DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-454/S-008

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 supplemental new drug application dated May 22, 2009, and received May 26, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TESTIM® 1% (testosterone gel).

We acknowledge receipt of your submissions dated June 22, July 20, August 28, and September 14, 15, and 17, 2009.

Reference is also made to our letter dated April 22, 2009, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for testosterone gel products. This information pertains to the risk of secondary exposure of children to testosterone due to drug transfer from adult males using testosterone gel products. The letter also notified you, under Section 505-1 of the FDCA, that you were required to submit a proposed Risk Evaluation and Mitigation Strategy (REMS) for Testim 1% (testosterone gel).

This supplemental new drug application provides for revisions to the labeling for Testim 1% (testosterone gel) and a proposed REMS. The agreed upon revisions to the Package Insert include the following changes regarding the risk of secondary exposure of children to testosterone.

- A new Boxed Warning was added:

WARNING: SECONDARY EXPOSURE TO TESTOSTERONE

- **Virilization has been reported in children who were secondarily exposed to testosterone gel.**
- **Children should avoid contact with unwashed or unclothed application sites in men using testosterone gel.**
- **Healthcare providers should advise patients to strictly adhere to recommended instructions for use.**

(See WARNINGS, Potential for Secondary Exposure to Testosterone)

- A subsection entitled "Potential for Secondary Exposure to Testosterone" was added to the **WARNINGS** section:

  Potential for Secondary Exposure to Testosterone

  - Secondary exposure to testosterone in children and women can occur with testosterone gel 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 testosterone gel should also be brought to the attention of a physician. Testosterone gel should be promptly discontinued until the cause of virilization has been identified.

- The list of precautions to minimize the potential for secondary exposure to testosterone, which was originally in the **PRECAUTIONS** section, was also added to the **WARNINGS** section. The list of precautions was expanded in both sections to include the following:
  - 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 (area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt).

- The Information for Patients subsection of the **PRECAUTIONS** section was revised to reference the Medication Guide.

- The following information was added to the Advise Patients of the Following subsection of the **PRECAUTIONS** section:

  Secondary exposure to testosterone in children and women can occur with the use of testosterone gel products in men. Cases of secondary exposure to testosterone have been reported in children with signs and symptoms including enlargement of the penis or clitoris, premature development of pubic hair, increased erections, and aggressive behavior.

  Unexpected sexual development including inappropriate enlargement of the penis or clitoris, premature development of pubic hair, increased erections, and aggressive behavior 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 testosterone gel also should be brought to the attention of a physician. Testosterone gel should be promptly discontinued until the cause of virilization is identified.

- A new subsection entitled "*Postmarketing Experience*" was added to the **ADVERSE REACTIONS** section and the following information was included:

  Secondary Exposure to Testosterone in Children

  Cases of secondary exposure to testosterone resulting in virilization of children have been reported in postmarketing surveillance of testosterone gel products. Signs and symptoms of these reported cases have included enlargement of the clitoris (with surgical intervention) or of the penis, development of pubic hair, increased erections and libido, aggressive behavior, and advanced bone age. In most cases with a reported outcome, these signs and symptoms were reported to have regressed with removal of the testosterone gel exposure. 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. In some of the cases, direct contact with the sites of application on the skin of men using testosterone gel was reported. In at least one reported case, the reporter considered the possibility of secondary exposure from items such as the testosterone gel user's shirts and/or other fabrics, such as towels and sheets (see WARNINGS).

We have completed our review of this supplemental application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the enclosed labeling. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission **"SPL for approved supplement NDA 21-454/S-008."**

In addition, within 21 days of the date of this letter, amend any pending applications for this NDA with content of labeling in structured product labeling (SPL) format to include the changes approved in this application.

Marketing the product with FPL that is not identical to the approved labeling text and in the required format may render the product misbranded and an unapproved new drug.

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on May 22, 2009, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and**

Container Labels for approved NDA 21-454/S-008." Approval of this submission by FDA is not required before the labeling is used.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

Since Testim 1% (testosterone gel) 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 products. We consider this information to be "new safety information" as defined in the Food and Drug Administration Amendments Act (FDAAA).

Your proposed REMS, submitted on September 17, 2009, and appended to this letter, is approved. The REMS consists of the Medication Guide included with this letter and the timetable for submission of assessments of the REMS.

The REMS assessment plan should include an evaluation of patients' understanding of the serious risks of Testim 1% (testosterone gel).

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), requirements for information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify submissions containing REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission:

NDA 21-454 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 21-454
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT FOR (NEW INDICATION FOR USE) FOR NDA 21-454
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Jeannie Roule, Regulatory 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

Enclosures: Labeling (Package Insert, Medication Guide)
REMS

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21454	SUPPL-8	AUXILIUM PHARMACEUTICALS	TESTIM 1% (TESTOSTERONE GEL)

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

/s/

SCOTT E MONROE
09/18/2009