CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION 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:	November 20, 2010
To:	Scott Monroe, MD, Director **Division of Reproductive and Urologic Products (DRUP)**
Through:	Claudia Karwoski PharmD, Director **Division of Risk Management (DRISK)**
From:	Shawna Hutchins, MPH, BSN RN Patient Labeling Reviewer **Division of Risk Management (DRISK)**
Subject:	DRISK Review of Proposed Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	Fortesta (testosterone) 2% gel
Application Type/Number:	NDA 21-463
Applicant/sponsor:	Endo Pharmaceuticals Inc. (Endo)
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 Risk Evaluation and Mitigation Strategy (REMS) and REMS Supporting Document for Fortesta (testosterone) 2% Gel.

Please send these comments to the Applicant and request a response within two weeks of receipt. Let us know if you would like a meeting to discuss these comments before sending to the Applicant.

The DRISK review of the Medication Guide will be provided under a separate cover. The DRISK review of the methodology and survey instruments to be submitted by the Applicant to evaluate the REMS will be provided under separate cover.

2. BACKGROUND

This is the third review cycle for NDA 21-463, Fortesta (testosterone) Gel 2%. The NDA received a complete response (CR) by the Agency on October 16, 2009 based on deficiencies noted during DSI audit. Endo resubmitted the complete response on June 30, 2010.

Prior to the October 16, 2009 action, FDA notified the Applicant that a REMS was necessary for Fortesta (testosterone) 2% Gel to ensure that the benefits of the drug outweigh the risks of secondary exposure of women and children to testosterone from men using the drug. The necessary components of the REMS includes a Medication Guide and Timetable for Submission of Assessments. DRISK completed an initial review of the proposed REMS on September 1, 2009. The proposed REMS submitted on June 30, 2010 as an amendment to the NDA resubmission, is the subject of this review.

3. MATERIAL REVIEWED

- FORTESTA (testosterone) 2% Gel Risk Evaluation and Mitigation Strategy (REMS) Notification Letter dated July 28, 2009.

- Proposed FORTESTA (testosterone) 2% Gel Risk Evaluation and Mitigation Strategy (REMS) and REMS Supporting Document, submitted on June 30, 2010, and received by DRISK on July 09, 2010.

4. RESULTS OF REVIEW

In our review of the proposed REMS, we have:

- Ensured it includes the elements outlined in the REMS Notification Letter.
- Ensured it meets the statutory requirements under the Food and Drug Administration Amendments Act (FDAAA) of 2007.

5. CONCLUSIONS AND RECOMMENDATIONS

DRISK concurs with the elements of the proposed REMS..

Please note, the timetable for submission of the assessment is required to be approved as part of the REMS, but not the Applicant's proposed information about the details of the REMS evaluation (methodology/instruments). The methodology and instruments do not need to be reviewed or approved prior to approval of the REMS.

We have the following comments and recommendations for the Applicant with regard to the proposed REMS.

Comments to DRUP:

Comments to Endo Pharmaceutical Inc.:

See the appended FORTESTA (testosterone) 2% Gel REMS proposal (Appendix A of this memo) for track changes corresponding to comments in this review.

a. **GOAL**

   Your proposed goal is acceptable.

b. Your Medication Guide distribution plan appears to be acceptable. Your detailed plan for how you plan to distribute the Medication Guide in accordance with 21 CFR 208.24 is more appropriate for the REMS Supporting Document.

   - We remind you that under 21 CFR 208.24, you are responsible for ensuring that sufficient numbers of Medication Guides are provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. You state that a Medication Guide will be placed in each carton with each pump, and additional copies will be available on the company website. We find your unit-of-use distribution plan acceptable.
   - We remind you that under 21 CFR 208.24, you are responsible for ensuring that the FORTESTA (testosterone) 2% Gel carton or container label contains a prominent statement that the Medication Guide should be dispensed to each patient. We suggest the following language if the product is enclosed in the carton.

     "Dispense accompanying Medication Guide to each patient."
   - See our editorial comments on this section of the proposed REMS (see Appendix A).

c. Your proposed timetable for submission of assessments (18 months, 3 years and 7 years) is acceptable.

d. Regarding your REMS Assessment Plan

   We acknowledge that you provided a brief description of the REMS Assessment Plan. We recommend that you submit for review the detailed plan you propose to use to evaluate patients' understanding about the safe use of FORTESTA (testosterone) 2% Gel. You may submit the proposed plan after approval of the REMS, however submit it at least 90 days before you conduct the evaluation.

Code the submission "REMS Correspondence." Make sure the submission includes all methodology and instruments used to evaluate the knowledge about the risks associated with and safe use of FORTESTA (testosterone) 2% Gel.

