 through 2012. Patients 50-59 years of age accounted for slightly more than a quarter of patients (28% of patients), followed by patients 40-49 years (25% of patients), and 60-69 years (19% of patients). Throughout this time period, male patients accounted for the majority of patients (96% of patients) with at least one prescription claim for testosterone injection. Among patients younger than 30 years old, there was a slightly higher proportion of female patients (13%) compared to all other age groups. Females accounted for 5% or less of patients overall.

Table 3: Nationally estimated number of patients with at least one prescription claim for injectable testosterone products, testosterone cypionate and testosterone enanthate, by patient age and sex in U.S. outpatient retail pharmacies, years 2009-2012 aggregated

	2009-2012						
	Total		Males			Females	
	Patient Count	Share	Patient Count	Vert. Share	Horiz. Share	Patient Count	Vert. Share
Injectable Testosterone	(b) (4)						
Age <30 yrs							
30-39 yrs							
40-49 yrs							
50-59 yrs							
60-69 yrs							
70+ yrs							
Unspecified Age							

Source Healthcare Analytics' ProMetis Lx[®]. Years 2009-2012. Extracted March 2013. File Name: SHALX 2013-252 Testosterone Inj 3-6-13.xls

3.3 WORLDWIDE DRUG USE INFORMATION - ENDO PHARMACEUTICALS SOLUTIONS, INC.

Information on the total sales of TU by vial is provided in the Endo's Summary of Clinical Safety and the EU Safety Risk Management Plan documents. Table 4 shows the total and the percent change in sales by year for 2003 through 2012. In the Summary of Clinical Safety, Endo reported total sales of (b) (4) vials from November 25, 2003 to November 24, 2011. The EU Risk Management Plan states that (b) (4) vials were sold between November 2003 and November 2012. This indicates an increase of 32% between 2011 and 2012, which is substantially larger than the increases seen from previous years. Endo does not note nor explain this sudden increase.

Table 4: Worldwide TU Sales by ampule, November 2003 – 2012*

Year	Total Ampules	Change from Prior Year
2003-2008	(b) (4)	
2008-2009		14%
2009-2010		14%
2010-2011		14%
2011-2012**		31%
Total 2003-2011		
Total 2003-2012**		

*Adapted from Endo’s S fety, pp161-182

** Adapted from Endo’s EU Safety Risk Management Plan, pp 15-16

In addition, Endo supplied IMS Health prescription information between June 2007 and July 2008 for a selected number of countries in the EU Safety Risk Management plan (page 17). **The following data should be interpreted with caution, as the use profile in the 5 countries was not verified in any way with the use profile in the other countries, and may not be representative of Nebido use in the other countries where it is approved.** Germany, France, Italy, Spain, and the UK combined had (b) (4) Nebido prescriptions during this time. Ninety-six percent of these prescriptions were for men whereas 4% (b) (4) prescriptions were for women. All of the female and 85% of the male prescriptions were for patients aged 21 to 64 years old. Among men, about 2% of prescriptions (b) (4) were for patients aged 16 to 20 years old, and the remaining 13% were for men over the age of 65 years.

3.3.1 Off-label Use

The EU Safety Risk Management Plan presented by Endo briefly discusses abuse and off-label use of TU (pages 43-46). The biggest potential source of abuse is use as a performance-enhancing drug among body builders and athletes. Although it is difficult to assess the level of anabolic steroid use as abuse, estimates range from 6% in high school athletes to almost 100% in body builders(13, 16). Endo believes that both the intramuscular administration and the length of time TU stays in the body, however, serve to discourage would-be abusers. In addition, the Endo states that additional measures designed to minimize theft and diversion of TU are in place, but do not describe these measures further.

According to the IMS Health data supplied by Endo, approximately 75% of TU prescriptions were for approved indications, while the intended indication could not be determined for 15%. Based on the available data, IMS concluded that 10% of the undetermined prescriptions were for off-label indications for Nebido, the majority of which were for unspecified ovarian and pituitary disorders in women, gender-identity disorder in men, and prostate hyperplasia. There was no evidence of use in children under the age of 16 years in the IMS indication data provided.

3.3.2 OSE/DEPI Comments on Drug Utilization

Endo's primary source of drug utilization data is worldwide wholesale sales of Nebido. Presumably, this method of estimating patient exposure was chosen to capture use information from the large number of countries in which Nebido is marketed and to compensate for the inability to obtain actual exposed patient counts. Obtaining estimates for the number of patients exposed to a drug administered in physician offices is difficult in many countries due to the varying reimbursement methods, and the inability to collect information on physician activities. Furthermore, in certain populations such as athletes, use of anabolic steroids such as Nebido for performance enhancement has been documented. It is plausible that a substantial proportion of anabolic steroids used for performance enhancement are obtained without prescriptions or a doctor's order, but that adverse events may be reported if the patient seeks medical attention. Therefore, while imprecise, Endo's method of estimating patient exposure is likely the best that can be accomplished to assess postmarketing risks.

The FDA has provided U.S. data for the other products in the testosterone market to provide trends in the market and to gain insight into the potential patient exposure that would be expected if marketing approval for Aveed is granted. An increase was seen in each database. U.S. sales (IMS) and patient utilization (ProMetis Lx) of TE and TC has increased approximately 35% between 2011 and 2012, and a similar increase (32%) in the worldwide sales of Nebido (IMS) was seen in the data reported by Endo. The reason for both increase in use of TE and TC in the U.S. and the large worldwide increase for Nebido is unknown but is likely due to increased marketing.

3.4 REPORTING RATES

3.4.1 Endo Pharmaceutical-Supplied POME and Anaphylaxis Reporting Rates

To support their application, the Endo provided reporting rates for anaphylaxis and POME for 2008 through 2012. Endo calculated the denominator for the reporting rate using the total number of 1000mg/4ml Nebido vials sold worldwide for the year in question. Endo assumed that each injection lasted an average of 12 weeks, and that patients received 4.3 injections per year. Years were measured from November 25th to November 24th of the next year, coinciding with the date of approval for the drug. Reporting rates were obtained by dividing the confirmed number of cases by the calculated total of person- (or treatment-) years of exposure for each year.

Tables 5 and 6 show the reporting rates for confirmed POME and anaphylaxis between 2004 and 2011. The reporting rate remained constant between 2008 and 2011, although sales of Nebido increased each year. A partial report, covering November 24th 2011 through April 30th, 2012 found five new POME cases and three cases of anaphylaxis (not included in the reporting rate calculations). In addition, in 2010, Endo reported 21 confirmed cases total of POME and anaphylaxis combined, resulting in a reporting rate of 0.4 per 10,000 treatment-years.

Table 5: Sponsor-reported TU POME reporting rates per 10,000 treatment-years

Year(s)	Number of POME Cases	Total Vials Sold	Total Patient-Years	Reporting Rate per 10,000 Treatment-Years	Reporting Rate per 10,000 injections
2004-10*	138	(b) (4)	454,396	3.0	7.1
2008-9	45	(b) (4)	136,622	3.3	
2009-10	189 suspected	(b) (4)			
	34 confirmed	(b) (4)	156,202	2.2	0.5
2010-11	63 suspected	(b) (4)			
	57 confirmed	(b) (4)	178,489	3.2	0.7

Adapted from PSUR 9, pp 33-4

pp 30-33

*Time period Jan 1 2004 through March 30 2010 and Table 9-1

Table 6: Sponsor-reported TU anaphylaxis reporting rates per 10,000 treatment-years

Year(s)	Number of Anaphylaxis Cases	Total Vials Sold	Total Treatment-Years	Reporting Rate per 10,000 Treatment-Years	Reporting Rate per 10,000 injections
2003-8	4	(b) (4)	336,045	0.1	0.04
2008-9	9	(b) (4)	136,621	0.7	0.20
2009-10	23 suspected	(b) (4)			
	12 included**	(b) (4)	156,202	0.7	
2010-11	7	(b) (4)	178,489	0.4	0.10

