CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021463Orig1s000

OTHER REVIEW(S)

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:	December 17, 2010
Application Type/Number:	NDA 021463
To:	Scott Monroe, MD Director, Division of Reproductive and Urologic Products
Through:	Todd Bridges, RPh, Team Leader Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Jibril Abdus-Samad, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name(s):	Fortesta (Testosterone) Gel, 10 mg per actuation
Applicant:	Endo Pharmaceuticals, Inc.
OSE RCM #:	2010-1504

1 INTRODUCTION

This review is written in response to a request from the Division of Reproductive and Urologic Products for a review of the revised Fortesta labels and labeling submitted on December 13, 2010, in response to the Division of Medication Error Prevention and Analysis' previous comments to the Applicant. DMEPA reviewed the initial proposed labels and labeling under OSE Review 2009-897, dated October 13, 2009.

2 MATERIALS REVIEWED

The Applicant provided revised label and labeling on December 13, 2010 (See Appendices A-F, no image of insert labeling). We also reviewed the recommendations in OSE Review # 2009-897.

3 DISCUSSION

Review of the revised labels and labeling show that the Applicant implemented DMEPA's recommendations. The Applicant's revisions did not introduce any additional areas of vulnerability that could lead to medication errors.

4 CONCLUSIONS AND RECOMMENDATIONS

The revised labels and labeling submitted by the Applicant adequately addresses our concerns from a medication error perspective. We do not have any additional comments at this time.

If you have further questions or need clarifications, please contact Karen Townsend, OSE Project Manager, at 301-796-5413.

5 REFERENCES

OSE Review #2009-897, Label and Labeling Review for Fortesta (Testosterone) Gel 2%, Abdus-Samad, J; October 13, 2009.

6 APPENDICES

Appendix A: Container label, one 60 g canister package

Appendix B: Container label, two 60 g canister packages

Appendix C: Container label, three 60 g canister packages

Appendix D: Carton labeling, one 60 g canister

Appendix E: Carton labeling, two 60 g canisters

Appendix F: Carton labeling, three 60 g canisters

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/s/

JIBRIL ABDUS-SAMAD
12/17/2010

TODD D BRIDGES
12/17/2010

CAROL A HOLQUIST
12/17/2010

SEALD LABELING: PI SIGN-OFF REVIEW

APPLICATION NUMBER	NDA 021463
APPLICANT	Endo Pharmaceuticals
DRUG NAME	Fortesta (testosterone gel)
SUBMISSION DATE	June 30, 2010
PDUFA DATE	December 30, 2010
SEALD SIGN-OFF DATE	December 16, 2010
OND ASSOCIATE DIRECTOR FOR LABELING	Ann Marie Trentacosti for Laurie Burke

This memo confirms that all critical prescribing information (PI) deficiencies found in the SEALD Labeling Review filed December 15, 2010, for this application have been addressed. SEALD agrees that the PI is ready for approval at this time.

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/s/

ANN M TRENTACOSTI
12/16/2010
Signing for Laurie Burke

SEALD LABELING REVIEW

This SEALD Labeling Review identifies major aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

APPLICATION NUMBER	NDA 021463
APPLICANT	Endo Pharmaceuticals
PRODUCT NAME	Fortesta (testosterone gel)
SUBMISSION DATE	6/30/2010
PDUFA DATE	12/30/2010
SEALD REVIEW DATE	12/14/2010
SEALD LABELING REVIEWER	Jun Yan, Pharm.D.

The following checked Selected Requirements for Prescribing Information items are outstanding labeling issues that must be corrected before the final draft labeling is approved.

Selected Requirements for Prescribing Information

For other regulatory requirements, see 21 CFR 201.56 and 201.57.

Highlights (HL)

- **General comments**
  - ☐ Highlights is in 8-point font, two-column format, with ½ inch margins.
  - ☐ Highlights is limited in length to one-half page. If greater than one-half page, a waiver has been granted previously or has been requested by the applicant in this submission.
  - ☐ There is no redundancy of information.
  - ☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
  - ☐ A horizontal line must separate the HL and TOC
  - ☐ All headings must be presented in the center of a horizontal line in upper-case letters and **bold** type.
  - ☐ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
  - ☐ Includes the following headings in the following order:

