DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-454

Auxilium Pharmaceuticals, Inc.
Attention: Benjamin Del Tito, Jr., Ph.D.
Senior Vice President, Quality and Regulatory Affairs
40 Valley Stream Parkway
Malvern, PA 19355

Dear Dr. Del Tito:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Testim™ 1% (testosterone gel), 50 mg and 100 mg.

Sections 505(o)(4) and 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorize FDA to require holders of approved drug and biological product applications to make safety related label changes and develop and comply with Risk Evaluation and Mitigation Strategies (REMS) based upon new safety information that becomes available after approval of the drug or biological product.

Since Testim was approved on October 31, 2002, we have become aware, through spontaneous postmarketing adverse event reports and peer-reviewed biomedical literature, of cases of secondary exposure of children to testosterone due to drug transfer from adult males using testosterone gel drug products. We consider this information to be "new safety information" as defined in FDAAA.

SAFETY LABELING CHANGES

In accordance with section 505(o)(4) of the FDCA, we are notifying you that, based on the new safety information described above, we believe that the new safety information should be included in the labeling for Testim as follows (additions are noted by underline and deletions are noted by ~~strikethrough~~):

- A **Boxed Warning** should be added and must include the following language:

WARNING: SECONDARY EXPOSURE TO TESTOSTERONE

- **Virilization in children and women can occur after secondary exposure to testosterone in testosterone gel products, including Testim.**
- **Children and women should avoid contact with Testim application sites on men using Testim.**
- **Testim users should adhere to recommended instructions for use.**
- **See WARNINGS**

WARNINGS

1. Men treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic carcinoma. Geriatric patients and other patients with clinical or demographic characteristics that are recognized to be associated with an increased risk of prostate cancer should be evaluated for the presence of prostate cancer prior to initiation of testosterone replacement therapy. In men receiving testosterone replacement therapy, surveillance for prostate cancer should be consistent with current practices for eugonadal men (see PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility and Laboratory Tests).
2. Potential for Secondary Exposure to Testosterone
    - Secondary exposure to testosterone in children and women can occur with Testim use in men. Cases of secondary exposure resulting in virilization of children have been reported in postmarketing surveillance of testosterone containing gel products. Signs and symptoms have included enlargement of the penis or clitoris, development of pubic hair, increased erections and libido, aggressive behavior, and advanced bone age. In most cases, these signs and symptoms regressed with removal of the exposure to testosterone. In a few cases, however, enlarged genitalia did not fully return to age-appropriate normal size, and bone age remained modestly greater than chronological age. The risk of transfer was increased in some of these cases by not adhering to precautions for the appropriate use of the testosterone gel product.
    - Inappropriate changes in genital size or development of pubic hair or libido in children, or changes in body hair distribution, significant increase in acne, or other signs of virilization in adult women should be brought to the attention of a physician and the possibility of secondary exposure to Testim should also be brought to the attention of a physician. Testim should be promptly discontinued at least until the cause of virilization has been identified.
3. **Strict adherence to the following precautions is advised in order to minimize the potential for secondary exposure to testosterone from Testim-treated skin:**
        - Children and women should avoid contact with Testim application sites on the skin of men using Testim.

- Testim should only be applied to the shoulders or upper arms.
- Patients should wash their hands immediately with soap and water after application of Testim.
- Patients should cover the application site(s) with clothing (e.g., a shirt) after the gel has dried.
- Prior to any situation in which skin-to-skin contact is anticipated, patients should wash the application site(s) thoroughly with soap and water to remove any testosterone residue.
- In the event that unwashed or unclothed skin to which Testim has been applied comes in direct contact with the skin of another person, the general area of contact on the other person should be washed with soap and water as soon as possible. Studies show that residual testosterone is removed from the skin surface by washing with soap and water.

4. Testim should not be applied to the abdomen.

5. Prolonged use of high doses of orally active 17-alpha-alkyl androgens (e.g., methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatitis, hepatic neoplasms, cholestatic hepatitis, and jaundice). Peliosis hepatitis can be a life-threatening or fatal complication. Long-term therapy with testosterone enanthate, which elevates blood levels for prolonged periods has produced multiple hepatic adenomas. Transdermal testosterone is not known to produce these adverse effects.

~~3. Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic carcinoma.~~ [This information moved to Item 1 above.]

~~4. Geriatric patients and other patients with clinical or demographic characteristics that are recognized to be associated with an increased risk of prostate cancer should be evaluated for the presence of prostate cancer prior to initiation of testosterone replacement therapy. In men receiving testosterone replacement therapy, surveillance for prostate cancer should be consistent with current practices for eugonadal men (see PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility and Laboratory Tests)~~ [This information moved to Item 1 above.]