Adapted from PSUR 9, pp 49

pp 33-41

**This changed to 11 cases in the 2010-11 PSUR, although the rate did not change

3.4.2 OSE/DEPI Comments on Reporting Rate Calculations

Endo provided reporting rates for both POME and anaphylaxis covering the entire marketing period, most likely for Nebido. For POME, the reporting rate has remained relatively stable since marketing; between 3.0 and 3.3 cases per 10,000 treatment-years for each calendar year, (2004-2010 are condensed). Reporting rates per injections follow a similar trend although the rates are generally lower. The reporting rates for anaphylaxis show a little more variation. For the first four years of marketing, the rate is 0.1 cases per 10,000 treatment-years. The rate

increased to 0.7 cases per 10,000 treatment years in 2008, and dropped to 0.4 cases per 10,000 treatment years in 2011. Reporting rates per injection follow a similar trend although the rates are generally lower. Endo does not attempt to provide an explanation for changes in reporting rates over time. Instead, Endo merely points out that the prescribing information describes both conditions, notes the difficulty of distinguishing POME from anaphylaxis in this particular setting and questions whether they occur separately or in combination. The absolute rate of change for vials sold is consistent until 2011-12 (a 31% increase), however, the same is not observed for reports of both POME and anaphylaxis. Moreover, no information is available specifically for Aveed.

In general, reporting rates are simple to construct and seemingly intuitive to understand. Endo provided reporting rates for other injectable products (Mesigyna, Androcur Depot, Testoviron Depot), however, they do not address several underlying conditions necessary for a valid and interpretable metric. The biggest concern is identifying the appropriate population at risk. To construct a rate, both the cases (i.e., the numerator) and the population at risk (i.e., the denominator) must be from the same population. If this is not the case, for example, if the cases are from a spontaneous reporting system and the population at risk is drug prescribing or sales information, the resulting ratio does not necessarily translate to a direct relationship between the event and the drug. This can be a challenge, except for rare cases when drugs are limited in distribution or use. For oral solid drug formulation, often the best available estimate is national-level prescription drug dispensing data. However, this may be insufficient for drugs with significant off-label use or abuse potential, such as opioids and anabolic androgen steroids (including TU). In these cases, it cannot be assumed that all vials sold were for a prescribed drug injection in a patient for an approved indication, especially when diversion might be a significant factor influencing those sales.

Another important consideration is accurately identifying cases of interest. For a suspected case to be reported to the manufacturer, a medical professional or patient must recognize it as such, determine that Nebido could be associated with the event, and take the time to report it to the manufacturer. Once there, the manufacturer then has to have enough information to determine what happened and if it could be causally related to the drug. Considering the process required for a suspected event to be counted, there is considerable potential for underascertainment of events for a wide variety of reasons, including failure to consider that a drug could have caused an event, not reporting the event, reporting it with insufficient information or not reporting an event when the initial symptoms were judged non-serious, which can be a subjective assessment. Further, as Endo notes in PSUR-10, there is no universally agreed-upon definition for anaphylaxis. This may increase the potential for subjective ascertainment of anaphylaxis cases and the possibility of overly stringent evaluation, especially for events not occurring immediately post injection. For these reasons, the numerator of a reporting rate is usually assumed to be an underestimation of actual cases.

In addition to an accurate evaluation of the population at risk, an assessment of postmarketing POME and anaphylaxis risk associated with Nebido would also need to consider the following:

- That sufficient information be available to definitively classify suspected cases. For example, although injectable TE was approved in the U.S. in 1953, FDA's Adverse Event Reporting System was not created until 1969.
- Unless Nebido is specifically identified in the report, the denominator will need to include all patients who were dispensed any testosterone-product instead of just those who received Nebido. This will inflate the denominator and may falsely minimize the risk.
- Since there are multiple settings of care where injectable testosterone may be administered, there is no way to obtain national patient counts for the use of these products in the US.
- A particular concern for injectable drugs is that the actual dose may be significantly different from what is recommended in the label, so it is not clear how much product a patient receives. For example, Gu et al administered 500 ml of TU per month, as did many of the contraceptive clinical studies described in the reports reviewed (5). These doses routinely exceeded the recommended dose of 1000 ml for Nebido in a 10-14 week period.

Once a reporting rate has been calculated, it may be tempting to compare it to an incidence rate as a way of providing context for a reporting rate. However, given the limitations of most reporting rates, particularly those that include sales information in the denominator, comparing it to an incidence rate can be misleading. Incidence rates are constructed in closed populations, so the numerator (cases) and denominator (actual exposed individuals) come from the same group of patients. Events of interest are generally serious enough for patients to seek medical attention and recorded in a standardized manner, although under-ascertainment may still occur if the event is not one of the outcomes of interest or if it is not readily recognized. Sometimes, use of reporting rates is the only information available to estimate a potential risk. Given the limitations of reporting rates in general, however, and for injectable drug products in particular due to the potential for self-injections and off-label use, reporting rates are considered a crude measure of risk at best, and should not be relied upon if any other measures, especially actual incidence rates, are available.

3.5 INCIDENCE RATES

In addition to reporting rates, Endo also provided incidence rates for TU studies in their clinical safety dataset as well as several postmarketing investigations. Eighteen clinical and postmarketing studies were included for TU: sixteen in Europe, one in the U.S., and a global study. An additional, ongoing study was not included in Endo's analysis. Thirteen of these studies (including the U.S. investigation) were in hypogonadal men; the remaining five were investigations of contraception in men. Appendix 3 provides a summary of the studies discussed.

Three thousand five hundred fifty-six men (3,556) participated in these studies, including 524 men (15%) from the U.S. Overall, 407 men were included in male contraception studies, while the rest were in clinical hypogonadal studies. Table 7 presents demographic information; all study patients were men. Participants in hypogonadal clinical studies had an average age between 50 and 54 years, and between 11.5% and 17.3% of men were over 65 years. The majority of patients were white, although 11% of patients in the 750 mg clinical hypogonadal studies and 12% in the postmarketing hypogonadal studies were black and Asian, respectively. The racial distribution likely reflects the US setting for the 750 mg clinical hypogonadal study and the fact that several of the postmarketing studies were conducted in China and Korea. Mean BMI for the hypogonadal studies ranged from 28 kg/m² to 32 kg/m². About 26% of men in the postmarketing hypogonadal studies had a BMI \geq 30 kg/m² compared to 45% and 60% for the 1000 mg and 750 mg clinical studies, respectively.

In contrast, the participants in the contraceptive studies were much younger, with an average age of about 30 years. No men over the age of 65 participated in these studies. The study population was mostly white, and the average BMI was approximately 24 kg/m² for both the 750 mg and 1000 mg study groups. A small percentage of each group, 2.6% in the 750 mg group and 2.8% in the 1000 mg group, had BMIs over 30 kg/m².

Table 7: Patient Demographic Data for Hypogonadal and Contraceptive Clinical and Postmarketing Studies

	Hypogonadal Studies			Contraceptive Studies	
	750 mg N=272	1000 mg N=453	1000 mg N=2424*	750 mg TU N=195	1000 mg TU N=212
Mean Age (years)	54.4	50.4	51.1	30.3	30.7
% \geq 65 years	17.3	11.5	14.6	N/A	N/A
% White	79	91.8	44.1	97.4	99.1
% Black	11.4	5.5	0.2	1.0	0
% Asian	0.7	0.7	11.9	0.5	0
Mean BMI (kg/m²)	32	30.3	28	24.2	24.1
% BMI \geq 30 kg/m²	59.6	44.8	26.6	2.6	2.8

Adapted from Endo Summary of Clinical Safety, Tables 6 and 7 (pp 39-43)

*Postmarketing studies

Table 8 shows the median duration of exposure, number of ampules, and person-years of exposure in patients who received 750 mg and 1000 mg doses of TU, respectively. Placebo groups were not included in these studies. Patients in the 750 mg dose group received a maximum of 13 injections, while those in the 1000 mg dose group received a maximum of 22 injections. These injections occurred over a 3.2-year period for those in 750 mg study arms (median 5 to 11 months) and 5

years in the 1000 mg study arm (median 11 months to 1.4 years). There were a total of 618.2 person-years of exposure for patients who received 750 mg injections and 3603.7 person-years of exposure for patients who received 1000 mg injections. A variety of dosing regimens were used in these investigations. A summary of these regimens can be found in Appendix 3. **Of note, most of the studies did not use the regimen under consideration for Aveed in the U.S.** The maximum number of injections and median weeks of exposure, therefore, reflect the experience of men who received 1000 mg TU injections.

