DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-015

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 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AndroGel® (testosterone gel) 1%.

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 AndroGel 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 AndroGel. 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 AndroGel as follows (additions are noted by underline and deletions are noted by ~~strikethrough~~):

- A **Boxed Warning** should be added to the **HIGHLIGHTS OF PRESCRIBING INFORMATION** and **FULL PRESCRIBING INFORMATION** sections and must include the following language:

> **WARNING: SECONDARY EXPOSURE TO TESTOSTERONE**
>
> - **Virilization in children and women can occur after secondary exposure to testosterone in AndroGel.**
> - **Children and women should avoid contact with AndroGel application sites on men using AndroGel (5.2).**
> - **AndroGel users should adhere to recommended instructions for use (17.2)**

- **WARNINGS AND PRECAUTIONS** (**HIGHLIGHTS OF PRESCRIBING INFORMATION)** section:
  - ~~Patients with benign prostatic hyperplasia (BPH) treated with androgens are at an increased risk for worsening of signs and symptoms of BPH (5.1)~~Patients treated with androgens may be at increased risk for prostate cancer (5.1)
  - ~~Cover application site and wash hands to prevent testosterone transfer to others (5.2)~~ Patients with benign prostatic hyperplasia (BPH) treated with androgens are at an increased risk for worsening of signs and symptoms of BPH (5.1)
  - Secondary exposure to testosterone in children and women can occur with use of AndroGel (5.2). Cases of secondary exposure resulting in virilization of children have been reported (6.2). To minimize the potential for transfer to others, strict adherence to the following is advised (17.2):
    - Children and women should avoid contact with AndroGel application sites on the skin of men using AndroGel.
    - AndroGel users should:
      - 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 with another person is anticipated.
  - Signs of virilization in children and women and the possibility of secondary exposure to AndroGel should be brought to the attention of the healthcare provider. AndroGel should be promptly discontinued until the cause of the virilization is identified (5.2).
  - Due to lack of controlled evaluations in women and potential virilizing effects, AndroGel is not indicated for use in women (5.3)
  - Exogenous administration of androgens may lead to azoospermia (5.4)
  - Edema may be a complication in patients with preexisting cardiac, renal, or hepatic disease (5.6, 6.2)
  - Gynecomastia, enlargement of breast, may develop (5.7)
  - Sleep apnea may occur in those with risk factors (5.8)
  - Monitor serum testosterone, prostatic specific antigen, hemoglobin, hematocrit, liver function test, and lipid levels periodically (2.3, 5.1, 5.9)
  - Alcohol-based gels are flammable until dry (5.10)

- **ADVERSE REACTIONS (HIGHLIGHTS OF PRESCRIBING INFORMATION)** section:

  Most common adverse reactions (incidence ≥ 5%) are acne, application site reaction, abnormal lab tests, and prostatic disorders. (6)

  Cases of testosterone secondary exposure resulting in virilization of children have been reported (6.2). Signs and symptoms have included inappropriate enlargement of the penis or clitoris, premature 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 AndroGel. 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.

  To report SUSPECTED ADVERSE REACTIONS, contact Solvay Pharmaceuticals, Inc. at 1-800-241-1643 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

- **Boxed Warning (FULL PRESCRIBING INFORMATION)** section:

  Insert as directed above in **HIGHLIGHTS OF PRESCRIBING INFORMATION** section.

- **WARNINGS AND PRECAUTIONS (FULL PRESCRIBING INFORMATION)** section:

  5.2 Potential for Secondary Exposure to Testosterone ~~Transfer to Others~~

  ~~Transfer of testosterone to others (including women and children) can occur when vigorous skin-to-skin contact is made with the application site *[see Clinical Studies (14.3)]*. The following precautions are recommended to minimize potential transfer of testosterone from AndroGel-treated skin to another person:~~

  Secondary exposure to testosterone (including in children and women) can occur with AndroGel 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 AndroGel. 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 AndroGel.

  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 AndroGel should also be brought to the attention of a physician. AndroGel should be promptly discontinued at least until the cause of virilization has been identified.

  AndroGel may cause fetal harm in a pregnant woman due to virilization of a female fetus *[see Use in Specific Populations (8.1)]*.