• **Highlights Limitation Statement** (required statement)
• **Drug names, dosage form, route of administration, and controlled substance symbol, if applicable** (required information)
• **Initial U.S. Approval** (required information)
• **Boxed Warning** (if applicable)
• **Recent Major Changes** (for a supplement)
• **Indications and Usage** (required information)
• **Dosage and Administration** (required information)
• **Dosage Forms and Strengths** (required information)
• **Contraindications** (required heading – if no contraindications are known, it must state "None")
• **Warnings and Precautions**
• **Adverse Reactions** (required AR contact reporting statement)
• **Drug Interactions** (optional heading)
• **Use in Specific Populations** (optional heading)
• **Patient Counseling Information Statement** (required statement)
• **Revision Date** (required information)

- **Highlights Limitation Statement**
  - ☐ Must be **bolded** and placed at the beginning of Highlights and read as follows: "**These highlights do not include all the information needed to use [insert name of drug product in UPPER CASE] safely and effectively. See full prescribing information for [insert name of drug product in UPPER CASE]**."

- **Product Title**
  - ☐ Must be **bolded** and include the proprietary and nonproprietary drug names, followed by the drug's dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**
  - ☐ Must include the 4-digit year of the initial U.S. approval of the new molecular entity (NME), new biological product, or new combination of active ingredients. If this is an NME, the year corresponds to the current approval action.

- **Boxed Warning**
  - ☐ All text in the boxed warning is **bolded**.
  - ☐ Summary must not exceed a length of 20 lines.
  - ☐ Requires a heading in upper-case bolded letters, containing the word "WARNING" and other words to identify the subject of the warning (e.g.,"**WARNING: LIFE-THREATENING ADVERSE REACTIONS**").
  - ☐ Must have the verbatim statement "***See full prescribing information for complete boxed warning***." If Highlights boxed warning is identical to FPI boxed warning, this statement is not necessary.

- **Recent Major Changes (RMC)**
  - ☐ Applies only to supplements and is limited to five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, Warnings and Precautions.
  - ☐ The heading and, if appropriate, subheading of each labeling section affected by the change must be listed with the date (MM/YYYY format) of supplement approval. For example, "Dosage and Administration, Coronary Stenting (2.2) --- 2/2010."
  - ☐ For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line ("margin mark") on the left edge.
  - ☐ A changed section must be listed in HL for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
  - ☐ Removal of a section or subsection should be noted. For example, "Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010."

- **Indications and Usage**

  ☐ If a product is a member of an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:

  http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm.

- **Contraindications**

  ☐ This heading must be included in HL and not omitted. If there are no contraindications, state “None.”

  ☐ All contraindications listed in the FPI must also be listed in HL.

  ☐ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug). If the contraindication is not theoretical, then it must be worded to explain the type and nature of the adverse reaction.

  ☐ For drugs with a pregnancy Category X, state “Pregnancy” and cross-reference to Contraindications section (4).

- **Warnings and Precautions**

  ☐ Pregnancy Category D drugs have positive human risk findings. These findings must be noted as a warning. Therefore, must state the following: “Pregnancy: Can cause fetal harm. Advise women of potential risk to the fetus.”

- **Adverse Reactions**

  ☐ Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” cannot be used. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).

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

- **Patient Counseling Information Statement**

  ☐ Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA approved patient labeling or Medication Guide”)**.

- **Revision Date**

  ☐ A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date will be the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- ☐ The heading – **FULL PRESCRIBING INFORMATION: CONTENTS** – must appear at the beginning of the TOC in UPPER CASE and **bold** type.
- ☐ The headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- ☐ All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- ☐ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:

  8.1 Pregnancy

  8.3 Nursing Mothers (not 8.2)

  8.4 Pediatric Use (not 8.3)

  8.5 Geriatric Use (not 8.4)
- ☐ When a section or subsection 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 the Contents: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI)

- **General Format**
  - ☐ A horizontal line must separate the TOC and FPI
  - ☐ The heading – FULL **PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
  - ☐ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).
- **Boxed Warning**
  - ☐ Must have a heading, in UPPER CASE **bold** type, containing the word "**WARNING**" and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the summary.
  - ☐ Must include a brief, concise summary of critical information and cross-reference to more detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).
- **Contraindications**
  - ☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.
- **Warnings and Precautions**
  - ☐ For Pregnancy Category D drugs, list pregnancy as a Warning and Precaution.

- **Adverse Reactions**

  ☐ Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as "adverse events" or "treatment-emergent adverse events," cannot be used.

  ☒ For the "Clinical Trials Experience" subsection, the following verbatim statement 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 clinical practice."

  Please add the word "clinical" in the sentence.