Table 8: Dose and Duration Totals Stratified by 750 mg vs. 1000 mg TU injections

	750 mg dose (N=467)	1000 mg dose (N=3089)	Overall (N=3556)
Max Injections Received	13	22	22
Total Ampules	3,149	17,068	20,217
Median (range) weeks of exposure	24 to 48 (0 to 168)	48 to 72 (0 to 264)	48 to 72 (0 to 264)
Person-Years of Exposure	618.2	3603.7	4221.9

Adapted from sponsor’s Summary of Clinical Safety, section 2.2.2 (pp 36-38)

Endo identified potential POME and anaphylaxis cases using similar approaches. First, records on all 3,556 study patients were searched using standardized queries for POME or anaphylaxis. Endo developed a standard terminology for POME, and used Standardized MedDRA Queries for anaphylaxis. Endo stratified cases by 1) events that occurred on the same day of the injection and 2) those that occurred more than one day afterwards. For POME, potential cases that did not occur on the same day of the injection were eliminated. All potential anaphylaxis cases underwent a clinical review regardless of the time elapsed since the TU injection. Since there is no universally accepted standard to determine anaphylaxis, those cases were reviewed using a variety of criteria.

3.5.1 Sponsor Reported POME Incidence Rates

Table 9 shows the results for POME. Four hundred sixteen potential cases were found when searching the database. Endo excluded 321 potential cases because they occurred more than one day after the injection, leaving 95 potential cases for adjudication. After review, there were nine POME confirmed cases in eight patients. This translates to an overall rate of 4.6 cases per 10,000 injections or 21.3 cases per 10,000 person-years. There were more POME cases at the higher dose level, suggesting a possible dose response.

Table 9: Incidence of POME in clinical and postmarketing studies

	750 mg dose (N=467)	1000 mg dose (N=3089)	Overall (N=3556)
--	--------------------------------	----------------------------------	-----------------------------

Potential cases from Query	162	254	416
Adjudicated Cases	1	8	9
Cases per 10,000 injections	3.2	4.7	4.5
Cases per 10,000 person-years	16.2	19.4	21.3

Adapted from sponsor's Summary of Clinical Safety, page 36, table 22 (page 75), table 24 (page 79)

To provide a comparison for these rates, POME rates are included from two postmarketing TU studies referenced by Endo. The first estimate is from a large observational study by Zitzmann et al. The purpose of this study was to assess the safety and tolerability of TU in hypogonadal men (17). It included a population of 1,438 men in 23 countries worldwide who received injections every 8 to 12 weeks for an average of 10 months. Over the four-year course of the study, 6,333 injections were administered. The second estimate is from Gu et al., who performed a long-term study of TU as a contraceptive in a group of Chinese men. For this study, 1,045 men were given 500 mg TU injections monthly over a two-year period. Unlike the current version of TU, the drug used in the Gu study contained tea seed oil instead of castor oil, although the preservative was not specified (5).

Table 10 shows the POME rates for each of these studies as presented by Endo. Note that the dosing regimens differed in these two studies from those for the approved product; participants in the Zitzmann study received a TU dose of between 1500 mg and 2000 mg every 12 weeks, while those in the Gu study received 1500 mg TU over the same time period(5, 17). In addition, the study populations were markedly different. The Gu study participants were between 20 and 45 years old and had an average body weight of 65 kg. Men in the Zitzmann study averaged 49.5 years of age, with 13% being above 65 years of age. The average weight for the Zitzmann study group was 87 kg. Despite these differences, both studies show POME incidence rates similar or higher to the ones seen for 1000 mg Nebido patients in the clinical trials.

Table 10: POME Incidence rates from selected TU studies

	POME per Patient (%)	POME per 10,000 Patients	POME per Injection (%)	POME per 10,000 Injections
Zitzmann (2013) (1000 mg every 8 to 12 weeks)	3/1438 (0.2%)	20.1	3/6333 (0.05%)	4.8
Gu (2009)** (500 mg monthly)	22/1054 (2.1%)	208.1	22/42,876 (<0.01%)	5.1

Adapted from PSUR 10, table 9-7 (page 43)

**Total number of injections not published. Range of total injections estimated based on dosing regimen and number of patients completing the study treatment phase in the published article.

3.5.2 Reported Anaphylaxis Incidence Rates - Endo Pharmaceuticals

Table 11 displays the results for the drug-related anaphylaxis analysis. The standardized query identified 90 potential cases. Twenty-three cases occurred on the day of the event, while 67 happened more than one day after the injection. All potential cases were sent for adjudication, and there were two cases in the final count. This translates to an overall rate of 4.7 cases per 10,000 injections or 32.4 cases per 10,000 treatment-years in men using the 1,000 mg Nebido dose.

Table 11: Incidence of anaphylaxis in clinical and postmarketing studies

	750 mg dose (N=467)	1000 mg dose (N=3089)	Overall (N=3556)
Potential cases from Query	35	55	90
Adjudicated Cases	0	2	2
Cases per 10,000 injections	0	1.2	0.9
Cases per 10,000 person-years	0	32.4	4.7

Adapted from sponsor's Summary of Clinical Safety, page 36, table 32 (page 85), table 33 (page 86)

The incidence rates for anaphylaxis vary widely in other studies that attempted to characterize it. In addition to lacking a standard definition for the condition, many studies that have attempted to quantify the incidence of anaphylaxis were limited to small or selective populations, or were not able to include likely points of contact of an anaphylaxis patient and the healthcare system, such as emergency medical technicians or emergency department visits(11). Flabbee et al reviewed several studies and found that in general, the rate for severe anaphylaxis ranged from 0.5 to 3 cases per 10,000 patients. For less severe disease, the rates ranged from 4 to 101 cases per 10,000 emergency department visits. Note that these rates did not discern the source of the reaction. Published drug-related anaphylaxis rates range from a

low of 0.99 cases per 10,000 patient-years for anaphylaxis to highs of 0.8 to 5 cases per 10,000 person-years (2, 15). Thong et al point out that while penicillin was once thought to be the main cause of drug-induced anaphylaxis, subsequent investigations have not supported that theory(15).

3.5.3 OSE/DEPI Comment on Reported Incidence Rates

In addition to attempting to calculate reporting rates, Endo also provided incidence rates for the EU and US clinical trials as well as several postmarketing TU studies. To enable comparison across all of the studies, incidence rates per 10,000 injections were calculated by OSE/DEPI from available information when not provided by Endo. For POME, the rates were 3.2 cases and 4.7 cases per 10,000 injections for the 750 mg and 1000 mg TU injections, respectively. In the case of anaphylaxis, there were no cases in the 750 mg TU dose group, and the rate for the 1000 mg TU dose group was 1.2 cases per 10,000 injections. Of note, only the U.S. clinical trial used the proposed dosing regimen of 750 mg TU over a 10-12 week period; the remaining studies used different doses and schedules (see Appendix 3).