If you plan to use a survey to conduct the assessment, we offer the following guidance as you develop your proposal.

1. Recruit respondents using a multi-modal approach. For example, you might recruit respondents through physicians' offices, pharmacies, managed care providers, consumer panels, or on-line.

   Explain how often you perform non-respondent follow-up or reminders.

   If you use an incentive or honorarium, provide details on what is offered and the estimated dollar value.

   Explain how you select recruitment sites.

   Submit for review any recruitment advertisements.

2. Describe the rationale for your sample size. Report the 95% confidence interval around the expected level(s) of patient knowledge for each key risk(s).

3. Define the expected number of people to be contacted to obtain the proposed sample size, and how the sample is determined (selection criteria).

4. Ensure the sample is demographically representative of the population who use the drug (patients).

5. When possible and appropriate, ensure the sample is diverse in terms of age, race, ethnicity, sex, socio-economic status, education level, and geographically.

6. List the inclusion criteria. For example, eligible patient respondents must be:

   - Age 18 or older
   - Currently taking FORTESTA (testosterone) 2% Gel or have taken the drug in the past 3 months
   - Not currently participating in a clinical trial involving FORTESTA (testosterone) 2% Gel
   - Not a healthcare provider

   Submit any screener instruments, and describe any quotas of sub-populations used.

7. Explain how you administer surveys and the intended frequency.

   Offer respondents multiple options for completing the survey. Be sure to include an option for the lower literacy population. For example, respondents might complete surveys online or through email, in writing or by mail, over the phone, and in person.

Explain how you train surveyors.

8. Explain how you control for limitations or bias associated with the methodology and survey instrument(s).
9. Submit for review the introductory text used to inform respondents about the purpose of the survey.

   Tell potential respondents that their answers will not affect their ability to receive or take (patients) the drug, and that their answers and personal information will be kept confidential and anonymous.
10. Clarify in your methodology that respondents are eligible for one wave of the survey only.
11. The assessment evaluates the effectiveness of the REMS in achieving the goal by evaluating patients' knowledge of the serious risks associated with use of the drug. The assessment does not evaluate consumer comprehension of the Medication Guide.

    According to regulation (21 CFR 208.24), patients receive the Medication Guide at the time the prescription is filled/dispensed. Do not offer respondents an opportunity to read or see the Medication Guide, Package Insert, or any other related educational materials again prior to taking the survey.
12. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in the Medication Guide.
13. Ensure the patient knowledge survey includes questions that ask about the specific risks or safety information conveyed in the Medication Guide to determine if the patient understands the information and knows what to do if they experience an adverse event.

    Derive the risk-specific questions from information located in the "What is the Most Important Information I should know about FORTESTA?" section of the Medication Guide.

    Ensure the risk-specific questions are not biased or leading, and that multiple choice questions include an instruction to "select all that apply." Ensure that each question has an "I don't know" answer option.

    Randomize the order of the multiple choice responses on each survey.
14. Order questions so the risk-specific questions are asked first, followed by questions about receipt of the Medication Guide. Collect demographic questions last or as part of any screener questions.

    Do not allow respondents the opportunity or ability to go back to previous questions in the survey.

    Explain if and when any education will be offered for incorrect responses.

15. Include questions about receipt of the Medication Guide in the patient survey as a way to fulfill the obligation to report on the distribution of the Medication Guide.

16. Prior to the questions about receipt of the Medication Guide, include text that describes a Medication Guide. For example,

    Now we are going to ask you some questions about the Medication Guide you may have received with FORTESTA (testosterone) 2% Gel. The Medication Guide is a paper handout that contains important information about the risks associated with use of FORTESTA (testosterone) 2% Gel and how to use FORTESTA (testosterone) 2% Gel safely. Medication Guides always include the title "Medication Guide" followed by the word FORTESTA and its pronunciation. The Medication Guide usually has sections titled "What is the most important information I should know about FORTESTA," "What is FORTESTA," and "Who should not take FORTESTA."

17. Use the following (or similar) questions to assess receipt and use of the Medication Guide.

    - Who gave you the Medication Guide for FORTESTA (testosterone) 2% Gel? (Select all that apply)
        a) My doctor or someone in my doctor's office
        b) My pharmacist or someone at the pharmacy
        c) Someone else - please explain: _____
        d) I did not get a Medication Guide for FORTESTA (testosterone) 2% Gel
    - Did you read the Medication Guide?
        a) All,
        b) Most,
        c) Some,
        d) None
    - Did you understand what you read in the Medication Guide?
        a) All,
        b) Most,
        c) Some,
        d) None
    - Did someone offer to explain to you the information in the Medication Guide?
        a) Yes, my doctor or someone in my doctor's office

b) Yes, my pharmacist or someone at the pharmacy

c) Yes, someone else – please explain: _____

d) No

- Did you accept the offer? Yes or No
- Did you understand the explanation that was given to you?

a) All,

b) Most,

c) Some,

d) None

- Did or do you have any questions about the Medication Guide? Yes or No (If Yes, list your question(s) below) Note: Group/code this open text field prior to submitting to FDA

18. Analyze results on an item-by-item or variable-by-variable basis. You may present the date using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables).

