



NDA 21-015/S-022

Solvay Pharmaceuticals, Inc.
Attention: Steven Wojtanowski, R.Ph., M.P.H.
Assistant Director, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Wojtanowski:

Please refer to your supplemental new drug application dated May 21, 2009, and received May 22, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for AndroGel (testosterone gel) 1% for topical use.

We acknowledge receipt of your submissions dated May 28, June 19, July 24, August 19, and September 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 AndroGel (testosterone gel) 1%.

This supplemental new drug application provides for revisions to the labeling for AndroGel (testosterone gel) 1% and 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 to the **HIGHLIGHTS OF PRESCRIBING INFORMATION** and the **FULL PRESCRIBING INFORMATION**:

WARNING: SECONDARY EXPOSURE TO TESTOSTERONE

See full prescribing information for complete boxed warning

- **Virilization has been reported in children who were secondarily exposed to testosterone gel (5.2, 6.2).**
- **Children should avoid contact with unwashed or unclothed application sites in men using testosterone gel (5.2).**
- **Healthcare providers should advise patients to strictly adhere to recommended instructions for use (5.2).**

- **WARNINGS AND PRECAUTIONS (HIGHLIGHTS)** – Added text included the following:
 - Secondary exposure to testosterone in children and women can occur with use of testosterone gel (5.2). Cases of secondary exposure resulting in virilization of children have been reported (6.2).
 - Children and women should avoid contact with unwashed or unclothed application site(s) in men using testosterone gel.
 - To minimize the potential for transfer to others, patients using AndroGel should apply the product as directed and strictly adhere to the following (5.2):
 - Wash hands with soap and water after application.
 - Cover the application site with clothing after the gel has dried.
 - Wash the application site thoroughly with soap and water prior to any situation where skin-to-skin contact of the application site with another person is anticipated.
 - Signs of virilization in children and women and the possibility of secondary exposure to testosterone gel should be brought to the attention of the healthcare provider. Testosterone gel should be promptly discontinued until the cause of the virilization is identified (5.2).
- **ADVERSE REACTIONS (HIGHLIGHTS)** – The following text was added:

Cases of testosterone secondary exposure resulting in virilization of children have been reported (6.2). Reported signs and symptoms have included enlargement of the penis or clitoris, premature 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 exposure to testosterone gel (5.2, 6.2). 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.
- **WARNINGS AND PRECAUTIONS (FULL PRESCRIBING INFORMATION),** Section 5.2 – Findings in children exposed to testosterone were added:

5.2 Potential for Secondary Exposure to Testosterone

Secondary exposure to testosterone in children and women can occur with testosterone gel use in men [*see Clinical Studies (14.3)*]. Cases of secondary exposure resulting in virilization of children have been reported in postmarketing surveillance. 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 gel. 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 testosterone gel.

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.

- **ADVERSE REACTIONS (FULL PRESCRIBING INFORMATION)** – The following text was added to Section 6.2 (**Postmarketing Experience**):

Secondary Exposure to Testosterone in Children

Cases of secondary exposure to testosterone resulting in virilization of children have been reported in postmarket surveillance. Signs and symptoms of these reported cases have included enlargement of the clitoris (with surgical intervention) or 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 fabric, such as towels and sheets [*see Warnings and Precautions (5.2)*].

- **PATIENT COUNSELING INFORMATION (FULL PRESCRIBING INFORMATION)** – This section was revised to include references to the FDA-approved Medication Guide and new text was added to Section 17.2 included the following:

17.2 Potential for Secondary Exposure to Testosterone and Steps to Prevent Secondary Exposure

Secondary exposure to testosterone in children and women can occur with the use of testosterone gel 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.

- Physicians should advise patients of the reported signs and symptoms of secondary exposure which may include the following:
 - In children; unexpected sexual development including inappropriate enlargement of the penis or clitoris, premature development of pubic hair, increased erections, and aggressive behavior
 - In women; changes in hair distribution, increase in acne, or other signs of testosterone effects
- The possibility of secondary exposure to testosterone gel should be brought to the attention of a healthcare provider
- Testosterone gel should be promptly discontinued until the cause of virilization is identified

Strict adherence to the following precautions is advised to minimize the potential for secondary exposure to testosterone from testosterone gel in men [*see FDA-Approved Medication Guide (17.5)*]:

- **Children and women should avoid contact with unwashed or unclothed application site(s)** of men using testosterone gel.

- **To minimize the potential for transfer** to others, patients using AndroGel should apply the product as directed and strictly adhere to the following:
 - **Wash hands** with soap and water after application.
 - **Cover the application site(s)** with clothing after the gel has dried.
 - **Wash the application site(s) thoroughly** with soap and water prior to any situation where skin-to-skin contact of the application site with another person is anticipated.
 - In the event that unwashed or unclothed skin to which testosterone gel has been applied comes in 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.

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 21-015/S-022.**”

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 21, 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 21-015/S-022.**” 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 AndroGel (testosterone gel) 1% was approved on February 28, 2000, 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 AndroGel (testosterone gel) 1%.

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 21-015 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 21-015
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT FOR (NEW INDICATION FOR USE)
FOR NDA 21-015
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-21015

SUPPL-22

UNIMED
PHARMACEUTICA
LS INC

ANDROGEL(TESTOSTERONE
GEL) 25MG/50MG

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