Endo selected two postmarketing TU studies to compare POME incidence; a study conducted in hypogonadal men and a contraceptive study (5, 17). Both studies had POME rates similar or slightly higher to those seen in the TU clinical trials, albeit the doses were higher than what is currently being recommended for the U.S. patients. An important consideration is that the Zitzmann study is included in both Endo's clinical trial POME calculation and as a comparator study. However, the incidence rate in the clinical trial patients when excluding this study is 4.6 cases per 10,000 injections. So, while large (this study contributed 1,438 of the 2,404 total 1000 mg TU patients), this study did not significantly alter the POME incidence rate.

Reliable estimates of anaphylaxis incidence are very difficult to obtain. This is primarily because there is no standardized definition for anaphylaxis. In addition, studies in single populations, such as hospitalized patients or registries, might miss more likely sources of anaphylaxis cases such as those seen only in emergency departments (9). In addition, the incidence rates appear to vary over time, and both within and across countries and populations (2, 9, 11, 15). Nevertheless, the rate of anaphylaxis seen in the clinical and postmarketing TU studies of 4.7 cases per 10,000 injections (or 32.4 cases per 10,000 person-years) is significantly higher than the estimated range for drug-induced anaphylaxis of between 0.8 and 5 per 10,000 person-years(15) reported in the literature.

The POME and anaphylaxis incidence rates in the clinical and postmarketing databases each indicate a consistent trend. The incidence of POME was constant in the clinical and postmarketing studies, under presumably ideal administration conditions. In addition, the POME rate has persisted over time despite increased publicity on the part of Endo and increased awareness by healthcare practitioners. Endo does not provide any additional suggestions for addressing this continuing risk; instead, they merely note that it seems to be a transient condition although they do propose a lower dose for U.S. patients. Concerning anaphylaxis, despite the difficulty of obtaining reliable incidence rates in the general population, the rate in

the TU studies is higher than other published rates. Endo does not comment on this fact either, other than to describe the difficulty of definitively adjudicating suspected anaphylaxis events. In summary, Endo does not acknowledge either of these trends and does not present any alternatives for tracking or reducing their occurrence in the general population of users.

4 DISCUSSION OF REPORTING AND INCIDENCE RATES

OSE/DEPI was asked to evaluate the reporting rates for POME and anaphylaxis submitted by Endo in support of the approval of Aveed. Calculating reporting rates for injectable drug products in general is not ideal for a number of reasons, chiefly, the inability to specify the appropriate population at risk. In addition, given the multiple dosing regimens used in worldwide TU studies and its possible abuse as an anabolic steroid, make it difficult to know how much of the product was actually administered to hypogonadal men based solely on sales data. OSE/DEPI does note some potential issues with Endo's submission. Whereas sales increase over time, particularly from November 2011 to November 2012, reports of POME and anaphylaxis cases do not increase at the same rate. The fact that the POME and anaphylaxis reporting rates remain consistent is likely an artifact of the large denominator used rather than a stable or decreasing number of events.

Endo also attempts to provide some insight into actual TU prescribing using a single year of information from five EU countries. Considering that TU is approved in 94 countries, and that Nebido has been widely available since 2003, this is likely not an accurate portrayal of TU use worldwide. Further evidence of this is provided by several clinical and postmarketing contraceptive studies that typically used doses of 1500 mg every 10 – 12 weeks (5, 10).

Endo's use of total exposed time resulted in an underestimation of the magnitude of the events in question. While the number of cases is unchanged, the time at risk should only encompass the first 24 hours of exposure, not the entire period between injections. For the reporting and incidence rates, the events per number of injections may be the more appropriate metric to use.

In addition to reporting rates, Endo provided incidence rates for POME and anaphylaxis based on clinical and postmarketing studies of TU. The incidence rates for POME were compared to two postmarketing studies highlighted in the documents provided; a contraceptive study and one in hypogonadal men (5, 17). These studies showed a consistent rate of POME over time, even in ideal study conditions. However, subjects in both studies were exposed to higher TU doses compared to what Endo is recommending for U.S. patients. While it is more difficult to determine rates of drug-induced anaphylaxis, the rate seen in Endo's data of 4.7 cases per injection or 32.4 cases per 10,000 patient-years is higher than published rates for drug-induced anaphylaxis in general of 0.8 to 5 cases per 10,000 patient-years(2, 15). Endo does not acknowledge either the consistency of the POME rate or the comparatively high anaphylaxis rates; their response to these conflicting findings is to describe the difficulty in adjudicating cases and note that these events are in the international prescribing information.

5 CONCLUSIONS

In summary, Endo's inability to characterize TU use accurately, the consistent POME and excess anaphylaxis incidence rates seen in the clinical and postmarketing databases, and Endo's unwillingness to acknowledge or effectively address these rates is concerning. It is unlikely that the incidence of either POME or anaphylaxis associated with TU has decreased in the postmarketing period, since these events still occurred under ideal study conditions. The risk of serious and life-threatening events should be carefully weighed against the benefit of a potentially longer period between TU injections, particularly given that there are multiple alternatives to TU, including other injectable testosterone preparations and other dose forms.

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APPENDICES

APPENDIX 1 - CHARACTERISTICS OF INJECTABLE TESTOSTERONE PREPARATIONS

Product	Excipients	Packaging	Dose Regimen	Indications	Warnings
Nebido® (Testosterone undecanoate) International, 2003	Castor oil, benzyl benzoate	1000 mg TU 4 ml single- dose vial	1000 mg every 10 to 14 weeks	-Confirmed Male Hypogonadism	-Use in women, children, and adolescents -Prostate diseases (incl. cancer) - Hypercalcemia -Liver tumor -Edema -Aggravation of epilepsy and migraine -Enhancing muscle development and athletic performance -POME
Depo Testosterone® (Testosterone Cypionate) U.S., 1979	Cottonseed oil, benzyl benzoate, benzyl alcohol	2000 mg TC 10 ml multi-dose vial	50 mg to 400 mg every 2 to 4 weeks	In males: -Primary Hypogonadism -Hypogonadal Hypogonadism	-Pregnancy Category X -Schedule III Controlled Substance - Hypercalcemia -Hepatic conditions (incl. cancer) -Prostate hyperplasia and cancer -Edema -Gynecomastia -Compromised adult stature
Delastryl® (Testosterone Enanthate) U.S., 1953	Sesame oil, chlorobutanol	1000 mg TE 5 ml multi- dose vial	50 mg to 400 mg every 2 to 4 weeks	In males: -Primary Hypogonadism -Hypogonadal Hypogonadism -Delayed Puberty	-Pregnancy Category X -Schedule III Controlled Substance - Hypercalcemia -Hepatic

Product	Excipients	Packaging	Dose Regimen	Indications	Warnings
				In females: -Inoperable Metastatic Mammary Cancer	conditions (incl. cancer) -Prostate hyperplasia and cancer -Edema -Gynecomastia -Enhancing athletic performance

APPENDIX 2: - DRUG USE DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Source Healthcare Analytics' ProMetis Lx®

The Source Healthcare Analytics' ProMetis Lx® database is a longitudinal patient data source which captures adjudicated prescription claims across the United States across all payment types, including commercial plans, Medicare Part D, cash, assistance programs, and Medicaid. The database contains approximately 4.8 billion prescriptions claims linked to over 190 million unique prescription patients, of which approximately 70 million patients have 2 or more years of prescription drug history. Claims from hospital and physician practices include over 190 million patients with CPT/HCPCS medical procedure history as well as ICD-9 diagnosis history of which nearly 91 million prescription drug patients are linked to a diagnosis. The overall sample represents nearly 30,000 pharmacies, 1,000 hospitals, 800 outpatient facilities, and 80,000 physician practices.