  ☐ For the "Postmarketing Experience" subsection, the listing must be separate from the listing of adverse reactions identified in clinical trials and include the following verbatim statement:

  - "The following adverse reactions have been identified during post approval use of drug X. 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."

- **Use in Specific Populations**

  ☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required.

- **Patient Counseling Information**

  ☐ This section is required and cannot be omitted.

  ☐ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement "See FDA-approved patient labeling (insert type of patient labeling)." should appear at the beginning of Section 17 for prominence. For example:

  - "See FDA-approved patient labeling (Medication Guide)"
  - "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
  - "See FDA-approved patient labeling (Patient Information)"
  - "See FDA-approved patient labeling (Instructions for Use)"
  - "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

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/s/

JUN YAN
12/15/2010

ANN M TRENTACOSTI
12/15/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

PATIENT LABELING REVIEW

Date:	**December 06, 2010**
To:	Scott Monroe, MD., Director **Division of Reproductive and Urologic Products (DRUP)**
Through:	LaShawn Griffiths, RN, MSHS-PH, BSN Acting Team Leader, Patient Labeling Reviewer **Division of Risk Management (DRISK)** Melissa Hulett, MSBA, BSN, RN Patient Labeling Reviewer **Division of Risk Management (DRISK)**
From:	Shawna Hutchins, MPH, BSN, RN Patient Labeling Reviewer **Division of Risk Management (DRISK)**
Subject:	DRISK Review of Patient Labeling (Medication Guide)
Drug Name (established name):	FORTESTA (testosterone)
Dosage Form and Route:	Gel for Topical Use CIII
Application Type/Number:	NDA 21-463
Applicant:	Endo Pharmaceuticals Inc.
OSE RCM #:	2010-1501

1. INTRODUCTION

This review is written in response to a request by the Division of Reproductive and Urologic Products (DRUP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG), for FORTESTA (testosterone) Gel for topical use.

The applicant submitted a New Drug Application (NDA) 21463 for FORTESTA (testosterone) Gel on June 03, 2002. Subsequently the applicant submitted an amendment on April 17, 2009 which received a class two Complete Response on October 16, 2009.

On June 30, 2010 the applicant resubmitted NDA 21463 for FORTESTA (testosterone) Gel for topical use for the treatment of males with a deficiency or absence of endogenous testosterone.

DRISK's Review of the Risk Evaluation and Mitigation Strategy (REMS) was submitted under separate cover to DRUP on November 20, 2010.

2. MATERIAL REVIEWED

- Draft FORTESTA (testosterone) Medication Guide (MG) received on June 30, 2010, revised by the Review Division throughout the current review cycle, and sent to DRISK on November 26, 2010.
- Draft FORTESTA (testosterone) prescribing information (PI) received June 30, 2010, revised by the Review Division throughout the current review cycle, and received by DRISK on November 26, 2010.
- Comparator labeling for Axiron (testosterone) Solution for topical use.

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 APHont 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 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 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)

- ensured that the MG is consistent with the approved comparator labeling where applicable.

4. CONCLUSIONS

The MG is acceptable with our recommended changes.

5. RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DRISK 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.

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

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/s/

SHAWNA L HUTCHINS
12/06/2010

LASHAWN M GRIFFITHS
12/06/2010

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: December 3, 2010

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

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

Re: **NDA 021463**
DDMAC labeling comments for Fortesta™ (testosterone) gel for topical use, CIII

Background

This consult is in response to DRUP's July 8, 2010 and September 24, 2010 request for DDMAC's review on labeling materials for Fortesta™ (testosterone) gel for topical use, CIII (Fortesta). DDMAC has reviewed the following labeling materials for Fortesta:

Healthcare Provider Directed:

- Prescribing Information (PI)

Consumer Directed:

- Medication Guide (Med Guide)

Please note that our comments are based on the substantially complete version of the draft label sent to DDMAC on November 26, 2010. In addition, we have considered the Axiron PI (approved November 2010), Testim PI (approved September 2009) and the Androgel 1% PI (September 2009) in our review of the draft Fortesta labeling.

We offer the following comments:

PI & Med Guide

Please see our attached comments.