6. Edema, with or without congestive heart failure, may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease. In addition to discontinuation of the drug, diuretic therapy may be required.

7. Gynecomastia occasionally develops and occasionally persists in patients being treated for hypogonadism.

8. The treatment of hypogonadal men with testosterone may potentiate sleep apnea in some patients, especially those with risk factors such as obesity or chronic lung diseases.

PRECAUTIONS

~~Transfer of testosterone to another person can occur when vigorous skin-to-skin contact is made with the application site (See Clinical Studies).~~

~~The following precautions are recommended to minimize potential transfer of testosterone from Testim™ treated skin to another person:~~ [This information moved to paragraph 3]

- ~~Patients should wash their hands thoroughly and immediately with soap and water after application of Testim. Studies of hand-washing show that Testim is effectively removed from the skin surface by thorough washing with soap and water.~~
- ~~Patients should cover the application site(s) with clothing after the gel has dried (e.g. a shirt).~~
- ~~Prior to any situation in which direct skin-to-skin contact is anticipated, patients should wash the application sites thoroughly with soap and water so as to remove drug residue.~~
- ~~In the event that unwashed or unclothed skin to which Testim has been applied does come in direct contact with the skin of another person, the general area of contact on the other person should be washed thoroughly with soap and water as soon as possible.~~

~~Changes in body hair distribution, significant increase in acne, or other signs of virilization of the female partner should be brought to the attention of a physician.~~

General

The physician should instruct patients to report any of the following:

- Too frequent or persistent erections of the penis.
- Any changes in skin color, ankle swelling or unexplained nausea and vomiting.
- Breathing disturbances, including those associated with sleep.

Information for Patients

Advise patients to carefully read the ~~information brochure~~ Medication Guide that accompanies each carton of 30 Testim™ single-use tubes.

Advise patients of the following:

1. Men with known or suspected prostate or breast cancer should not use Testim.
2. Secondary exposure to testosterone in children and women can occur with the use of testosterone gel products. Cases of secondary exposure to testosterone have been reported in children with signs and symptoms including enlargement of the penis or clitoris (one case underwent clitoral reduction surgery), premature development of pubic hair, increased erections, and aggressive behavior.

   Inappropriate changes in genital size or premature development of pubic hair or libido in children, or changes in hair distribution, increase in acne, or other signs of testosterone effects in adult women should be brought to the attention of a physician and the possibility of secondary exposure to Testim also should be brought to the attention of a physician. Testim should be promptly discontinued at least until the cause of virilization is identified.

3. **Strict adherence to the following precautions is advised in order to minimize the potential for secondary exposure to testosterone from Testim-treated skin:**

    - Children and women should avoid contact with Testim application sites on the skin of men using Testim.
    - Testim should only be applied to the shoulders or upper arms.
    - Patients should wash their hands immediately with soap and water after application of Testim.
    - Patients should cover the application site(s) with clothing (e.g., a shirt) after the gel has dried.
    - Prior to any situation in which skin-to-skin contact is anticipated, patients should wash the application site(s) thoroughly with soap and water to remove any testosterone residue.
    - In the event that unwashed or unclothed skin to which Testim has been applied comes in direct contact with the skin of another person, the general area of contact on the other person should be washed with soap and water as soon as possible. Studies show that residual testosterone is removed from the skin surface by washing with soap and water.

Also advise patients of the following:

- Testim should not be applied to the scrotum, penis or abdomen.
- Testim should be applied once daily at approximately the same time each day to clean dry skin of the shoulders and/or upper arms.
- Washing or swimming may lessen testosterone levels; when washing occurs two or more hours post drug application, however, serum testosterone levels remain within the normal range.

- ~~Testim™ should not be applied to the scrotum, penis, or abdomen.~~ [Moved above]
- ~~Testim™ should be applied once daily at approximately the same time each day to clean dry skin of the shoulders and/or upper arms.~~ [Moved above.]
- ~~Washing or swimming may lessen testosterone levels; however, when washing occurs two or more hours post drug application, serum testosterone levels remain within the normal range.~~ [Moved above.]
- ~~Testim™ may be transferred to another person by vigorous contact with the application site. Potential for transfer may be reduced by washing hands thoroughly after application, by wearing clothing to cover the sites, and by washing the application sites thoroughly with soap and water prior to any direct skin-to-skin contact.~~

HOW SUPPLIED

Disposal

Keep out of the reach of children.