    You may stratify the data by any relevant demographic variable, and presented in aggregate. Submit with your assessments all methodology and instruments utilized.

Please let us know if you have any questions.

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/s/

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CLAUDIA B KARWOSKI
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concur

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:	September 01, 2009
To:	Scott Monroe, MD, Director **Division of Reproductive and Urologic Products (DRUP)**
Through:	Claudia Karwoski, PharmD, Director **Division of Risk Management (DRISK)** Jodi Duckhorn, MA, Team Leader **Division of Risk Management**
From:	Shawna Hutchins, BSN, R.N., Patient Labeling Reviewer **Division of Risk Management**
Subject:	DRISK Review of Proposed Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	FORTESTA (testosterone) 2% Gel
Application Type/Number:	NDA 21-463
Applicant/sponsor:	ProStrakan, Inc.
OSE RCM #:	2009-1038

1 INTRODUCTION

This memorandum is in response to a request by the Division of Reproductive and Urologic Products (DRUP) for the Division of Risk Management (DRISK) to review the proposed Risk Evaluation and Mitigation Strategy (REMS) for FORTESTA (testosterone) 2% Gel. Please send these comments to the Applicant and request a response within two weeks of receipt. Please let us know if you would like a meeting to discuss these comments before sending to the Applicant. The Medication Guide is being reviewed by DRISK and will be provided under separate cover.

2 MATERIAL REVIEWED

- FORTESTA (testosterone) 2% Gel Evaluation and Mitigation Strategy (REMS) Notification Letter dated July 28, 2009
- Proposed FORTESTA (testosterone) 2% Gel Risk Evaluation and Mitigation Strategy (REMS), dated August 19, 2009
- FORTESTA (testosterone) 2% Gel Evaluation and Mitigation Strategy (REMS) Supporting Document dated August 19, 2009

3 CONCLUSIONS AND RECOMMENDATIONS

DRISK concurs with the elements of the REMS.

Please note, the timetable for submission of the assessments is required to be approved as part of the REMS, but not the Applicant's proposed information about the details of the REMS evaluation (methodology/instruments).

We have the following comments and recommendations for the Applicant with regard to the proposed REMS.

Comments to ProStrakan Inc.:

See the appended FORTESTA (testosterone) 2% Gel REMS proposal (Appendix A of this memo) for track changes corresponding to comments in this review.

a. GOAL

Revise your goal as follows:

The goal of this REMS is to inform patients about the serious risks associated with the use of FORTESTA (testosterone) 2% Gel.

b. The Medication Guide distribution plan is generally acceptable.

We have some editorial comments in this section of the proposed REMS.

c. We remind you of the requirement to comply with 21 CFR 208.24:

- A required statement alerting the dispenser to provide the Medication Guide with the product must be on the carton and container of all strengths and formulations. We recommend the following language

dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

"Dispense the enclosed Medication Guide to each patient." or

"Dispense the accompanying Medication Guide to each patient."

d. Your proposed timetable for submission of assessments (18 months, 3 years, and 7 years) is acceptable.

You will need to prominently identify the submission containing the REMS assessments with the following wording in bold capital letters at the top of the first page of the submission:

<<Insert application #>> REMS ASSESSMENT

You should consider whether or not it is appropriate to submit the assessments within the Periodic Reports.

e. Please submit for review a detailed plan to evaluate patients' understanding about the safe use of FORTESTA (testosterone) 2% Gel. Your detailed plan should be submitted as part of the REMS supporting document. This information **does not** need to be submitted for FDA review prior to approval of your REMS, however it should be submitted at least 90 days before you plan to conduct the evaluation. The submission should be coded "REMS-Other." If you plan to conduct this assessment using a survey, your submission should include:

- All methodology and instruments that will be used to evaluate the patients' understanding about the safe use of FORTESTA (testosterone) 2% Gel. This should include, but not be limited to:
  - Sample size and confidence associated with that sample size
  - How the sample will be determined (selection criteria)
  - The expected number of patients to be surveyed
  - How the participants will be recruited
  - How and how often the surveys will be administered
  - Explain controls used to minimize bias
  - Explain controls used to compensate for the limitations associated with the methodology
- The survey instruments (questionnaires and/or moderator's guide).
- Any background information on testing survey questions and correlation to the messages in the Medication Guide.

Please let us know if you have any questions.

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/s/

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