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

- Beth Carr (Consumer directed materials)
  (301) 796-3674, or beth.carr@fda.hhs.gov

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

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/s/

JANICE L MANIWANG
12/03/2010

SEALD LABELING REVIEW

This SEALD Labeling Review identifies major aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

APPLICATION NUMBER	NDA 021463
APPLICANT	Endo Pharmaceuticals
PRODUCT NAME	FORTESTA™ (testosterone) gel
SUBMISSION DATE	30 June 2010
PDUFA DATE	30 Dec 2010 (tentative 23 Dec 2010)
SEALD REVIEW DATE	Dec 3 2010 (Label entitled "Label from Endo December 2 2010 CLEAN.doc posted in the eroom on Dec 3 2010)
SEALD LABELING REVIEWER	Jun Yan

The following checked Selected Requirements for Prescribing Information items are outstanding labeling issues that must be corrected before the final draft labeling is approved.

Selected Requirements for Prescribing Information

For other regulatory requirements, see 21 CFR 201.56 and 201.57.

Highlights (HL)

- **General comments**
  - ☐ Highlights is in 8-point font, two-column format, with ½ inch margins.
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  - ☐ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
  - ☐ Includes the following headings in the following order:

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• **Drug names, dosage form, route of administration, and controlled substance symbol, if applicable** (required information)
• **Initial U.S. Approval** (required information)
• **Boxed Warning** (if applicable)
• **Recent Major Changes** (for a supplement)
• **Indications and Usage** (required information)
• **Dosage and Administration** (required information)
• **Dosage Forms and Strengths** (required information)
• **Contraindications** (required heading – if no contraindications are known, it must state "None")
• **Warnings and Precautions**
• **Adverse Reactions** (required AR contact reporting statement)
• **Drug Interactions** (optional heading)
• **Use in Specific Populations** (optional heading)
• **Patient Counseling Information Statement** (required statement)
• **Revision Date** (required information)

- **Highlights Limitation Statement**
  - ☐ Must be **bolded** and placed at the beginning of Highlights and read as follows: "**These highlights do not include all the information needed to use [insert name of drug product in UPPER CASE] safely and effectively. See full prescribing information for [insert name of drug product in UPPER CASE]**."

- **Product Title**
  - ☐ Must be **bolded** and include the proprietary and nonproprietary drug names, followed by the drug's dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**
  - ☐ Must include the 4-digit year of the initial U.S. approval of the new molecular entity (NME), new biological product, or new combination of active ingredients. If this is an NME, the year corresponds to the current approval action.

- **Boxed Warning**
  - ☐ All text in the boxed warning is **bolded**.
  - ☐ Summary must not exceed a length of 20 lines.
  - ☐ Requires a heading in upper-case bolded letters, containing the word "WARNING" and other words to identify the subject of the warning (e.g.,"**WARNING: LIFE-THREATENING ADVERSE REACTIONS**").
  - ☐ Must have the verbatim statement "***See full prescribing information for complete boxed warning***." If Highlights boxed warning is identical to FPI boxed warning, this statement is not necessary.

- **Recent Major Changes (RMC)**
  - ☐ Applies only to supplements and is limited to five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, Warnings and Precautions.
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- **Indications and Usage**

  ☐ If a product is a member of an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:

  http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm.

- **Contraindications**

  ☐ This heading must be included in HL and not omitted. If there are no contraindications, state “None.”

  ☐ All contraindications listed in the FPI must also be listed in HL.

  ☐ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug). If the contraindication is not theoretical, then it must be worded to explain the type and nature of the adverse reaction.

  ☐ For drugs with a pregnancy Category X, state “Pregnancy” and cross-reference to Contraindications section (4).

- **Warnings and Precautions**

  ☐ Pregnancy Category D drugs have positive human risk findings. These findings must be noted as a warning. Therefore, must state the following: “Pregnancy: Can cause fetal harm. Advise women of potential risk to the fetus.”

- **Adverse Reactions**

  ☐ Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” cannot be used. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).

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

- **Patient Counseling Information Statement**

  ☐ Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA approved patient labeling or Medication Guide”)**.

- **Revision Date**

  ☒ A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date will be the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- ☐ The heading – **FULL PRESCRIBING INFORMATION: CONTENTS** – must appear at the beginning of the TOC in UPPER CASE and **bold** type.
- ☐ The headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- ☐ All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- ☐ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:

  8.1 Pregnancy

  8.3 Nursing Mothers (not 8.2)

  8.4 Pediatric Use (not 8.3)

  8.5 Geriatric Use (not 8.4)
- ☐ When a section or subsection 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 the Contents: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI)

- **General Format**
  - ☐ A horizontal line must separate the TOC and FPI
  - ☐ The heading – FULL **PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
  - ☐ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).
- **Boxed Warning**
  - ☐ Must have a heading, in UPPER CASE **bold** type, containing the word "**WARNING**" and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the summary.
  - ☐ Must include a brief, concise summary of critical information and cross-reference to more detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).
- **Contraindications**
  - ☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.
- **Warnings and Precautions**
  - ☐ For Pregnancy Category D drugs, list pregnancy as a Warning and Precaution.