Used Testim™ tubes should be discarded in household trash in a manner that prevents accidental ~~application or ingestion by~~ exposure of children or pets; contents flammable.

Medication Guide

- In addition to the changes to labeling described above, you should convert your patient package insert to a Medication Guide for Testim. Your Medication Guide must include information about the serious risk of secondary exposure to testosterone and will be considered part of the proposed REMS described below. Your proposed Medication Guide should be consistent with 21 CFR 208.20. Information included in the Medication Guide should reflect the changes requested in the Physician Labeling which are outlined in this letter. Specifically, the changes made to the **WARNINGS** and **PRECAUTIONS** sections of the Physician Labeling should be included in the Medication Guide in language appropriate for patients.
- In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a supplement proposing changes to the approved labeling for Testim in accordance with this letter, or notify FDA that you do not believe a labeling change is warranted and submit a statement detailing the reasons why such a change is not warranted.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Testim to ensure that the benefits of the drug outweigh the risk of secondary exposure of children to testosterone due to drug transfer from adult males using testosterone gel drug products.

Your proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Testim poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Testim. FDA has determined that Testim is a product that has a serious risk (relative to benefits) of which patients should be made aware because information concerning the risk could affect patients' decisions to use, or continue to use, Testim. FDA has also determined that Testim is a product for which patient labeling could help prevent serious adverse events.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Testim.

The approved Medication Guide described above under Safety Labeling Changes will be considered part of the REMS.

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments of the REMS that shall be no less frequent than by 18 months,

3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Your assessment of the REMS should include an evaluation of:

a. Prescribers' and patients' understanding of the serious risk of secondary exposure due to drug transfer from adult patients to children
b. The distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
c. Failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
d. Whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

In accordance with section 505(o)(4) and section 505-1, within 30 days of the date of this letter, you must submit a prior-approval supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted. In accordance with section 505-1, you must also submit a proposed REMS within 30 days of the date of this letter. The supplement or statement about the safety labeling change and the proposed REMS should be included in the same submission. The REMS, once approved, will create enforceable obligations.

We suggest that your proposed REMS submission include two parts: a "Proposed REMS" and a "REMS Supporting Document." Attached is a template for the Proposed REMS that you should complete with concise, specific information (see Appendix A). Once FDA finds the content acceptable, we will include this document as an attachment to the approval letter that includes the REMS.

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

The safety labeling changes portion of the supplement should contain the Medication Guide for Testim. Include labeling in both Microsoft Word format and content of labeling in structured product labeling (SPL) format as described at: http://www.fda.gov/oc/datacouncil/spl.html.

Under 21 CFR 208.24(d), you are also responsible for ensuring that the label of each container or package, where the container label is too small, includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and state how the Medication Guide is provided. The safety labeling changes portion of the supplement should contain marked up package or container labels of all strengths

and formulations with the required statement alerting the dispenser to provide the Medication Guide. 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."

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

NEW SUPPLEMENT FOR NDA 21-454
PROPOSED REMS
AND
SAFETY LABELING CHANGES UNDER 505(o)(4) – PRIOR APPROVAL SUPPLEMENT

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – CHANGE NOT WARRANTED

Prominently identify subsequent submissions related to the proposed REMS and/or the safety labeling changes with the following wording in bold capital letters at the top of the first page of the submission:

SUPPLEMENT <<insert assigned #>>
PROPOSED REMS-AMENDMENT

AND/OR

SUPPLEMENT <<insert assigned #>>
SAFETY LABELING CHANGES UNDER 505(o)(4) - AMENDMENT

If you do not submit electronically, please send 5 copies of your proposed REMS.

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

Sincerely,

{See appended electronic signature page}

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

APPENDIX A: MEDICATION GUIDE REMS TEMPLATE

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name
Address
Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide

If a Medication Guide is included in the proposed REMS, include the following:

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

APPENDIX B:

REMS SUPPORTING DOCUMENT TEMPLATE
MEDICATION GUIDE REMS

This REMS Supporting Document should include the following listed sections 1 through 6. Include in section 4 the reason that the Medication Guide proposed to be included in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents

2. Background

3. Goals

4. Supporting Information on Proposed REMS Elements

    a. Medication Guide

    b. Timetable for Assessment of the REMS (for products approved under an NDA or BLA)

5. REMS Assessment Plan (for products approved under an NDA or BLA)

6. Other Relevant Information

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

/s/

Scott Monroe

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