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

- Children and women should avoid contact with AndroGel application sites on the skin of men using AndroGel.
- AndroGel should only be applied to the shoulders, upper arms, and/or abdomen.
- Patients should wash their hands immediately with soap and water after application of AndroGel.
- 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 AndroGel 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.

~~• Patients should wash their hands immediately with soap and water after application of AndroGel.~~ [Moved to 3rd bullet above]

~~• Patients should cover the application site(s) with clothing after the gel has dried (e.g., a shirt).~~ [Moved to 4th bullet above]

~~• In the event that unwashed or unclothed skin to which AndroGel 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 with soap and water as soon as possible. In vitro studies show that residual testosterone is removed from the skin surface by washing with soap and water.~~ [Moved to the 6th bullet above]

~~• Women and children should avoid skin contact with AndroGel application sites in males. Changes in body hair distribution, significant increase in acne, or other signs of virilization should be brought to the attention of a physician. AndroGel may cause fetal harm in a pregnant woman due to virilization of a female fetus *[see Use in Specific Populations (8.1)].*~~

- **ADVERSE REACTIONS (FULL PRESCRIBING INFORMATION)** section:

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of AndroGel. Because the 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.

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 have included enlargement of the penis or clitoris (one reported case underwent clitoral reduction surgery), 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 testosterone 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 most of the cases, direct contact with the sites of application on the skin of men using AndroGel was reported. In at least one reported case, the reporter considered the possibility of secondary exposure from items such as the AndroGel user's shirts and bed linens.

[The remainder of subsection 6.2 (including Table 4) is unchanged from the current labeling]

- **PATIENT COUNSELING INFORMATION (FULL PRESCRIBING INFORMATION)** section:

17.1 Use in men with known or suspected prostate or breast cancer

Men with known or suspected prostate or breast cancer should not use AndroGel.

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

Secondary exposure to testosterone (including in children and women) can occur with the use of AndroGel in men. Cases of secondary exposure to testosterone have been reported in children with signs and symptoms including enlargement of the penis or clitoris (one reported 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 AndroGel also should be brought to the attention of a physician. AndroGel should be promptly discontinued at least 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 AndroGel in men:

- Children and women should avoid contact with AndroGel application sites on the skin of men using AndroGel.
- AndroGel should only be applied to the shoulders, upper arms, and/or abdomen once daily, preferably in the morning.
- Patients should wash their hands immediately with soap and water after application of AndroGel.

- 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 testosterone residue.
- In the event that unwashed or unclothed skin to which AndroGel 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.

17.~~1~~3 Potential Adverse Reactions with Androgens

[Wording in this subsection remains unchanged from the wording in subsection 17.1 of the current label]

17.~~2~~4 Instructions for Use of AndroGel

- Patients should be informed to apply AndroGel once daily (preferably in the morning) to clean, dry skin of the shoulders and upper arms and/or abdomen. **To prevent ~~transfer~~ secondary exposure of testosterone from AndroGel to others, patients should wash their hands after application and cover the application site with clothing *[see Potential for Secondary Exposure to Testosterone (17.2)]*.**
- 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 testosterone residue.
- **Advise patients that AndroGel is an alcohol based product and is flammable, therefore avoid fire, flame or smoking until the gel has dried**.
- Counsel patients on the importance of adhering to all recommended monitoring by their healthcare professional.
- Advise patients to report any changes in their state of health, such as changes in urinary habits, breathing, sleep, and mood.

Medication Guide

- In addition to the changes to labeling described above, you should convert your patient package insert (currently 17.3 FDA-Approved Patient Labeling) to a Medication Guide for AndroGel. 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** and

PATIENT COUNSELING INFORMATION 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 AndroGel 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 AndroGel to ensure that the benefits of the drug outweigh the risk of secondary exposure children to testosterone due to drug transfer from adult patients using AndroGel.

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 AndroGel 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 AndroGel. FDA has determined that AndroGel 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, AndroGel. FDA has also determined that AndroGel 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 AndroGel.

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 AndroGel
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 AndroGel. 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 21-015
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 submission.

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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