- **Adverse Reactions**
  - ☐ Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as "adverse events" or "treatment-emergent adverse events," cannot be used.
  - ☐ For the "Clinical Trials Experience" subsection, the following verbatim statement 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 clinical practice."
  - ☐ For the "Postmarketing Experience" subsection, the listing must be separate from the listing of adverse reactions identified in clinical trials and include the following verbatim statement:
    - "The following adverse reactions have been identified during post approval use of drug X. 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."

- **Use in Specific Populations**
  - ☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required.

- **Patient Counseling Information**
  - ☐ This section is required and cannot be omitted.
  - ☐ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement "See FDA-approved patient labeling (insert type of patient labeling)." should appear at the beginning of Section 17 for prominence. For example:
    - "See FDA-approved patient labeling (Medication Guide)"
    - "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
    - "See FDA-approved patient labeling (Patient Information)"
    - "See FDA-approved patient labeling (Instructions for Use)"
    - "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

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/s/

JUN YAN
12/03/2010
Fortesta SEALD Labeling Review

ANN M TRENTACOSTI
12/03/2010

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: October 20, 2010

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: Resubmission (Class 2 Complete Response) for NDA 21-463 - FORTESTA (testosterone) Gel, 2% - Indicated for testosterone replacement therapy in hypogonadal males.
Sponsor: Prostrakan

Materials reviewed: Draft Label for Fortesta (NDA 21-463) found in the EDR.

Background:

In a consult request dated June 30, 2010, the Division of Reproductive and Urologic Products (DRUP) requested that CSS review the proposed language in the draft label of Fortesta (testosterone gel) 2% (NDA 21,463) with regard to scheduling of the product. The draft labeling was provided in September 2010, in response to a class 2 Complete Response resubmission. In a memo dated August 19, 2009, CSS provided some initial language for the label under section 9 entitled "DRUG ABUSE AND DEPENDENCE" along with a scientific basis for this language.

Recommendation

We recommend the Division to accept the Sponsor's proposed language for Section 9 entitled "DRUG ABUSE AND DEPENDENCE," as submitted in September 2010, with the addition to the end of Section 9.3 of the following statement:

> *The withdrawal syndrome following discontinuation of prolonged, high dose anabolic steroid use may include depressed mood, fatigue, restlessness, anorexia, and decreased libido.*

CSS Review

Below is the proposed language for section 9 entitled "DRUG ABUSE AND DEPENDENCE," as proposed by the Sponsor in the current draft of the product label for Fortesta.

(b) (4)

With one exception, the proposed language in the current draft label regarding section 9 entitled "DRUG ABUSE AND DEPENDENCE" is identical to that proposed by CSS in its August 19, 2009, memo to the Division. The one exception is the deletion of the following sentence proposed by CSS:

(b) (4)

A review of the literature suggests there is sufficient documentation to describe a withdrawal syndrome following discontinuation of prolonged, high dose anabolic steroid use. This syndrome includes depressed mood, fatigue, restlessness, anorexia, insomnia, and decreased libido (Allnutt and Chaimowitz, 1994; Brower, 1997, 2002; Brower et al., 1990, 1991; Jan van Amsterdam et al., 2010; Kanayama et al., 2008, 2009, 2010; Malone and Dimeff, 1992; NIDA Research Report Series: Anabolic Steroid Abuse (2006); Pope and Brower, 2009). Therefore, it is advised that the following sentence regarding the withdrawal syndrome be added at the end of Section 9.3 of the label:

The withdrawal syndrome following discontinuation of prolonged, high dose anabolic steroid use may include depressed mood, fatigue, restlessness, anorexia, and decreased libido.

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/s/

JAMES M TOLLIVER
10/20/2010

SILVIA N CALDERON
10/20/2010

MICHAEL KLEIN
10/20/2010

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:	October 13, 2009
To:	Scott Monroe, MD Director, Division of Reproductive and Urologic Products
Through:	Todd Bridges, RPh, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Division Director Division of Medication Error Prevention and Analysis
From:	Jibril Abdus-Samad, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Fortesta (Testosterone) Gel, 2%
Application Type/Number:	NDA 21-463
Applicant:	Endo Pharmaceuticals, Inc.
OSE RCM #:	2009-897

CONTENTS

1 INTRODUCTION

This review is written in response to a request from the Division of Reproductive and Urologic Products for assessment of labels and labeling for Fortesta (Testosterone) Gel from a medication error perspective.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis[1] (FMEA) to evaluate the labels and labeling submitted as part of the April 17, 2009. The Applicant submitted updated container and carton labeling on September 18, 2009. See Appendix A through F.