APPENDIX 3 – SUMMARY OF STUDIES

Summary of Studies included in Calculation of Incidence Rates from Sponsor Clinical and Postmarketing Trials (Endo Pharmaceuticals Table 1, Summary of Clinical Safety, page 23)					
Study Number/	Indication	Title	Type	Study Design	Treatments
US Clinical Study					
IP157-001 Completed	Hypogonadism	A 2-arm, open-label, randomized, multicenter pharmacokinetic and long-term safety study of intramuscular (IM) injections of testosterone undecanoate (TU) 750 mg and 1000 mg in hypogonadal men This is a 5-part protocol that includes 2 IM treatment arms in Part A, 2 IM treatment arms in Part B, a single IM treatment arm in Part C, a single IM treatment arm in Part C2, and 2 subcutaneous (SC) treatment arms in Part D.	Phase III	Randomized, 2-arm, active-controlled, multiple-dose	Part A: TU 750 mg IM TU 1000 mg IM Part B: All subjects received TU 1000 mg IM initial dose followed by two arms of: TU 750 mg IM TU 1000 mg IM Part C: TU 750 mg IM Part C2: TU 750 mg IM Part D: TU 1000 mg SC (Part A subjects)
European Clinical Studies					
JPH01495 Completed	Hypogonadism	Study to investigate the pharmacokinetics of TU after single IM injection	Phase I	Open-label, single-arm, single-dose	TU 1000 mg IM

Summary of Studies included in Calculation of Incidence Rates from Sponsor Clinical and Postmarketing Trials (Endo Pharmaceuticals Table 1, Summary of Clinical Safety, page 23)

Study Number/	Indication	Title	Type	Study Design	Treatments
JPH04995 (includes LTFU study) Completed	Hypogonadism	Study to investigate the pharmacokinetics and efficacy of TU after multiple IM injections in hypogonadal men	Phase II/III	Open-label, single-arm, multiple-dose	TU 1000 mg IM
ME98096 (includes 2 LTFU studies) Completed	Hypogonadism	Open-label study to evaluate safety and pharmacokinetic parameters of total and free testosterone after repeated IM administrations of TU 1000 mg (5 injections over	Phase II	Open-label, single-arm, multiple-dose	TU 1000 mg IM
ME97029 (includes 2 LTFU studies) Completed	Hypogonadism	Study to investigate the efficacy and safety of TU vs. testosterone enanthate (TE) after IM injection in hypogonadal men	Phase III	Randomized, open-label, parallel-group, 2-arm, active-	TU 1000 mg IM TE 250 mg IM

Summary of Studies included in Calculation of Incidence Rates from Sponsor Clinical and Postmarketing Trials (Endo Pharmaceuticals Table 1, Summary of Clinical Safety, page 23)

Study Number/	Indication	Title	Type	Study Design	Treatments
306605 (includes LTFU study) Completed	Hypogonadism	Open-label, 1-arm study to investigate safety and efficacy of IM injections of TU 1000 mg in hypogonadal men at variable intervals during a 136-week to 192-week treatment including pharmacokinetics of TU during steady state in a subgroup of 30 subjects Long-term safety and efficacy of IM injections of TU including pharmacokinetics during steady	Phase III	Open-label, single-arm, multiple-dose	TU 1000 mg IM
303934 Terminated Early ^a	Male andropause	A monocenter, prospective, randomized, double-blind, parallel- group, placebo-controlled, long- term clinical trial to investigate the effects of a long-acting IM preparation of TU on andropause- related	Phase II	Randomized, double-blind, parallel-group, 2-arm, placebo-controlled,	TU 1000 mg IM Placebo 4 mL IM
European Male Contraception Studies					
97028 Completed	Male contraception in healthy males	Male contraception with TU vs. combined administration of TU and levonorgestrel (LNG) - a double- blind, randomized, single-center comparative study	Phase II	Randomized, double-blind, parallel-group, 2-arm, placebo-	TU 1000 mg IM + oral placebo TU 1000 mg IM +oral LNG

Summary of Studies included in Calculation of Incidence Rates from Sponsor Clinical and Postmarketing Trials (Endo Pharmaceuticals Table 1, Summary of Clinical Safety, page 23)

Study Number/	Indication	Title	Type	Study Design	Treatments
97173 Completed	Male contraception in healthy males	Male contraception with a sequential regimen of cyproterone acetate (CPA) and TU followed by a lower dose of CPA and TU in normal men	Phase II	Randomized, single-blind, 3-arm, placebo-controlled, multiple-dose	<p>Induction Phase: All subjects received TU 1000 mg IM + CPA 20 mg/day oral</p> <p>Maintenance Phase: Randomized to 1 of the following 3 regimens: TU 1000 mg IM + CPA 20 mg/day oral TU 1000 mg IM + CPA 2 mg/day oral TU 1000 mg IM + daily oral placebo</p>
98016 Completed	Male contraception in healthy males	A single-center, prospective, 1-arm, uncontrolled study to investigate the efficacy and safety of male contraception with TU and norethisterone enanthate (NET-EN) over 24 weeks	Phase II	Open-label, single-arm, multiple-dose	TU 1000 mg IM + NET-EN 200 mg IM
99015 Completed	Male contraception in healthy males	Study on efficacy and safety of male contraception with TU and NET combined in different application regimens	Phase II	Randomized, open-label, parallel-group, 3-arm, active-	TU 1000 mg IM + NET-EN 200 mg IM TU 1000 mg IM + NET-EN 400 mg IM TU 1000 mg IM + NET-A 10 mg/day oral

Summary of Studies included in Calculation of Incidence Rates from Sponsor Clinical and Postmarketing Trials (Endo Pharmaceuticals Table 1, Summary of Clinical Safety, page 23)

Study Number/	Indication	Title	Type	Study Design	Treatments
42306 Completed	Male contraception in healthy males	A phase IIb, double blind, placebo-controlled, randomized, multicenter, multiple dose trial investigating the efficacy, safety and pharmacokinetics of a subcutaneous etonogestrel (ENG) rod combined with IM TU for male fertility control	Phase IIb	Randomized, double-blind, parallel-group, 7-arm, placebo-controlled, multiple-dose	TU 750 mg IM + Low Release ENG Implant every 10 weeks TU 750 mg IM + Low Release ENG Implant every 12 weeks TU 1000 mg IM + Low Release ENG Implant every 12 weeks TU 750 mg IM + High Release ENG Implant every 10 weeks TU 750 mg IM + High Release ENG Implant every 12 weeks TU 1000 mg IM + High Release ENG Implant every 12 weeks Placebo IM + Placebo Implant
Postmarketing Studies					
AWB 0105 Completed	Androgen deficiency	Efficacy and tolerability of Nebido®	Post-marketing surveillance: prospective, non-intervention	Open-label, single-arm, multiple-dose	TU 1000 mg IM
39732 (NE060 1 IPASS) Completed	Hypogonadism	International, multicenter post authorization surveillance study on the use of Nebido® to assess tolerability and treatment outcomes in daily clinical practice (IPASS Nebido®)	Post-marketing surveillance: non-interventional	Open-label, single-arm, multiple-dose	TU 1000 mg IM

Summary of Studies included in Calculation of Incidence Rates from Sponsor Clinical and Postmarketing Trials (Endo Pharmaceuticals Table 1, Summary of Clinical Safety, page 23)

Study Number/	Indication	Title	Type	Study Design	Treatments
14329 (Czech NEO) Completed	Hypogonadism	NEO; Observational post-marketing study (NEbido)	Post-marketing surveillance: Non-interventional	Open-label, single-arm, multiple-dose	TU 1000 mg IM
NB02 Completed	Hypogonadism	NEBIDO Therapy in Hypogonadal Male Patients With Paraplegia With Osteoporosis Compared With Conventional Osteoporosis	Post-marketing surveillance: Non-interventional	Open-label, 3-arm, multiple-dose, single center	TU 1000 mg
TG09 Completed	Hypogonadism	Efficacy and tolerability of Testogel/Nebido in combination with a standardized exercise and diet programme in hypogonadal male patients with abdominal obesity compared with exercise	Post-marketing surveillance: Non-interventional observational	Open-label, 2-arm, multiple-dose, single center	TU 1000 mg, Testogel
14853 Terminated Early ^b	Hypogonadism	Effect of exercise alone or in combination with testosterone replacement on muscle strength and quality of life in older men with low testosterone concentrations; a randomized double-blind, placebo controlled	Post-marketing surveillance: Interventional	Randomized, Double blind, parallel-group, 2-arm, placebo controlled	TU 1000 mg, Placebo

Data Source: Data Integration Plan for EN3331 Integrated Summary of Safety (dated 30-May-2012) (5.3.5.3, AVEED ISS [Appendix E]).