2.1 FDA'S ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE SEARCH

Because testosterone gel is currently marketed, DMEPA conducted a search of the Adverse Events Reporting System (AERS) database to determine if medication errors related to the use of this product have been reported. The search was conducted on May 29, 2009, using the following terms: Trade Name "Androgel" and "Testim", Verbatim Names "Andro%" and "Testi%", the MedDRA reactions "Medication Errors" (HLGT), and "Product Quality Issue" (PT).

The reports were manually reviewed to determine if a medication error occurred and remove duplicate reports from review. Those cases that did not describe a medication error with testosterone gel were excluded from further analysis. If an error occurred, the staff reviewed the case to determine if the root cause could be associated with the labels or labeling of the product, and thus pertinent to this review. The cases that described a medication error possibly relevant to this review of this product were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors.

3 RESULTS

3.1 AERS RESULTS

The FDA Adverse Event Reporting System (AERS) search retrieved a total of 47 cases involving testosterone gel. Of the 47 cases, 13 cases were excluded from further analysis because these cases mainly described adverse events or involved errors unique to other product formulations of testosterone.

The 34 remaining cases involved medication errors related to testosterone gel. These cases were categorized as accidental exposure (30), product quality issue (3), and incorrect route of administration (1).

3.1.1 *Accidental Exposures (n=30)*

Thirty cases describe a secondary exposure to the product by transfer from the actual user. These cases, which led to adverse events, occurred between 2001 and 2009 and involved children and adults. FDA released a press announcement on May 7, 2009, entitled *Testosterone Gel Safety Concerns Prompt FDA to Require Label Changes, Medication Guide*[2], which addressed these accidental exposures, subsequent

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

[2] http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm149580.htm, last accessed September 18, 2009

adverse events, and the newly required labeling changes for the currently approved topical testosterone gel products (Androgel 1% packets and Testim 1% tubes). Additionally, a Medication Guide will be provided with Fortesta to comply with the labeling requirements for testosterone gel detailed in the aforementioned press release.

3.1.2 *Product Quality Issue (n=3)*

Three cases of reported product quality issues occurred between 2002 and 2008. The first case was a complaint in which a patient reported Androgel was not improving his Testosterone levels and questioned the quality of the product. The second case in 2004, involved a patient reporting the potency of Androgel varied month to month and that the lot of Androgel he was using did not contain the active ingredient, testosterone. It was unclear how this was determined and no further information was reported. The last case in 2008, involved a physician reporting his patients on Androgel Metered Dose Pump have had their testosterone levels return to pre-treatment levels. The physician has returned several pumps to the manufacturer for analysis however has not received any results.

3.1.3 *Incorrect Route of Administration (n=1)*

The case of an incorrect route of administration was reported in 2004. A physician reported a patient injected Androgel subcutaneously rather than applying topically. The cause of the error was not stated. The patient required hospitalization, antibiotics, and psychiatric treatment.

4 DISCUSSION AND RECOMMENDATIONS

The reports of product quality and incorrect route of administration are not relevant to the review of this product. Although secondary exposure to the product by transfer from the actual user can occur with Fortesta, the labeling informs health care providers and patients about the risk of secondary exposure and the steps that should be taken to minimize the risk. We noted areas where information on the labels and labeling can be clarified and improved upon to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 4.1, *Comments to the Division*. Section 4.2, *Comments to the Applicant,* contains our recommendations for the container label and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant.

We would be willing to meet with the Division for further discussion, if needed. 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 the please contact OSE Project Manager, Maria Wasilik, at 301-796-0567.

4.1 COMMENTS TO THE DIVISION

4.1.1 *Insert Labeling*

1. We noted the use of trailing zeros and the symbols > and < in the DOSAGE AND ADMINISTRATION section of the insert labeling. The use of trailing zeroes and the symbols > and < is considered a source of medication errors and are included on ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations[3] which states they should never be used when communicating medical information. As part of a joint (FDA and ISMP) national campaign, FDA agreed to not allow the use of dangerous abbreviations, symbols, and dose designations to appear in the approved labels and labeling of products. We request that all trailing zeros be removed and the symbols > and < be replaced with the words "greater than" and "less than".

[3] http://www.ismp.org/Tools/errorproneabbreviations.pdf, last accessed September 18, 2009.

2. In the DOSAGE AND ANDMINISTRATION sections of the FULL PRESCRIBING INFORMATION and in the HIGHLIGHTS OF PRESCRIBING INFORMATION, the expression of dosing includes the number of grams of gel and the corresponding milligrams of testosterone. For example, the recommended starting dose of FORTESTA is a total of 2 g gel (40 mg of testosterone) applied once daily.

   The actual number of pump depressions is what health care providers need to communicate to whoever is administering FORTESTA (i.e. nurse or patient). Thus, providing the number of pumps in the dosing and administration instructions may help eliminate the risk involved in any calculations errors due to converting grams of gel or milligrams of testosterone to the corresponding number of depressions.

   Currently, there are approved medication products that are dispensed with metered dose devices that provide a specific amount of drug per actuation. These types of products provide dosing information in terms of the number of device actuations such as inhalations or sprays for oral and nasal inhalers, respectively. Furthermore, a similar product, Androgel (testosterone) gel, which is also dispensed in a metered-dose pump device, provides similar dose instructions in terms of grams of gel and number of pump actuations. Healthcare providers are familiar with these dose instructions and there were no medication reports retrieved from AERS involving confusion with Androgel 1% metered pump in the insert labeling dose instructions. We acknowledge that these products are not interchangeable, however we anticipate healthcare providers may perceive these products as being similar since the have the same active ingredient (testosterone), dosage form (gel), route of administration (topical), dosing device (metered pump), and expression of strength (%). Thus, healthcare providers may expect similar units of measure for describing dose instructions. Indicating the proper number of depressions will provide clear dose instructions.

   DMEPA recommends the revising the expression of dosing to include the corresponding number of pumps depressions throughout the insert labeling. For example, revise "2 g gel (40 mg of testosterone)" to read "2 g gel (40 mg testosterone or 4 depressions)".

3. FORTESTA 2% will be the second approved testosterone gel dispensed in a metered dose pump. The recommended starting dose and dose adjustments for this product differ from the currently marketed products. However, we anticipate healthcare providers may perceive these products as being similar since the have the same active ingredient (testosterone), dosage form (gel), route of administration (topical), dosing device (metered pump), and strength designation (%). Healthcare providers may attempt to interchange these products based upon comparing the milligrams of testosterone, grams of gel, or percentage strength. Thus, a statement should be in the DOSAGE AND ADMINISTRATION sections that these testosterone products are not interchangeable and prescribers should consult the package insert for dosing.

4.2 COMMENTS TO THE APPLICANT

4.2.1 *Canister Container Label and Carton Labeling*

1. Ensure that the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
2. Relocate the Medication Guide statement to the principle display panel.
3. Remove the bolding of "Keep out of reach of children" and bold the statement "**For external use only**". This may help ensure the correct route of administration.

4. The dosing instructions for this product contain detailed information to ensure appropriate use and there is not adequate space available to place the dosing instructions on the container label and carton labeling. Thus, per 21 CFR 201.55, revise the statement "Apply to the skin as instructed by your doctor" to read:

"See package insert for dosage information".

4.2.2 *Container Label*

1. Decrease the prominence of the net quantity, 60 g, by decreasing the font size and removing the color surrounding it. The net quantity statement should not be more prominent than the strength. The strength should have greater prominence, since it is an important aspect of identifying the correct drug product.
2. Relocate the medication guide statement to the principal display panel. Additionally, the manufacturer information may be relocated to the right side of the label to provide space on the principal display panel.
3. Add the statement "Rx Only".

4.2.3 *Carton Labeling*

1. Relocate the medication guide statement to the principal display panel.
2. Relocate "Rx Only" to the principal display panel.
3. Relocate the statement "**For external use only**" to the principal display panel to decrease the likelihood of an incorrect route of administration error. Since this product is not for oral use, the correct route of administration should be prominently displayed.