^a Terminated early

^b Terminated early due to slow recruitment rate.

CPA=Cyproterone acetate; ENG=Etonogestrel; IM=Intramuscular; LNG=Levonorgestrel; LTFU=Long-term follow up; NET-A=Norethisterone acetate; NET-EN=Norethisterone enanthate; SC=Subcutaneous; TE=Testosterone enanthate; TU=Testosterone undecanoate.

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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**

Provision of Pharmacovigilance Data

Date: February 13, 2013

Reviewer(s): Office of Surveillance and Epidemiology
Teresa Rubio, Pharm.D., Safety Evaluator
Division of Pharmacovigilance I

Team Leader(s): Office of Surveillance and Epidemiology
Adrienne Rothstein, Pharm.D., Team Leader
Division of Pharmacovigilance I

Product Name(s): Aved, testosterone undecanoate (injectable)

NDA Number: 22-219

Subject: Oil embolism in the lungs (also referred to as pulmonary oil microembolism, or POME) and potential anaphylactic reactions.

Applicant/Sponsor: Endo Pharmaceutical Solutions, Inc.

RCM #: 2013-252

1 INTRODUCTION

A joint meeting of the Repro/DSARM (Reproductive/Drug Safety and Risk Management) advisory committees is planned for April 18, 2013, to discuss NDA 22-219, AVEED, testosterone undecanoate (injectable). This product is being reviewed by DRUP in consultation with DPARP (Division of Pulmonary, Allergy, and Rheumatology Products).

DRUP is concerned about a potential safety signal related to reports of oil embolism in the lungs (also referred to as pulmonary oil microembolism, or POME) and potential anaphylactic reactions following injection of Aved. As part of the preparation for the AC meeting, on 1/22/2013 DRUP requested that the Division of Pharmacovigilance (DPV) search the FDA Adverse Event Reporting System (FAERS) database for cases of POME with other injectable testosterone products and to provide a summary of the search results. In order to limit the heterogeneity in case adjudication and minimize bias, DPV and DPARP agreed that the DPARP clinical reviewer should adjudicate the US case reports from postmarketing (PM) sources in addition to their adjudication of the sponsor's Aved case reports submitted for the application.

2 METHODS AND MATERIALS

The FDA Adverse Event Reporting System (FAERS) was searched with the strategy described in Table 1.^a

Date of search	1/29/2013
Time period of search	01/01/1969* - 01/29/2013
Product Terms	TESTOSTERONE%
MedDRA Search Terms (MedDRA version 15.1)	Sponsor's Search Criteria listed in Sponsor's Appendices 1 & 2**, plus additional Preferred Terms (PTs): Haemoptysis, Lung infiltration, Asphyxia, Pulmonary Oil Microembolism
Country of occurrence:	USA

* *AERS implementation date*

** *NDA 22-219, FDA submission date 03/21/2012, Appendices 1 & 2.*

^a FAERS is a database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. FAERS data do have limitations (e.g., variable quality and quantity of information provided, cannot determine causality, voluntary reporting system, reporting biases). Additionally, FAERS cannot be used to calculate the incidence of an adverse event in the U.S. population. FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

3 DATA- LINE LISTING OF CASES (N=183)

The search results from the FAERS database were reviewed and reports for topical testosterone products were removed. In total there were 183 US reports of serious events with injectable testosterone products. The following line listing for the 183 reports was provided to Dr. Stacy Chin in DPARP for her case adjudication. In addition paper copies of the 183 reports were provided.



POME_US_Serious_1
nj_Testosterone_201

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/s/

TERESA RUBIO
02/14/2013

ADRIENNE M ROTHSTEIN
02/14/2013



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: August 19, 2009

To: Scott Monroe, M.D., Director
Division of Reproductive and Urologic Products

Through: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff (CSS)

From: James M. Tolliver, Ph.D., Pharmacologist, CSS

Subject: Consult on NDA 22-219 - AVEED (testosterone undecanoate) IM Injection - Indicated for testosterone replacement therapy in hypogonadal males.
Sponsor: Endo Pharmaceuticals

Materials reviewed: All materials submitted and comprising NDA 22-219.

Background:

The Division of Reproductive and Urologic Products has submitted a consult to CSS requesting verification on the scheduling status of AVEED and an assessment of the labeling for AVEED as it applies to abuse and dependence.

AVEED will be marketed in amber glass vials containing 3 mL of 250 mg/mL (750 mg) testosterone undecanoate sterile injectable solution consisting of refined castor oil (885 mg/3 mL) and benzyl benzoate (1500 mg/3 mL). It is intended for intramuscular injection, as an oil-based depot, for testosterone replacement therapy in males deficient in endogenous testosterone due either to primary hypogonadism (congenital or acquired) or to hypogonadotropic hypogonadism (congenital or acquired). The dosage regimen will be 3 mL injected intramuscularly at initiation of therapy, at 4 weeks and every 10 weeks thereafter. The proposed labeling indicates that injections should be done in a healthcare facility or physician's office in case there is a need to manage a potential anaphylactic reaction.

CSS Review and Recommendations

Testosterone undecanoate, and therefore the product AVEED, is in Schedule III of the Controlled Substances Act (21 U.S.C 801 et seq.). Testosterone is specifically designated

a Schedule III anabolic steroid under 21 U.S.C. 802(41)(A)(xlvii). Esters of testosterone are also Schedule III anabolic steroids pursuant to 21 U.S.C. 802(41)(A)(xix). Due to the abuse potential associated with AVEED, this product would not be excluded from control under 21 U.S.C. 811(g)(3)(C).

Proposed Labeling of AVEED

Currently, the draft labeling under "9. DRUG ABUSE AND DEPENDENCE" reads as follows:

9.1 Controlled Substance

AVEED contains testosterone undecanoate, a Schedule III controlled substance

(b) (4)

CSS recommends that the labeling under "9. DRUG ABUSE AND DEPENDENCE" be changed to read as follows:

9.1 Controlled Substance.

AVEED contains testosterone undecanoate, a Schedule III controlled substance in the Controlled Substances Act (CSA).

9.2 Abuse and Addiction

Anabolic steroids, such as testosterone, are reported to be abused. Abuse is often associated with adverse physical and psychological effects.

9.3 Dependence

(b) (4)
[Redacted text]

. In general, anabolic steroid dependence is characterized by any three of the following:

- 1) taking more drug than intended
- 2) continued drug use despite medical and social problems
- 3) significant time spent in obtaining adequate amounts of drug
- 4) desire for anabolic steroids when supplies of the drugs are interrupted
- 5) difficulty in discontinuing use of the drug despite desires and attempts to do so
- 6) experience of a withdrawal syndrome upon discontinuation of anabolic steroid use.

(b) (4)
[Redacted text]

Discussion

With respect to scheduling status, the label should state that AVEED is in Schedule III under the Controlled Substances Act of 1970 (b) (4)

Currently, the labeling suffers from a lack of information regarding abuse or dependence and should be updated. We recommend that some general class information regarding anabolic steroid abuse and dependence be added to the Abuse and Dependence section of the label. This information would at least alert the reader that abuse and dependence development is a possibility and should be considered when they store, dispense or use an anabolic steroid. Similar general information should be considered for the labeling of other products containing testosterone and other anabolic steroids.

Over the years, a considerable scientific and medical literature has accumulated documenting the abuse of anabolic steroids by athletes and bodybuilders; patterns of abuse and physical and psychiatric adverse effects are described. Several recent review articles on this topic include Brower (2002), Hartgens and Kuipers (2004), Trenton and Currier (2005), and Pope and Brower (2009). In addition, there is evidence that abuse of high doses of anabolic steroids can lead to dependence. A number of studies with athletes using high doses of anabolic steroids examine dependence according to the DSM diagnostic criteria for substance abuse dependence (Brower et al, 1991; Gridley and Hanrahan, 1994; Pope and Katz, 1994; Malone et al., 1995; Copeland et al., 1998; Midgley et. al., 1999; Perry et al, 2005; and Kanayama et al., 2009). In addition, a specific withdrawal syndrome upon termination of prolonged high dose anabolic steroids has been identified. Recently, a group of researchers published a paper in the American Journal of Psychiatry suggesting the future addition in DSM-V of specific diagnostic criteria for dependence to anabolic-androgenic steroids (Kanayama et al., 2009). Recent review articles concerning dependence on anabolic steroids include Brower (2002), Pope and Brower (2009), Quaglio et al, 2009 and Wood (2008).

References

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Quaglio G, Fornasiero A, Mezzelani P, Moreschini S, Lugoboni F and Lechi A (2009). Anabolic steroids: dependence and complications of chronic use. *Intern Emerg. Med.*, 4: 289-296.

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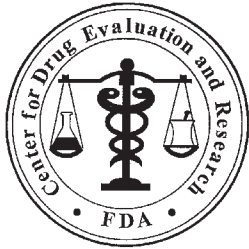
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/s/

JAMES M TOLLIVER
08/19/2009

SILVIA N CALDERON
08/19/2009

MICHAEL KLEIN
08/19/2009



**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 14, 2009

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

Through: Denise Toyer, PharmD, Deputy Director
Division of Medication Error Prevention and Analysis

From: Carlos Mena-Grillasca, RPh, Acting Team Leader
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name: Aveed (Testosterone Undecanoate) Injection
750 mg/3 mL (250 mg/mL)

Application
Type/Number: NDA 22-219

Applicant: Endo Pharmaceuticals

OSE RCM #: 2009-510

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1 INTRODUCTION

This review is in response to a request from the Division of Reproductive and Urologic Products for a review of the revised Aved label and labeling in response to the Division of Medication Error Prevention and Analysis' previous comments to the applicant.

2 MATERIALS REVIEWED

The Applicant provided revised label and labeling on August 14, 2009. We also evaluated the recommendations pertaining to the previous revision in OSE RCM# 2009-510 dated August 11, 2009 and August 13, 2009.

3 RECOMMENDATIONS

Our evaluation noted areas where information on the label and labeling can be improved to minimize the potential for medication errors. We provide recommendations in Section 3.1 *Comments to the Applicant*. We request the recommendations in Section 3.1 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Maria Wasilik, Project Manager, at 301-796-0567.

3.1 COMMENTS TO THE APPLICANT

A. Carton Labeling

We recommend deleting the storage requirement and the "See package insert..." statements from the Principal Display Panel (as this information is already provided on the side panel) in order to provide adequate space to present the Medication Guide statement in a prominent and conspicuous manner, to comply with 21 CFR 208.24.

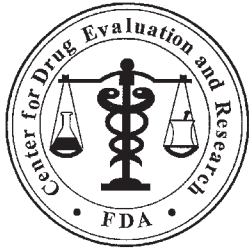
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/s/

CARLOS M MENA-GRILLASCA
08/14/2009

DENISE P TOYER
08/14/2009



**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 11, 2009

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

Through: Carlos Mena-Grillasca, R.Ph., Acting Team Leader
Denise Toyer, Pharm D., Deputy Director
Division of Medication Error Prevention and Analysis

From: Walter Fava, R.Ph., Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name: Aveed (Testosterone Undecanoate) Injection
750 mg/3 mL (250 mg/mL)

Application Type/Number: NDA 22-219

Applicant: Endo Pharmaceuticals

OSE RCM #: 2009-510

CONTENTS

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2	METHODS AND MATERIALS	3
3	RECOMMENDATIONS	3
3.1	Comments To The Division.....	3
3.2	Comments to the Applicant.....	3
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1 INTRODUCTION

This review is in response to a March 20, 2009 request from the Division of Reproductive and Urologic Products for an evaluation of the labels and labeling for Aveed to identify areas that could lead to medication errors. DMEPA has identified areas on the labels and labeling where revisions can be made to minimize the potential for confusion. Our comments are provided in Section 3.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis (FMEA) in our evaluation of the container labels, carton and insert labeling, and medication guide submitted on June 8, 2009.

3 RECOMMENDATIONS

Our evaluation noted areas where information on the label and labeling can be improved to minimize the potential for medication errors. We provide recommendations in Section 3.1 *Comments to the Division* and Section 3.2 *Comments to the Applicant*. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Maria Wasilik, Project Manager, at 301-796-0567.

3.1 COMMENTS TO THE DIVISION

A. Prescribing Information

1. Preparation and Handling (Full Prescribing Section 2.4)
Remove the statement, (b) (4) and include the statement, 'Discard unused portion'.
2. Dosage Form and Strength (Highlights Section and Full Prescribing Section 3)
Revise the presentation of the strength statement, (b) (4) to read '750 mg/3 mL (250 mg/mL)'.
3. How Supplied/Storage and Handling (Full Prescribing Section 16)
 - a. Revise according to A1 and A2 above.

B. Medication Guide

Revise the word (b) (4) to read 'injection' throughout the medication guide.

3.2 COMMENTS TO THE APPLICANT

A. General Comments

DMEPA notes that the light grey font color used to present important information on the container labels and carton labeling is not easy to read. We recommend you revise the presentation of all light grey text to a darker font color to make the labels and labeling easier to read.

B. Container Label and Carton Labeling

1. Revise the presentation of the proprietary name to use title case font (e.g. Aveed). As currently presented, [REDACTED] (b) (4) makes the proprietary name difficult to read.
2. Ensure the presentation of the established name is at least half the size of the proprietary name in accordance to 21 CFR 201.10(g)(2), which requires that the establish name shall be printed in letters that are at least half as large and with a prominence commensurate to the proprietary name, taking into consideration all pertinent factors, including typography, layout, contrast and other printing features. In addition, we note that the condensed font used in the presentation of the established name makes it difficult to read.
3. Revise the spelling of the [REDACTED] (b) (4) in the established name to 'undecanoate'.
4. Include the statement [REDACTED] (b) (4) on the side panel of the container label to be consistent with the presentation of this information on the carton labeling.

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/s/

CARLOS M MENA-GRILLASCA
08/11/2009

DENISE P TOYER
08/11/2009



**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 7, 2009

To: Scott Monroe, Director
Division of Reproductive and Urologic Products

Through: Jodi Duckhorn, MA, Team Leader
Division of Risk Management

From: Sharon R. Mills, BSN, RN, CCRP
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide)

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

Application Type/Number: NDA 22-219

Applicant/sponsor: Endo Pharmaceuticals Solutions Inc.

OSE RCM #: 2009-560

1 INTRODUCTION

This review is written in response to a request by the Division of Dermatology and Dental Products (DDDP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for Aveed (testosterone undecanoate) injection. Please let us know if DDDP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant. The proposed REMS is being reviewed by DRISK and will be provided to DDDP under separate cover.

2 MATERIAL REVIEWED

- Draft Aveed (testosterone undecanoate) injection Prescribing Information (PI) submitted March 2, 2009, revised by the Review Division throughout the current review cycle and provided to DRISK on July 21, 2009, July 28, 2009, and August 7, 2009.
- Draft Aveed (testosterone undecanoate) injection Medication Guide (MG) submitted on July 21, 2009.

3 RESULTS OF REVIEW

In our review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

Many of the revisions in this review were made to be consistent, as appropriate, with the revisions made in the MGs for other testosterone products (Androgel and Testim).

Please let us know if you have any questions.