5 REFERENCES

ADVERSE EVENTS REPORTING SYSTEM (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufacturers that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

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/s/

JIBRIL ABDUS-SAMAD
10/13/2009

TODD D BRIDGES
10/13/2009

CAROL A HOLQUIST
10/13/2009

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

Memorandum

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

Date: **October 6, 2009**

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

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

Subject: **NDA 21-463**
DDMAC Medication Guide comments for Fortesta (testosterone gel) 2% for topical use

DDMAC has reviewed the proposed Medication Guide for Fortesta (testosterone gel) 2%. Please note that DRISK provided comments on the Fortesta Medication Guide on October 1, 2009, and our comments are based on the DRISK version of the Medication Guide. DDMAC agrees with DRISK comments and offers the following additional comments. If you have any questions or concerns regarding my comments, please contact me.

How should I use FORTESTA?

- This section presents the claim, '(b) (4) The Administration section of the draft PI states, '(b) (4) (emphasis added) Please consider revising the language in the Medication Guide to be consistent with the PI.

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 A NEWCOMER
10/06/2009

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:	October 1, 2009
To:	Scott Monroe, M.D., Division Director
	Division of Reproductive and Urologic Products
	(DRUP)
Through:	Mary Willy, PhD, Deputy Division Director
	Division of Risk Management (DRISK)
	LaShawn Griffiths, MSHS-PH, BSN, RN
	Patient Product Information Reviewer, Acting Team Leader
	Division of Risk Management
From:	Melissa Hulett, MSBA, BSN, RN
	Patient Product Information Reviewer
	Division of Risk Management
Subject:	DRISK Review of Patient Labeling (Medication Guide)
Drug Name(s):	FORTESTA 2% (testosterone gel)
Application Type/Number:	NDA 21-463
Applicant/sponsor:	Endo Pharmaceuticals Inc.
OSE RCM #:	2009-1038

1 INTRODUCTION

This review is written in response to a request by the Division of Reproductive and Urologic Products (DRUP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for Fortesta (testosterone gel). Please let us know if DRUP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant. DRISK's review of the proposed REMS was sent to DRUP under separate cover dated September 2, 2009.

2 MATERIAL REVIEWED

- Draft Fortesta (testosterone gel) Prescribing Information (PI) submitted April 17, 2009 and revised by the Review Division throughout the current review cycle.
- Draft Fortesta (testosterone gel) Medication Guide (MG) submitted on April 17, 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.

Please let us know if you have any questions.

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/s/

MELISSA I HULETT
10/01/2009

MARY E WILLY
10/01/2009
I concur with this review

M E M O R A N D U M
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 21-463 - FORTESTA (testosterone) Gel, 2% - Indicated for testosterone replacement therapy in hypogonadal males.
Sponsor: Prostrakan

Materials reviewed: Materials submitted and comprising NDA 21-463.

Background:

The Division of Reproductive and Urologic Products has submitted a consult concerning NDA 21-463 to CSS requesting verification on the scheduling status of FORTESTA (testosterone) Gel 2% and an assessment of the labeling for FORTESTA (testosterone) Gel 2% as it applies to abuse and dependence.

FORTESTA (testosterone) Gel 2% is intended for testosterone replacement therapy in adult males deficient in testosterone due to either primary hypogonadism (congenital or acquired), secondary (hypogonadotrophic) hypogonadism (congenital or acquired) or age related primary or secondary hypogonadism. The recommended starting dose is a total of 2.0 g gel (40 mg of testosterone) applied once daily to clean, dry, intact skin at the front of both thighs (topically). It is supplied in 60 g metered dose canisters with a pump that delivers 0.5 g gel (10 mg of testosterone) per complete depression. Dose adjustment is between 0.5 g gel (10 mg of testosterone) and a maximum of 3.5 g gel (70 mg of testosterone) and is based on the total serum testosterone levels.

CSS Review and Recommendations

Testosterone, and therefore the product FORTESTA (testosterone) Gel 2%, is in Schedule III of the Controlled Substances Act. Testosterone is specifically designated a Schedule III anabolic steroid under 21 U.S.C. 802(41)(A)(xlvii).

Labeling of FORTESTA (testosterone) Gel 2%

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

(b) (4)

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

(b) (4)

Discussion

With respect to scheduling status, we recommend that the label state that FORTESTA is in Schedule III under the Controlled Substances Act of 1970, and not under the Anabolic Steroids Control Act. This latter legislation simply amended the Controlled Substances Act to place anabolic steroids, including testosterone and its esters into Schedule III.

Currently, the labeling suffers from a lack of information regarding abuse or dependence and needs to 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 needs to be considered when they store, dispense or use an anabolic steroid. Similar general information needs to 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).

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/s/

JAMES M TOLLIVER
08/19/2009

SILVIA N CALDERON
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