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/s/

SHARON R MILLS
08/07/2009

JODI M DUCKHORN
08/07/2009

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: July 23, 2009

To: Jeannie Roule, Regulatory Project Manager
Division of Reproductive and Urologic Products (DRUP)

From: Carrie Newcomer, PharmD
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: DDMAC comments on proposed Medication Guide for Aveed
(testosterone undecanoate) injection
NDA: 22-219

DDMAC reviewed the proposed patient package insert (PPI) for Aveed (testosterone undecanoate) injection and we provided comments on July 15, 2009. There is now a proposed Medication Guide for Aveed, which is similar to the previously proposed PPI. Please apply our July 15, 2009, comments on the PPI to the proposed Medication Guide. In addition, we have the following comments. Please note that these comments are based on the revised version of the draft labels sent to DDMAC on July 22, 2009. If you have any questions or concerns regarding my comments, please contact me.

(b) (4)

- Should the title of this section be revised to state, "**What should I tell my doctor before (b) (4) AVEED?**" (as this section includes health problems and medications that patients should discuss with their doctor before taking Aveed).

What are possible (b) (4) side effects of AVEED?

(b) (4)

Thank you. If you have any questions, please contact Carrie Newcomer at 301.796.1233 or Carrie.Newcomer@fda.hhs.gov

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/s/

Carrie Newcomer
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DDMAC CONSUMER REVIEWER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

*****PRE-DECISIONAL AGENCY MEMO*****

Date: July 15, 2009

To: Jeannie Roule
Project Manager
Division of Reproductive and Urologic Products (DRUP)

From: Janice Maniwang, Pharm.D., M.B.A.
Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Carrie Newcomer, Pharm.D.
Regulatory Review Officer
DDMAC

Re: **NDA 22-219**
DDMAC Labeling Comments for Aveed™ (testosterone undecanoate) injection

Background

DDMAC has reviewed the following label materials for Aveed, submitted on March 2, 2009 [EDR path: \\FDSWA150\NONECTD\N22219\N_000\2009-03-02]:

Healthcare Provider Directed:

- Prescribing Information (PI)
- Vial Labeling
- Carton Labeling

Consumer Directed:

- Patient Product Information (PPI)

Please note that our comments are based on the revised version of the draft labels sent to DDMAC on July 13, 2009. In addition, we have considered the Delatestryl (testosterone enanthate injection) PI (approved July 25, 2007) and the AndroGel (testosterone gel, 1%) PI in our review of the draft Aveed PI. We offer the following comments:

PI

(b) (4)

5.6 Potential for adverse effects on spermatogenesis

(b) (4)

- Please consider revising this sentence to, “At large doses of exogenous androgens, spermatogenesis may be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH) which could possibly lead to adverse effects on semen parameters including sperm count” (emphasis added) to be consistent with the AndroGel 1% PI.

5.7 Hepatic adverse effects

(b) (4)

6.1 (b) (4)

- Please consider adding placebo rates to Table 1.

6.2 Post-marketing Experience

(b) (4)

- Please consider replacing (b) (4) with “AVEED.” (b) (4)

(b) (4)

(b) (4)

12 CLINICAL PHARMACOLOGY

(b) (4)

(b) (4)

(b) (4) We recommend deleting or revising this section to be consistent with the AndroGel 1% PI, which states, “Male hypogonadism has two main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter’s Syndrome or Leydig cell aplasia, whereas secondary hypogonadism is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (FSH, LH).”

Metabolism

(b) (4)

(b) (4)

14.1 Testosterone Replacement Therapy

(b) (4)

(b) (4)



Vial Label
Carton Label

DDMAC cannot provide comments on the vial and carton labels at this time [redacted] (b) (4)

PPI

DDMAC has reviewed the proposed patient package insert (PPI) for AVEED (testosterone undecanoate) injection and we offer the following comments.

What is [redacted] (b) (4)

This section presents the claim, [redacted] (b) (4)
[redacted] (b) (4) The draft PI states. [redacted] (b) (4)
[redacted] (b) (4) Please consider adding the word “adult” to the PPI to be consistent with the PI.

This section presents the claims. [redacted] (b) (4)
[redacted] (b) (4)
[redacted] (b) (4) These claims may be used promotionally. Are these claims supported by substantial evidence?

Who should NOT [redacted] (b) (4)

The draft PI lists “breastfeeding” as a contraindication. Please include “breastfeeding” to this list in the PPI.

- This section states, “breast cancer (b) (4) Please consider deleting the phrase (b) (4) from the PPI, as this statement is not necessary and is not presented in the Patient Labeling for AndroGel.

What should I tell my doctor before (b) (4)

- The Warnings and Precautions section of the draft PI states, (b) (4)
(b) (4) Please consider adding this information in consumer friendly language to the PPI.
- The Drug Interactions section of the draft PI states, “Changes in anticoagulant activity may be seen with androgens (b) (4) (b) (4) Please add this drug interaction in consumer friendly language to the PPI.
- The draft PPI states, (b) (4) It appears that this drug interaction was deleted from the draft PI. If so, please delete this drug interaction from the PPI so that it is consistent with the PI.

What are possible side effects (b) (4)

- This section states, (b) (4)
(b) (4)
(b) (4) The draft PI states, (b) (4)
(b) (4) (emphasis added) Please consider adding context to the PPI to be consistent with the PI (b) (4)
- This section states, (b) (4) liver problems.” Please consider adding context to this section to state that **serious** liver problems, including cancer, could occur.
- This section states, (b) (4) increased risk for (b) (4) prostate cancer.” (emphasis added). Please consider deleting the term (b) (4) from this sentence, as this term is not included in the draft PI and it implies that this risk only pertains to (b) (4) Please consider replacing the term (b) (4) with “AVEED” to make it clear that this risk applies to patients taking AVEED. Finally, please consider bulleting this risk to be consistent with the other risks presented in the PPI.
- The draft PI states, “Patients with BPH treated with androgens are at an increased risk of worsening signs and symptoms of BPH.” Please consider including this information in the PPI. For example, the Patient Labeling for AndroGel states that patients should contact their healthcare professional if they experience “Changes in urinary habits such as increased urination at night, trouble starting your urine stream, passing urine many times during the day, having an urge that you have to go to the bathroom right away, having a urine accident, being unable to pass urine and weak urine flow.”

- The Warnings and Precautions section of the draft PI includes “Potential for adverse effects on spermatogenesis.” Is it important to convey this risk to consumers? If so, please consider including this risk in consumer friendly language in the PPI.
- The Warnings and Precautions section of the draft PI includes, “Edema with or without congestive heart failure may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease.” Is it important to convey this risk to consumers? If so, please consider including this risk in consumer friendly language in the PPI.
- The Highlights section of the draft PI lists “cough” as a commonly reported adverse reaction. Please consider adding “cough” to the list of common side effects in the PPI to be consistent with the PI.

DDMAC appreciates the opportunity to provide comments on these materials. If you have any questions, please contact:

- Janice Maniwang (Professional directed materials)
(301) 796-3821, or janice.maniwang@fda.hhs.gov
- Carrie Newcomer (Consumer directed materials)
(301) 796-1233, or carrie.newcomer@fda.hhs.gov

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/s/

Janice Maniwang
7/15/2009 04:54:52 PM
DDMAC PROFESSIONAL REVIEWER



Memorandum

Pre-Decisional Agency Information

Date: January 8, 2008

To: John Kim
Regulatory Health Project Manager
DRUP

From: Amy Toscano, Pharm.D., CPA
Regulatory Review Officer
DDMAC

Subject: DDMAC comments on Nebido® (testosterone undecanoate) intramuscular injection
draft PI

Background

I have considered the current AndroGel (testosterone gel) 1% PI in my review of the Nebido draft PI.

DDMAC appreciates the opportunity to review the proposed product labeling for Nebido, and provides the following comments and proposed changes (see track changes throughout).

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/s/

Amy Toscano
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DDMAC REVIEWER